Failure Modes and Effects Analysis Guide

1 Overview

Failure Modes and Effects Analysis (FMEA) is commonly used in a variety of industries for Risk Management, where simple quantification of risk is insufficient, and where identification of root causes of risks and means of mitigation are paramount. FMEA is one of the most useful and effective tools for developing designs, processes and services. The goal of FMEA is to align the risks as closely as possible with its source. This enables the determination of the root cause of the risk, and allows the selection of ways to detect the occurrence of a particular failure and/or to find options to prevent or mitigate the effects of a particular failure. Good FMEA methodology allows for the identification and documentation of potential failures of a system and their resulting effects. It also allows for the assessment of the potential failure to determine actions that would reduce severity, reduce occurrence, and increase detection.

During FMEA, all steps are analyzed for potential failure opportunities; the ultimate effect to product quality or patient safety and/or efficacy as a result of each potential failure opportunity is then quantified; and then adjusted based on capabilities to detect or mitigate, to reach a final assigned score of risk.. The risk for each failure is often times entered into a risk score matrix which enables easy determination of the priority and/or level of attention required to be applied to each step based on its total risk priority number (RPN). The outcome of the FMEA is a list of recommendations to reduce overall risk to an acceptable level, and can be used as a source for designing a control strategy.

This document presents guiding principles for the execution of Failure Modes and Effects Analysis (FMEA). Successful application of any risk management model requires that the tools are used in concert with an overall quality risk management process, similar to that described by ICH Q9.

1.1 Use

Failure Modes and Effects Analysis can be a useful tool in:

- selection and optimization of drug product formulation
- defining the design space for manufacturing processes for drug substances and drug products
- design and manufacture of devices

A list of advantages and disadvantages of the FMEA tool is provided as follow:

Advantages	***Disadvantages***
- Accepts a high degree of complexity. - Uniform quantification of risk can be applied. - Results can be correlated directly with actual risks. - The effect of various methods of mitigation/detection on risk can be modeled easily. - Provides a well-documented record of improvements from corrective actions implemented. - Provides information useful in developing test programs and in-line monitoring criteria. - Provides historical information useful in analyzing potential product failures during the manufacturing process. - Provides new ideas for improvements in similar designs or processes.	- Requires significant effort in establishing clearly defined terms. - Requires significant effort in assigning scores to each step.

2 Risk Assessment

2.1 Define Goal of Risk Assessment

The first step in any risk assessment is to define the goal of the risk assessment. Components of the FMEA are:

- Severity: if a failure were to occur, what effect would that failure have on the product quality and on the patient (if any)?
- Probability of occurrence: how likely is it for a particular failure to occur?
- Detectability: what mechanisms are in place (if any) to detect a failure if it were to occur?

Each of the above metrics require clear definitions and a corresponding scale to rank or score the projected impact (i.e. a scale for Severity; a scale for Probability; and a scale for ability to Detect).. In addition, a composite score would then need to be calculated (e.g. severity multiplied by Proabality multiplied by ability to detect) and matrixed so that final team recommendations are based on a calculated and unambiguous fashion.

2.2 Define overall process and process increments (unit operations, steps)

Initiation of a FMEA requires the assembling of a team usually comprised of a facilitator, a team lead, and functional experts from development, ,manufacturing, quality, regulatory, etc., as appropriate. The assembled team should first describe the process in general unit operations, and then section each unit operation into its component parts. Use of a detailed flow chart of the process or schematic of the design under evaluation is recommended. It is also important that team members gain input from key stakeholders who will be responsible for implementing any resulting recommendations to ensure feasibility.

Sectioning of the unit operation should be done in process increments of sufficient size to enable accurate risk assessment for each unit operation and in turn the entire manufacturing train. It is critical to describe each step in sufficient detail so that the team can adequately assign the proper risk score to the step. Careful attention to detail is needed so that common practices that affect risk are captured in the step description. While these additional levels of detail provide greater accuracy, they also require greater effort. The appropriate level of detail is a matter of judgment for each team and depends on the perceived overall significance of the project and the corresponding risk involved; for example introduction of a new technology versus an established core competency.

FMEA Team Start-Up

1.Identify a facilitator, team lead and person responsible for taking minutes and maintaining records
2.Define the scope of the FMEA. Include a clear definition of the product or process to be studied.
3.Assemble team members. Ensure that al keyl impacted functional areas are represented, e.g. development, manufacturing, quality, regulator, etc.
4. Ensure that the necessary range of knowledge and experience are represented on the teams(e.g. is it necessary to have a skilled operator from manufacturing involved instead of only engineers or scientists?)
5.Define FMEA Team's boundaries of freedom - What aspect of the FMEA is each team/ subteam responsible for ?e.g. FMEA Analysis, recommendations for improvement, implementation of improvements, etc.?
6. Also define project deadline, team member time constraints, etc. to ensure all are preparted to support the initiative. 8.Do team members have specific time constraints?
9. What is the procedure if team needs to expand beyond the established boundaries?
10.How should the FMEA be communicated to others?

2.3 Establish Clear Definitions

As indicated in Section 2.1, risk in an FMEA evaluation has three components: ***Severity, Probability, and Detectability***. The definitions for the various levels of severity, probability, and detectability should be clearly articulated. Examples of definitions for each level are presented in the tables below. For each of these risk profile attributes, a five-point rating scale was developed and utilized to ensure that the risk rating had:

- appropriate levels of differentiation in order to support meaningful risk prioritization
- clearly apparent meaning in the context of the overall risk to process and product quality

FMEA

- *Is dependent on a complete sectioning of the overall risk into risks associated with the smallest increment step in the process.*
- *Requires an agreed-upon set of clearly defined terms for the component parts of risk (severity, probability, and detectability), and the corresponding scores.*
- *Provides a means to determining the level of attention to be applied to each step, and summarizes recommendations to reduce the risks. at each step*

- consistency across the risk profile attributes (severity, occurrence and detection) to ensure that no attribute contributed disproportionately to the overall prioritization of risk.

It is important to note that the definitions, levels and numbers assigned to the different levels can vary depending on the system under evaluation or previously established definitions by the organization or company. However, once a set of definitions are established for FMEA evaluation of a system, the definitions should be piloted with a limited number of examples to validate their clarity so as to build consistency across the unit operations within a project.

In general, the same rating scale should be applied to the components of severity, occurrence and detection to avoid the appearance of skewing the resulting RPN (a calculation of the assessed severity rating multiplied by occurrence rating and multiplied again by the detection rating). Additionally, it has proven useful that nonconsecutive numbers (e.g. 1,3,5,7,10) are more useful than consecutive numbers e.g, 1,2,3,4,5, as the use of non-consecutive numbers allows more distinction between ratings and less debate amongst team members. As an alternative, the team may want to put more emphasis on the severity criteria for example, in which case a non-linear scoring scale can be utilized (e.g. 1, 4, 9,16, 25)

Note, the below definitions for Severity, Probability and Detection were developed for a FMEA involving a new process development; these will change based on the subject under assessment.

Severity Criteria for FMEA

In general, severity assesses how serious the effects would be should the potential risk occur. In the example of a manufacturing process for a drug substance, the severity score is rated against the impact of the effect caused by the failure mode on the batch quality. A non-linear scoring scale can be applied to augment the effect of the severity criteria as shown in the table below.

Severity		
Value	Description	Criteria
1	Irrelevant	No impact to product quality and process robustness
4	Slight	No impact to product quality
9	Important	Noticeable impact to product quality, but can be recovered by reprocessing
16	Critical	Definite impact to product quality that may require rework
25	Disastrous	Batch failure, not recoverable by rework

Probability of Occurrence Criteria for FMEA.

In general, the probability of occurrence evaluates the frequency that potential risk(s) will occur for a given system or situation. The probability score is rated against the probability that the effect occurs as a result of a failure mode. The example below applies a linear scoring scale to the probability of occurrence of failure modes associated with the manufacturing process of a drug substance.

Probability		
Value	Description	Criteria
1	An unlikely probability of occurrence	Failure has **never** been seen in any relevant lab experiments, or scale-up batches yet but it is theoretically possible.
3	A remote probability of occurrence	Failure only seen **once or twice** in relevant lab experiments, never in scale-up batches.
5	An occasional probability of occurrence	Failure potential has been noted in **several** relevant lab experiments, or at scale-up. If procedures are followed the failure potential is minimal.
7	A moderate probability of occurrence	Failure potential has been noted in several relevant lab experiments, or at scale-up, in-process control maybe required to avoid failure.
9	A high probability of occurrence	Failure potential has been noted in several relevant lab experiment, or at scale-up, an active non-standard feed back control loop may be required.

Detectability Criteria for FMEA.

In general, detectability is the probability of the failure being detected before the impact of the failure to the system or process being evaluated is detected. The detectability score is rated against the ability to detect the effect of the failure mode or the ability to detect the failure mode it self. The example below applies a linear scoring scale to the detectability criteria in an FMEA for a drug substance manufacturing process.

Detection		
Value	Description	Criteria
1	High degree of detectability	A: Validated automatic detection system that is a direct measure of failure. B: Two or more manual operated validated detection systems, direct or indirect. (e.g. Control range and IPC)
3	Good detectability	A: Single manually operated validated detection system that is a direct measure of failure. (e.g. IPC of failure, validated PAT)
5	Likely to detect	A: Single manually operated validated detection system that is not a direct measure of failure. (e.g. PAT measurements or IPC's not directly linked to failure)
7	Fair detectability	A: Non validated (manual or automated) detection. (e.g. visual level check, visual inspection of vessels).
9	Low or no detectability	No ability to detect the failure

2.4 Risk score matrix

The composite risk score for each unit operation step is the product of its three individual component ratings: severity, probability, and detectability. This composite risk is called a risk priority number (RPN). .

RPN = S x P x D

The RPN number is not absolute and should be considered in context with other factors that influence the product risk outside the scope of this evaluation. The RPN provides a relative priority for taking action - the bigger the RPN, the more important to address the corresponding failure being assessed.

Table 2.4 is an example of a FMEA Table/Form. For each formulation component or manufacturing processing step under evaluation, the function of the component or processing step, potential failure mode and effect of the failure mode should be recorded. A severity score is then assigned. The root cause of the failure is described and a score is assigned to the probability of occurrence of the failure. Controls that are currently in place to detect the failure are listed and a detectability score is then assigned. The RPN number is calculated. The action(s) that need to be taken to reduce or mitigate the risk are listed and individuals or departments responsible for implementing the actions are identified with target dates for completion.

Table 2.4: EXAMPLE OF A FAILURE MODE AND EFFECTS ANALYSIS (FMEA) FORM

SYSTEM/PROJECT: FMEA NUMBER:
SUBSYSTEM/PROBLEM:
REFERENCE DRAWING:
CORE TEAM:
PREPARED BY: FMEA DATE:

Part/Process	Failure Mode	Failure Effects	SEVERITY	Causes	OCCURRENE	Controls	DETECTION	RPN	Actions	Responsibility & Target Completion Date	Actions taken	SEV	OCC	DET	RPN
(What is the function of each step)	(Describe what could go wrong)	(How does the failure affect the function of the step)		(What is the root cause or reason for the failure)		(What controls are currently in place to catch or prevent this failure									

3 Risk Control

There are two ways to control or reduce the risk at each unit operation step: mitigation and detection. In the case of mitigation, the step is changed to reduce the impact of a failure (severity) or the likely hood (probability) of a failure occurring. Detection refers to adding additional controls or feedback mechanisms that can result in a reduction of either the severity or probability (or both).

3.1 Detection

Additional physical (e.g. inspection) and/or analytical tools can be added to a process that can increase the ability to monitor the performance of the process, with or without real-time feedback. Monitoring without feedback could reduce the probability of a failure, but real-time feedback will reduce both the probability and severity of a failure. Implementation of such a feedback mechanism is dependent on balance between the degree of risk reduction and cost/resource requirements.

3.2 Mitigation options

A process step can be modified such that a failure become highly unlikely or that if there was a failure, the impact to the patient is small. This typically requires identification of a root cause or source of the failure, and removal of the root cause. This provides for a more robust process. By identifying possible risk mitigation options and re-evaluating the results, teams can identify the mitigation options that will have the most beneficial impact to overall risk.

4 Risk communication and Review

The outcome of the risk assessment and option analysis should be presented in an increasing level of detail. This enables the reader of the report to focus on the recommendations and only delve into the details of interest. This maintains the readers interest and ensures that relevant parts of report are given due scrutiny.

The outcome of a risk assessment and option analysis should be reviewed with all key stake holders to ensure their understanding and buy-in, since they are usually responsible for subsequent implementation of the recommendations. It is also important to stipulate any residual risks remaining after implementation. Residual risks are risks that were identified "as low as reasonably possible". These need periodic review to ensure that the risks associated with affected unit operation steps do not creep from medium to high.

5 Summary of Steps for Performing FMEA

1. Describe the product or process.
2. Review a block diagram of the product or flow chart of the process.
3. Complete the headers of FMEA table as customized for the specific need.
4. Break down the product or process into its components or steps and list each step or component under the column with the header of "Parts/Components" in the FMEA Table.
5. Identify all potential failure modes associated the product component or process step.
6. List all potential failure modes for each item (product component or process step under the "Failure Mode" column in the FMEA Table.
7. Describe the effects of each of the listed failure modes and assess the severity of each of these effects on the product or process. Assign a severity rating to each effect on the FMEA Table.
8. Identify the possible cause(s) of each failure mode.
9. Quantify the probability of occurrence of each of the causes of a failure mode.
10. Identify all existing controls (Current Controls) that contribute to the prevention of the occurrence of each of the causes of a failure mode.
11. Determine the ability of each of the listed controls in preventing or detecting the failure mode or its cause. Assign a ranking score to indicate the detection effectiveness of each control.
12. Calculate the Risk Priority Number (RPN) = (SEV x OCC x DET).
13. Identify actions to address potential failure modes that have a high RPN
14. Assign an individual responsible for implementation of the defined action(s) and a target date for completion.
15. After the defined actions have been implemented the overall effect on the failure mode that the actions were supposed to address must be re-assessed and a new RPN calculated.
16. The new RPN will help to determine if further action needs to be taken.
17. Update the FMEA Table every time there is a significant change in the product design or process.

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