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Review Article

A REVIEW ON "FAILURE MODE AND EFFECTS ANALYSIS – A TOOL OF QUALITY RISK MANAGEMENT" BASED ON ICH Q9

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ABSTRACT

Risk management principles are effectively utilized as quality risk management in the pharmaceutical industries, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system. Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources. Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Failure Mode and Effect Analysis (FMEA) is a tool, a living document and always reflect the latest design level, as well as the latest relevant actions, including those occurring after the start of production operations. It helps in Quality risk management that supports a scientific and practical approach to decision-making. 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 detectability of the risk. Potential Applications of Quality Risk Management (QRM): as a part of, Integrated quality management: Documentation, Training and Education, Quality defects, Auditing / Inspection, Periodic review, Change management / change control, Continual improvement and Regulatory Operations: Inspection and assessment activities, Industry operations, Development, Facilities, equipment and Utilities, Materials Management.

Keywords: Failure Mode and Effect Analysis, FMEA, Quality Risk Management, ICH Q9.

INTRODUCTION TO THE QUALITY RISK MANAGEMENT[1-3]

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. In relation to pharmaceuticals, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better

and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

By developing the effective Quality Risk Management for the packaging operations, leads to the minimizing risks related to packaging of the finished product, improving the quality of the packaging and developing a system to easily identify the possible risks and mitigation of that risk.

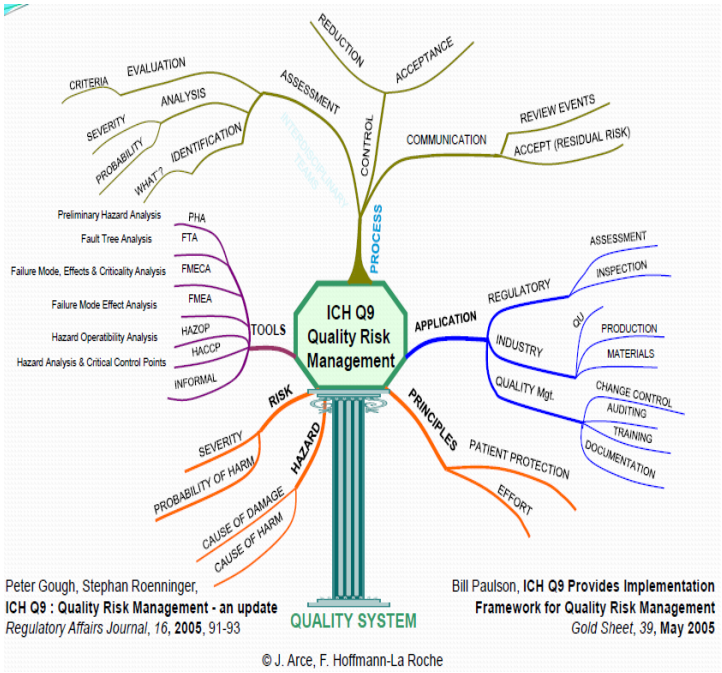


Fig. 1.1: ICH Quality Road Map

RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision-making. 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.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures).

- ✓ **Basic risk management facilitation methods**
  (Flowcharts, check sheets etc.).
- ✓ **Failure Mode Effects Analysis (FMEA)**
  Breaks down the large complex processes in to manageable steps.
- ✓ **Failure Mode, Effects and Criticality Analysis (FMECA)**
  FMEA & links severity, probability & detectability to criticality.
- ✓ **Fault Tree Analysis (FTA)**
  Tree of Failure Mode Combinations with logical operators.
- ✓ **Hazard Analysis and Critical Control Points (HACCP)**
  Systematic, proactive and preventive method on criticality.
- ✓ **Hazard Operability Analysis (HAZOP)**
  Brain storming technique.
- ✓ **Preliminary Hazard Analysis (PHA)**
  Possibilities that the risk event happens.
- ✓ **Risk ranking and filtering**
  Compare and prioritize risks with factors for each risk.
- ✓ **Supporting statistical tools**
  - ✓ Control charts
  - ✓ Design of Experiment (DOE)
  - ✓ Pareto Chart
  - ✓ Probabilistic Risk Assessment (PRA)

- ✓ Process Capability Analysis

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.

Table 1.1: Example to choose the right tool for the task

A possible aid where to use methods / tools	General → Detail			
	System Risk (facility & people)	System Risk (Organization)	Process Risk	Product Risk (Safety & Efficacy)
Risk ranking & Filtering	X	X	X	
Failure mode effect analysis		X	X	
Hazard analysis and critical control points		X	X	
Process mapping			X	
Flow chart			X	X
Statistical tools				X
Check sheets	X			X

INITIATING A QUALITY RISK MANAGEMENT PROCESS

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;
- ✓ Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- ✓ Identify a leader and necessary resources;
- ✓ Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

RISK ASSESSMENT

It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

FMEA (FAILURE MODE EFFECT ANALYSIS)

The FMEA is a living document and should always reflect the latest design level, as well as the latest relevant actions, including those occurring after the start of production operations.

Failure Modes: All ways in which a product (including each of its specific parts) or process can fail to perform its intended function. More than one failure mode can exist for a given part or process. Also, some failures may be gradual and/or partial, whereas others may occur immediately and completely.

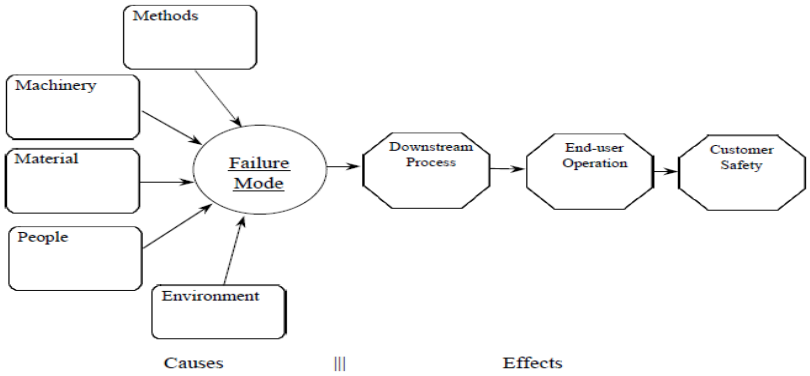


Fig. 1.2: FMEA Cause and Effect Diagram

Types

There are two types of FMEA

1. Design FMEA (DFMEA)
2. Process FMEA (PFMEA)

Use

These are analytical techniques utilized by

1. Design responsible engineer/team or
2. Manufacturing responsible engineer/team

These tools are used to assure that potential product failure modes and their associated causes have been considered and addressed in the design or manufacturing process.

DFMEA

Supports design process in reducing risk of failures by

- ✓ Aiding in the objective evaluation of design requirements and design alternatives
- ✓ Aiding in the initial design for manufacturing and assembly
- ✓ Increasing the probability that potential failure modes and their effects on systems and product operation have been considered in the design & development process
- ✓ Providing additional information to aid in the planning of efficient design testing and product development programs
- ✓ Developing a list of potential failure modes ranked according to their effect on the "customer," thus establishing a priority system for design improvements and development testing
- ✓ Providing an open issue format for recommending and tracking risk reducing actions
- ✓ Providing future reference to aid in analyzing field concerns, evaluating design changes and developing advanced designs.

PFMEA

THE PROCESS FMEA

- ✓ Identifies potential product related process failure modes
- ✓ Assesses the potential customer effects of the failures
- ✓ Identifies the potential manufacturing or assembly process causes and identifies process variables on which to focus controls for occurrence reduction or detection of the failure conditions
- ✓ Develops a ranked list of potential failure modes, thus establishing a priority system for corrective action considerations
- ✓ Documents the results of the manufacturing or assembly process

FMEA APPLICATIONS IN MANUFACTURING SETTINGS

DFMEA

- ✓ Should be initiated before or at design concept finalization
- ✓ Should be continually updated as changes occur or additional information is obtained throughout the phases of product development
- ✓ Should be fundamentally completed before the drawings are released for tooling, or other manufacturing needs
- ✓ Addresses the design intent and assumes the design will be manufactured and assembled to this intent
- ✓ Does not rely on process controls to overcome potential weaknesses in the design, but it does take the technical and physical limitations of a manufacturing or assembly process into consideration.

PFMEA

- ✓ Should take into account all manufacturing operations, from individual components to assemblies
- ✓ Does not rely on product design changes to overcome weaknesses in the process
- ✓ Does take into consideration a product's

design characteristics relative to the planned manufacturing or assembly process
- ✓ Assures that, to the extent possible, the resulting product meets customer needs and expectations.

KEY RESOURCES NECESSARY TO CONDUCT SUCCESSFUL FMEA PROGRAMS
- ✓ Commitment of top management
- ✓ Knowledgeable individuals, i.e. Expertise in: Design, Manufacturing, Assembly, Service, Quality, Reliability.
- ✓ Individuals attentive to FMEA timeliness, i.e. Achieve greatest value: before a design or process failure mode has been unknowingly designed into the product
- ✓ People resources may be internal or external to the business, or a combination thereof.

PRINCIPLES DRIVING CUSTOMER SATISFACTION
- ✓ Teamwork
- ✓ Managing processes
- ✓ Statistical process control

FMEA REQUIRES TEAMWORK

Build quality into people through training and committed leadership.

MANAGING PROCESSES

Utilize a style of management that is also people oriented in contrast to one that is solely oriented toward results

Process-oriented management

Support and stimulate efforts to improve the way employees do jobs Reinforces “long term” outlook

Management criteria
- ✓ Discipline, Time management, Skill development, Participation & involvement, Morale, Communication, Process incorporation,
- ✓ A process includes some combination of: Methods, Materials, Machines, Manpower, Environment, Measurement.
  - ✓ These are incorporated to complete tasks, such as producing a product or performing a service. A process has measurable inputs and outputs.

FMEA PROJECTS SELECTION & PURPOSE TANGIBLE EFFECTS
- ✓ Successful development of new products
- ✓ Shortening of product development time
- ✓ Increased market share
- ✓ Increased sales volume
- ✓ Development of new markets
- ✓ Increased production volume
- ✓ Fewer processes
- ✓ Improved quality
- ✓ Reduced defect costs
- ✓ Fewer customer complaints

INTANGIBLE EFFECTS
- ✓ Increased quality-consciousness and problem-consciousness
- ✓ More confidence in new product development
- ✓ Improved standardization
- ✓ Improved quality of work
- ✓ Improved information feedback
- ✓ FMEA project implementation

Quantitative methods
- ✓ Severity ranking
- ✓ Occurrence ranking
- ✓ Detection ranking
- ✓ Risk priority number (RPN)

Qualitative Methods
- ✓ Similar past experiences
- ✓ Brainstorming analysis
- ✓ Customer(s) input
- ✓ Financial impact

Identification of the Failure mode
- ✓ Use the template for Risk Assessment including the tabular form for FMEA, and list all failure modes that may be associated with the product/activity being analyzed.
- ✓ Failure modes may be identified based on the experience similar processes, brainstorming, review of development documents, previous failures related to activities etc.
- ✓ Identify failure modes in both normal and fault conditions.
- ✓ For each failure determine potential effect on the product, patient, user or process;
  - ➢ Consider worst case scenario
  - ➢ Consider indirect effect that result from the failure
- ✓ Determine possible cause of the failure by;
  - ➢ Documenting all possible causes
  - ➢ Causes may be determined by brainstorming and story boarding exercises, review of historic data etc.
  - ➢ Involving each individual
- ✓ Failure/cause/effect combination are entered on to the FMEA template a separate line item as a failure mode may have multiple causes and each cause may have different frequency, this in turn will result in different risk priority number.

Assessment of quantitative risk associated with each failure mode

Quantitative risks associated with each failure mode are related to Patient, GMP, Business, Employees, neighborhood area, Environment etc.

An **example** is presented below **Table 1.2**: **Risk categories** to understand this that how the risks are categorized and what different impacts it can generate to different levels.

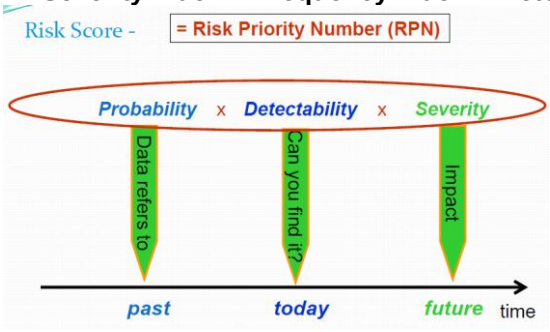
Table 1.2: Risk categories

Class	Rating	Consequences	
IV	Catastrophic	Patient:	Fatalities, non-reversible side effects
		Stock:	Interruption: permanent stock-out
		GMP:	close down of site / drug shortage; withdrawal of product or loss of marketing authorization etc.
		Business:	Financial Loss: Extreme Image: severely damaged internationally
		Employees, neighborhood:	fatalities, evacuation outside the site area
		Environment:	Irreversible, long-term damage outside site area
III	Critical	Patient:	Reversible side effects
		Stock:	Interruption:<12 weeks
		GMP:	Recall, process interruption, unable to get new products approved etc.
		Business:	Financial Loss: Excessive Image: severely damaged nationally
		Employees, neighborhood:	Serious injuries, affected outside the site area
		Environment:	Reversible, short-term damage outside site area
II	Marginal	Patient:	No side effects but patient can observe the defect
		Stock:	Interruption; < 4 weeks
		GMP:	Issue, investigation reports, market complaints etc.
		Business:	Financial Loss: Marginal Image: local
		Employees, neighborhood:	Minor injuries, affect inside the site area
		Environment:	Only site area affected
I	Negligible	Patient:	No side effects
		Stock:	Interruption: < 2 weeks
		GMP:	Corrective actions possible, deviation report etc.
		Business:	Financial Loss: Minor Image: No effects
		Employees, neighborhood:	No effects
		Environment:	No effects

PREPARING A RISK PROFILE: CONSEQUENCES

The risk assessment for each failure mode is made by expressing it as a quantitative value, the Risk Priority Number (RPN) using the following equation:

Figure 1.3: RPN = Severity Index X Frequency Index X Detectability Index



Estimating Severity Index

- ✓ Severity of the failure shall be estimated based on the effect it may have on the process/product/patient.
- ✓ Assign a quantitative value to the possible effect of each hazard according to the scale shown in Table 2.
- ✓ When estimating severity, take any defined assumption in to consideration. In call cases, make a conservative estimate of severity, cautioning on the side of safety.
- ✓ Document the severity index value in the appropriate column of FMEA template.

Table 1.3: Severity Index

Effect	Criteria: SEVERITY of Effect	Ranking
Hazardous-without warning	Very high severity ranking when a potential failure mode affects safe operation and/or involves noncompliance with regulations without warning.	10
Hazardous-with warning	Very high severity ranking when a potential failure mode affects safe operation and/or involves noncompliance with regulations with warning.	9
Very high	Product/item inoperable, with loss of primary function.	8
High	Product/item operable, but at reduced level of performance. Customer dissatisfied.	7
Moderate	Product/item operable, but may cause rework/repair and/or damage to equipment.	6
Low	Product/item operable, but may cause slight inconvenience to related operations.	5
Very Low	Product/item operable, but possesses some defects (aesthetic and otherwise) noticeable to most customers.	4
Minor	Product/item operable, but may possess some defects noticeable by discriminating customers.	3
Very Minor	Product/item operable, but is in noncompliance with company policy.	2
None	No effect.	1

Estimating Frequency Index

- ✓ Estimating frequency index based on the frequency of occurrence of each identified cause.
- ✓ Frequency may be interpreted as probability of occurrence whose quantitative value shall be assigned based on the scale shown in the table.
- ✓ Document the frequency index value in the appropriate column of FMEA template.

Table 1.4: Frequency / Occurrence Index

Probability of Failure	Possible Failure Rates	Ranking
Very High: Failure is almost inevitable	1 in 2	10
	1 in 3	9
High: Repeated Failures	1 in 8	8
	1 in 20	7
Moderate: Occasional Failures	1 in 80	6
	1 in 400	5
	1 in 2,000	4
Low: Relatively Few Failures	1 in 15,000	3
	1 in 150,000	2
Remote: Failure is Unlikely	1 in 1,500,000	1

Estimating Detectability Index

- ✓ Assign detectability index based on the ability to detect the event prior to or during its occurrence and thereby preventing the hazard of effect.
- ✓ Assign quantitative values for detectability based on the scale shown in the table.
- ✓ Document the detectability index value in the appropriate column of FMEA template.

Table 1.5: Detectability Index

Detection	Criteria: Likelihood of DETECTION by Design Control	Ranking
Absolute Uncertainty	Design Control will not and/or cannot detect a potential cause/mechanism and subsequent failure mode; or there is no Design Control.	10
Very Remote	Very remote chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	9
Remote	Remote chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	8
Very Low	Very low chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	7
Low	Low chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	6
Moderate	Moderate chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	5
Moderately High	Moderately high chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	4
High	High chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	3
Very High	Very high chance the Design Control will detect a potential cause/mechanism and subsequent failure mode.	2
Almost Certain	Design Control will almost certainly detect a potential cause/mechanism and subsequent failure mode.	1

FMEA TEMPLATE / WORKSHEET

The details should be reported in the standard format as per below **Table 1.6.**

QUALITY RISK ANALYSIS OF PACKAGING OPERATIONS WITH RESPECT OT PATIENT RISK BY FAILURE MODE EFFECTS ANALYSIS																
											Action Results					
Sr. No.	Process / Activity	Point of Failure / Risk	Effect(s) of Failure on the Process / Product (Severity)	Potential Cause(s)	S *	F *	Controls/ System in place for Detection	D *	RPN *	Mitigation/ Corrective Action(s)	S *	F *	D *	RPN *	Action Taken (Yes / No)
1.															
2.															

*S = Severity, F = Frequency, D = Detection, RPN = Risk Priority Number

The format filled with the details provide the overall idea

Calculation of Risk Priority Number (RPN)

Calculate estimated risk associated with each failure mode based on the assigned severity, frequency and detectability values identified as shown above.

- ✓ The estimated risk shall be referred to as quantitative Risk Priority Number (RPN). Calculate the RPN as follows:

RPN = Severity Index X Frequency Index X Detectability Index

Enter the RPN in to the FMEA format in the space provided.

- ✓ RPN are an estimated quantitative expression of the risk that is helpful in prioritizing mitigations intended to reduce risk. It helps to estimate the extent to which the risks must be mitigated in order to assure patient safety.

Review of Risk Value

- ✓ The calculated risk factors shall be analyzed to determine the need for mitigation, CAPA, etc. The below table describes recommended action based on a calculated risk factor.
- ✓ After mitigation / taking appropriate action to reduce the risk for a given operation / activity, the FMEA may be carried out again to calculate the RPN for the activity and for documenting the residual risk.

Table 1.7: Analysis of the Risk-based on the result of FMEA

Occurrence

Rating	1	2	3	4	5	6	7	8	9	10	Rating
10	100	200	300	400	500	600	700	800	900	1000	10
9	81	162	243	324	405	486	567	648	729	810	9
8	64	128	192	256	320	384	448	512	576	640	8
7	49	98	147	196	245	294	343	392	441	490	7
6	36	72	108	144	180	216	252	288	324	360	6
5	25	50	75	100	125	150	175	200	225	250	5
4	16	32	48	64	80	96	112	128	144	160	4
3	9	18	27	36	45	54	63	72	81	90	3
2	4	8	12	16	20	24	28	32	36	40	2
1	1	2	3	4	5	6	7	8	9	10	1

Severity

Detectability

Risk Category
Unacceptable Risk
ALARP region of acceptable risk
Negligible risk

Table 1.8: Review of Risk Value

Risk Category	Risk Factor (RPN)	Interpretation
Unacceptable Risk	>320	Risk categorized as too severe to be tolerated. A risk in this region must be reduced to ALARP region prior to implementation of the activity / product etc.
ALARP region of acceptable risk	64-320	Tolerable risk, only if the reduction is impractical or cost of reduction grossly disproportionate to improvement. Acceptable risk is established on case to case basis.
Negligible risk	1-63	Risk is Negligible. Mitigation not necessary.

*ALARP: As Low as risk possible

Implement and verify the appropriateness of mitigations

The Initiator shall conclude the appropriateness of the risk reduction measure(s) taken and to evaluate any unforeseeable “risk” introduction after implementation of the “risk-reduction” measure(s).

Table 1.9: FMEA overview

Tool Concept:	Assess failure modes and then determine whether the failure could be detected and whether prevention, detection and response controls are adequate.
Tool Approach:	Bottom-up approach that considers what could go wrong and what the related risks are. Methodically divides the analysis of complex processes in to smaller manageable considerations to facilitate the assessment.
Risk Focus:	Failure Modes (similar to faults)
Quantitative vs. Qualitative:	Either depending upon application. Risk Priority Number (RPN) concept favors quantitative approaches to risk rating.
Key assumption:	Failure modes are intuitive, well known, or have been previously identified.
Key Strengths:	Ability to rank risks and appoint effort accordingly. Wide acceptance in the industry, with many case studies available. Best method for prioritizing and ranking risks, Effectively summarizes modes of failure the factor causing the failures and their effects.
Key Limitations:	Forces the user to rate risks in terms that may not be well understood (for example, human factors or process anomalies are difficult to rate for probability of occurrence or the ability to detect) Analyses can be highly detailed and tedious for complex system having multiple components.
Scope Management:	Scope must be actively managed –Team must put assumptions and /or limitations in place to manage scope from becoming unnecessary detailed.
Risk Ranking Capability:	Risk Prioritization numbers (RPN) commonly used to correlate risk level to required mitigation effect.
Output format:	Tabular
Key guidance:	IEC International Standards 812 (also referred to as Standard 60812)

CONCLUSION

The Risk associated with the system can be minimized by the use of FMEA model. The highest risk priority number (RPN) shows the highest risk associated with the event that can be minimized by corrective actions and preventive actions (CAPA) measures. After implementing the CAPA plans again the RPN calculated and checked whether it reduces to the acceptable number. By this way the root cause of the risk analyzed and minimized to an acceptable limit.

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