e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

REVIEW ON QUALITY RISK MANGEMENT

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ABSTRACT

In the Pharmaceutical industry every product and every process associated with risks. To maintain product quality throughout the product life cycle, too much time and resources are allocated. Risk is described in -recent guidance as a combination of the probability of occurrence of harm and the severity of that harm. The Quality Risk Manage IN the pharmaceutical indument (QRM) approach initiated by regulatory agencies with recognized management tools along with support of statistical tools in combination allows for a risk-based approach towards quality management, thus ensuring that resources are deployed in a timely and expeditious manner to areas that need them most.

Evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the safety of the patient. For any pharmaceutical organization, quality risk management should aim at raising the level of protection for the patient, by reduction of the risk to which that patient is exposed at the time he/she receives a drug product. All kinds of quality, quality risk assessment, and also the risk management have been covered with extreme detail through the seminar report in the current scenario.

Keywords: Quality Risk Management, Risk Assessment, FMEA, Probability, Severity, ICH, GM.

I. INTRODUCTION

Risk management is not anything new – we all do it informally. Techniques for risk management have been around for nearly a century. In the 1960s, reliability engineering methods were developed; examples include FEECA and HACCP. ISO 13485 became an established risk management standard across the entire product life cycle. Risk management in the pharmaceutical industry is no more the newcomer. There is significant influence of the 2005 publication ICH Q9 —Quality Risk Management‖ on the pharmaceutical industry. The concepts were embraced by the FDA and other relevant regulatory bodies. 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 potential risks to quality. Generally Q9 gives a broad level direction about identification, estimation and evaluation, controlling.

Monitoring and recording the risk management process. Q9 defines the risk as the combination of the probability of occurrence of harm and the severity that harm.[1]

Today, several industries such as finance, insurance, occupational safety, public health, pharmacovigilance, and agencies regulating these practice risk management principles. Quality risk management is being utilized by pharmaceuticals today, but its application is very limited, far from the extensive contributions that risk management has to provide. Quality systems have equally important roles in the pharmaceutical industries, and it has increasingly become apparent that the quality of risk management is an important constituent of an overall quality system. While the term "risk" is understood most broadly to refer to the probability of occurrence of harm and the severity of that harm. It is nonetheless difficult to achieve mutual understanding of the application of risk management among different stakeholders because of different types of perceived potential harms, varied levels of probability attached to the occurrence of each type of perceived potential harm, and differential severities attributed to each type of perceived potential harm. With regard to medicines, it does not matter that in the case of such products as medicines, for instance, the number of stakeholders on both sides- patients and doctors versus government and industry-is by no means small; protection of the patient by managing the risk to quality should be regarded as of prime importance.[2]

II. WHAT IS QRM?

Quality Risk Management is the systematic process for the assessment, control, "communication and review of risks to the quality of the medicinal product across the product lifecycle." (ICH Q9) They are called enablers

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because they constitute a tool or process which provides the means to achieve an objective. The importance of QRM is such that a whole ICH guideline, Q9, has been devoted to it. "A Quality Risk Management process organizes 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." (ICH Q9) The QRM 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 and the level of effort, formality and documentation of the QRM process is commensurate with the level of risk. A quality risk management system, therefore, can be applied both proactively and retrospectively.[3]

SCOPE:

1. Principles of QRM can be applied to MRAs, pharmaceutical manufacturers and MRAs
2. MRAs: systematic and structured planning of reviews and inspections. Even the programs for submission review and inspection can work in a coordinated and synergistic manner.
3. Manufacturers: medicine drug research and development, production, and distribution. RM is a fundamental part of any organisational culture.
4. Science-based decision-making can be embedded into practice
5. Restrictive and unnecessary practices can be avoided
6. MRAs: regulatory scrutiny adjusted to level of process understanding. Improvement and innovation by manufacturers is encouraged.
7. Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Real-time batch release is feasible. Innovation and the adoption of latest scientific advances in manufacturing and technology are supported
8. .MRAs: company decisions easier to scrutinize. Acceptance of residual risks through understanding the RM decisions involved.
9. Manufacturers: quality decisions and filing commitments can be based on science based process understanding and RM (quality by design). Process control focused on critical attributes. Uncertainty can be addressed explicitly. c) Resources can be focused on risks to patients
10. MRAs: RM can be used to determine best allocation of inspection resource, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks. Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.
11. Manufacturers: evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient. Supports a corporate culture to focus on the patient as a primary stakeholder in all activities.
12. Restrictive and unnecessary practices can be avoided
13. MRAs: regulatory scrutiny adjusted to level of process understanding. Improvement and innovation by manufacturers is encouraged.
14. Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Real-time batch release is feasible. Innovation and the adoption of latest scientific advances in manufacturing and technology are supported. e) Communication and transparency are facilitated
15. MRAs: facilitated dialogue with pharmaceutical manufacturers and tailoring of the inspection programme. Improved clarity of a company's decision-making process and judgement on critical issues.
16. Manufacturers: matrix team approach, stakeholders kept informed via science-based decisions. Culture of trust and "one-team" mindset with focus on product and patient. QRM is the overall and continuing process of minimizing risks to product quality throughout its life-cycle in order to optimize its benefit/risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product.
17. It can be applied both proactively and retrospectively. QRM should ensure the evaluation of risk to quality based on scientific knowledge and experience that ultimately links to the protection of the patient. This

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guideline will align with the general framework described within other current international papers on this subject [4]

PRINCIPLES OF QUALITY RISK MANAGEMENT:

- Evaluate the risk of quality based on scientific knowledge and 3 ultimately to be linked to protecting the patient.
- The approach toward QRM needs to be dynamic, iterative, and responsive to change;
- The QRM process should be informal or formal and documented according to the risk.
- QRM process should include the potential to continually enhance and improve it further. [5]

INITIATING A QUALITY RISK MANAGEMENT :

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following: • Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk

• Collect background information and/or data regarding the possible hazard, harm or human health impact relevant to the risk assessment • Identify a leader and critical resources • Define a timeline, deliverables and appropriate level of decision making for the risk management process [4]. RISK ASSESSMENT Risk assessment includes identification of hazards and analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments are typically initiated by a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and types of information that will address the risk question will be more readily identifiable. Three fundamental questions often serve as an aid in clearly defining the risk(s) for risk assessment purposes: 1 What might go wrong? . 2 What is the likelihood (probability) it will go wrong? . 3. What are the consequences (severity)[6].

Risk control:

Includes decision making to minimize or accept risks. The aim of risk control is to decrease the risk to a tolerable amount. The quantity of effort put into control of risks must be commensurate with the magnitude of the risk. Decision makers may rely on various processes, such as benefit-cost analysis, to comprehend the optimal amount of risk control. Control of risks may involve addressing questions such as:

1. Is the risk above an acceptable level?
2. What can be done to reduce or eliminate risks?
3. What is the appropriate balance among benefits, risks and resources?
4. Are new risks introduced as a result of the identified risks being controlled?

Risk reduction :

focuses on process for the mitigation or avoidance of quality risks when it exceeds a specified (acceptable) level (see Fig. 1). Reduction of risk could include activities related to the mitigation of harm both in terms of the severity and probability. The processes that enhance the detectability of hazards and quality risks may be employed in conjunction as part of a risk control strategy. The implementation of risk reduction measures may introduce new risks into the system or increase the significance of other existing risks. Thus, it may be appropriate to revisit the risk assessment in an attempt to identify and evaluate any possible change in risk after the implementation of a risk reduction process. Risk acceptance is a decision to accept risk. Risk acceptance is a formal decision regarding the residual risk or can be done in a passive way where residual risks are not specified. In some cases, best quality risk management practices may not totally eliminate risk for types of harms. Given these, it would be acceptable that an appropriate quality risk management has been applied and the quality risk is reduced to a specified (acceptable) level. That specified acceptable level will depend on many parameters and should be decided on a case-by-case basis .[5,6]

Risk Communication:

Risk communication is the exchange of information regarding risk as well as risk management between the involved decision makers and others. All parties can communicate at any phase of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately

communicated and documented (see Fig. 1: solid arrows). Communications may involve those among interested parties-for example, regulators and industry; industry and the patient; within a company, industry, or regulatory authority. The information provided may be about the presence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication does not need to be done for every one and every risk acceptance. The industry needs to communicate with the regulatory authorities about

quality risk management decisions might be effected through existing channels as specified in regulations and guidances. [7]

Risk Review :

Risk management should be an integral part of the quality management process. A mechanism to review or monitor events should be instituted. The output/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 instituted, that process should continue to be employed for events 63 www.ajptr.com Mandhare et. al., Am. J. PharmTech Res. 2018;8(2) ISSN: 2249-3387 that may impact the transition to the rated original quality risk management decision, whether those events are planned-for example, results of product review, inspections, audits, change control or not planned for example, root cause from failure investigations, recall The frequency of any review shall be determined by risk level Risk review may include a review of previously accepted risk decisions [8]

Quality Risk Assessment:

This includes hazard identification and analysis and evaluation of risks generated by exposure to those hazards (as defined below). When hazard identification and risk analysis is carried out safety issues must be separated from quality issues. An initial assessment should be carried out based on an understanding of the business processes. Understanding can be acquired from user requirements, design specifications, operating procedures, regulatory requirements, and known functional areas. 9. The QRM team should identify all hazards that may reasonably be expected to happen at every step from production, testing and distribution up to the point of use. It should then do a hazard analysis in order to identify for the QRM plan which hazards are of such a nature that their elimination or reduction to acceptable levels is essential. A detailed risk analysis should be conducted to ensure that control measures are effective. It is advisable to carry out a two-stage risk analysis. In the first stage, the team should have the review of material, activities, equipment, storage, distribution, and intended use of the product. A list of hazards, which might be introduced, increased, or controlled in each step, should be drawn. The QRM team shall then determine which of the hazards identified should be covered within the QRM plan, and which of the control measures, if any, is in place that could be applied for each of the hazards. A hazard identified for a step at which control is necessary to ensure safety, where no control measure exists at that step or elsewhere, shall be modified, either at such a step, or earlier or later, so that such control measure is included. More than one control measure may need to be used to control a particular hazard and more than one hazard may be controlled by a given control measure. This exercise can be aided by the use of a decision-tree, which assists in a logical approach. The way that a decision-tree is utilised will depend on the operation concerned, e.g. production, packing, reprocessing, storage or distribution. At least the following should be considered to help determine the potential hazards:

- Materials and ingredients;
- Physical characteristics and composition of the product;
- Processing procedures; www.ajptr.com 64 Mandhare et. al., Am. J. PharmTech Res. 2018; 8(2)
- Microbial limits, where applicable;
- Premises;
- Equipment;
- Packaging;
- Sanitation and hygiene;
- Personnel – human error; and ISSN: 2249-3387

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• Risk of explosions. The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix .The scoring system and trigger points for mitigating action are

Subjective so the justification for score classification should be delineated as much as possible. If supported by factual evidence then it should be more apparent what mitigating action is necessary-the mitigating action is as important as the score determined. Professional judgment should be applied to interpreting factual evidence but must be open to justification. The expectation of QRM is the analysis of risks to the medicinal product and patient and control both to an acceptable level. It is prudent that companies review their control systems so as to put in place the best controls so as to achieve product quality and patient safety. If this can be achieved in a more cost-effective way while maintaining or decreasing the risk to the product and patient then this is also acceptable. Inappropriate risk assessment and mitigation that could be undertaken to save cost but may work to the disadvantage of the patient should be avoided.[6]

III. RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision-making in support of the highest quality and safety decision. It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and, sometimes, detectability of the risk. Historically, risks to quality have been assessed and managed in a variety of informal ways, for example, based on compilation of observations, trends, and other information (empirical and/or internal procedures). These approaches continue to provide useful information that might support topics such as handling complaints, quality defects, deviations, and resource allocation. In addition, the pharmaceutical industry and regulators can review and control risks through accepted risk management tools and/or internal procedures, such as standard operating procedures. The following is a non-exhaustive list of some of these tools:

1. Basic risk management facilitation methods
2. (Flowcharts check sheets, etc.)
3. Failure Mode Effects Analysis (FMEA
4. Failure Mode, Effects, and Criticality Analysis (FMECA)
5. Fault Tree Analysis (FTA) 6. Hazard Analysis and Critical Control Points (HACCP)
7. Hazard Operability Analysis (HAZOP)
8. Preliminary Hazard Analysis (PHA)
9. Risk ranking and filtering
10. Supporting statistical tools

It may be appropriate to apply these tools for targeted use in certain areas of drug substance and drug product quality. Quality risk management methods and the enabling statistical tools can be used together-for example, Probabilistic Risk Assessment. The combined use offers flexibility that can make it easier to apply the principles of quality risk management. The degree of intensity and formality applied to quality risk management should be proportional to available knowledge and the complexity and/or criticality of the issue to be addressed. It should also be realized that Mindshare et. the tool or group of tools, applicable for any situation when a quality risk management procedure is followed.

1. Basic Risk Management Facilitation Methods :

Some of the simple techniques that are commonly 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)

2. **Failure Mode Effects Analysis (FMEA)**

In FMEA analysis, possible failure modes for processes and their probable impact on results and/or product performance can be analyzed. Identification of failure modes facilitates the application of risk reduction by way of either eliminating, containing, reducing, or controlling potential failures. FMEA requires product and process knowledge. FMEA methodically breaks down the sometimes arduous task of examining intricate processes into a manageable sequence. It is a highly effective summarizing tool for critical modes of failure, causes which lead

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to these failures, and what probable effects are from these types of failures. Possible Application Areas: FMEA can be applied in prioritizing risks as well as monitoring the effectiveness of activities associated with the control of risk. FMEA can be applied in equipment and facilities. FMEA can be used in looking into a manufacturing operation and how it would impact product or process. This explains those elements/operations in the system.[10]

Potential Areas of Use(s)

5. Hazard Analysis and Critical Control Points (HACCP)

A risk FMEA is a method that can be used in prioritizing risks and assessing the effectiveness of risk control activities. For manufacturing operation, it can be used in the analysis of a process or equipment FMEA to understand its effect on a product or process. It points out elements/operations within the system that make it vulnerable. The results of an FMEA output can then form a foundation for design or further analysis or direct resource deployment. 3. Failure Mode, Effects, and Criticality Analysis (FMECA) FMEA can be expanded to include examination of the severity of the effects, their probabilities of occurrence and their detectability thus become a Failure Mode, Effects and Criticality Analysis. To carry out such an analysis the first thing to be defined are the specifications for the product or process in question. FMECA can 2identify areas where additional preventive actions might be appropriate to minimize risks. Potential Areas of Use(s) FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it's not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which can then be used to rank the modes on a relative risk basis.[11] HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety .It is a structured approach that applies technical and scientific 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.[12]

IV. CONCLUSION

The main purpose of risk management at the organizational level is to apply risk management to formality in risk-informed decision making that could easily be linked with resource allocation and patients' safety. The bottom line is to apply the right amount of analytical sophistication to address the appropriate level of complexity. Finally, applying risk management to the pharmaceutical industry should decrease the number of threats or mitigate their impact through the consistent use of the tools/methods and review at specified intervals. The output of the risk management supports the organization in its endeavor to meet defined goals towards protection of public health.

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