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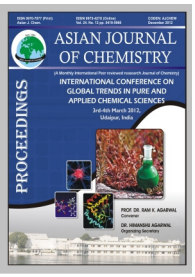

Quality Risk Management in Pharmaceutical Industry-A Overview†

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Risk is defined as combination of the probability of occurrence of harm and severity of that harm. Quality risk management is a systemic process for the assessment, control, communication and review of risk to the quality of the medicinal product. It can be applied both proactively and retrospectively. The quality risk management system should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient. The risk management is applied to different aspects of the pharmaceutical industry. These aspects includes development, manufacturing, distribution, inspection, preparation of the quality part of the marketing authorization dossiers and handling of suspected quality defects throughout the life-cycle of the drug substance, drug product, biological, biotechnological products, raw materials, solvents, excipients, packing and labeling materials. The risk to its quality is just one component of the overall risk. The quality of the product should be maintained throughout the life-cycle of the product.

Key Words: Risk, Quality risk management, Risk assessment, Risk evaluation, Quality risk management process, Life-cycle.

INTRODUCTION

Pharmaceutical industry being an important industry which are directly related to the health of people in society hence risk associated with the pharmaceutical industry are need to be evaluated. Every pharmaceutical product and every process has an associated risk. As per ICH Q9, combination of the probability of occurrence of harm and the severity of that harm[1].

The risk management is applied to different aspects of the pharmaceutical industry. These aspects includes development, manufacturing, distribution, inspection, preparation of the quality part of the marketing authorization dossiers and handling of suspected quality defects throughout the lifecycle of the drug substance, drug product, biological, biotechnological products, raw materials, solvents, excipients, packing and labeling materials. Quality risk management (QRM) must therefore provide an effective mechanism for identifying the risk and determining the potential harm that risk may cause to the various stakeholders such as users, (final dosage manufacturers) medical practitioners, regulators and above all, the patient. Of prime importance is product quality which must be maintained for the entire life-cycle.

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.

The quality risk management system should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process. The risk to its quality is just one component of the overall risk. The quality of the product should be maintained throughout the life cycle of the product.

The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk. Risk management is the process that helps to identify problems, analyze them and then to create an action plan to avoid or manage these problems. Risk characterization is used as a part of the basis for risk management decisions on appropriate measures to handle the risk. Total quality management is defined as an integrated organizational effort designed to improve quality at every level. Total quality management is also defined as quest of excellence, fitness for use, value for money, customer satisfaction, *etc*. The international organization for standards (ISO) defines total quality management as total quality management is a management approach for an organization, centered on quality, based on participation of all its members of the organization and to society[2].

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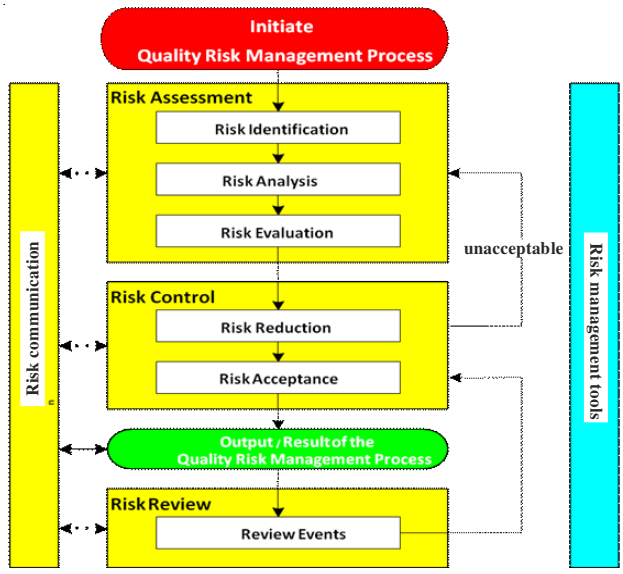
Risk management process: It is systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk to quality of the product[3-10].



ICH Q9

Risk assessment

Risk identification: A systematic use of information to identify hazards referring to the risk question or problem such as historical data, theoretical analysis, informed opinions, concerns of stakeholders.

Risk analysis: It is the process of identification of the root cause. The estimation of the risk associated with the identified hazards. It is a qualitative or quantitative process of linking the likelihood of occurrence and severity of harm. In risk analysis delectability is considered if applicable.

Risk evaluation compares the identified and analyzed risk against given risk criteria. It maintains a robust data set. The data provided must be reliable and accessible.

Risk control

Decision-making activity: Risk control shall focus on the following: Is the risk above an acceptable level? What can be done to reduce or eliminate risks? What is the appropriate balance between benefits, risks and resources? Are new risks introduced as a result of the identified risks being controlled?

Residual risk: The residual risk consists of *e.g*. Hazards that have been assessed and risks that have been accepted. Hazards which have been identified but the risks have not been correctly assessed. The hazards that have not yet been identified. Hazards which are not yet linked to the patient risk. Is the risk reduced to an acceptable level?

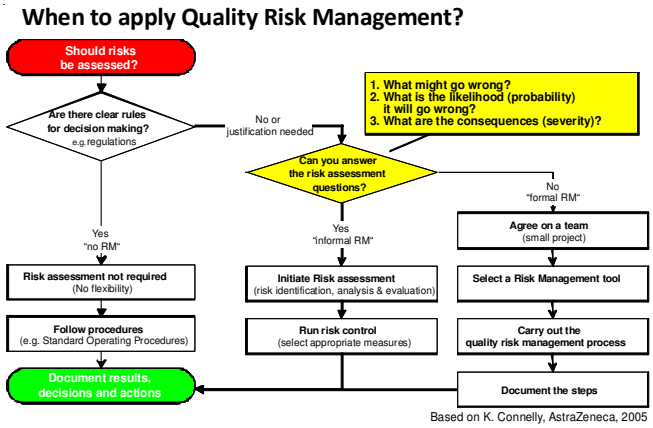
Risk reduction: Risk reduction is a proactive means of addressing potential process failures through design, incorporation of safety features or instructions whose end result is risk reduction to the patient. The amount of risk reduction should be proportional to the impact of that risk.

Risk control: If the risk is acceptable, then the process may remain as it is or reasonable steps considered to further reduce that risk. It may require support by (senior) management. It applies to both industry and competent authorities. It is always be made on a case-by-case basis.

Risk review: The output/results of the quality risk management process has to be reviewed on a regular basis. It is important to continue to review events that may impact the original quality risk decision whether these events are planned (results of product review, inspections, audits, change control *etc*.) or unplanned (root cause from failure, recall, *etc.*). Follow up of action items, summary and evaluation: *e.g*. annual product review, product quality review, follow-up report.

Risk communication: Relevant information shall be reported to all stake holders at every stage of the quality risk management review. The communications can take the form of an informal electronic record to a more formal approved document depending on the level of risk and the point in the risk assessment. The modes of communication are frequent interactions (*e.g.* short daily meeting), informal meetings, scheduled regular meetings (minutes), training.

When to initiate and plan a quality risk management process: First define the question which should be answered (*e.g.* a problem and/or risk question) including pertinent assumptions identifying the potential for risk. Then assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk. Identify a leader and necessary resources. Specify a timeline, deliverables and appropriate level of decision making for the quality risk management process.



Based on K. Connelly, AstraZeneca, 2005

Basic risk management facilitation methods: The selection of particular risk management tools is completely dependent upon specific facts and circumstances.

ˆ Flowchart, check sheets, process mapping, cause and effect diagrams (Ishikawa/fish bone): To associate multiple possible causes with a single effect, constructed to identify and organize possible causes for it.

ˆ Failure mode effects analysis: Break down large complex processes into manageable steps.

ˆ Failure mode, effects and criticality analysis: Failure mode, effects and criticality analysis and links severity, probability and detectability to criticality.

ˆ Fault tree analysis: Tree of failure modes combinations with logical operators.

ˆ Hazard analysis and critical control points: Systematic, proactive and preventive method on criticality.

ˆ Hazard operability analysis: Brainstorming technique.

ˆ Preliminary hazard analysis: Possibilities that the risk event happens.

ˆ Risk ranking and filtering : Compare and prioritize risks with factors for each risk.

ˆ Supporting statistical tools acceptance control charts, control charts, Shewhart control charts.

Importance of risk management as a technique

ˆ Improves decision making.

ˆ Identifies what gives most benefit to the patient.

ˆ Is scientific and data-driven.

ˆ Reduces subjectivity.

ˆ Ranks risk-allows prioritization.

ˆ Better use of resources.

ˆ Means of building in quality.

ˆ Improves transparency- inside organisation and builds trust with competent authorities.

ˆ Enables regulatory flexibility.

ˆ Benefits apply throughout product lifecycle.

Potential applications areas:

1. Integrated quality management; 2. Regulatory operations; 3. Development; 4. Facilities, equipment and utilities; 4. Materials management; 5. Production; 5. Laboratory control and stability studies; 7. Packaging and labeling.

RESULTS AND DISCUSSION

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

Quality risk management is not for Hiding risks, justifying poor quality of product and/or processes, writing half the truth (*e.g.* in an investigation report).

Quality risk management results should contain:

ˆ The rationale and output have to be communicated after decision making.

ˆ The means and records of what is communicated will vary in individual circumstances.

ˆ The choice from short summary to detailed report is case dependant.

ˆ When you decide, through a risk management process, that a certain residual risk is acceptable, you can close your QRM process for that particular risk.

ˆ The need to review or not should be decided based upon the level of accepted risk and other cumulative factors (*e.g.* process changes, events).

ˆ How the problems have been solved?

ˆ What corrective and preventive measures have been taken?

ˆ Inspectors/audits might review/inspect.

The decision makers should take the responsibility of co-coordinating quality risk management across various functions and department of organization. Also assure that quality risk management is defined, deployed and reviewed and adequate resources are available.

Quality risk management is a useful process for decision-making during process development, facility design, equipment selection, change control and failure investigation as well as validation activity planning and prioritization. The approach used for quality risk management shall be practical, useful, not overtly burdensome and commensurate to the task at hand. It is important to remain objective when evaluating process steps in order to avoid preconceived notions and conclusions and to resist using the risk assessment process to justify opinions and desired results.

Available quality risk management guidelines are exhaustive and we can feel the approach is arbitrary. All over the guidelines are roadmap which elaborates various methodologies and their limits based on some scientific and logical evidences. It is the responsibility of the organization to establish a robust quality risk management which assess and resolve the risk across the various operations from different departments of the organization.

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