RESEARCH ARTICLE

Risk Assessment of Product Before the Regularization of the Process

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ABSTRACT

Risk or uncertainty are two words frequently used and replaced by one another. In Wherein case of uncertainty, the output is unknown; risky situations give the possible outcomes and the necessary arrangements to deal with it. Thus, risk can actually be quantified, whereas uncertainty cannot be. The study discusses the assessment of the risk involved in different cases that were tried during the procedure.

The process of determining the severity and likelihood of adverse effects that may result from exposure to chemical, biological, or physical hazards is known as risk assessment. It is an essential part of the modern advanced pharmaceutical quality. This study provides a general overview of risk assessment which was done before regularization of the process in a pharmaceutical industry (API Plant). It is important to identify the potential causes and risks involved in the manufacturing process before the regularization of the process and suggest the additional controls or CAPA to be taken in case of process identified as a high-risk category.

The paper covers the identification of risks that are associated with the process. Thereafter, risk priority number is found out which would help us in comparison of different risks outlined. Subsequently based on the severity, corrective measures are suggested. The study concludes by ensuring that process of continuous quality improvement can be made. Associated riskhave been assessed and controls found to be effective.

Keywords: Quality Risk Management, Risk Assessment, Failure Mode, Effects Analysis.

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INTRODUCTION[1,2,3,4]

The regulatory framework outlined in the International Council for Harmonisation (ICH) guidance Q8 (R2) pharmaceutical development, ICH Q9 quality risk management, and ICH Q10 pharmaceutical quality systems (PQS) was introduced to improve pharmaceutical product quality and provide regulatory flexibility for the industry to improve their manufacturing processes.

What is Quality Risk Assessment?

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1).

Two Primary Principles of Quality Risk Management are

- the intension should be to protect the patient and should have a firm and robust scientific knowledge to back it up;
- Any discrepancy in quality should be detected at the experimental stage so that it doesn't pass on to the patients.

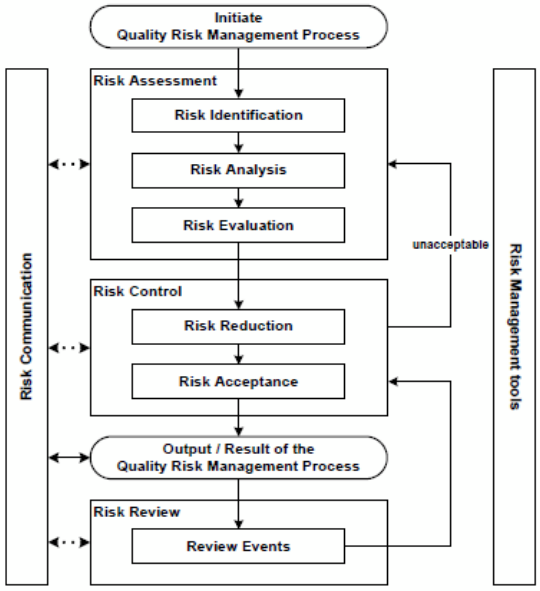

Figure 1: Overview of a typical quality risk management process

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Need to do Quality Risk Assessment

When the cycle advances from the idea stage to feature stage and then finally production, it is prone to many risks during the course of product development. The initial idea may not be feasible. It may have certain durability issues, may require frequent maintenance, may break even after a relatively long time period etc. Quality risk assessment (QRA) gives us an estimate regarding the associated risks with various actions or could be taken in the future. Instead of countering the risks involved, it is always beneficial to avoid probable risks. For example, rework and scrap costs of a product are much higher than in house quality issues. Thus, quality risk assessment helps the makers to assess the risks involved and accordingly take remedial measures for the same.

Reasons for Quality Risk Assessment

When the ideas that are put on paper need to be implemented in case of product development, the uncertainty associated with such decisions is huge. As a result, the party is at the risk of losing out on many resources that it could have saved has they have analyzed the risk involved in the process. The entire lifecycle needs to be studied properly, and the risk assessment needs to be made. The risk assessment has many advantages like the improved pace of the process, avoid unnecessary wastage, proper allocation of resources such as raw materials, labor, capital, etc.

Benefits of Quality Risk Assessment

Some benefits of Quality Risk Assessment are highlighted as shown below-

The QRA enables one to be proactive towards approaching risk. Instead of reacting to any event and incurring correction costs, it is always advisable to incur prevention costs.

If QRA is performed correctly, it can help in saving critical resources. In turn, it help to increase the efficiency of the process.

QRA helps in the efficient and effective use of resources. Example – The number of staff that needs to be employed, where they need to be employed etc., would be easier to judge based on the assessment of risks involved.

METHODS

Failure Mode Effects Analysis (FMEA)[5-7]

FMEA is a management tool that helps us in providing the different methods or modes in which a failure can occur and how it would eventually affect the customers. Failure here refers to unwanted situations that can crop up or has more likelihood of occurrence. There can be different kinds of failures and they can be categorized based on how serious their consequences are (severity), what is the frequency of the error or defect coming up (frequency), and the ease with which it can be detected (Detection). The process of FMEA/FMECA process is shown in Figure 2.

Another advantage of FMEA is the database that gets formed in the process of analyzing the potential risks. Over a period of time, this database provides for a handbook and would result in efficient and quicker response by the team. Also, since it is used during the design phase of product development, it helps us avoid the rework costs or failure costs associated with the product. FMEA can not only be applied to products but also to processes, machinery etc. Apart from the above advantages, it helps us in understanding the criticality of the processes involved. This knowledge of process's significance would help the team allocate resources appropriately. As a matter of fact, FMEA finds varies applications in various sectors like Design, Health etc. but the approach remains similar.

Benefits of FMEA

There are many benefits of using FMEA as listed below:

- Given that it is a proactive tool, it helps us in reduction of manufacturing costs, rework or scrap costs, costs related to modification of process, product etc.
- Enabling us to know about the probable risks, it reduces the product development time and costs involved.
- If a proper database is maintained, it would help in better decision making if a similar kind of problem is encountered any time in future.
- It improves the quality of the process, the reliability of the procedures and reduces the safety hazards if any in the process.
- The entire process ensures faster response to changing customer needs and would help in increased customer satisfaction.

Identification and Comparison of Risks in Process while performing QRM

The entire process of assessment of risk could be based on either qualitative or quantitative approach or both of them. Risk priority number (RPN) is a quantitative number that is

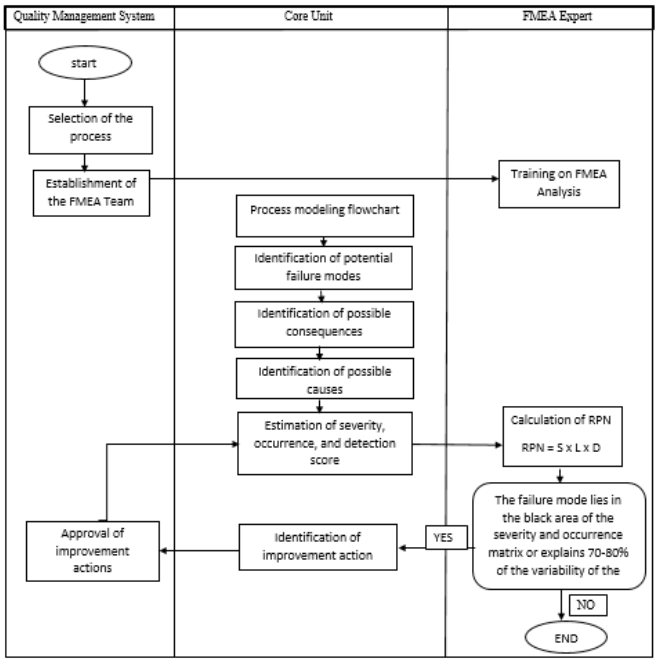

Figure 2: Swimlane flowchart of the FMEA/FMECA process.

assigned to different associated risks. The purpose of RPN is to enable easy comparison between the risks and thereby decide which risk needs to be focused on first or given more importance. RPN is calculated by multiplying the likelihood of occurrence, frequency of occurrence and the ease of detection of a particular risk. RPN is a technique to identify, compare and review the different risks that had been identified using the FMEA method. Given below in the Figure 3 is a general FMEA structure that is followed:

As can be observed from the above picture, the early stages of FMEA involved identification of risks but the later stages involve assigning a quantitative number i.e. RPN to the risk involved. The number is assigned by industry experts and those with a plethora of experience in the field. It is with their experience that the team would understand the degree of risk to which the process is prone to. Accordingly, preventive or remedial measures could be taken.

Overview of RPN

Where FMEA is performed to identify the potential risks associated with the process, the RPN is assigned to these risks that help us easy comparison between the process. The team is then responsible for converting the identified risk into a quantitative number. This conversion is based purely on one's perspective. Thus, more experienced professionals more would be the accuracy of the rating. The rating is done based on three different scales as described below:

- Likelihood, which determines the probability of occurrence of failure
- Severity, which determines the criticality of the failure
- Detection, which determines the probability of detecting the risk before it makes some real difference in functioning or in market.

The rating can be given on either a five-point scale or a 10-point scale. The choice of the rating scale is totally upon the discretion of the individual or the organization. A higher rating signifies that the particular risk is more prone to occurrence than one with a lower rating. Thus, based on the rating (given to different problems, risks or errors), it would signal the team about the step in the cycle that needs to be addressed first. The higher the risk chances, higher would be the rating and accordingly more would be the attention to detail to the particular process.

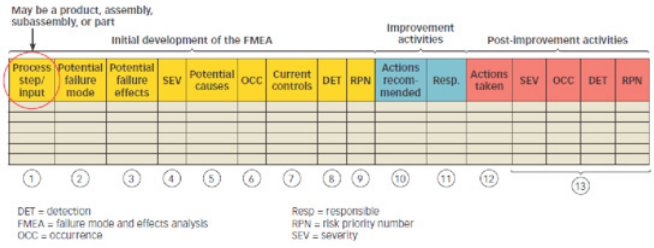

Figure 3: Typical FMEA Structure

Selection Criteria

Severity (S) - which is represented in Table 1.
Likelihood (L) is represented in Table 2 and
Detection (D) is represented in Table 3
RPN is then calculated using the following formula –

RPN = Severity × Likelihood × Ease of detection

Once the RPN number is calculated after the assessment of the risk, it is then reviewed. If the RPN number lies within the control range, suitable preventive measures are supposed to be taken. This could be either replacement of certain raw materials, changes in order of process etc. But in cases where the RPN is very high, immediate action needs to be taken by the team. Based on the number, it may be even be required at times to stop the entire development at once, fix the problem and only then commence the process or production. The range

Table 1: Severity ranking

Effect	*Criteria: Severity of the effect*	*Ranking*
High	Severe impact on Product Quality impact on Efficacy of potential drug risk to the patient	4
Medium	Impact on quality and no adverse impacts/risk to patient	3
Moderate	May affect the quality however impact is less No risk to Patient	2
Minor	No Impact/ negligible	1

Table 2: Likelihood ranking

Likelihood	*Probability of failure*	*Ranking*
High	The Possibility of occurrences are high based on trend/expertise opinion	4
Medium	Repeated failures in the history /Negative studies evidenced the possibility of failures	3
Moderate	Occasional Failures	2
Low	Remote chances of failures based on the evidenced trend and Design of Experiment	1

Table 3: Detection ranking

Detection	*Probability of detection in time*	*Ranking*
High	Highest chances of risk detection and ample time for necessary correction	4
Medium	Good chances of risk detection but lesser time to react to subsequent changes	3
Moderate	Low chances of detection of failure and almost negligent time to react	2
Low	Very Less probability of detection of a future failure	1

Table 4: Results of risk assessment

S. No.	*Description of the item/ activity*	*Risk involved*	*Failure mode/ effect of risk*	*Potential causes*	*Existing control (s)*	*S*	*L*	*D*	*RPN*	*Risk Category*	*Additional controls /action plan /CAPA*
1	Vendor identification and Vendor Qualification for list of raw materials used in the manufacturing process	Usage of less quality Raw material	Product risk Quality failures	No Proper/ Specified Procedure for Quality vendor Identification.	Following are the SOP Procedure for Qualification and Evaluation of the Vendor. Initially, vendor samples analysis, Filled vendor questionnaire and all the relevant documents. Procurement of materials, analysis and validation completion. Vendor audit and permanent approval of the vendor.	4	1	4	16	Low	NA
2	Sampling and Dispensing of Raw materials	Cross Contamination	Product risk Quality failures	Non-availability of Proper Sampling Procedure and training	Sampling performed for KSMs and for raw materials followed by the "Sampling of the materials" and the SOP "Dispensing of Raw and Packing materials" The sampling & dispensing are as per the procedure to eliminate the cross contamination Concerned individuals would undergo the training as per "Training SOP''	4	1	14	16	Low	NA
3	Testing of the materials	Product quality risk	Quality failures	Non-Availability of specified specs Improper training on testing Instruments fail to work accurately	Testing is performed as per the approved specifications Necessary training is performed for the testing persons All the analytical instruments are qualified prior to the analysis as	4	1	4	16	Low	NA
4	Sampling and Dispensing of Raw materials	Cross Contamination	Product risk Quality Failures	Non-availability of Proper Sampling Procedure and training	Sampling performed for KSMs & for raw materials followed by the "Sampling of the materials" and the SOP "Dispensing of Raw and Packing materials" The sampling & dispensing are as per the procedure to eliminate the cross contamination Concerned individuals would undergo the training as per "Training SOP''	4	1	14	16	Low	NA

S. No.	Description of the item/ activity	Risk involved	Failure mode/ effect of risk	Potential causes	Existing control (s)	S	L	D	RPN	Risk Category	Additional controls /action plan /CAPA
5	Men	Untrained Persons handling the operations	Product risk Human risk from the product.	Non-Availability of training facility on the working procedures and operations	Any new recruit training program is carrying out as per the SOP "Training (and training shall be given to the respective individuals before commencement of operations and Personnel qualification. Wearing the suitable PPE (hand gloves, helmet and mask) to handle the product to avoid the risk.	4	1	4	16	Low	NA
6	Cleaning and Sanitation	Product risk Safety	Contamination of product	Cleaning not performed or suitable solvents not used	Cleaning performing with a suitable solvent. Cleaning solvent selected as per the solubility criteria and performing the daily sanitation.	4	1	4	16	Low	NA
7	In process, Intermediate and finished sampling	Product risk	Cross Contamination.	Poor sampling procedures followed	In process sampling shall be performed as per BMR by the trained persons only. Approved In process, finished STP and work books are using for analysis. All the persons involved in the sampling and analysis are undergone training prior to perform the activity.	4	1	4	16	Low	NA
8	Product processing	Product quality risk	Cross contamination of product	Poor Processing process followed	Suitable environment for processing Verification of the status of the raw materials used before charging. Calibrated balances used for weighing of the packed product. If any deviations are identified shall be resolved as per the SOP "Handling of deviations"	4	1	4	16	Low	NA
9	Sampling and analysis of Final product	Product risk Cross contamination	Cross Contamination.	Poor sampling procedures followed	Sampling is performed from each container as per the SOP "Sampling of the materials." Approved STP and workbooks are used for analysis	4	1	4	16	Low	NA

S. No.	Description of the item/ activity	Risk involved	Failure mode/ effect of risk	Potential causes	Existing control (s)	S	L	D	RPN	Risk Category	Additional controls /action plan /CAPA
10	Packing of the final product	Product risk	Product contamination	Poor packing procedures followed	In the packing area only one product shall be packed at any point of time; after packing of the material area will be cleaned so there is no probability of cross-contamination.	4	1	4	16	Low	NA
				No Proper Storage facility	Quarantine, approved and rejected (If any) materials are stored separately at dedicated places with identification labels.						
11	Storage and packing conditions of the product	Product risk	Product contamination	Poor packing procedures followed	Product storage conditions follow as per BMR instructions.	4	1	4	16	Low	NA
					"Handling and storage of Intermediate and API materials" - SOP						

is decided by a team of expert professionals who based on their previous knowledge, decide upon which risk could be easily be mitigated and hence delayed and the risks which need immediate attention. The results of risk assessment are discussed in Table 4.

RESULTS AND DISCUSSIONS

The findings of the study are discussed in Table 4, which was identified, described, analyzed and classified based on the severity, likelihood and detectability to control the risk involved/ associated. The Risk Priority Number was calculated, and further, the risks were classified based on low, medium and high and Corrective and Preventive Actions (CAPA) was suggested respectively.

SUMMARY AND CONCLUSION

Summary

The facility is evaluated for Risk Assessment, all unit operations (Charging, Reaction, Distillation, Drying) are involved, and risk involved in the manufacturing of the product "XX-02-0018" were identified and categorized. Identified risks are evaluated for severity and likelihood of occurrence and Level of Detection. The risk level for all the operations are low so no additional control/ mitigations are required.

CONCLUSION

Each of the above risk has been evaluated and found to be at low risk and existing controls in place are effective. The controls proposed are at each operation/activities are effective to manage the system as per the CGMP requirements. It is concluded that the Quality Risk Assessment shall be implemented on a continuous basis wherever required and if any individual risk assessed for this product shall be enclosed as an amendment and hence this process can be regularized.

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