

Impact of Quality Risk Management Process in Pharmaceutical Industry to Curtail the Non-Conformity

Aachchhadita Sharma, Raju Mari Jeyaprakash*, Rinchi Bora, Abinash Chandra

Department of Pharmaceutical Analysis, JSS College of Pharmacy, Ooty-643001, Tamil Nadu, India

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ABSTRACT

Risk is intertwined with every drug product in a market. This article's intent is to provide ground rule and praxis of different tools for quality risk management (QRM) in various aspects of pharmaceutical science. QRM comprises of tools and processes which helps in establishing objectives. Hence they are also known as Enablers. Enablers help in risk mitigation of product quality throughout a lifecycle in such a way that benefit outweighs the risk. The key properties of Enablers or QRM, i.e., attempts made, solemnness and records shall be compatible with risk scale. The Enablers accomplishment gives recognized, obvious and steps of Enabler process produced by regeneratable methods which is based on customary comprehension to evaluate feasibility, ability to find out risk prejudice. The QRM or Enabler tools can assist the manufacturing company and regulatory bodies to scrutinize, handle, notify, and inspect the risk.

Keywords: Applications, Investigation parameters, QRM Methods, Quality risk management process, Tools.

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INTRODUCTION

The QRM or Enablers are a fundamental feature of the regulatory bodies for a quality product. In the US, during the Mexican-American War of 1846–1848, many deaths occurred. The reason was not a slaughter scene in wartime only, but also due to a lack of safety and efficacy of imported drugs. The United States Import Drug Act 1848 was authorized for testing and assuring the safety and purity of imported drugs before crossing the border. The modern finding of risk management for drug and biological products arose with a 1999 risk management report to the Food and Drug Administration (FDA) Commissioner by Task Force. A conception for proactive risk management including internal Risk and external Risk was approved in August 2002 with the declaration of a new Food and Drug Administration proposal entitled “Pharmaceutical cGMPs for the 21st Century- A Risk-based approach”. In September 2004, the conclusive report on the FDA proposal emerged. The report foretold that industry and FDA should adopt the quality systems model for quality management and regulations.¹ The olden ways to assure quality in product and process are Trends review, Changes review, Flow charts, Checklists, Observation compilations (Complaints, Deviations, etc.). Now quality risk management ground rules are implemented across the industry with the help of predictable QRM or Enabler tools hold up with statistical tools.

THE QUALITY RISK MANAGEMENT

ICH states that “Quality Risk Management (QRM) is a systematic process for the assessment, control, communication, and review of risk to the quality of the medicinal product across the product lifecycle.³ The entire ICH-Q9 guideline is devoted to quality risk management as QRM or enablers play an important role in producing a quality product. QRM or Enablers ascertain that the quality risk evaluation is based on customary comprehension, absolute process awareness, and eventually keeping patients safe. QRM or Enablers could be a proactive or retrospective strategy.

TOPICS ENCLOSED BY ENABLERS OR QRM

- Praxis of risk analysis, QMS risk, and risk of CAPA systems.
- Praxis of risk assessment for product-market complaints monitoring.
- Praxis of risk analysis in pharmaceutical manufacturing compliance and audit.
- Praxis of risk principles to actuate or bring into operation, product qualification, and product validation.
- Quality risk management master plan advancement.
- Hazard analysis and critical control point (haccp) in manufacturing and operation monitoring.
- ICH Q9- Pharmaceutical quality risk management.

*Author for Correspondence: jpvvis7@gmail.com

- Ground rules of risk management (analysis, control, and conduct).
- Risk analysis and control praxis in design or program control.
- Regulatory guidance to make use of QRM or enablers in pharmaceuticals- ICH, EU/TGA/PICS, FDA.
- Quality by Design- Risk analysis in the design and development of products.

APPROACH ON QUALITY RISK MANAGEMENT AS PER THE FDA²

As per the FDA, a conservation plan is formulated to reduce the threat to product quality by utilizing single or multiple tools, which is known as Quality Risk Management. The FDA suggested that the sponsor submitting the application for approval of the product shall plan a strategy to lower the risks while the product is in the commercial market for use. Quality Risk Management may include product packaging and labeling, risk examination, pharmacovigilance, and hindrance in peculiar studies.

The FDA looks forward to follow the underlying process for Risk Management, such as:

<i>FDA Guidelines</i>	<i>QRM Elements</i>
Educating about and interpreting product's profits and risks.	Risk detection technique, Risk assessment technique, risk, and issue management technique.
Designing and implementing interventions to minimize the product's risks.	Risk and issue management plan, Risk response planning.
Evaluating interventions.	Risk and issue management plan.

QUALITY RISK MANAGEMENT PRINCIPLES^{3,4}

- It should be dynamic, iterative and responsive to change.
- The appraisal of the risk to quality should be established as per scientific knowledge and ultimately relates to the protection of the patient.
- The level of formality, effort and documentation of the QRM process should be suitable to the level of risk.
- The capability for enhancement and continual development should be rooted in the QRM process.

QUALITY RISK MANAGEMENT PROCESS IN COMMON

The key parameters of Quality risk management comprises of detection, dissection and appraisal of the risk with respect to the vulnerability of the hazards that takes place. The organized structure comprises of various elements which help to build a vigorous course of action. The significance of each element may vary from event to event with respect to a particular hazard. QRM model is outlined in the diagram below.^{6,7}

INITIATING OF QUALITY RISK MANAGEMENT PROCESS

Steps involved³

- The dilemma or query of risk comprises of relevant theory detecting the probability of risk should be well defined.

- Backdrop facts about hazard probability, damage, and effect on human health concerning the risk appraisal should be gathered.
- A person in charge and an interdisciplinary team of basic assets should be recognized.
- Target completion date should be stated.

RISK ASSESSMENT

Risk assessment should start with a thorough account on the query of risk defining the difficulty to facilitate the selection of an appropriate QRM tool and to identify the kind of facts required to tackle the query of risk.⁵ Three vital queries should be employed:

- What may be incorrect?
- What is the likelihood that it will be incorrect?
- What are the probable outcomes?

STEPS INVOLVED IN THE RISK ASSESSMENT ARE^{7,8}

Assemble and Systemize the Facts

- Relevant facts, suitable context appraisal review should be gathered and detect the hypothesis.
- Information could be categorized with the help of various tools.
- The limits of the QRM workouts should be mentioned.

Originate the Query of Risk

- It is the initial point of the QRM workout.
- The synopsis containing details about the difficulty and the intention for performing QRM workout comprising of risk causes should be prepared.
- The scope of the difficulty and associated specification limits should be stated.

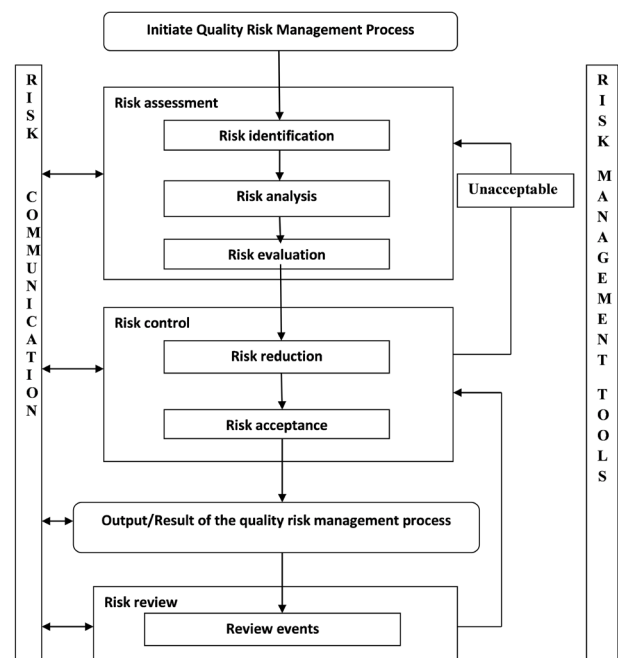


Figure 1: Overview of typical QRM process³

Opt Tools

- Basic risk management facilitation methods (flowcharts, check-sheets, etc.)
- Failure Mode Effect Analysis and Failure Mode Effects and Criticality analysis
- Fault Tree Analysis
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard and Operability Analysis
- Preliminary Hard Analysis
- Risk Ranking and Filtering
- Supporting Statistical Tools

Recognize Risk Causes and Associated Vulnerability

- Possible damage to the health of patients could be caused by hazards.
- Hazards could be classified into the following aspects: operator, environmental, systemic, reagent, and sampling.
- It might be simpler to discover the sort of control measures to be taken for unnecessary risk reduction.

Describe the Risk Constituents and Range⁶

$$\text{RISK} = \text{PRIORITY} \times \text{DETECTABILITY} \times \text{SEVERITY}$$

Where,

- Severity- Product complications
- Priority- Site difficulties
- Detection- Audit record

Appraise the Risk for Every Danger

- It decides how often the failure will occur.

Determine the Acceptability of Risks

- It looks after the critical aspects of harm to conclude acceptance or rejection of risk.

Establish Action Initiation

- It limits out of which activities will take place or not.

Install the Tool

- Scrutinize the detailed information about the risks and quantify the risks.
- Based on the initiation of action, determine what assessment should be done.

RISK IDENTIFICATION

Risk identification is a step to discover hazards relating to the risk query or account of difficulty that took place. Details might comprise theoretical analysis, chronological records, knowledgeable suggestions, and stockholder concerns. It addresses “What might be incorrect?” query and discovering probable outcome. Risk Identification should be built a foundation for other QRM steps to process further.

RISK ANALYSIS

Risk analysis is the process of finding out the risk intertwined with recognized danger. It helps in relating the probability of incidence and rigorousness of problems qualitatively and quantitatively. In few QRM tools, the evaluation of risk also comprises the factor harm detection ability.

RISK EVALUATION¹⁴

Risk evaluation is the comparison between risk recognized, and risk scrutinized versus specified criteria. The potency of facts or data for all queries related to risk is significant for risk evaluation.

Table 1: Severity

Severity Rating	Description
4.	<ul style="list-style-type: none"> • Service of the product is influenced. • Specifications corresponding to patient safety and efficacy failed to meet. • No batch re-processed, leading to an inspection, product out of stock. • Plant shutdown due to compliance or audit issue. • Regulatory investigation findings with a significant impact on the plant. (e.g., warning letter, a shipment of product is not approved from the plant). • Death or life-threatening injury to the patient due to failure.
3.	<ul style="list-style-type: none"> • The quality of product is influenced; the failure mode effect failed to meet up with quality specifications. • During the investigation, minor flaws discovered. • Inspection result containing details of man-hour impact affected by batch re-process. • Regulatory investigation findings without a significant impact on the plant.
2.	<ul style="list-style-type: none"> • Quality of Product quality is influenced; the failure mode effect failed to meet up with aesthetic properties. • Agreeable Risk: Aesthetic flaw encountered during the investigation. • Feasible yield impact: Production inadequacy. • Deviation closed without any additional investigation.
1.	<ul style="list-style-type: none"> • Agreeable risk: product quality and service is not harmed. • Product safety and service is not influenced. Feasible patient trouble if minor modification is done in the product.

Table 2: Probabilities

Probability Rating	Description
5.	Almost certain (every time): Risk incident anticipated to take place every time, seen several times a year.
4.	Likely: Risk incident more eventual than not to take place. Seen to happen more than once a year.
3.	Potential: Risk incident may or may not to take place. Seen every 1–2 years.
2.	Unlikely: Risk incident less eventual than not to take place. Seen every 2–5 years.
1.	Very rare: Risk incident not anticipated to take place. Seen every 5–10 years.

Table 3: Detection

<i>Detectability Rating</i>	<i>Detectability</i>
1.	Is always detected
2.	Is likely to be detected
3.	Is probable to be detected
4.	Is unlikely to be detected
5.	Is never detected

Risk Priority Number

The risk priority number (RPN) is a numeric assessment of risk assigned to a process, or steps in a process, as part of failure mode, effects and criticality analysis (FMECA).¹⁴

Detection ratings:

$$\text{RPN} = (\text{Severity/Consequences}) \times (\text{Probability of occurrence}) \times (\text{Chances of Detection})$$

A high RPN indicates that the risk is high, and a low RPN indicates that the risk is low. Ranking (scoring) and criteria for severity, occurrence, and detection is mention in Tables 3:

OUTPUT OF RISK ANALYSIS

The outcome of a risk appraisal should be risk estimated quantitatively, or intensity of risk described qualitatively. Quantitative risk estimation or assessment provides a set of risk generating events or numerical probability of a definite situation at a time. When the risk is expressed qualitatively, a qualitative descriptor, such as “high,” “medium,” or “low,” is used. Qualitative descriptors should contain thorough details. A “risk score” helps to determine relative risk on the whole by combining multiple grades of severity and occurrence. Both qualitatively and quantitatively risk could be used within a scoring process by the intermediate steps.

RISK CONTROL

It includes reducing risks to an acceptable level. The attempts made to control the risk should correspond to the consequences of the risk.¹⁴

- Measures taken to control risk should employ the following queries:
- Was the risk beyond the tolerable level?
- What actions might have been taken to lessen or eradicate risks?
- What was the adequate sense of balance between resources, advantages, and risks?
- Were new risks came into the frame was the outcome of the control efforts taken for acknowledged risk?

RISK REDUCTIONS

When quality risk surpasses the specified limit, measures are taken to lessen and avert the risk this process is known as Risk Reduction. It might include measures to reform the efficiency of detecting the harms and risks, lessen the severity and occurrence. The determined attempts made for reducing the risks should correspond to the impact of the hazards or risks. The steps taken for minimizing risks could bring forth new risks or boost up existing risks. Hence, after executing reduction process of risks, it is favorable to go through the risk

assessment again for classifying and analyzing any probable alteration to be done.

Ponder over events that would:⁸

- Reduce severity: prevent collapse before noteworthy impact, reject, and recall.
- Reduce probability: Examine deficiencies in the batch.
- Raise detection: Taking in concern clarifying events tools are reapplied and verified whether new risks occurred during clarifying events, shift from labor-intensive to a mechanical inspection.

RISK ACCEPTANCE

As risk control measures are applied, but lasting risks are not mentioned in the reactive conclusion, then a formal judgment is taken to accept the lasting risk; this process is known as risk acceptance. In some kind of hazards, the best QRM practices might not eliminate the risk entirely. In such events, QRM strategy has been implemented effectively, and whether the risk is under the acceptable limit should be assured. This tolerable limit would be depending on numerous factors and identified based on various events that took place.

RISK REVIEW

QRM is an ongoing component of quality management. The final QRM output/ result is as per the updated data, and practices should be reviewed at regular intervals. Risk assessment should be done in case of acquired knowledge from audits, field alert reports (FAR), recalls, deviations and Temporary change control proposals, etc. As QRM process is started, it should take over charge of all the events that might affect the original QRM decisions; they might be planned events (e.g., outcome of a product review, inspections, audits, change control proposal) or unplanned events (e.g., root cause failure investigations, product recall). Reviewing of Risk might include a reassessment of the risk acceptance decision. The periodic interval at which risk should be reviewed regularly depends on the severity level of risks.

RISK COMMUNICATION

Risk communication includes information related to the reality, environment, type, likelihood, severity, tolerability, control, handling, ability to detect, or other risk features affecting quality. Stakeholders may communicate at any stage of the QRM process. Communicating risk is the allocation of risk data and strategies to overcome the risks between the company and regulators, company, and patient. The final QRM output/ Result should be adequately documented, approved, conveyed, and applied. For every risk acceptance that took place, it is not necessary to convey information. Existing channels as mentioned

in guidelines and regulations might affect QRM, which should be communicated among industry and regulatory authorities.

COMMON QUALITY RISK MANAGEMENT METHODOLOGY TOOLS⁴

Table 4: Quality risk management tools

<i>Quality risk management tools</i>	<i>Description</i>	<i>Praxis</i>
<i>Basic tools</i>		
Basic Risk Management Methods: Diagram analysis, Flow charts, Check sheets, Process mapping and Effect diagram	<ul style="list-style-type: none"> • Easy system of working that helps to collect and systematize information, organize quality risk management processes, and assist decision-makers. 	<ul style="list-style-type: none"> • Compilations of explanation, trends, and other experimental information to support a less range of complex deviations, flaws, complaints, and other events.
Risk ranking and filtering	<ul style="list-style-type: none"> • System to evaluate and risk ranking. • Usually comprises of assessment of miscellaneous qualitative and quantitative components for every risks, risk score and weighting factors. 	<ul style="list-style-type: none"> • Prioritize working areas or site for inspection/evaluation. • When risks and miscellaneous fundamental outcomes are possible and difficult to judge with one tool, this is efficient.
<i>Advanced tools</i>		
Fault tree analysis (FTA) ⁸	<ul style="list-style-type: none"> • Method applied to identify root cause of all predicted flaws or breakdown. • Applied to assess system or sub-system breakdown single at a time, if casual chains identified merge miscellaneous breakdown factors. • Count greatly on thorough process understanding to recognize casual factors. 	<ul style="list-style-type: none"> • Investigate product Complaints. • Evaluate deviations
Hazard operability analysis (HAZOP) ⁹	<ul style="list-style-type: none"> • Presumes that risk circumstances occurred due to deviations by the design and operating profoundness. • The shift from ordinary use or design profoundness to the organized system to identify probable deviations. 	<ul style="list-style-type: none"> • The approach production process, equipment, and services. • It usually helps to examine hazards related to procedure safety.
Hazard analysis and critical control point (HACCP) ¹¹	<ul style="list-style-type: none"> • Consistently and effectively preventing hazardous events from taking place by identifying and implementing process controls. • It helps to find out ideas on how to prevent hazards from taking place and growing. • Emphasizes on prevention control rather than detectability. • Before initiating the evaluation, thorough knowledge of the process and the CCP'S should be defined. Tools ensure that CPP's are met. 	<ul style="list-style-type: none"> • More suitable for preventive praxis rather than reactive. • A more suitable forerunner for process validation. • Examination of the critical process parameter's effectiveness and consistent execution ability in any process.
Failure mode effect analysis (FMEA) ¹⁰	<ul style="list-style-type: none"> • Product functioning and probable failure mode of the process is evaluated. • Potential failures are eliminated, reduced or controlled to perform risk reduction steps, as failure mode is analyzed. • Extremely depend on considerate of product, process and services under assessment. • Result is the central part of the risk for every failure. 	<ul style="list-style-type: none"> • To predict severe risk steps or critical parameters by evaluating facilities, equipment, and analyzing the production process.
Preliminary hazard analysis	<ul style="list-style-type: none"> • The occurrence of the risk incident is detected probably. • The level of probable harm to health is qualitatively evaluated. • The detection of possible corrective measures. 	<ul style="list-style-type: none"> • Early in the advancement, existing methods are analyzed, and hazards are emphasized. • PHA is helpful in a project with reserved knowledge of the plan or manufacturing process. It will act as a forerunner in advance studies to be carried out in the future.
Support statistical tools	<ul style="list-style-type: none"> • It holds up and assists QRM. They help in the examination of data effectively and understanding the significance of the data sets and assists in taking more sound decisions. 	<ul style="list-style-type: none"> • Data Assessment.

QUALITY RISK MANAGEMENT INVESTIGATION
17**Table 5:** Investigation Parameters

<i>Parameters</i>	<i>Causes</i>
Material	Variation due to source of materials, alteration in the procedure, age of materials vs. stability, packing material, test result at incoming stage/retest, condition of storage, correctness of quality, etc.
Method	Is the procedure definite? Critical control points and adequacy of control parameters, the robustness of the process, experience, training, processability, recent change if any, deviation in implementation, trend analysis of process parameters, safety mechanism, and challenges.
Document	Documents used for a specific time period or temporarily, which is not an approved process or procedure.
Operator	Variation due to skill, comprehension, competence, and attitude; Adequacy of supervision and support, clarity about the job role, experience, training, shift in which the activity is done, conduct work environment, availability of tools/equipment, verbal or written communication problem.
Equipment	Variation due to age of equipment, calibration and maintenance record, preventive measures, machineability, operating of machine or equipment not as per validated procedure, operating parameters, improper Installation Qualification/ Operational Qualification, Out of tolerance, machine parts are defective, inappropriate parts, failure of electrical power and computer system.
Environment	Variation due to errors in air circulation management, working of HVAC system, and water treatment system.
Schedule	Variation due to divergence from the customary framework, which includes preventive measures, environmental monitoring, calibration plan, and testing process.
Vendor	Variation due to vendor performance, alteration or missing vendor documentation, faults in lab testing, and shipment.
Administrative	Variation due to inadequate administrative control and supervision, groundwork defects, inappropriate resource distribution, details not clearly defined, distributed, and applied.
Others	Reason belongs to different classes or categories not mentioned or where the reason cannot be defined.

PHARMACEUTICAL APPLICATIONS OF QRM⁴**Training and Education**

Employees should be educated, trained, and assisted in developing necessary skills, having access to suitable resources to accomplish QRM ground rules effectively. The training program should be held at a regular interval, which clarifies the strategy of QRM activities, working instructions, procedure, and describe the duty of appropriate personnel responsible for Quality Risk Management. QRM is important in producing and supplying safe pharmaceuticals whose success relies on teaching, management training, and staff.

Responsibilities

All personnel should understand the responsibilities involved in QRM activities. Cross functional-matrix should be designed for assigning responsibilities and accountabilities with all employees involved in QRM. QRM team includes Subject Matter Expert (SME) from every department or area (e.g., regulatory affairs, production operations, quality control unit, business development, marketing and sales, engineering, statistics, and clinical) and persons familiar and skilled in QRM process.

Decision Maker's Responsibilities

- QRM processes are explained in detail, organized, appraised and accessibility of adequate resources should be assured.
- Coordination among various departments of an organization for the effective functioning of QRM should be accomplished.

QRM Application During Marketable Manufacturing

QRM execution should not prevent the company from acting following regulatory authorities' expectations (regulatory requirement, filling, and investigation commitments). QRM events should permit the smooth functioning of risk evaluation and preventive measures taken as per the suitable risk level in the company. Risk assessment and risk control are the special focus point during the product lifecycle and may include:

- Product quality risk
- Quality deficiency of product leading to harm of patient's physical condition
- Intermission in the supply of product to a patient
- Good Manufacturing Process risk and risk to comply with regulatory norms
- Multisite risks
- Multiproduct risks
- Latest facilities and alteration in accessible facilities e.g., setups, latest marketable production procedures, technology transfer and product cease.
- Efficiency of risk control measures should be evaluated.
- Alteration in examined risk and present control measures should be evaluated.

QRM Application During Qualification And Validation

In process validation, data generated all the way through the process, i.e., from R and D to production, should be evaluated, which assures the product is of desired quality produced in the manufacturing area based on scientific facts. Validation or conformance batches intensify the science or risk-based decisions during product development and should manifest that all identified critical sources of variability under controlled conditions. Examine any unintended variation in batch or between batches and make use of appropriate arithmetical tools, e.g., trend analysis, for process control verification. QRM ground rules can be used to accomplish the qualification scope. The maintenance, monitoring, calibration, and requalification can be organized in the most favorable schedule with the help of QRM.

Quality Risk Management Incorporation with Key Quality System Elements

QRM should be incorporated in accessible components of a quality system, linked with commercial practices, and recorded properly. Benefits of QRM in various operations are:

- Integrated quality management: training and education, documentation, change control management/proposal (include services, equipment, utility and information technology systems), quality defects, audit/inspection, constant upgrading, and CAPA.
- The facility, equipment, and utility: e.g., blueprint, qualification, maintenance, decommission of particular facility/equipment, equipment cleaning, control of environmental conditions, calibration/preventive measures, computer system, and processor-controlled equipment.
- Supplier, material, and contract service management: an appraisal of supplier and contract manufacturer, preliminary material, materials use, storage space, planning, and allocation situations.
- Technology transfer: e.g., starting from R&D to production region, all through marketable production among plants, from marketable production to product ceases.

QRM Praxis in Manufacturing of the Product

The QRM could assist the decision “How we have to do it?” Thus ensuring product will meet up adequate standards of efficacy, safety and regulatory compliance. To appraise and manage quality risks, QRM looks after the following actions:

- Production: risks related to the manufacturing process, validation, In-process testing and controls, planning of production, deviation and investigation administration, and change management.
- Control of laboratory and stability study: outcomes of out-of-specification, retest periods, expiry date, and procedure transfer.
- Packaging and labeling: packages design, container selection and closure technique, control of labels.
- Storage space, transportation, and allocation: e.g., cold chain.

CONCLUSION

The QRM could be enforced to diverse aspects of pharmaceutical quality, including advancement, production, allocation, scrutiny, capitulation and appraisal processes throughout the drug substance and product lifecycle. By scrutinizing and comparing accessible data as per quality perspective, QRM improves alertness and detection of potential risk. For managing quality of the product, production processes, and compliance, QRM plays a significant role. The productivity of risk management gives compliance to external and internal requirements and supports the organization to meet the defined goals.

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