International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.6, No.3, pp 908-914, July-Aug 2014

Quality Risk Management in Pharmaceutical Industry: A Review

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Abstract: 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.Quality Risk Management is an overall and continuing process of minimizing risks to product quality throughout its life-cycle in order to optimize its benefit and balance the risk. It is a systematic process for the evaluation, control, communication and review of risks to the quality of the medicinal product. The basic QRM process should include the level of effort, formality and documentation of QRM process which should commensurate with level of risk. QRM principles are utilized effectively in many areas of business and government including business, insurance, work-related safety, public health, pharmacovigilance and by agencies regulating these industries. The risk assessment process should be carried out by analyzing, identifying and evaluating the risk and the QRM plans should be reviewed after their follow up. The QRM implementation provides documented, clear and reproducible methods to accomplish steps of QRM process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk. Using QRM tools, the pharmaceutical industry and regulators can evaluate, control, communicate and review the risks. Effective QRM implementation can facilitate better and well-versed decisions which can provide regulators with greater assurance of a company's ability to deal with possible risks.
Keywords: Quality Risk Management,Risk- based approach, Patient safety, Product quality.

Introduction

Since a couple of years Quality Risk Management (QRM) has become a mandatory regulatory requirement towards healthcare organizations. QRM is an overall and continuing process of minimizing risks to product quality throughout its life-cycle in order to optimize its benefit and balance the risk. 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, Training etc. Quality Risk Management principles are effectively utilized in many areas including business, insurance, work related safety, public health, pharmacovigilance, and by agencies regulating these industries. Even though 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 relation to pharmaceuticals, though there are a variety of stakeholders, including medical practitioners and patients as well as government and industry, the safety of the patient by managing the risk to quality should be considered prime importance. The manufacturing and use of a drug product, including its components, necessarily involve some degree of risk. An effective QRM approach can further ensure the high quality of the drug product to the patient by

identify and control potential quality issues during development and manufacturing. Use of QRM can improve the decision making if a quality problem arises. Effective QRM implementation can facilitate better and well-versed decisions which can provide regulators with greater assurance of a company's ability to deal with possible risks.[1,3]

Principles of Quality Risk Management[1,2]

Four primary principles of QRM are:

- 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 capability for continual development and enhancement should be embedded in the QRM process.

General Quality Risk Management Process

Quality Risk Management is a systematic process for evaluation, control, communication and review of risks to the quality of the drug product across the product lifecycle. Risk can be defined as the combination of the probability of occurrence of harm and the severity of that harm.[4,5]

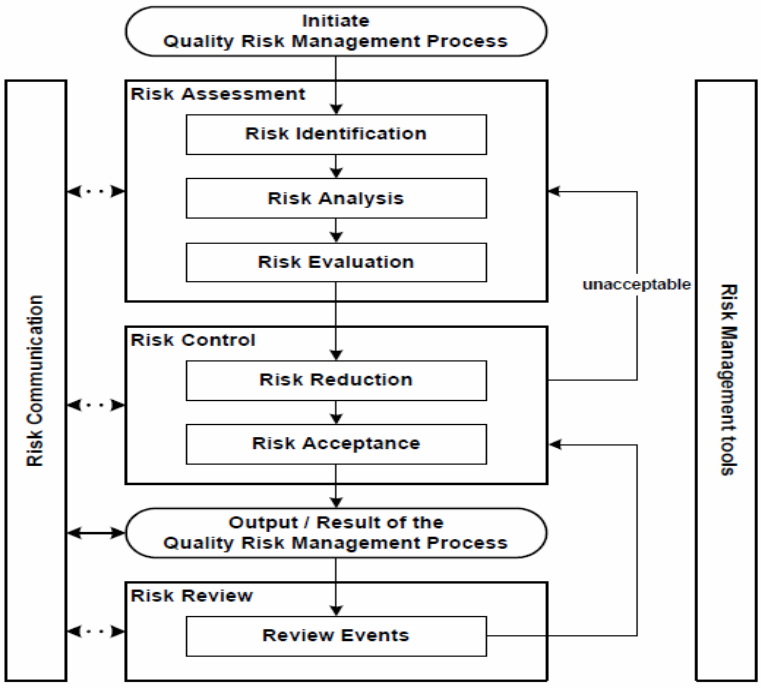


Figure 1: Overview of a typical Quality Risk Management process[1]

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:[1]

- Define the problem and/or risk question, including relevant assumptions identify the potential for risk.
- Assemble background information and/or data on the potential hazard, harm or human health impact applicable to the risk assessment.
- Specify a timeline, and appropriate level of decision making for the risk management process.

Risk Assessment

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.[5] Three fundamental questions are often helpful.

1. What might go wrong?
2. What is the possibility that it will go wrong?
3. What are the consequences?

Risk identification is a organized use of information to identify hazards referring to the risk. Information can include historical data, theoretical analysis, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis 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. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

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

1. 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.e
2. 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
3. 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.
4. 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..
5. Define the Risk Components &Scales[4]

RISK = PRIORITY * DETECTABILITY * SEVERITY

Where,

Severity- Criticality of the product.

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

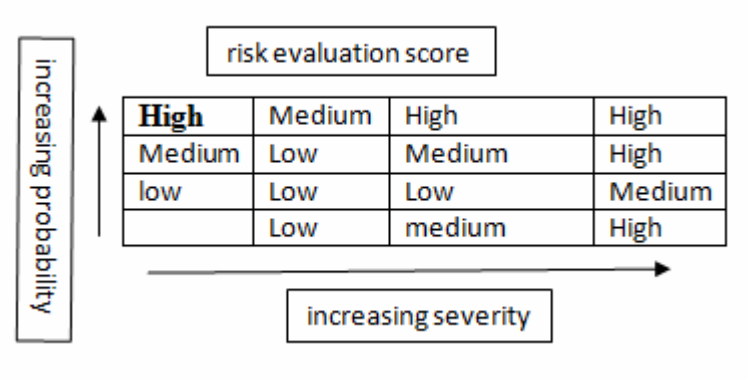
Detection- Audit history.

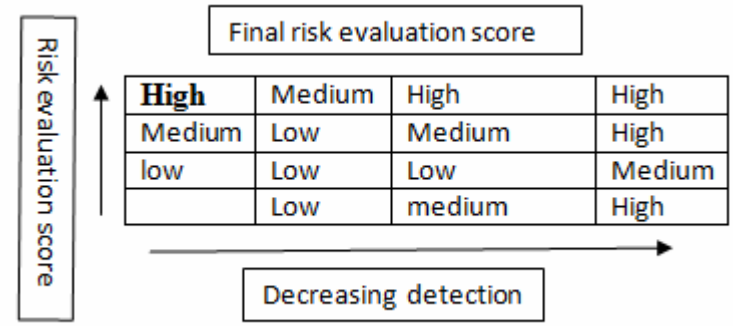
6. Evaluate the risk for each hazard.

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

7. Determine acceptability of risks[6,7]

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





8. Determine Action Threshold

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

9. 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.

Risk Control

Risk control includes decision making to reduce and/or accept risks. The intention of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk[12,13]

Risk control might focus on the following questions:

- ➢ Is the risk above an acceptable level?
- ➢ What actions might take 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 focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified level. Risk reduction might include actions taken to mitigate the severity and probability of harm. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Consider measures/actions that could:[6]

1. Decrease the severity
   - Stop failure before significant consequences, reject, recall
2. Decrease the probability
   - Inspect defect out of batch
3. Increase the detection
   - Move from manual to machine inspection
4. Reapply the tool taking the mitigating measures into consideration
5. Determine if the mitigations/actions have introduced new risks

Risk acceptance is a decision to accept risk. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate 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 decided on a case-by-case basis.

Risk Review is theoutput/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision. Risk review might include reconsideration of risk acceptance decisions

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

The approach described can be used to[14]:

- 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[2]

Risk management tool	Description/attributes	Potential applications
Basic tools		
➢ 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 weighting factors and risk scores	➢ Prioritize operating areas or sites for audit/assessment ➢ Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Advanced tools		
Fault tree analysis (FTA)[8]	➢ 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)[9]	➢ 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)[11]	➢ 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 ➢ Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that CPPs will be met.	➢ Better for preventative applications rather than reactive ➢ Great precursor or complement to process validation ➢ Assessment of the efficacyof CPPs and the ability to consistently execute them for any process
Failure modes effects analysis (FMEA)[10]	➢ Assesses potential failure modes for processes and the probable effect on outcomesand/or product performance ➢ Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures	➢ Evaluate equipment and facilities; analyze a manufacturing process to identify high risk stepsand/or critical parameters

	➢ Highly dependent upon strong understanding of product, process and/or facility under evaluation ➢ Output is a relative "riskscore" for each failure mode	

Conclusion

Quality Risk Management is a systematic process for evaluation, control, communication and review of risks to the quality of the drug product across the product lifecycle. Effective Quality Risk Management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight.

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