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Pharmaceutical Quality Risk Management System: Current Concept

Palak Sharma, Hariharanand Sharma

Email : palak0sharma@gmail.com

Abstract: Every product and every process has an associated risk. Every enterprise should have a methodology for identifying and evaluating the risks it faces and it should have a process for generating intervention plans to reduce the risks to an acceptable level. This process is generally referred to as a Risk Management Plan (RMP)

Pharmaceutical Industry being an important industry which is directly related to the health of people in society hence risks associated with the Pharmaceutical Industry are need to be evaluated. Every pharmaceutical product and every process has an associated risk. As per **ICH Q9,** Risk is defined as Combination of the probability of occurrence of harm and the severity of that harm the word "risk" is widely used in general and technical applications with different Meanings. Every product and every process has an associated risk.

This article aims to provide principles and examples of tools for Quality Risk Management (QRM) that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, inspection and submission of review processes throughout the lifecycle of drug substances, drug products and biological products.

Key words : Quality management , risk management, FMEA

Introduction:

In earlier days risk in the product quality and process had been assessed in the following informal ways.

- Trends review
- Check lists
- Flow charts
- Observations compilation [From complaints, deviations etc.]
- Changes review

Now the risk management approach initiated by regulatory agencies with recognized management tools along with support of statistical tools in combination, which make easy for application of quality risk management principles across the industry. A Risk Management Program starts with identifying the possible risks associated with a product or with the process used to develop, manufacture, and distribute the product. An effective quality risk management ensures the high quality of drug product to the patient. In addition quality risk management improves decision making if a quality problem arises. It should include systemic processes designated to co-ordinate, facilitate and improve science-based decision-making with respect to risk.[1]

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full Contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry, and it is becoming evident that quality risk Management is a valuable component of an effective quality system.

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. However, achieving a shared understanding of the application of risk management among diverse stakeholders is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.[2][3]

Quality Risk Management is a systemic process for the assessment, control, communication & review of Risk to the Quality of the medicinal product.

PRINCIPLES OF QUALITY RISK MANAGEMENT

Four primary principles of quality risk management are [1][4]

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.
- QRM should be dynamic, iterative and responsive to change.
- The capability for continual development and enhancement should be embedded in the QRM process.

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General Quality Risk Management Process [1]

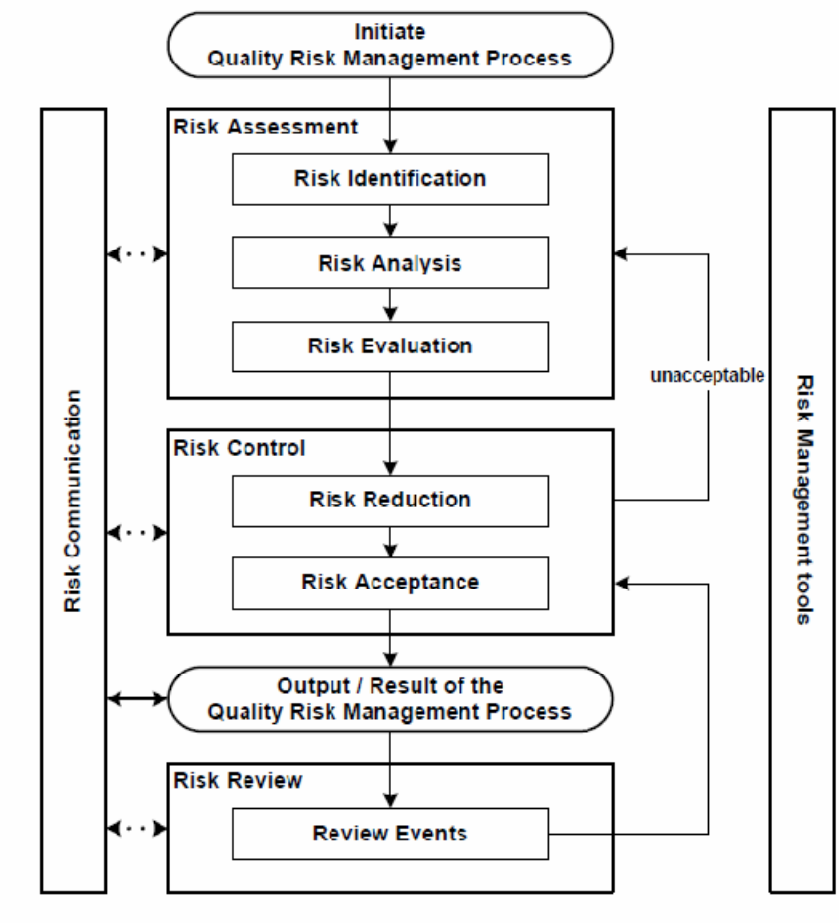


Figure 1: Overview of a typical Quality Risk Management process [1]

1. Initiating a QRM process:

QRM activities should be performed using systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk. Possible steps used to initiate and plan a QRM process might include the following *(Ref. ICH Q9)*:

• define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;

• assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment;

• identify a leader and necessary resources; and

• specify a timeline, deliverables and appropriate level of decision-making for the risk management process.

2. Personnel involved in QRM:

The implementing party, i.e. pharmaceutical manufacturer or regulatory authority, should assure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities. The personnel should be able to:

(a) Conduct a risk analysis.

(b) Identify and analyze potential risks.

(c) Identify, evaluate risks and determine which ones should be controlled and which ones can be accepted;

(d) Recommend and implement adequate risk control measures.

(e) Devise procedures for risk review, monitoring and verification.

3. Knowledge of the product and process:

Any activity of QRM would need to be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle. Where necessary, a flow diagram may be helpful, covering all operations and controls in the process under evaluation. When applying QRM to a given operation, the steps preceding and following that operation should

also be considered. A block-type diagram may be sufficiently descriptive. Amendments to the flow diagram may be made where appropriate, and should be documented.

4. Risk assessment:

When risk assessment is conducted safety and efficacy need to be considered in addition to the quality concerns. During the assessment all the risks that may be reasonably expected to occur in the activity under evaluation should be listed. This is usually applied during its initiation when there is a change or a concern and may also be applied to existing processes. An analysis should be conducted to identify which risks are of such a nature that their elimination or reduction to acceptable levels is essential. A thorough risk analysis is required to ensure an effective risk control. It should review the materials, activities, equipment, storage, distribution and intended use of the product. Typically a list of the potential risks (biological, chemical and physical) which may be introduced, increased or controlled in each step should be drawn up. In the risk analysis the following basic questions should be addressed:

- What is the nature of possible risks?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

It should then be decided which potential risks should be addressed by the QRM activities and what control measures, if any, should be implemented for each risk. If a risk has been identified at a step where control is necessary for safety, and no control measure exists at that step or at any other, the product or process should be modified at that step, or at an earlier or

later stage, to include such a control measure. More than one control measure may be required to control a specific risk and more than one risk may be controlled by a specified control measure. Risk assessment can be facilitated by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned. Normally, potential risks in relation to the following should be considered:

- Materials and ingredients;
- Physical characteristics and composition of the product;
- Processing procedures;
- Microbial limits, where applicable;
- Premises;
- Equipment;
- Packaging;
- Sanitation and hygiene;
- Personnel
- Human error;
- Utilities;

Different Steps Involved In the Risk Assessment Are [5] [6]

I. Collect & organize the information.

- Gathering relevant information, reviewing appropriate references & identifying assumptions.
- Tools can be used to categorize the information.
- Define the limits of the QRM exercise.

II. Formulate the Risk Question:

- It is the starting point of the QRM exercise, high level statement outlining the issue & purpose for conducting the QRM exercise including risk factors, the scope of the issue and any related limits or constraints.

III. Choose Tool different tools include-

- Basic risk management facilitation methods (flowcharts, check sheets etc).
- Failure Mode Effects Analysis and Failure Mode Effects and Criticality Analysis.
- Fault Tree Analysis.
- Hazard Analysis and Critical Control Points.
- Hazard & Operability Analysis.
- Preliminary Hazard Analysis.
- Risk Ranking & Filtering.
- Supporting statistical tools.

IV. Identify Risks Factors and Related Hazards

- A hazard is a failure that could cause potential harm to the patient. Once the hazards are recognized, they can then be categorized into one of five areas: Operator, Environment, System, Reagents, or Specimen. These categories will make it easier to later identify types of controls necessary to reduce unwanted risk.

V. Define the Risk Components &Scales[7]

RISK = PRIORITY * DETECTABILITY * SEVERITY

Where,

Severity- Criticality of the product.

Priority- Complexity of the site (multi-product).

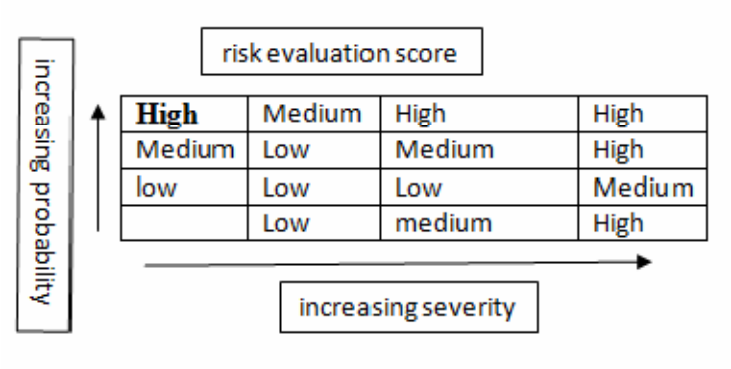
Detection- Audit history.

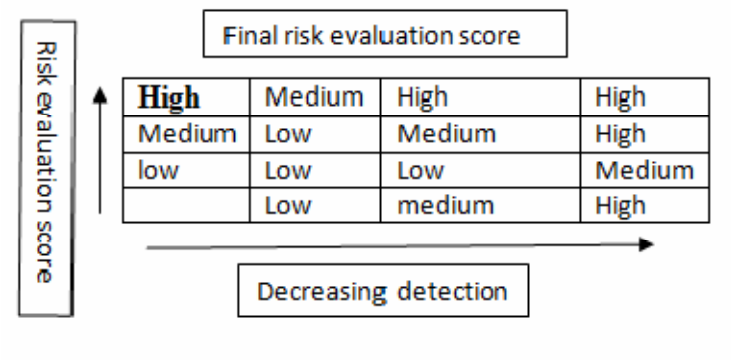
VI. Evaluate the risk for each hazard.

- This is the step where you decide how often that a failure will occur.

VII. Determine acceptability of risks[6,8]

- Once the risks are assigned, the next step is to look at severity and probability of harm to determine whether the risks are acceptable.





VIII. Determine Action Threshold

- A level or value above which an action will take place and below which it will not.

IX. Apply the tool

- Analyze the detailed risks and quantify those risks using the scales for severity, probability and detection to provide a risk score.

- Conclude what actions are required based on the threshold for action.

5. Risk control:

Risk control is a decision-making activity designed to reduce and/or accept risks. It usually occurs after risk assessment, and at a fundamental level its purpose is to reduce the risk to an acceptable level. During risk control activities the following key questions should be asked:

- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk control activities usually involve identifying controls and measures which may reduce or control the risk associated with a failure mode or negative event. Risk control activities can serve to determine critical process parameters for certain controls, how they will be monitored, and the level of qualification and validation which may be required, if any, for such controls.

6. Risk review:

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring. Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded. All records and documents associated with risk review should be signed and dated by the person(s) carrying out the review and by a responsible official(s) of the quality unit of the company.

The approach described can be used to [9]

- Thoroughly analyze products and processes to ensure the best scientific rationale is in place to improve the probability of success
- Identify important knowledge gaps coupled with processes that need to be understood to properly identify risks
- Provide a communication process that will best interface with all relevant parties involved in the Risk Management Plan
- Make possible to transfer process knowledge and product development history to ease product progression and to supplement generic corporate knowledge
- Enable the pharmaceutical industry to adopt a risk-based approach to development as described in external regulatory guidance. The Risk Management outputs will potentially very as reference documents to support product development and control strategy discussions in regulatory filings.

Discussion

Table 1: Common Risk Management Tools [4]

Risk management tool	Description/attributes	Potential applications
Basic Tool		
➢ Diagram analysis ➢ Flowcharts ➢ Check sheets ➢ Process mapping ➢ Cause/effect ➢ diagrams	➢ Simple techniques that are commonly used to gather and organize data, structure RM processes and facilitate decision making	➢ Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances
Risk ranking and filtering	➢ Method to compare and rank risks ➢ Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and	➢ Prioritize operating areas or sites for audit/assessment ➢ Useful for situations when

	weighting factors and risk scores	the risks and underlying consequences are diverse and difficult to compare using a single tool
Advanced tools		
Fault tree analysis (FTA)[	➢ Method used to identify all root causes of an assumed failure or problem ➢ Used to evaluate system or sub-system failures one at a time, but can combine multiple causes of failure by identifying causal chains ➢ Relies heavily on full process understanding to identify causal factors	➢ Investigate product complaints ➢ Evaluate deviations
Hazard operability analysis (HAZOP)	➢ Tool assumes that risk events are caused by deviations from the design and operating intentions ➢ Uses a systematic technique to help identify potential deviations from normal use or design intentions	➢ Access manufacturing processes, facilities and equipment ➢ Commonly used to evaluate process safety hazards
Hazards analysis and critical control points (HACCP)	➢ Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring ➢ Bottom-up approach that considers how to prevent hazards from occurring and/or propagating ➢ Emphasizes strength of preventative controls rather than ability to detect	➢ Better for preventative applications rather than reactive ➢ Great precursor or complement to process validation ➢ Assessment of the efficacy of CPPs and the ability to consistently execute them for any process
Failure modes effects analysis (FMEA)	➢ Assesses potential failure modes for processes and the probable effect on outcomes and/or product performance ➢ Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures ➢ Highly dependent upon strong understanding of product, process and/or facility under evaluation ➢ Output is a relative “riskscore” for each failure mode	➢ Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps and/or critical parameters

Conclusion

The risk management program consists of four major components: risk assessment, risk control, risk review, and risk communication. All four components are essential. All the above methods should address the mentioned four basic components. Team selection and method selection are also plays a vital role in the risk management process, so care should be taken while selection of risk management team and method.

Potential Areas for Risk Management Application

The following areas are identified as potential in the pharmaceutical industry for quality risk management application.

- Documentation [SOPs, Batch records etc.]
- Training [Schedules and effectiveness]
- Quality defects [Complaints, deviations, OOS etc.]
- Audits [Compliance]
- Periodic reviews [Revalidation assessment]
- Change controls [Impact assessment]
- Development reports [Process and controls verification]
- Facilities, Equipment and Utilities [Components, maintenance etc.]
- Material management [Receipt, storage and distribution]
- Packaging and labeling [Container closure system and labeling]

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