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Review Article

# Risk Assessment and Management Tools in Quality Assurance

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**Abstract:** *The aim of this article is to provide better understanding in the application of the International Conference on Harmonization Q9 guideline. This paper reflects the need of quality risk management in pharmaceutical industry to improve and consistently working with quality. Quality risk management (QRM) can be applied at various stages in the industry consisting of manufacturing, distribution, inspection, and review of pharmaceutical products and any biological product throughout its lifecycle. QRM includes risk evaluation, risk control, and risk review. The risk evaluation provides regulator brief information about the severity of the risk and depending on severity of the risk appropriate risk management tool. The various risk management tools are described in this paper. Risk pertaining in the quality of product declining the firm's growth so as to maintain the market response firm has to be consistent with the product quality. QRM shows how to implement, evaluate, control, and review the risk.*

**Keywords:** Failure mode effect analysis, hazard management, international conference on harmonization guidelines, quality risk management, risk management

## I. INTRODUCTION

The International Conference on Harmonization (ICH) Q9-quality risk management (QRM) dispense wonderful framework for the use of risk management in pharmaceutical product development and manufacturing quality decision-making applications**.** It has been part of the pharmaceutical industry since decades failure mode effect analysis (FMEA) and hazard analysis and critical control points (HACCP) were created in 1960 as quality risk management tools. International organization for standardization also adopted risk management standard throughout the product life cycle. The aspects consist of development, manufacturing, distribution, and the inspection and submission/review processes throughout the life cycle of drug substances, drug products, and biological and biotechnological products.[1]

QRM is evolved by the expert working group of the ICH of technical essential for registration of pharmaceuticals for human use which explains a model for a pharmaceutical quality system by giving principles and examples of tools for QRM and approach to identify, scientifically evaluating and controlling potential risks to quality 1 (ICH, 2005).[1] It is a systematic process for the evaluation, control, communication, and review of risks to the quality of the medicinal product. It supports science based and practical decisions when integrated into quality systems, examples of quality systems include validation, quality defects investigation, auditing, inspection, documentation, and training 2 (Reddy *et al*., 2014).[2]

### QRM

The QRM system safeguards that the evaluation of the risk to quality builds on scientific knowledge, experience with the process and eventually relates to the preservation of the patient, and the degree of effort and documentation of the QRM process are proportional with the level of risk 3 Q9 ICH, 2006).[3]The terminologies of QRM are defined in Table 1.

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**PRINCIPLES OF QRM**

1. The evaluation of the risk to quality should be depend on scientific knowledge and finally relates to the protection of the patient.
2. The amount of input, formality, and documentation of QRM process should be commensurate with the level of risk.
3. The evaluation principle constitutes four stages of an effective QRM process as defined by ICH Q9. Al four components are important, i.e., risk assessment, risk control, risk communication, and risk review 1 (ICH, 2005, Lotlikar, 2013).[1]

**QRM PROCESS**

QRM is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for QRM is outlined in the flowchart [Figure 1].

1. Initiating QRM process: The initiating phase of QRM process involves understanding the risk event by defining and agreeing the context, the scope,and the tolerability criteria for the QRM, together with any underlying assumptions. It should involve all the stakeholders, all the relevant information are assembled and shared.[1]
2. Quality risk assessment: Quality risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.[4-8]

- Quality risk identification: It consists of the use of information to identify hazards or potential risks. Information used to identify risk includes historical data, theoretical analysis, and informed opinions.
- Quality risk analysis: It is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms.
- Quality risk evaluation: Quality risk evaluation includes comparison of identified and analyzed risk against predefined acceptance criteria and consideration of probability, severity, and detectability.

**Table 1: The terminologies of QRM[1]**

| | |
|---|---|
| Risk | The merger of the prospect of event of harm andthe grievousness of that harm |
| Risk acceptance | The determination to accept risk |
| Hazard | The potential origin of harm |
| Risk analysis | The evaluation of the risk pertaining with hazards |
| Risk assessment | Anefficient operation of arranging information to support a risk determination to be made within a risk management process |
| Risk control | Actions implementing risk management decisions |
| Risk evaluation | The collation of the evaluated risk to given risk criteria using aquantitative or qualitative scale to decide the notable of the risk |
| Risk identification | The formal use of information to evaluate potential origin of harm referring to the risk-related problem description |
| Risk management | The standard application of quality management policies, procedures, and practices to the work of assessing, controlling, communicating, andreviewing risk |
| Risk reduction | Steps taken to reducethe probability of reoccurrence of harm andthe grievousness of that harm |
| Risk review | Review or observing of output/results of the risk management process considering new knowledge about the risk |
| Severity | Calculate of the possible results of a hazard |
| Detectability | The capacity to govern the existence, presence, or actuality of ahazard |
| Harm | Harm to health, including the harm that can cause from loss of product quality or availability |

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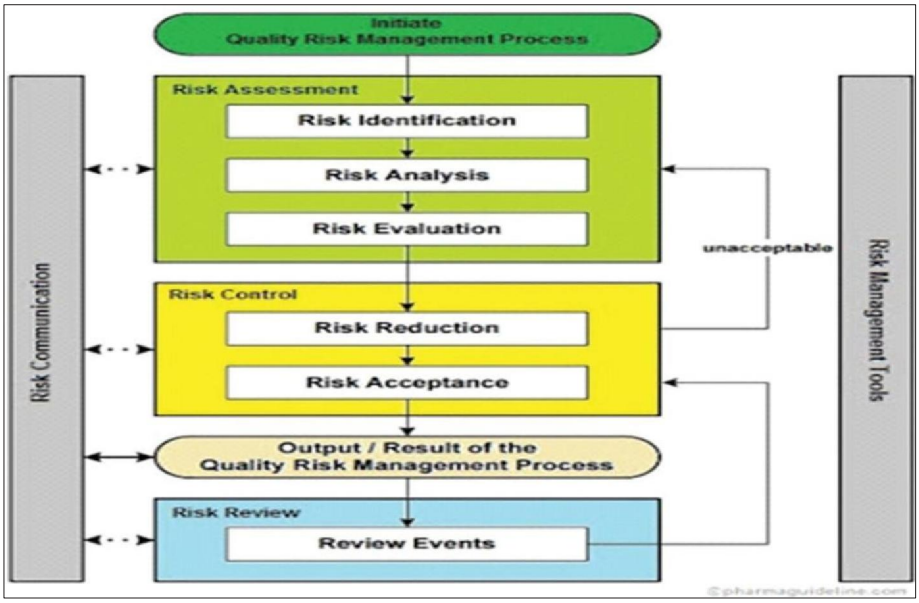


**Figure 1:** Overview of quality risk management process[1]

3. Risk control: It includes decision-making to reduce and/or accept risks. Its purpose is to reduce the risk to an acceptable level. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.The steps for risk control include:
- Risk reduction: Risk reduction includes actions taken to lessenthe probability of the occurrence of harm andseverity of that harm usually by corrective action and preventive action and change control.
- Risk acceptance: Decision to accept risk. It can be a formal decision to accept the residual risk or can be a passive decision in which residual risks are not specified.

4. Risk communication: It is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process. The output/ r esult of the QRM process should be appropriately communicated and documented.
5. Risk review: It should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented. The output/results of the risk management process should be reviewed to take into account new knowledge and experience.[7]

## QRM TOOLS

A key early step in the execution of a risk analysis is to determine the appropriate risk assessment methods or tools.There is no single best choice for anygiven assessment process, and the selection of the appropriate risk methodology should be based on the depth of analysis required, complexity of the subjectrisk of concern, and the familiarity with the assessment tool.[1] The list of recognized risk-management tools given in Figure 2 and their description and applications are explained inTable 2.

## POTENTIAL APPLICATION OF QRM

The selection of particular risk management tools is completely dependent on specific facts and circumstances. These examples are provided for illustrative purposes and only suggest potential uses of QRM 2 (ICH, 2005).

### QRM as Part of Integrated Quality Management Documentation

- Training and education: To determine the appropriateness of initial and/or ongoing training sessions based on education, experience, and working habits of staff, as well as on a periodic assessment of previous training, for example, its effectiveness.

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- Quality defects: To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, trend, deviation, investigation, and out of specification result.
- Auditing/inspection: To define the frequency and scope of audits, both internal and external, taking into account factors such as existing legal requirements, overall compliance status and history of the company, and robustness of a company's QRM activities.
- Periodic review: To select, evaluate, and interpret trend results of data within the product quality review, to interpret monitoring data.
- Continual improvement: To facilitate continual improvement in processes throughout the product lifecycle

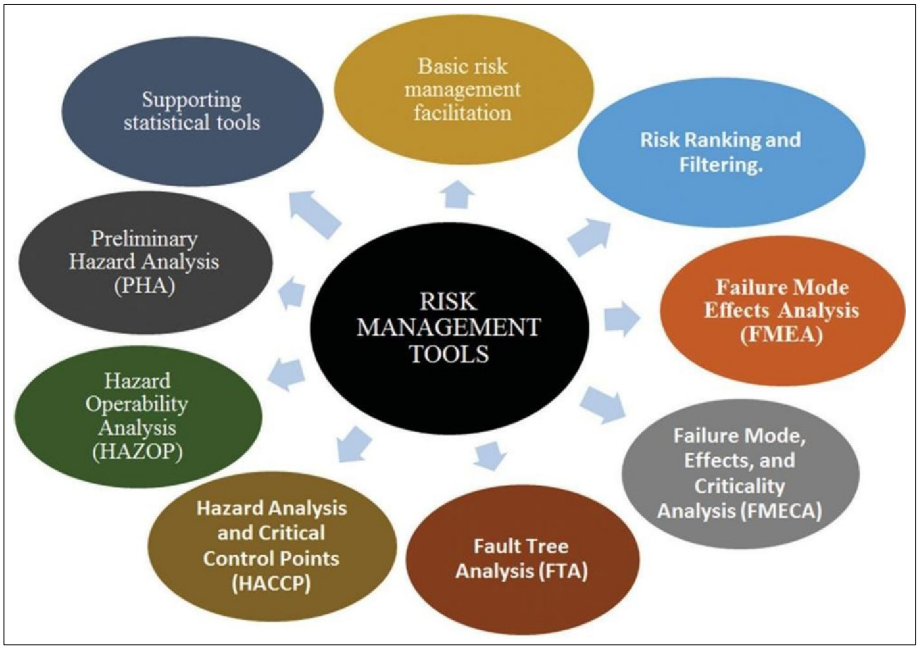


**Figure 2:** Risk management tools[2,9]

**Table 2: Risk management tools with their description and application[10]**

| S. No. | Risk management tools | Description | Potential application |
|---|---|---|---|
| 1 | Basic risk management facilitation methods (Diagram analysis) | It is a simple technique. Commonly used to structure risk management by gathering or organizing data and facilitating decision-making by flowcharts check sheets process mapping cause and effect diagrams | Compilation of observations, trends, or other empirical information to support a variety of less complex deviations, complaints, defaults |
| 2 | Risk ranking and filtering | For risk ranking of complex systems, it evaluates multiple diverse quantitative and qualitative factors for each risk. It is useful when management needs to evaluate both quantitatively assessed and qualitatively assessed risks within the same organizational framework | Prioritize manufacturing sites for inspection/audit by regulators or industry |
| 3 | FMEA | Evaluate potential failure modes for processes, and the probable effect on outcomes and/or product performance | Evaluate equipment and facilities; analyze a manufacturing process to identify high-risk steps/critical parameters |

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| | | | |
|---|---|---|---|
| 4 | FMECA | It is extension of FMEA that includes acriticality analysis which is used to chart the probability of failure modes against the severity of the consequences | It identifies the places where additional actions can be appropriate to minimize risk |
| 5 | FTA | It is a top-down deductive failure analysis. It identifies all root causes of an assumed failure or problem | Investigate complaints and deviations. Understand their root cause and resolve the issue |
| 6 | HACCP | It is systematic, proactive, andpreventive tool for assuring aproduct quality, reliability, and safety | Emphasizes on preventive controls rather than ability to detect |
| 7 | HAZOP | Based on a theory that assumesthat risk events are caused by deviations from the design or operating intentions | Evaluate manufacturing processes, equipment, and facilities for drug substance |
| 8 | PHA | Analysis conducted based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations, andcircumstances events that might cause harm, as well as to estimateextensive technique from being their probability of occurrence for agiven activity, facility, product, or system | Evaluating existing systems or prioritizing hazards where used |
| 9 | Supporting statistical tools | Support andfacilitate quality risk management. Commonly usedtools are as follows: Control charts DOE histograms Paretocharts process capability analysis | The yenable effective data assessment, aid in determining the significance of the data set (s), and facilitate more reliable decision-making |

FMEA: Failure mode effects analysis, HACCP: Hazard analysis and critical control points, FMECA: Failure mode, effects, and criticality analysis, FTA: Fault tree analysis, HAZOP: Hazard operability analysis, PHA: Preliminary hazard analysis, DOE: Design of experiments

**QRM as Part of Regulatory Operations Inspection and Assessment Activities**

To frame the inspection planning, its frequency and assessment intensity, to identify risk and it should be communicated between inspector and accessor and to facilitate better understanding of how risk can be controlled.

**QRM as part of development**

To design manufacturing process to consistently deliver the product of intended performance with materialattributes for example particle size distribution, moisture content, flow properties and process parameters.

**QRM for facilities, equipment, and utilities design of facility/equipment**

To determine appropriate area when designing buildings and facilities, for example, flow of material and personnel, prevention of mix- ups, dedicated or segregated facilities/equipment. To determine compatibility between product and equipment material / packaging material i.e. selection of stainless steel grade.

**Computer systems and computer controlled equipment**

To select the design of computer hardware and software i.e. to determine the extent of Computer system validation for example, identification of critical performance parameters, selection of the requirements, and design.

**QRM as part of materials management assessment and evaluation of suppliers and contract manufacturers**

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing and supplier quality agreements).

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- Starting material: To assess differences and possible quality risks associated with variability in starting materials (e.g., age and route of synthesis).
- Use of materials: To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing), to determine appropriateness of reprocessing, reworking, and use of returned goods.
- Storage, logistics, and distribution conditions: To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, and container design).

**QRM as part of production**

- Validation: To identify the scope and extent of verification, qualification, and validation activities (e.g., analytical methods, processes, equipment, and cleaning method).
- In-process sampling and testing: To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control), to evaluate and justify the use of PAT in conjunction with parametric and real-time release.

**QRM as part of laboratory control and stability studies**

- Out of specification results: To identify potential root causes and corrective actions during the investigation of out of specification results.
- Retest period/expiration date: To evaluate adequacy of storage and testing of intermediates, excipients, and starting materials.

**QRM as part of packaging and labeling**

- Design of packages: To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).
- Selection of container closure system: To determine the critical parameters of the container closure system.
- Label controls: To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

## II. CONCLUSION

Well-accessed methodology structured to find current quality risk assessment, that is, ICH Q9 guideline. Here above in this paper given number of applications and risk management tools. It is a process consisting of evaluation, control, and review of the risk emerging out for quality. The common risk management tools used in application of risk to thequality are risk ranking, FMEA, and HACCP. The first step is to identify appropriate risk methodology subsequent to the risk. These verity of the risk is taken into account. QRM provides better ability to handle the risk pertaining in the quality of product throughout its lifecycle.

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