Review Article

Quality Risk Management: A Review

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ABSTRACT

Risk is associated with every product in the pharmaceutical industry. In the recent guidance risk is described as a combination of the probability of occurrence of harm and severity of that harm. Quality Risk Management (QRM) is an overall and continuing process of minimizing risks to product quality throughout its lifecycle in order to optimize its benefits and balance the risk. It is the systematic process for the evaluation, control, communication and review of risks to the quality of the medicinal product. Using QRM tools, the pharmaceutical industry and regulators can evaluate, communicate, control and review the risk. In pharmaceutical industry there are many preferable methods for risk management such as FMEA, FMECA, FTA, HACCP, HAZOP, PHA, Risk ranking and filtering and supporting statistical tools analysis all together provides high reliability, better quality, increased safety and cost saving leads to decreased development time and reduced waste and non-value added operations.

Keywords: Quality Risk Management; QRM tools; Harm; Pharmaceutical industry.

INTRODUCTION

Risk management has been an important tool for the pharmaceutical industry. QRM is an overall and systematic process of minimizing risks to product quality throughout its life-cycle in order to optimize its benefit and balance the risk. ICH —Q9 QRM is developed by the Expert The publication of ICH Q9 —Quality Risk Management have major impact on pharmaceutical industry. The FDA and other regulatory bodies, is implementing the Q9 concepts. ICH —Q9 QRM is developed by the Expert Working Group (Quality) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use which describes a model for a pharmaceutical quality system by providing principles and examples of tools for quality risk management and approach to identifying, scientifically evaluating and controlling possible risks to quality. Quality Risk Management principles are efficiently utilized in many areas including business, insurance, work related safety, public health, pharmacovigilance, and by of the use of quality risk management in the pharmaceutical industry. In addition, the significance of *quality systems* has been accepted in the pharmaceutical industry and it is becoming obvious that quality risk management is a valuable element of an efficient quality system.[1, 2]

The Q9 defines risk as the combination of the probability of occurrence of harm and the severity of that harm. The manufacturing and use of a drug product, including its components, essentially engross some degree of risk. An efficient QRM approach can further ensure the high quality of the drug product to the patient by recognize and control possible quality issues during development and manufacturing. Use of QRM can progress the decision making if a quality problem arises. Effective QRM execution can facilitate better and well versed decisions which can provide regulators with greater assurance of a company's capability to deal with possible risks.[3, 4]

Definitions[5]

Risk:

Combination of both probability of occurrence of harm and severity of that harm.ISO 14971.

Harm:

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

Quality:

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

Requirements:

Needs or expectations that is stated, generally implied or obligatory by the patients or their surrogates (e.g. health care professionals, regulators and legislators)

Principles of Quality Risk Management:

Four primary principles of QRM are:

The evaluation of the risk to is based on technical and process-specific knowledge and eventually linked primarily to the protection of the patient.

- The assessment of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.

- QRM should be dynamic, iterative and responsive to change.
- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk
- The potential for continual development and enhancement should be implanted in the QRM process.

Quality Risk Management Process

Quality risk management is a systematic process for the assessment, control, communication and review of risks towards the quality of the drug (medicinal) product across the product lifecycle. The prominence on each element of the framework may be different from case to case however a robust process will incorporate deliberation of all the elements at a level of element that is corresponding with the specific risk.A model for quality risk management is outlined in Figure 1.

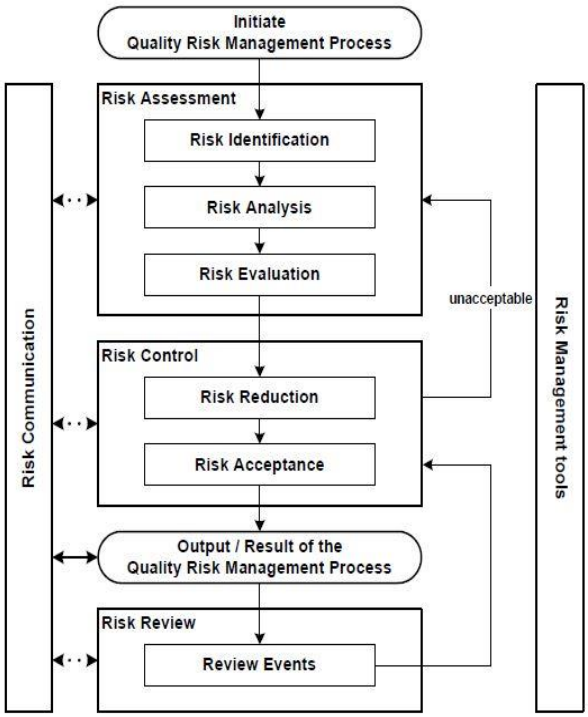

Figure 1: Overview of a Quality Risk Management Process

Initiating a Quality Risk Management Process

Quality Risk Management should include systematic processes designed to organize, facilitate and improve science-based decision making with respect to risk. Steps used to initiate and plan a quality risk management process might include the following:

Steps used to initiate and plan a quality risk management process might include the following:

- Describe the problem and/or risk question, including significant assumptions identify the potential for risk.
- Collect background information and/or data on the potential hazard, harm or human health impact related to the risk assessment.
- Indicate a timeline, and suitable level of decision making for the risk management process.

Risk Assessment

Risk assessment is a methodical process of organizing information to support a risk decision to be made within a risk management process.[6, 7] Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. It includes risk identification, risk analysis and risk evaluation. Three essential questions are frequently helpful.[8, 9]

1. What may go wrong?

2. What is the possibility that it will go wrong?

3. What are the consequences?

Risk identification

Risk identifications a planned use of information to recognize hazards referring to the risk. Information can incorporate historical data, theoretical analysis, and the concern of stakeholders. Risk identification addresses the "What may go wrong?" question, as well as identifying the possible consequences. This provides the source for further steps in the quality risk management process.

Risk analysis

Risk analysis the evaluation of the risk associated with the known hazards. It is the qualitative or Quantitative process of relating the probability of incidence and severity of harms. In some risk management tools, the capacity to detect the harm (detectability) also factors in the assessment of risk.

Risk evaluation

Risk evaluation compares the recognized and analyzed risk against given risk criteria. Risk evaluations consider the strength of confirmation for all three of the essential questions.

Risk Priority Number

The Risk Priority Number is a mathematical product of the numerical Severity, Probability, and Detection ratings:

RPN = (Severity / Consequences) x (Probability of occurrence) x (Chances of Detection)

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

Ranking (scoring) and Criteria for severity, Occurrence and Detection is shown in Table 1, Table 2 and Table 3.

Risk Control

Risk Control includes decision creation to decrease and/or accept risks. The function of risk control is to decrease the risk to an acceptable level.

Table 1: Criteria for severity

Ranking (Scoring)	Criteria
1	Insignificant: No Additional control measures required/ No impact to product quality and process robustness
2	Minor: No impact to product quality
3	Moderate: Noticeable impact to product quality
4	Major: Define impact to product quality that may require rework
5	Disastrous: Product failure/ Batch failure/ Threat to life/ Irreversible damage.

Table 2: Occurrence of Risk

Ranking (Scoring)	Criteria
1	Unlikely probability of occurrence: One occurrence every six months to one year or one occurrence in 10000 events.
2	Remote probability of occurrence: One occurrence every six months to one year or one occurrence in 10000 events
3	Occasional probability of occurrence: One occurrence every three months or three occurrences in 1000 events
4	Moderate probability of occurrence: One occurrence per week or a probability of 5 occurrences in 100 years
5	High probability of occurrence: Very high probability of failure

Table 3: Detection of Risk

Ranking (Scoring)	Criteria
1	High degree of detectability: The defect is obvious or there is 100% to detect the failure
2	Good detectability: Chances of detection are high.
3	Likely to detect: Detection possibility is moderate.
4	Fair detectability: Difficult to detect. Product or failure is accepted on the basis of no defectives in a sample
5	Low / No detectability: The failure is not detectable

The sum of effort used for risk control should be proportional to the consequence of the risk. Decision makers may use different processes, including benefit-cost analysis, for accepting the optimal level of risk control. [10, 11]

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- 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 reduction

Risk reduction focuses on processes for improvement or prevention of quality risk when it exceeds a specified level. Risk reduction might include actions taken to moderate the severity and probability of harm. Processes that improve the detecting ability of hazards and quality risks might also be used as part of a risk control policy. The execution of risk reduction process can introduce new risks into the system or increase the consequence of other existing risks. Hence, it might be suitable to revisit the risk assessment to identify and evaluate any potential change in risk after implementing a risk reduction process.

Risk acceptance

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For various types of harms, even the best quality risk management practices might not completely eliminate risk. In these conditions, it might be agreed that a proper quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be determined on a case-by-case basis.

Risk Communication

Risk communication is the contribution of information about risk and risk management between the decision makers and others. The output/result of the quality risk management process must be properly communicated and documented. The included information might relate to the existence, nature, form, probability, severity, suitability, control, treatment, detectability or other aspects of risks to quality.

The approach described can be used to:

- Thoroughly analyse products and processes to make sure the best methodical rationale is in place to improve the probability of success
- Identify significant data gaps coupled with processes that need to be understood to accurately identify risks
- Provide a communication process that will be greatest interface with all related parties involved in the Risk Management Plan
- Make a potential to transfer process knowledge and product development history to relieve

product evolution and to supplement generic corporate knowledge.

- Enable the pharmaceutical industry to accept 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.[12]

Risk Review

Risk reviews the output/results of the risk management process have to be reviewed to take into account new information and knowledge. Once the quality risk management process has been initiated, that process should continue to be utilized for events that may impact the original quality risk management decision. Risk review might include modification of risk acceptance decisions.

Risk Management Methods

The pharmaceutical industry and regulators can access and manage risk using standard risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools

- Basic risk management methods (flowcharts, check sheets etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools.

Basic Risk Management Facilitation Methods

Some of the uncomplicated techniques that are regularly used to structure risk management by organizing data and facilitating decision-making are:

- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

Failure Mode Effects Analysis (FMEA)

- FMEA provides for an estimation of potential failure modes for processes and their possible effect on outcomes and/or product performance.
- Once failure modes are recognized, risk reduction can be used to eliminate, reduce or control the potential failures.
- FMEA relies on product and process understanding.
- FMEA systematically breaks down the analysis of complex processes into manageable steps.
- It is a powerful tool for summarizing the significant modes of failure, factors causing these failures and the possible effects of these failures.

Potential Areas of Use

- FMEA can be used to prioritize risks and monitor the efficiency of risk control activities.
- FMEA can be applied to equipment and facilities and might be used to analyse a manufacturing process and its effect on product or method.
- It identifies elements/operations in the system that render it vulnerable.
- The output/ results of FMEA can be used as a basis for design or additional analysis or to guide resource deployment. [13]

Failure Mode, Effects and Criticality Analysis (FMECA)

- Failure Mode, Effects and Criticality Analysis (FMECA) FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of incidence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis.
- In order for such an analysis to be performed, the product or process specifications have to be established.
- FMECA can identify places where additional preventive actions might be suitable to minimize risks.

Potential Areas of Use

- FMECA application in the pharmaceutical industry should be utilized for failures and risks related with manufacturing processes though, it is not limited to this application.
- The output of an FMECA is a relative risk “score” for each failure mode, which is used to rank the modes on a relative risk basis.

Fault Tree Analysis (FTA)

- The FTA tool is an approach that assumes failure of the functionality of a product or process.
- This tool evaluates system (or sub-system) failures one at a time but can combine various

causes of failure by identifying fundamental chains.

- The results are represented pictorially in the structure of a tree of fault modes.
- At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.).
- FTA relies on the experts' process understanding to identify fundamental factors.

Potential Areas of Use

- FTA can be used to establish the pathway to the root cause of the failure.
- FTA can be used to inspect complaints or deviations in order to completely understand their root cause and to make sure that intended improvements will completely determine the issue and not lead to other issues (i.e. solve one problem yet cause a different problem).
- Fault Tree Analysis is a successful tool for evaluating how multiple factors influence a given issue.
- The output of an FTA includes a visual demonstration of failure modes. It is useful both for risk assessment and in developing monitoring programs. [14]

Hazard Analysis and Critical Control Points (HACCP)

- HACCP is a methodical, practical, and preventive tool for assuring product quality, reliability, and safety.
- It is a structured approach that applies scientific and technical principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

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

Potential Areas of Use

- HACCP might be used to identify and manage risks related with physical, chemical and biological hazards (including microbiological contamination). HACCP is mainly useful when product and process understanding is sufficiently complete to support identification of critical control points.
- The output of a HACCP analysis is risk management information that facilitates monitoring of essential points not only in the manufacturing process but also in other life cycle phases.[15]

Hazard Operability Analysis (HAZOP)

- HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions.
- It is a methodical brainstorming system for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are functional to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions.
- It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use

- HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products.
- It has also been used mainly in the pharmaceutical industry for evaluating process safety hazards.
- As is the case with HACCP, the output of a HAZOP analysis is a list of essential operations for risk management.[16]
- This facilitates regular monitoring of critical points in the manufacturing process.

Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to assess their probability of incidence for a given activity, facility, product or system.

The tool consists of

1) The identification of the potential that the risk incident happens

2) The qualitative assessment of the level of possible injury or damage to health that might effect

3) A relative ranking of the hazard using a combination of severity and probability of occurrence

4) The identification of possible corrective measures.

Potential Areas of Use

- PHA might be useful when analyzing existing systems or prioritizing hazards where conditions prevent an additional extensive technique from being used.
- It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product.
- PHA is most frequently used early in the development of a project where there is modest information on design details or operating procedures; thus, it will frequently be a precursor to further studies.
- Usually, hazards are identified in the PHA are further assessed with other risk management tools such as those in this section.

Risk Ranking and Filtering

- Risk ranking and filtering is a tool for comparing and ranking risks.
- Risk ranking of complex systems usually requires estimation of multiple diverse quantitative and qualitative factors for each risk.
- The tool involves breaking down a basic risk question into as many components as required to capture factors involved in the risk.
- These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use

- Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry.
- Risk ranking methods are mainly helpful in situations in which the selection of risks and the fundamental consequences to be managed are diverse and difficult to compare using a single tool.
- Risk ranking is useful when management needs to assess both quantitatively-assessed and qualitatively-assessed risks within the same organizational structure.

Supporting Statistical Tools

Statistical tools can support and assist quality risk management. They can facilitate effective data evaluation, assist in determining the significance of the data set(s), and facilitate more reliable decision making.

A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

- Control Charts
  - Acceptance Control Charts Control Charts with Arithmetic Average
  - Warning Limits Cumulative Sum Charts
  - Shewhart Control Charts
  - Weighted Moving Average
- Design of Experiments (DOE)
- Histograms
- Pareto Charts
- Process Capability Analysis

CONCLUSION

The investigation of risk is a scientific activity and expression of culture. The use of risk-based approach helps to understand and influence the factors (Hazard) which has impact on the quality of the product and provides a reliable process for manufacturing high quality drug products which are associated with resource allocation and ensuring patient safety. Eventually, QRM provides assurances that risks are adequately managed and also helps in making consistent and traceable decisions to pharmaceutical industry that will reduce risk through the consistent use of the tools/methods and periodic review. The output of risk management gives compliance to external and internal requirements and supports the organization to meet the defined goals.

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