OVERVIEW ON RISK ASSESSMENT AND MITIGATION STRATEGIES

Introduction

It is important to have a quality risk assessment process before executing the project/activity. This helps to identify the potential risk involved in the quality of the product and what mitigation to be taken to control the risk identified. Generally, the process is called the ***Quality Risk Management*** (QRM). It provides the proactive approach to identify and scientifically control the potential risk to the quality. It also facilitates the improvement in the process performance and product quality throughout the product life cycle. The Quality Risk Management process is described as guideline in International Conference for Harmonisation of Pharmaceutical products In Human Use (ICH) Under ICH Q9. Here, will discuss about what is the risk, how to assess the risk and what strategies to be adopted to control the identified risk.

What is Risk?

Risk is defined as combination of the ***probability*** of occurrence of harm and ***severity*** of that harm as defined in the ICH guideline.

Risk = Probability X Severity of the harm

Quality Risk Management (QRM)

A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle as defined in the ICH guideline. The QRM aspects can be applied in the development, manufacturing, distribution, inspection, submission/review throughout the life cycle of product for drug substance and drug product. The QRM process consist of risk assessment, risk control and risk review. It is depicted in the below simple diagram.

QRM Process – Diagram -1

Risk Assessment

Risk assessment is the process of identifying the potential hazard and analysis then followed by evaluation of the risk associated with the exposure of that hazard. It is important to have a well-defined problem statement for the risk in question. In the risk assessment process, there are three fundamental questions need to be raised for evaluation.

1. What might go wrong?
2. What is the probability of occurrence?
3. What is the severity?

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Risk assessments consist of three step process.

1. **Risk identification**
   Risk identification is the systematic use of information's to identify the potential hazard of the risk in question. The information can be from previous trend data, theoretical analysis, informed opinions, and concerns of the stake holders. This step provides the answer to the question of what might go wrong? including the possible consequences.

2. **Risk analysis**
   Risk analysis is the estimation of risk associated with the identified hazards. It may be qualitative or quantitative process. In case of qualitative risk analysis, the risk is classified as No risk/Low risk, medium risk, and high risk. In case of quantitative analysis, the risk is quantified through risk score for the combination of probability of risk, severity of the risk and detectability of the risk.

3. **Risk evaluation**
   In the risk evaluation process, compares the identified and analysed risk against the given risk category.

Risk management methodology

Number of risk management methodology available for the assessing the risk. It might be qualitative or quantitative. Please find the list of tools available for evaluating risk.

- ✓ Basic methods like check sheet and flow charts etc
- ✓ Failure Mode Effect 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

How a simple tool is powerful for determining and assessing the risk of identified hazard. The below diagram depicts the risk assessment process qualitatively. Refer the **Diagram -2**

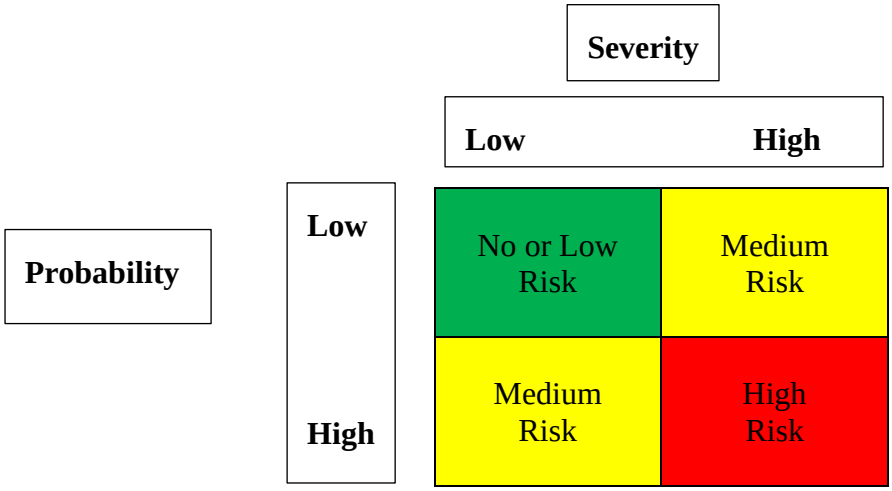


Diagram -2

Risk Control/Mitigation

The next step in the risk management activity is risk control or risk mitigation. It is a decision-making process either to accept and/or reduce the risk. The main purpose of the risk mitigation is to reduce the risk to acceptable. The level of effort taken to mitigate the risk is proportional to the significance of the risk. Generally, a cost benefit analysis is used for making the decision process to mitigate the risk.

Risk management strategies

There are five principal of risk management strategies. The type of mitigation to be used is based on the type of risk and possible probability, severity, and detectability of the risk.

a) Risk Acceptance

In this mitigation process simply accept the risk identified if the identified risk is very low in terms probability of occurrence and severity of the risk and very high detectability. Here the decision of acceptance is applied based on the cost benefit analysis.

b) Risk Avoidance

In this mitigation process simply avoid the risk identified if the identified risk is very high in terms of probability of occurrence and severity of the risk and very high detectability. Further, if the risk mitigation process does not help much in reduction in risk and very high cost involved for reduction hence better to avoid it.

c) Risk Mitigation

In this process some of the risks are either cannot be accepted or avoid. In such cases a suitable control process should be implemented hence the identified risk are under control. For example, controlling the probability of occurrence of hazard.

d) Risk Reduction

In this process the identified risk can be reduced by adding additional control measures. It helps the reduction in the risk however it needs to review again to find any chances of risk further because of introduction of additional control measure. For example, introducing the additional control to reduce the risk to very low.

e) Risk Transfer

In this process, the risk can be transferred to others if the identified risk is neither accept, avoid, control or reduction. It is cost effective way of stopping the further damage due to risk and better to transfer.

Risk Communication

It is a communication process to transfer the information gathered during the risk management process between decision makers and others. The out put of the quality risk management should be communicated and documented. The communication process should include the following but not limited to identified risk, risk control measure, risk review process, probability of risk, severity of risk and detectability of risk.

Risk Review

The final step in the risk management process consists of periodic risk review which include the decision on the earlier acceptance of risk and control measure introduced. The frequency of review of risk based on the level of risk identified.

Usage of Quality Risk Management Process

The Quality risk management process can be applied in the pharmaceutical operations including but not limited to Quality management, development, facility, equipment, utilities, materials management, production, laboratory control, stability testing, inspection, and assessment etc.

Typical example of QRM application in the pharmaceutical industry

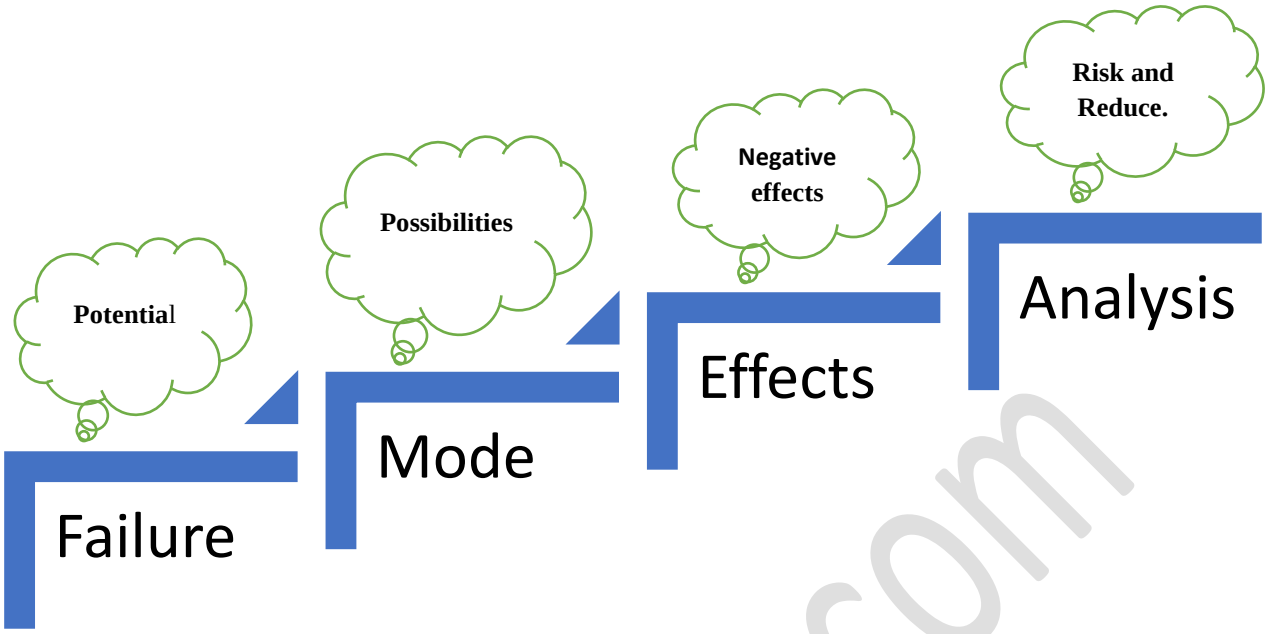
FMEA Tool – Failure Mode Effects Analysis

As per ICH - **FMEA** is defined as evaluation of potential failure mode for processes and their effects on outcome and/or product performance.

Once failure mode is established, a risk reduction can be used to eliminate, contain, reduce, and control potential failures.

FMEA methodology breaks down the process into a simple step from a complex process to a manageable way.

FMEA is depicted simply as below in the **Diagram -3**



What Can Go Wrong in the Process or Product

Diagram -3

FMEA is evaluated in the below table by considering the possible occurrence of the process failure, severity, and possibility of detectability. It is calculated as Risk Priority Number (RPN) by using the numerical numbers from the scale of 1 to 5 (Very Low to Very high). i.e.,**1-Very Low, 2- Low, 3- Medium, 4- High and 5- Very High**

Process step	**Potential Failure mode**	**Potential effect**	**Severity (S)**	**Potential causes**	**Occurrence (O)**	**Current process control**	**Detectability (D)**	**Risk Priority Number RPN = S x O x D**
What is the process step?	What way the process steps can go wrong?	What is the impact of failure?	What is the severity of failure?	What are the causes of failure?	What is frequency of occurrence?	What is current control to prevent?	What is possible detection?	Risk Priority Rank Or concerns

Based on the above evaluation and calculation the RPN is determined. If RPN is 125 then the risk is very high hence an immediate attention is needed and additional control to be introduced to reduce the risk with the acceptable limit.

RPN = S x O x D = 5 x 5 x 5 = 125 – Risk is very High – Need Additional Control

If the RPN is 27 then the risk is medium. Though the risk is medium, the severity and possible occurrence is on higher side hence additional control need to be introduced to reduce the risk with acceptable limit.

RPN = S x O x D = 3 x 3 x 3 = 27 – Risk is Medium - Need Additional Control

If the RPN is 8 then the risk is Low. Hence no additional control is required and the existing risk acceptable.

RPN = S x O x D = 2 x 2 x 2 = 8 – Risk is Low - No Additional Control

In some cases, if RPN is in the acceptable limit however the severity and occurrence is very high in that cases an additional control needs to be introduced to reduce the risk further.

There is a possibility of ***missing the detectability of occurrence of process failure*** in such cases the RPN is calculated by eliminating the detectability.

RPN = Severity x Occurrence

FMEA process helps to identify the potentials failure, assess the failure, its impact, causes of failure and additional controls required to reduce the risk to bare minimum. This tool is effectively used in the pharmaceutical industry in all the areas.

Conclusion

In this article, an overview of risk assessment and mitigation strategies are described in detail. Also explained the steps in the Quality Risk Management Processes i.e., Risk assessment, Risk control and Risk review. The scientific tool can be used for evaluation of QRM which is presented over here. How the FMEA can be applied in the pharmaceutical process steps is also described in detail. Risk identification, assessment of potential failure, its impact and causes are evaluated by FMEA process through Risk Priority Number. Its emphasis the important of evaluating the RPN only through severity and occurrence, where the possibility of detection is missing.

Quality Risk Management is process that supports science based and practical decisions when it is integrated into the quality system. It is very much important to have a risk review to understand the accepted risk is fine or any other possibility of the risk is emerged due to introduction of additional control applied to reduce the potential failure. The QRM process can be applied in pharmaceutical industry from development of the product to retirement of the product i.e., the entire Product Life Cycle. It is effective and essential tool one must apply in the process or product to understand the risk involved for the potential failure. This will help us the reduce the risk by adding additional control in the process step or product so the process or product can go through without having any failure, or if any failure is found we have a mitigation strategy to handle such cases.

References

1. ICH Q9 _ Quality Risk Management guideline
2. USFDA guideline

About the Author

The author is born in India and his highest education qualification is post graduate chemistry from Bharathidasan university. His additional qualification is Master in Business Administration from Bharathidasan university. Currently pursuing higher study in M. Tech – Pharmaceutical administration and management from BITS, Pilani.

He has worked in various organisation like SPIC Petro, Sanmar Speciality chemicals, Ranbaxy, Glenmark, Lupin, Microlabs and Cipla at various level. Currently, heading the Quality control department in Aurobindo pharma of one of the Active Pharmaceutical Manufacturing Unit in India.

He has a vast experience in the field of Quality control, Quality assurance, Analytical, Corporate quality assurance, and training.

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