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Research Article

QUALITY RISK MANAGEMENT – CAPA TO PREVENT POTENTIAL QUALITY ISSUES

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ABSTRACT

In the pharmaceutical industry there are number of risks and failure involved in each and every pharmaceutical product throughout the life cycle. Risk are managed in our day to day life and ensure that preventive measures are taken to avoid any hazards in our life, similarly quality risk management is the tool using which potential quality issues can be avoided to occur for the pharmaceutical products throughout the lifecycle of the product. The principle of QRM can be applied proactively or retrospectively at many stages of pharmaceutical quality such as product development, technology transfer, production, pharmacokinetic evolution, distribution, inspection, validation, submission/review process and life cycle management in product development. It finds useful application in selection of raw materials, solvents, excipients, packaging and labelling materials, formulation development, process development and process improvement. This article discusses general principles and several tools for risk management which can be used successful to identify the potential quality issues. The quality risk management theory and applications for controlling the risk to pharmaceutical quality has identified various potential quality issues and allowed the pharmaceutical industry to manufacture the quality and safe products for the patients.

Key words- Quality risk Management, FMEA, RPN, CAPA, ICH

INTRODUCTION

Human life comprises of success and failures and the various risks associated with the personal voyage called as life. Similarly, it may be considered that there are number of risks and failure involved in each and every pharmaceutical product throughout the life cycle. However as we manages the risk in our day to day life and ensure that preventive measures are taken to avoid any hazards in our life, similarly quality risk management is the tool using which potential quality issues can be avoided to occur for the pharmaceutical products throughout the lifecycle of the product. In fact, Quality risk management is a source of initiating preventive action and allows mitigating the risk pro-actively.

Risk can be defined as combination of probability of occurrence of the harm and Severity of the harm. It is, therefore, a measure of the likelihood of a specific undesired event and its unwanted consequences. Risk management has been effectively utilized in many industries like Automobile industry, insurance industry and organizations like banking, finance, and safety. Now Pharmaceutical Industry is taking interest to follow Quality Risk Management (QRM) Principle and Tools.

This article discusses general principles and several tools for risk management which can be used successful to identify the potential quality issues. The quality risk management theory and applications for controlling the risk to pharmaceutical quality has identified various potential quality issues and allowed the pharmaceutical industry to manufacture the quality and safe products for the patients.

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Quality risk management (QRM) is a systematic approach or tool in understanding risks, their root cause and impact on quality. According to the International conference on harmonization (ICH)Q9 guidance document "Quality risk management is a systematic process for the identification, assessment and control of risks to the quality of pharmaceutical products across the product lifecycle". It includes elements such as risk assessment, mitigation, elimination, communication and review. The guidance provides the scientific knowledge based evaluation of risk to the quality of product and links it to the patient's safety.

The principle of QRM can be applied proactively or retrospectively at many stages of pharmaceutical quality such as product development, technology transfer, production, pharmacokinetic evolution, distribution, inspection, validation, submission/review process and life cycle management in product development it finds useful application in selection of raw materials, solvents, excipients, packaging and labelling materials, formulation development, process development and process improvement.

QRM History

Risk management is a preventive and predictive – not reactive-tool[1].Concept of quality risk management is not new and historically, it has been being followed in various organization and industries since long.

- Year 1949: US Armed Forces Military described the procedures document MIL-P-1629 Which was amended in year 1980 as MIL-STD-1629A)[4].
- Year 1960s: NASA (National Aeronautics and Space Administration) of USA have been using Failure Mode, effects and criticality analysis (FMECA) or Failure Mode and Effect analysis (FMEA) successfully. NASA programs using FMEA variants included Apollo, Viking, Voyager, Magellan, Galileo[10].
- Year 1967: The Society for Automotive Engineers released the first publication to address FMECA[10].
- Year 1970: the Motor Company (M/s Ford) introduced FMEA to the automobile industry for safety and regulatory consideration[10]. They applied the same approach to processes (PFMEA) to identify the potential process induced failures prior to launch of their products in market.
- FMEA methodology is now widely used in various industries including semiconductor processing, food service, plastics, software, and healthcare. One step further, Toyota used FMEA with its "Design Review Based on failure mode" known as "DRBFM" approach developed by Tatsuhiko Yoshimura, a Quality Expert and a professor at Japan's Kyushu University[11].

But it was not until 1990 that the United States Food and Drug Administration (USFDA) became the first regulatory authority to establish risk management standards for the medical device industry[1].

Various regulatory agencies were enforcing pharmaceutical industry to conduct risk analysis to perform a scientific study and issued the guidance to address as a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the life cycle of pharmaceutical drug product. In 2006, the FDA announced the ICH Harmonized Tripartite Guideline: Quality Risk Management Q9 with the purpose of offering a systematic approach to QRM[2]. It is a land mark document that acknowledges risk management as a standard and acceptable quality system practice to assist with decision-making in risk identification, resource prioritization, and mitigation/elimination, as appropriate. Two years later, the European Medicines Agency (EMEA) announced the Annex 20 of its regulation "EU Guidelines to Good Manufacturing Practice Medicinal products for Human and Veterinary Use "Volume 4, that adopts ICH Q9 guideline[5] and in November 2005, International Organization for Standardization (ISO) approved the regulation 31000 that provides principles and generic guidelines on risk management[6].At the same time, ISO published ISO Guide 73: 2009 that provides the definitions of generic terms related

to risk management as a complement to this regulation[7].

CAPA and Quality Risk Management relationship

CAPA is the process for continuous improvement of the product, process and quality management system in the organization. If we expand CAPA, it has two components (a) CA i.e. corrective action and (b) PA i.e. Preventive action. Corrective action is defined as action taken to avoid the recurrence of the existing non-conformity or quality issue and it is reactive approach to address the quality issues while preventive action is defined as action taken to avoid the occurrence of the potential non-conformity or quality issue which has not happened and it is pro-active approach[8]. Now the question is how do we identify the potential quality issue and the answer is Quality Risk Management (QRM).The integration of both the systems shall ensure that risks are identified at the early stages pro-actively and all the risks are mitigated by eliminating the cause or reducing the occurrence to an acceptable level and introducing the system to detect the quality issue. Refer Figure 1 for the flow chart for relationship of QRM and CAPA systems.

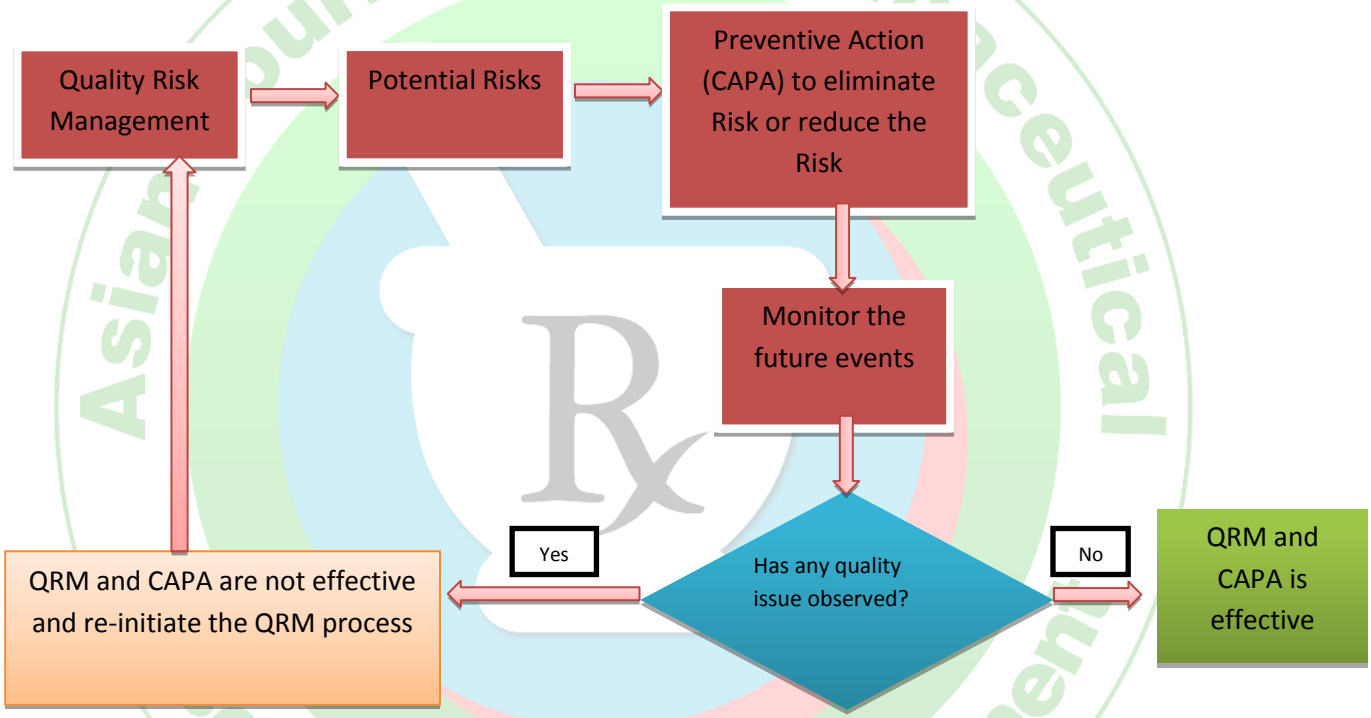

Figure 1: Relationship of QRM and CAPA

Advantages of QRM: Following are the advantages of the Quality Risk Management

- Proactive tool to identify potential quality issues and take preventive action
- Helps to take science based decision in case any potential Quality issue may arises
- Facilitate better and educated decision
- Greater assurance to the regulator
- Built the quality in product
- More scientific and data driven: Reduces Subjectivity.
- Ranks Risk and allow prioritization: Better use of resources.
- Improves transparency: Enables Regulatory flexibility.
- Beneficial throughout product life cycle: Provides economical profits.

Quality Risk management Principles:

There are primarily two basic principles[2] for performing the quality risk management –

- 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

Process flow of Quality Risk Management:

Quality Risk management is a Systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk to quality of the product and safety of the patients.An effective risk management approach can assure highest Quality of drug product to the patients in providing means to identify and mitigate Quality issues at the early stages of product development. A model for the quality risk management is outlines in the diagram (figure 2)

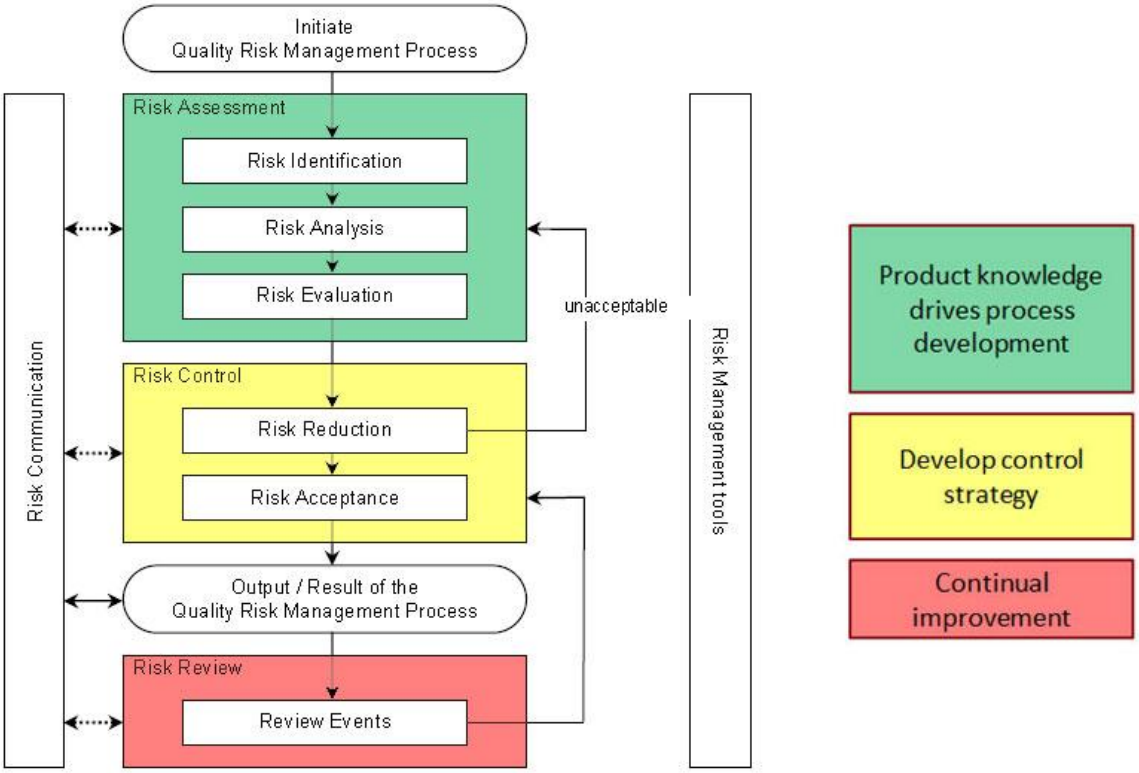

Figure 2: Overview of a typical Quality risk management process

Source: Quality Risk Management ICH Q9, version 4

MHRA, regulatory agency UK, suggested to follow below key attributes to be observed for a good risk assessment as [9] -

- Identify the process to be assessed and what the harm/risk is associated and what potential impact could be on the patient safety
- Ensure systematic identification of possible risk factors
- Take full account of current scientific knowledge
- Personnel with experience in the risk assessment process shall be part of the process
- Factual evidence supported by expert assessment shall be used to reach conclusions
- Unjustified assumptions shall not be included
- Identify all reasonably expected risks – with a accurate assessment and proposed mitigation
- Appropriate documented findings of the process
- Ensure that QRM process study is linked to the safety of the patient
- Ensure risk mitigation plans are included.

A planned risk assessment is one that is conducted in advance of conducting an

activity, either before any activity is conducted or before further activity is conducted. This would often allow quality to be built in to activities and risk reduced (quality by design) e.g. design of facilities for manufacture of cytotoxic products or organization/design of a label printing room. An unplanned risk assessment is one that is conducted to assess the impact of a situation that has already occurred, e.g. impact of a deviation from normal ways of working[9].

Following are the major steps while performing Quality Risk Management[3]–

- Quality risk Management process initiation
- Risk Assessment,
- Risk Control,
- Output/Result of the QRM process
- Risk Review,
- Risk Communications

Quality Risk Management Process Initiation

QRM should include systematic processes designed to co-ordinate, facilitate and improve science based decision making with respect to risk. Planning of the QRM process shall include[3] –

- Defining the problem statement, scope, known assumptions and expected outcome
- Identifying the appropriate team of SMEs and a trained facilitator
- Determining the level of formality and selecting the appropriate tools to deliver the expected outcome
- Determining how the QRM activities will be documented
- Identifying and collecting relevant background information, reference documents and data related to the potential risks or product and patient impact.
- Stating a deliverables with target completion date and appropriate levels of decision making for the risk management process.

Risk Assessment

The risk assessment process comprises of following three steps –

- Risk identification,
- Risk analysis
- Risk evaluation.

The level of rigor and type of risk assessment should be proportionate with the potential impact on product quality and patient safety and knowledge of risk associated with a risk question, problem statement[3].

Irrespective of the product, process, risk question, problem statement all risk assessment requires the same fundamental activities in a common sequence of events:

- Identify the owner of the QRM process
- Identify the stakeholders of the QRM exercise and individual responsible for its execution.
- Identify the areas of expertise required for the exercise and build the risk assessment team of cross functional Subject Matter Experts (SMEs).
- Describe the product, process or system for which QRM is to performed
- Define the risk question, problem description or problem statement
- Determine the appropriate risk management tools to be used
- Identify the criteria for risk evaluation
- Assemble background information and data on the potential hazard, harm or human impact relevant to the risk assessment.

Risk identification

Risk identification is a systematic use of information to identify risks referring to the problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders.

Three fundamental questions are asked to clearly define the risk(s) for Quality risk assessment purposes[2]:

1. What might go wrong?

   This question raises the possibilities of harm from exposures to hazards

2. What is the likelihood (probability) it will go wrong?

   This question focuses on the probability of occurrence of specific harms

3. What are the consequences (severity)?

   This question focuses on the severity of outcomes, given that the risk event occurs

Risk analysis

Risk analysis is the assessment of the risk associated with the identified hazards. It can be either qualitative or quantitative process which links with the likelihood of occurrence (probability) or severity of harms. The ability to detect (detectability) the harm also factors in the assessing the risk.

Risk analysis is beneficial when conducted with a multi-functional team of SMEs. This assures that risks are analysed from multiple perspectives. Team discussion is particularly useful so that different perceptions of the risk can be surfaced[2].

Risk evaluation

The identified and analyzed risks are compared against pre-defined risk criteria during risk evaluation. The output of a risk assessment can be a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be articulated using qualitative descriptors, such as "high", "medium", or "low". These descriptors should be defined in detail for better clarity while assigning the rating. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Hence, quantitative risk assessment is useful for one particular consequence at a time[2].

Risk Control

Risk control includes decision making either to reduce or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should commensurate to the significance of the risk identified. Benefit-cost analysis or any appropriate tool shall be used by the decision makers for understanding the optimal level of risk control.

Risk control might focus on the following questions[2]:

- 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 focuses on reducing the severity and probability of occurrence by implementing appropriate product, process, and system controls. Each identified risk should be assessed to determine if it is broadly acceptable, or unacceptable / intolerable. For unacceptable / intolerable risks, the risk reduction strategy should define the CAPA to attempt to reduce the risks to an acceptable level[2].

Refer below table for risk evaluation using qualitative factors –

Table:1 Risk Evaluation

Severity → / Probability of Occurrence ↓	Critical	Moderate	Minor
High	**Intolerable risk**	**Intolerable risk**	**Unacceptable risk**
Medium	**Intolerable risk**	**Unacceptable risk**	**Acceptable risk**
Low	**Unacceptable risk**	**Acceptable risk**	**Acceptable risk**

Processes that improve the detect ability of possible harm and quality risks shall also be used as part of a risk control strategy. It is worth to note that implementation of improvement measures for risk reduction can introduce new risks into the system or increase the significance of other existing risks. Hence, it is appropriate to re-examine the risk assessment to evaluate

any possible change in risk after implementing a risk reduction process.

Risk reduction should preferentially focus on prevention rather than detection. Prevention can be achieved in several ways such as:

- Build in safety by design
- Add protective measures in product or manufacturing process
- Add safety warnings

Improvement of detection mechanisms can also be useful in reducing risks especially where prevention controls are insufficient.

Risk acceptance is a formal process in which decision makers review the risks associated with a specific activity. The decision maker shall determine whether the risks are acceptable or reduction is needed. For some types of harms, even the best quality risk management practices might not entirely remove the risk, hence an appropriate quality risk management strategy shall be applied in such circumstances and that quality risk is reduced to an acceptable level which depends on many parameters and shall be decided on a case-by-case basis.

Output/Results of the QRM process

For meaningful execution of formal QRM activities, relevant supporting data, salient information, and facts should be clearly documented and communicated. Risk assessment outcomes including risk reduction and risk acceptance decision, level of residual risk and their acceptability, and risk review requirement should be documented and approved by the appropriate decision makers. QRM documents should be archived properly[3].

Risk Communication

Risk communication means to share information about risk and outcome of the risk management between the stake holders and the decision makers. Communication can be made any stage of the risk management process. The output/result of the quality risk management process shall be adequately communicated and documented. Stake holders might include interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc.

Communication activities are recognised as fundamentally important to the risk management process outlines in the ISO risk management standard, ISO 31000. This is underline by the recognition that a high performance in risk management activities is associated with organization that has a high level of regard for continual and timely communications with external and internal stake holders[2].

Risk Review

Risk management should be an on-going part of the quality management process. A structured mechanism for periodic review or monitoring the events should be implemented to understand new knowledge and experience gained from the output/results of the risk management process. Quality risk management process should continue to be utilized for planned or unplanned events that might impact the original quality risk management decision. Examples of planned events are results of product review, inspections, audits, change control and the examples of unplanned events are the root cause from failure investigations, recall. The frequency of any review should be based upon the level of risk and risk review might include revisiting the risk acceptance decisions[2].

Quality Risk Management Tools

The most commonly used basic QRM tools to facilitate decisions are:

- Flowcharts;
- Check Sheets;
- Process Mapping;
- Fishbone Diagrams;
- Risk Ranking and Filtering.

The most popularly used QRM tools for more sophisticated analysis are:

- 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(HOP);
- Preliminary Hazard Analysis (PHA)[2].

Failure Mode and Effects Analysis (FMEA):

FMEA is effective and popular tool for developing designs, processes, and services. The goal of FMEA is to align risks as closely as possible with their source. This process helps to determine the possible cause of the potential risks and probability of occurrence of a particular failure is specified from the knowledge base data. The FMEA team proposes the options for prevention and mitigation of the potential effects. FMEA allows for the assessment of the potential failure and focuses to eliminate and/or reduce severity and occurrence and increase the detect ability of the harms. Thus FMEA tool helps to improve the reliability and safety of the process and reduces wastage, rejection, reprocess, and rework thus saves money.

Following are the three main components of the FMEA process

- **Severity (S):** Severity would assess how serious the effects on the product quality and patient safety in case the potential risk actually occurred. The severity score is rated against the impact of the effect caused by the failure mode on the batch quality.
- **Probability of occurrence (P):** Probability of occurrence evaluates the frequency that potential risk (s) will occur for a possible failure. The probability score is rated against the frequency that the effect occurs as a result of a failure mode.
- **Detectability (D):** Detectability is the possibility of the failure being detected before the impact of the failure to the system or process. The detectability score is rated against the ability to detect the effect of the failure mode or the ability to detect the potential failure.

These three factors are used to composite a risk score for each unit operation step which is calculated by multiplying these factors. Composite risk is called a risk priority number (PRN) and The RPN provides a relative priority for taking action.

RPN = (Severity) x (Occurrence) x (Detection)

In summary, the basic steps for performing FMEA are[1]:

- Describe the product / system / process identified for the quality risk assessment;
- Form a cross functional team including SMEs and team lead
- Team shall prepare the Process flowchart
- Use the FMEA table and complete the headers which can be customized for the specific need;
- Break down the product / system / process into its sub-components
- Team shall brainstorm to Identify all potential failure modes related to the product /system/ process;
- List all potential failure modes for each item under the “Failure Mode” column of the FMEA table;
- Describe the effects of each of listed failure mode and assess the severity of each of these effects on the product / system / process;
- Assign a severity rating to each effect on the FMEA table ;
- Identify the possible cause (s) of each failure mode;
- Quantify the probability of occurrence of each of the cause of a failure mode;
- Identify existing measure or controls that is capable to prevent the occurrence of each of the cause of a failure mode;
- Determine the detect ability of each of the listed failure mode or the cause
- Assign a ranking score for indicating the detect ability of each control;
- Calculate the Risk Priority Number (can be qualitative or quantitative);
- Team shall discuss to Identify actions for mitigating potential failure modes that have a high RPN;
- Assign responsibility for implementation of the recommendation/ action(s) along with target date for completion;
- Re-assess and calculate new RPN after all the actions are implemented

Table 2: FMEA Table

Item and function/ process step	Potential failure mode	Potential Effect(s) of failure	Severity	Potential cause (s) of failure	Occurrence	Current controls	Detection	RPN	Recommended action	Responsibility and target date	*Action taken*	*Severity*	*Occurrence*	*Detection*	*RPN*

Case Study Discussion

FMEA for a pharmaceutical industry with problem statement "Mix-up of the products" is performed. A cross functional team was formed. Team agreed to have following ratings for each factor (i.e. Severity, Occurrence and detectability).

Table 3: Rating table

Rating	Severity	Probability of Occurrence	Detectability
1	No effect or negligible effect on product quality and patient safety	No known occurrences	Certain – Defect / Failure will be caught
2	Minor effect on product quality and patient safety	Low (relatively few failures)	Almost Certain
3	Moderate effect on product quality and patient safety	Moderate (occasional failures)	Moderate
4	High effect on product quality and patient safety and reversible damage to the patient health	High (repeated failures)	Low
5	Very high effect on product quality and patient safety and irreversible damage to the patient health	Very high (failure is almost inevitable)	Very Low - Defect / Failure will be passed to customer undetected

Team got together for brain storming and question "what can go wrong" was asked. All the potential failure modes were discussed and the details were documented in the below table.

Team discussed and agreed for the recommendations (Preventive actions) to eliminate the occurrence of the quality issue. CAPA forms were opened for each action items where in responsible person was identified with target completion date (TCD). The progress of action was monitored by the team lead and ensured the completion. Team again gathered and re-calculated the RPN after 12 months of production. The rating for severity remained same, however there were no incidence reported in 12 months means occurrence were reduced to lowest level with improved detectability. This exercise performed at the design stage before starting the operations ensured that all potential quality issues / risk can be prevented thus improving the quality, reducing the risk of patient safety and increasing the profitability in the organization.

Table 4: FMEA for Mix-up of the products

Item and function/process step	Potential failure / Unwanted event	Potential Effect(s) of failure	Severity	Potential cause(s) of failure	Occurrence	Current controls	Detection	RPN	Recommended action	Responsibility and TCD	*Action taken*	*Severity*	*Occurrence*	*Detection*	*RPN*
Mix-up of the products	Product mix may take place if the different products are stored together on same pellets	Serious GMP issue and patient safety issue if the mix up remain unnoticed	5	Mix up will have serious health hazards	5	Current Standard operating procedure does not require for storage of 2 products on separate pellets	5	125	SOP shall be revised to include to mention for the storage of different products on different pellets	XYZ	SOP revised	5	1	1	5
Mix-up of the products	Product mix may take place each if the product container is not labelled	Serious GMP issue and patient safety issue if the mix up remain unnoticed	5	Mix up will have serious health hazards	5	Current Standard operating procedure does require to label each container from out side	3	75	SOP shall be revised to include for labelling each product containers from outside and inside. Each product label shall be unique in colour for visual identification	XYZ	SOP revised	5	1	1	5
Mix-up of the products	Product mix may take place if the cleaning procedure is not adequate	Serious GMP issue and patient safety issue if the mix up remain unnoticed	5	Mix up will have serious health hazards	5	Current Standard operating procedure does identify hard to see the location where previous product could be hidden	4	100	SOP for cleaning shall be revised to include pictorial diagrams depicting hard to see locations which shall be critically examined during cleaning operation	XYZ	SOP revised	5	1	1	5
Mix-up of	Product mix	Serious	5	Mix up	5	Current	3	1	A cleaning	XY	SO	5	1	1	5

the products	may take place if the cleaning adequacy is not verified by another person	GMP issue and patient safety issue if the mix up remain unnoticed		will have serious health hazards		Standard operating procedure does require to get the cleaning activity verified by another person		00	checklist shall be prepared which shall include all the critical steps for the cleaning and shall be counter verified by second person after completion of cleaning	Z	Revised			

CONCLUSION

Quality Risk Management is very effective process to identify the potential risk / quality issues at the early stage of various processes of pharmaceutical industry. Once the potential risks are identified, it is vital to eliminate the source of occurrence. If the elimination is not possible than the frequency of occurrence shall be reduced and shall be monitored. System shall be strengthened to detect the quality issues. Failure Mode effective analysis (FMEA) has been proved to be successful tool to perform the Quality risk management where the Risk priority number helps to prioritise to mitigate the risk in the process and revisiting the RPN after implementation of the risk helps to understand whether preventive action (CAPA) implemented to reduce the risk is effective or not. Effective Quality risk management integrated with CAPA system would reduce the quality issues and increase the profitability of the organizations.

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