DECODING PHARMA

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
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1.0 PURPOSE

This guideline defines the procedure for Quality Risk Management (QRM) for product, facility, organization, people, business etc. to produce quality products and control, to communicate, Review risks to product quality, safety and efficacy throughout the product life cycle.

2.0 SCOPE

2.1 This guideline shall be applicable for QRM concept and process for carrying out risk evaluation. It is applicable to all the functions, which may impact patient safety and efficacy and quality of the product directly and (or) indirectly, manufactured at different site of ……and its group of companies.

2.2 This scope includes, but not limited to following:

2.2.1 Quality Management, Regulatory Operations, Product Development (Dosage forms), Facility, Equipments, Utilities, Material Management & Logistics, Product & Process Validation, Manufacturing, Laboratory control, Stability studies, and Packaging & Labeling.

2.2.2 Additionally, case by case the approach may also be adopted for evaluation of risk being perceived due to deviation, market complaint or any other quality decision.

3.0 REFERENCE(S) & ATTACHMENTS

3.1 References

3.1.1 ICH 09 Quality Risk Management.

3.1.2 ICH Q10, 2008 Pharmaceutical Quality system.

3.1.3 ICH Q8 (Revision 2), 2009 Pharmaceutical Development.

3.1.4 Pharmaceutical CGMPs for the 21st Century - A Risk Based Approach 2004.

3.1.5 WHO TRS 981 Annex 2.

3.1.6 PICs - PE009-12.

3.1.7 EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines.

3.2 Attachments

3.2.1 Attachment-I: Risk Management Checklist

3.2.2 Attachment-II: Risk Assessment Model

3.2.3 Attachment-Ill: Risk Assessment Report

3.2.4 Attachment-IV: Failure Mode & Effect Analysis Worksheet

3.2.5 Attachment-V: Severity Ratings

3.2.6 Attachment-VI: Probability of occurrence Ratings

3.2.7 Attachment-VII: Control Effectiveness (Detecting) Ratings

3.2.8 Attachment-VIII: FMEA Rating Scale & RPN Result Action

3.2.9 Attachment-IX: QRM in the Product Life Cycle

3.2.10 Attachment-X: 5 Why Analysis

3.2.11 Attachment-XI: Root cause analysis by fish bone diagram

4.0 DEFINITION & ABBREVIATION(S)

4.1 Definitions

4.1.1 **Fault:** Inability to function in a desired manner, or operation in an undesired manner, regardless of cause.

4.1.2 **Failure:** A fault owing to breakage, wear out, compromised structural integrity, etc.

4.1.3 **Failure Mode:** The manner in which a fault occurs. i.e., the way in which the element faults.

4.1.4 **Hazard:** The potential source of harm associated with physical, chemical and biological.

4.1.5 **Quality Risk Management:** A systematic process for the assessment, control, communication, and review of risks to the quality of the drug product throughout the product lifecycle.

4.1.6 **Quality System:** The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

4.1.7 **Risk:** The combination of the probability of occurrence of harm and the severity of that harm.

4.1.8 **Risk Acceptance:** The decision to accept risk.

4.1.9 **Risk Analysis:** The estimation of the risk associated with the identified hazards.

4.1.10 **Risk Assessment:** A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

4.1.11 **Risk Communication:** The sharing of information about risk and risk management between the decision maker and other stakeholders

4.1.12 **Risk Control:** Actions implementing risk management decisions.

4.1.13 **Risk Evaluation:** The comparison of the estimated risk to given risk criteria using a quantitative and/or qualitative scale to determine the significance of the risk.

4.1.14 **Risk Identification:** The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

4.1.15 **Risk Management:** The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk

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4.1.16 **Risk Reduction:** Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

4 1.17 **Risk Review:** Review or monitoring of outputs/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

4.1.18 **Severity:** A measure of the possible consequences of a hazard.

4.1.19 **Stakeholder:** Any individual, group, or organization that can affect, be affected by, or perceive itself to be affected by a risk. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

4.1.20 **Trend:** A statistical term referring to the direction or rate of change of a variable(s).

4.1.21 **Root Cause analysis (RCA):** Root cause analysis is a problem solving technique for identifying the basic or casual factors that underlie the occurrence or possible occurrence of an adverse event.

4.2 Abbreviations

4.2.1 API: Active Pharmaceutical Ingredients

4.2.2 CQA: Corporate Quality Assurance

4.2.3 CPP: Critical Control Parameter

4.2.4 CAPA: Corrective Action & preventive Action

4.2.5 FMEA: Failure Mode and Effects Analysis

4.2.6 GD: Guideline Document

4.2.7 ICH: International Conference on Harmonization

4.2.8 IND: Investigational New Drug

4.2.9 ISPE: International Society for Pharmaceutical Engineering

4.2.10 NDA: New Drug Application

4.2.11 SME: Subject Matter Expert

4.2.12 SOP: Standard Operating Procedure

4.2.13 QRM: Quality Risk Management

4.2.14 QA: Quality Assurance

4.2.15 QMS: Quality Management System

4.2.16 WHO TRS: World Health Organization Technical Report Series

5.0 RESPONSIBILITY

5.1 Corporate Quality Assurance:

5.1.1 To prepare the guideline.

5.1.2 To ensure implementation of the guideline.

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5.1.3 To issue global CAPA if required.

5.2 Team Leader:

5.2.1 Communicate, promote and coordinate quality risk management across the various functions and departments of their site.

5.2.2 Summarize Quality Risk Assessment (QRA) and communicate strategy to Senior Management and Quality Management.

5.3 Quality Assurance /Quality Control (QA/QC) Head:

5.3.1 To provide the necessary support regarding data backup.

5.3.2 To assuring that a quality risk management process is defined, deployed, reviewed and adequately documented.

5.3.3 To communicate, promote and coordinate quality risk management across the various functions and departments of their site.

5.3.4 Periodic review of progress of QRM and notification to management.

5.4 Plant Head:

5.4.1 QRM strategy including the level of acceptance or control of identified risks.

5.4.2 Provide leadership for QRM as an ongoing process.

5.4.3 Provide multi-disciplinary teams of qualified personnel from all stakeholders.

5.4.4 Evaluate that the risk to quality is based on scientific knowledge and ultimately link to the protection of the patient.

5.4.5 Ensure adherence to QRM policy of the organization.

5.4.6 To ensure implementation of system as per guideline.

6.0 Distribution:

I. Quality Assurance
II. Quality Control
III. Production
IV. Ware house
V. Engineering
VI. Human resource and Administration
VII. Environment, Health and safety

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7.0 PROCEDURE:

7.1 Quality Risk Management (QRM) Concept and Process:

7.1.1 QRM is holistically defined as a process to formally identify hazards and understand risks to assist decision making for implementation of appropriate approaches for risk control.

7.1.1.1 QRM relies upon qualitative and quantitative data; commensurate with the level of risk; and assists in decision making and device control strategies to manage the risks to patient, product and operating personnel.

7.1.2 **Initiation (of QRM process):**

7.1.2.1 Based on perceived risk and impact, QRM process is prioritize and followed as under:

7.1.2.1.1 Identify a Team leader, shall be SME, facilitating QRM studies.

7.1.2.1.2 Identify a cross-functional team with knowledge, experience and regulations.

7.1.2.1.3 Define the problem/failure of the system being studied and document the scope of QRM. It can be for complete process or for a portion of the process.

7.1.2.1.4 Define Critical Process Parameters (CPP) and Critical Quality Attributes (CQA).

7.1.2.1.5 Define responsibility and procedure to collect data, background information and/or data on the potential hazard, harm or impact relevant to the risk, proposed QRM tools.

7.1.2.1.6 Define criteria for Risk Evaluation.

7.1.2.1.7 Define timeline, deliverables and appropriate level of decision making for the QRM process.

7.1.3 **Risk Assessment:**

7.1.3.1 Intends to identify the critical aspects of the system, define problem or risk question necessary to manage.

7.1.3.2 Quality Risk Assessment (QRA) consists of the identification of product quality hazards, analysis and evaluation of risk associated with the identified hazard, regardless of tools used. QRA shall address following:

7.1.3.2.1 What might go wrong? (Detectability, D): A systematic use of information to identify hazards referring to the risk question or problem such as historical data, theoretical analysis, informed opinions, concerns of the stakeholders.

7.1.3.2.2 What are the consequences? (Severity, S): Compare the identified and analyzed risk against given risk criteria.

7.1.3.2.3 What is the likelihood? (Probability, P): Will it go wrong? The estimation of the risk associated with the identified hazards. A qualitative &/or quantitative process of linking the likelihood of occurrences and severity of harm.

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7.1.3.3 **Risk Identification:**

7.1.3.3.1 Systematic use of information to identify hazards or risk problem; information can include historic data, theoretical analysis, informed opinions, and the concerns of stakeholders. The data shall identify Delectability and severity of the risk.

7.1.3.4 **Risk Analysis:**

7.1.3.4.1 Risk analysis is an estimation of risk associated with the identified hazards. It is a qualitative or quantitative process to ascertain the likelihood of occurrence and severity of consequences. The approach shall include:

7.1.3.4.2 The initiating event or circumstance that can lead to the failure.

7.1.3.4.3 The context and sequence of events that could lead to failure.

7.1.3.4.4 The likelihood of arising such situations.

7.1.3.4.5 The nature of potential failure.

7.1.3.4.6 Based on the nature of study, additional information / data can also be referred, but not limited to the following:

7.1.3.4.6.1 Published Standards

7.1.3.4.6.2 Scientific Technical Data

7.1.3.4.6.3 Historical Data

7.1.3.4.6.4 Usability Test

7.1.3.4.6.5 Clinical evidences — Knowledge from literature, product literature, IND/NDA data or any such source.

7.1.3.4.6.6 Outcome of Investigations

7.1.3.4.6.7 Expert Opinion

7.1.3.4.6.8 Supplier's Knowledge

7.1.3.4.6.9 External quality assessment

7.1.3.4.6.10 Global CAPA

7.1.3.4.6.11 All the Risk shall be listed in the Attachment-I.

7.1.3.5 **Risk Evaluation:**

7.1.3.5.1 Based on Risk Analysis and evidences, risk shall be compared and analyzed with respect to acceptance criteria. The risk may either be expressed qualitatively or quantitatively. The information shall then be used in decision making to accept or reduce or eliminate the risks under the risk control strategy.

7.1.4 **Risk Control:**

7.1.4.1 Risk control is a process used continually during lifecycle of the system and includes decision making to eliminate, reduce and (or) accept the identified risk ensuring consistent product quality and patient safety.

7.1.4.2 The amount of effort for risk control shall be proportionate to the significance of the risk. Risk control shall focus on:

7.1.4.2.1 Is the risk above acceptance level?

7.1.4.2.2 What can be done to reduce or eliminate the risk?

7.1.4.2.3 Appropriate balance among benefits, risks and resources?

7.1.4.2.4 Is any new risk being introduced as a result of control of identified risk?

7.1.4.3 When the level of risk is not dear, the most conservative approach shall be followed.

7.1.4.4 **Risk Reduction:**

7.1.4.4.1 Plan quality risk mitigation, avoidance or elimination with a focus on the severity and/or detectability followed by probability of the harm. A decision making activity to determine if the risk is above an acceptable level; what can be done to reduce or eliminate the risk considering the appropriate balance between benefits, risks and resources.

7.1.4.4.2 Risk reduction plan may include more than one of the following approaches:

7.1.4.4.2.1 **Elimination:** completely eliminate the risk. There may be practical limitation to the extent to which this may be achieved.

7.1.4.4.2.2 **Substitution:** replace the high cause of risk with low or no risk alternate.

7.1.4.4.2.3 **Reduction:** reduce potential of risk through additional controls, alarms dedicated/closed systems.

7.1.4.4.2.4 **Administrative Controls:** SOP, QMS, spatial arrangement, flow of materials and Personnel, segregation, training, behaviors, cultural controls, redundancies.

7.1.4.4.2.5 **Personnel Protective Equipment (PPE): Safety** procedures, Good Personnel Hygiene practices, Housekeeping procedures, Gowning procedure, Cleaning & Sanitation procedures, Do's & Don't at work place.

7.1.4.5 **Risk Acceptance:**

7.1.4.5.1 On review of risk management solutions, a decision shall be made whether the residual risk after implementation is acceptable.

7.1.4.5.2 Methodology to verify the risk control measures shall be documented and monitored for effective implementation. It shall be demonstrated and documented that the residual risk is suitably managed and controlled to an acceptable level.

Documentation and the acceptance of residual risk shall commensurate with level of risk.

7.1.4.5.3 Despite all efforts, it may not be possible to eliminate the risk in entirety. In such case, it shall be ensured that quality risk is reduced to a specified/ acceptance level.

It shall be able to demonstrate that the proposal is effective and the decision is acceptable to the market authorization and stakeholders being affected by the risk.

This acceptable level may depend on many parameters and shall be decided on a case-by-case basis.

7.1.5 **Conclusion/Report:**

7.1.5.1 Risk evaluation shall be summarized as a report.

7.1.5.2 It shall be ensured that the report contains all the data/information being relied upon through QRA.

7.1.5.3 The report shall be handled as per site procedure on Document & data Control.

7.1.5.4 Based on the necessary measures suggested in the report for effective QRM, individual department shall be responsible to ensure implementation.

7.1.6 **Risk Communication:**

7.1.6.1 Output from risk evaluation shall be communicated to Management. Whether the risk is acceptable and initiating action to eliminate or reduce the risk.

7.1.6.2 Communication can occur at any stage of the QRM process.

7.1.6.3 In case identified risk can have common impact across all locations/departments, a global CAPA shall be issued to ensure risk management across all locations / departments.

7.1.7 **Risk Review:**

7.1.7.1 QRA shall be evaluated periodically for monitoring effectiveness of risk elimination reduction plan for:

7.1.7.1.1 Need for any re-assessment to ensure that original assumptions and performance data remain valid.

7.1.7.1.2 Any change in risk profile shall be documented and communicated to the management.

7.1.7.1.3 The review may either prove the risk assessment is correct or need further improvement.

7.1.7.1.4 Review outcome shall be communicated to Location Head and documented along with the earlier report.

7.1.8 **Documentation:**

7.1.8.1 Ensure all documentation related to the Quality Risk Management (ORM) activities are completed in a defined time frame.

7.1.8.2 Documents shall have traceability and accessibility to relevant staff, reviewers &/or Regulatory Reviewers.

7.1.8.3 All documentation related to the Quality Risk Management activities shall be maintained in the Quality Risk Management File in accordance with site document control procedures.

7.1.8.4 Prior to implementation, any introduction of a new method or process, proposed change an existing method or process or any investigation of a method or process failure shall be documented using proper risk management assessments and change control procedures.

7.1.8.5 Following document shall be filled at the time of Risk management activities;

(i) Risk Management Checklist (Attachment-I)

(ii) Risk Assessment Model (Attachment-II)

(iii) Risk Assessment Report (Attachment-Ill)

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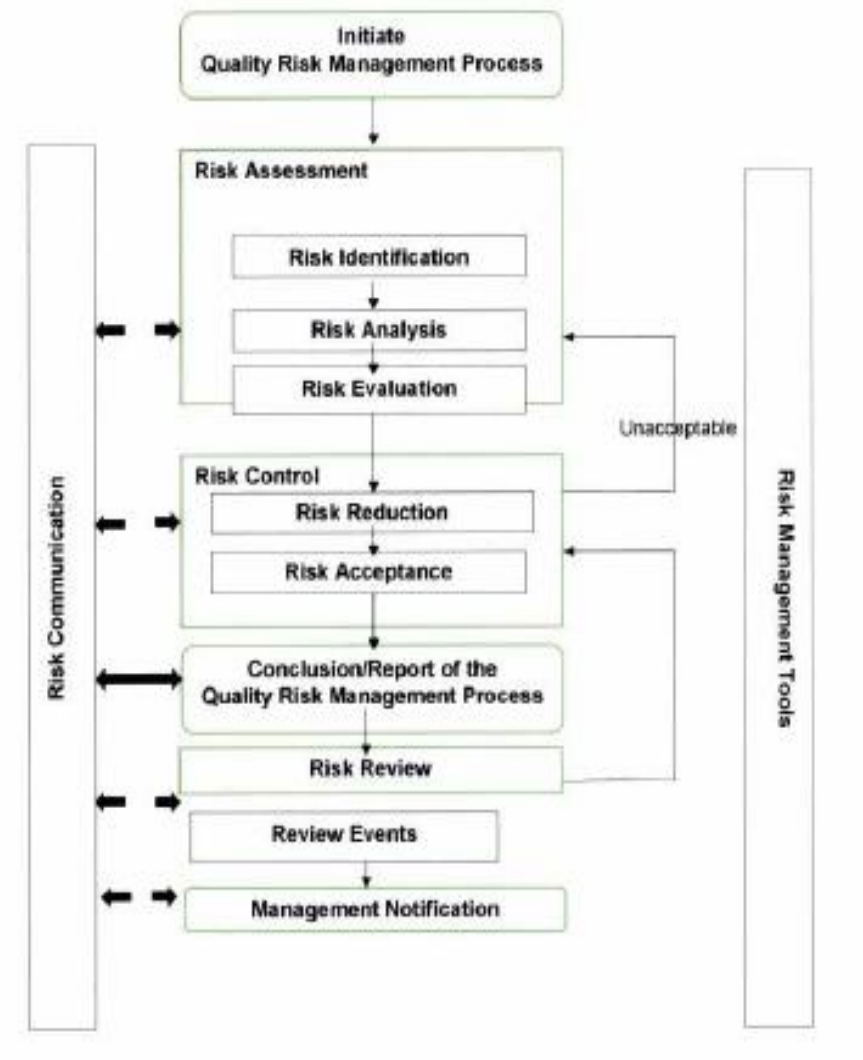
Schematic Representation of the Quality Risk Management Process (ICH Q9)



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7.2 Potential Applications for Quality Risk Management:

7.2.1 Effective quality risk management can facilitate better and more informed decisions,
can provide regulators with greater assurance of a site's/company's ability to deal with potential risks and might affect the extent and level of direct regulatory oversight.

7.2.2 Quality risk management shall be integrated into existing operations and documented appropriately.

7.2.3 Following are the applications in which the use of the quality risk management process provides information that can be used in a variety of pharmaceutical operations:

7.2.3.1 **Quality Risk Management as Part of Integrated Quality Management:**

7.2.3.1.1 **Documentation:**

To review current interpretations and application of regulatory expectations.

7.2.3.1.2 **Training and Education:**

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience, and working habits of staff, as well as a periodic assessment of previous training (e.g., its effectiveness).

To identify the training, experience, qualifications, and physical abilities those allow personnel to perform an operation reliably and with no adverse impact on the quality.

7.2.3.1.3 **Quality Defects:**

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc. To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

7.2.3.1.4 **Auditing/Inspection:**

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements
- Overall compliance status and history of the company or site
- Robustness of a company's/site's quality risk management activities
- Complexity of the site
- Complexity of the manufacturing process
- Complexity of the product and its therapeutic significance
- Number and significance of quality defects (e.g., recall)
- Results of previous audits/inspections

- Major changes of building, equipment, processes, and key personnel
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches)
- Test results of quality control laboratories

7.2.3.1.5 **Periodic review:** To select, evaluate, and interpret trend results of data within the product quality review. To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).

7.2.3.1.6 **Change management/change control:**

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing.

To evaluate the impact of the changes on the availability of the final product. To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process, or technical transfers.

To determine appropriate actions preceding the implementation of a change, e.g. additional testing, (re)qualification, (re)validation, or communication with regulators.

7.2.3.2 **Quality Risk Management as Part of Development:**

7.2.3.2.1 To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options, and process parameters etc.

7.2.3.2.2 To assess the critical attributes of raw materials, solvents, active pharmaceutical ingredient (API) starting materials, excipients, or packaging materials.

7.2.3.2.3 To establish appropriate specifications, identify critical process parameters, and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing).

7.2.3.2.4 To decrease variability of quality attributes:

7.2.3.2.4.1 Reduce product and material defects.

7.2.3.2.4.2 Reduce manufacturing defects.

7.2.3.2.5 To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer.

7.2.3.3 **Quality Risk Management for Facilities, Equipment and Utilities:**

7.2.3.3.1 **Design of Facility/Equipment:**

To determine appropriate zones when designing buildings and facilities, e.g.

- Flow of material and personnel.

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- Minimize contamination.
- Pest control measures.
- Prevention of mix-ups.
- Open versus closed equipment.
- Clean rooms versus isolator technologies.
- Dedicated facilities/equipment
- To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants).
- To determine appropriate utilities (e.g., steam; gases; power source; compressed air, heating, ventilation, and air conditioning (HVAC); water system.
- To determine appropriate preventive maintenance for associated equipment (e.g. inventory of necessary spare parts).

7.2.3.3.2 **Hygiene aspects in facilities:**

To protect the product & personnel from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns).

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured.

7.2.3.3.3 **Qualification of facility/equipment/utilities:**

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods).

7.2.3.3.4 **Cleaning of equipment and environmental control:**

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single purpose, batch versus continuous production). To determine acceptable (specified) cleaning validation limits.

7.2 3 3.5 **Calibration/ preventive maintenance:**

To set appropriate calibration and maintenance schedules.

7.2.3.3.6 **Computer systems and computer-controlled equipment:** To determine the extent of validation, example.

- Identification of critical performance parameters.
- Selection of the requirements and design.
- Code review.
- The extent of testing and test methods.
- Reliability of electronic records and signatures.

7.2.3.4 **Quality Risk Management as Part of Materials Management:**

7.2.3.4.1 **Assessment and evaluation of suppliers and contract manufacturers:**

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

7.2.3.4.2 **Starting material:**

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

7.2.3.4.3 **Use of materials:**

To determine whether it is appropriate to use material under quarantine (e.g... for further internal processing).

7.2.3.4.4 **Storage, logistics and distribution conditions:**

7.2.3.4.4.1 To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design).

7.2.3.4.4.2 To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidance.

7.2.3.4.4.3 To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance).

7.2.3.4.4.4 To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

7.2.3.5 **Quality Risk Management as Part of Production:**

7.2.3.5.1 **Validation:**

7.2.3.5.1.1 To identify the scope and extent of verification, qualification, and validation activities (e.g., analytical methods, processes, equipment, and cleaning methods).

7.2.3.5.1.2 To determine the extent for follow-up activities (e.g. sampling, monitoring, and revalidation).

7.2.3.5.1.3 To distinguish between critical and noncritical process steps to facilitate design of a validation study.

7.2.3.5.2 **In-process sampling & testing:**

7.2.3.5.2.1 To evaluate the frequency and extent of in- process control testing (e.g., to justify reduced testing under conditions of proven control) .

7.2.3.5.2.2 To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

7.2.3.5.3 **Production planning:**

7.2.3.5.3.1 To determine appropriate production planning (e.g., dedicated/campaign, and

concurrent production process sequences).

7.2.3.6 **Quality Risk Management as Part of Laboratory Control and Stability Studies**

7.2.3.6.1 **Out of Specification Results:**

To identify potential root cause(s) and corrective actions during the investigation of out of specification results.

7.2.3.6.2 **Retest Period/Expiration dating:**

To evaluate adequacy of storage and testing of intermediates/excipients/starting materials.

7.2.3.7 **Quality Risk Management as Part of Packaging and Labeling:**

7.2.3.7.1 **Design of Packages:**

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

7.2.3.7.2 **Selection of Container Closure System:**

To determine the critical parameters of the container closure system.

7.2.3.7.3 **Label controls:**

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label

7.3 Risk Management Methods & Tools:

7.3.1 A variety of tools that support science-based decisions are available.

7.3.2 No one or set of tools is applicable to every situation in which quality risk is being evaluated.

7.3.3 The selection of a tool shall be commensurate with nature of evaluation and the level of risk.

7.3.4 Any alternate approach is also acceptable if the objective of that tool & set of tools is understood and elaborated.

7.3.5 Below is the list of commonly used QRM approach and tools: Apart from the below mentioned tools, other tools can also be used for risk management:

- Brainstorming
- Five (05) Why's
- Charting
- Process Mapping — visual representation of work flow inputs and outputs
- Fish Bone Diagrams — suited for defining process variables and process elements.
- Decision Trees
- Event Tree Analysis

- Statistical Tools
- Preliminary Hazard Analysis (PHA) — focuses on hazardous situations
- FMEA (Failure Mode and Effect Analysis)/FMECA (Failure Mode Effects and Criticality Analysis) — suited for Prospective Analysis to predict multiple effects
- HACCP (Hazard Analysis and Critical Control Points) — supports identification of critical control points in a process
- Variation Risk Management
- Probabilistic Risk Analysis
- FTA (Fault Tree Analysis) — suited for Retrospective Analysis
- Risk Ranking and Filtering
- Root Cause Analysis — suited for Retrospective Analysis

Note: Appropriate tool can be used in specific areas pertaining to product quality. Quality risk management methods and the supporting statistical tools can be used in combination.

7.3.6 **Failure Modes & Effects Analysis (FMEA) - Concept & Process:**

7.3.6.1 The FMEA process is an on-going, bottom-up approach typically utilized in three areas of product realization and use, namely design, manufacturing and service. A design FMEA examines potential product failures and the effects of these failures to the end user, while a manufacturing or process FMEA examines the variables that can affect the quality of a process. The aim of a service FMEA is to prevent the misuse or misrepresentation of the tools and materials used in servicing a product.

7.3.6.2 The Failure Modes and Effects Analysis (FMEA), is a systematic method by which potential failures of a product or process design are identified, analyzed and documented.

7.3.6.3 FMEA is a crucial reliability tool that helps avoid costs incurred from product failure and liability.

7.3.6.4 FMEA is used to evaluate processes for possible failures and to prevent them by correcting the processes proactively rather than reacting to adverse events after failures have occurred.

7.3.6.5 FMEA is designed to:

7.3.6.5.1 Identify and fully understand potential failure modes and their causes, and the effects of failure on the system or end users, for a given product or process.

7.3.6.5.2 Assess the risk associated with the identified failure modes, effects and causes, and prioritize issues for corrective action.

7.3.6.6 Typically, the main elements of the FMEA are:

7.3.6.7.1 The ***failure mode*** that describes the way in which a design/process/system fails to perform as intended or according to specification.

7.3.6.7.2 The **effect** or the impact on the customer resulting from the failure mode.

7.3.6.7.3 The ***cause(s)*** or means by which an element of the design/process/system resulted in a failure mode.

7.3.6.8 The relationship between and within failure modes, effects and causes can be Complex. For example, a single cause may have multiple effects or a combination of causes could result in a single effect.

7.3.6.9 **Types of FMEAs:**

7.3.6.9.1 **System FMEA** is the highest-level analysis of an entire system, made up of various subsystems. The focus is on system-related deficiencies, including system safety, system integration, interfaces or interactions between subsystems or with other systems, interactions with the surrounding environment, human interaction, service, and other issues that could cause the overall system not to work as intended.

7.3.6.9.2 **Design FMEA** focuses on product design, typically at the subsystem or component level. The focus is on design related deficiencies, with emphasis on improving the design and ensuring product operation is safe and reliable during the useful life of the product. Design FMEA usually assumes the product will be manufactured according to specifications.

7.3.6.9.3 **Process FMEA** focuses on the manufacturing or assembly process, emphasizing how the manufacturing process can be improved to ensure that a product is built to design requirements in a safe manner, with minimal downtime, scrap and rework.

The scope of a Process FMEA can include manufacturing and assembly operations, shipping, incoming parts, transporting of materials, storage, conveyors, tool maintenance, and labeling. Process FMEAs most often assume the design is sound.

7.3.6.10 **Objectives of FMEA:**

7.3.6.10.1 For System FMEAs, the objective to improve the design of the system.

7.3.6.10.2 For Design FMEAs, the objective is to improve the design of the subsystem or component.

7.3.6.10.3 For Process FMEAs, the objective is to improve the design of the manufacturing process.

7.3.6.10.4 Identify and prevent safety hazards.

7.3.6.10.5 Minimize loss of product performance or performance degradation.

7.3.6.10.6 Improve test and verification plans (in the case of System or Design FMEAs).

7.3.6.10.7 Improve Process Control Plans (in the case of Process FMEAs).

7.3.6.10.8 Consider changes to the product design or manufacturing process.

7.3.6.10.9 Identify significant product or process characteristics.

7.3.6.10.10 Develop Preventive Maintenance plans for in-service machinery and equipment.

7.3.6.11 **FMEA Success Factors:**

7.3.6.11.1 There are six broad success factors that are critical to uniformity of success in the application of FMEA.

7.3.6.11.2 Implementing these FMEA success factors help ensure FMEAs achieve safe, reliable and economical products and processes.

i. Understanding the fundamentals and procedures of FMEAs, including the concepts and definitions.

ii. Selecting the right FMEA Activity.

iii. Preparation steps for each FMEA Activity.

iv. Applying lessons learned and quality objectives.

v. Providing excellent facilitation.

vi. Implementing an effective company-wide FMEA process.

7.3.6.12 **Understanding the Fundamentals and Procedures of FMEA:**

7.3.6.12.1 Time spent toward understanding the fundamental concepts and definitions of FMEAs shorten the time in meetings and help ensure high quality results.

7.3.6.12.2 This methodology is based on ICH Q9 guideline, WHO, PICS and ISPE, Volume 7 "Risk based Manufacture of Pharmaceutical products". It is a generic approach for QRM: however, alternate approach and criteria can also be adopted.

7.3.6.12.3 The methodology is based on FMEA analysis and quantitation of risk. Individual risk is evaluated for its Severity, Probability and Detectability followed by Risk Priority Number (RPN): RPN = S X P X D

Where S means ***Severity,*** P means ***Probability*** and D means ***Detestability***

7.3.6.12.4 The risk priority number (RPN) shall be calculated for all possible failure modes identified in the process being evaluated. The possible score in this range can range from 1 (1 x 1x 1) to 1000 (10 x 10 x 10). Where 1 represents the least to no risk The data is assessed for prioritizing the risk and mitigation strategy.

7.3.6.12.5 The following ten steps provide a basic approach that can be followed in order to conduct a basic FMEA. Attachment IV provides a sample format for completing FMEA worksheet.

Step 1: Identify Items/Components and Associated functions - To identify all of the items/components to be evaluated. This may include all of the parts that constitute the product or, if the focus is only part of a

product, the parts that make up the applicable sub-assemblies. The function(s) of each part within in the product should be briefly described.

Step 2: Identify Failure Modes - The potential failure mode(s) for each part should be identified. Failure modes can include but are not limited to:

- complete failures • intermittent failures
- Partial failures • Failures over time
- Incorrect operation • Premature operation
- Failure to cease functioning at allotted time • failure to function at allotted time.

Step 3: Identify Effects of the Failure Modes - For each failure mode identified, the consequences or effects on product, property and people should be listed.

These effects can be best described as seen through the eyes of the customer. An "effect" is the consequence of the failure on the system or end user. This can be a single or multiple description of the effect for each failure mode. However, typically the FMEA team should use the most serious of the end effects for the analysis.

Step 4: Determine Severity of the Failure Mode - The severity or criticality rating indicates how significant of an impact the effect has on the customer. Severity can range from insignificant to risk of fatality. The advantage of a numeric rating is the ability to be able to calculate the Risk Priority Number (RPN). Severity ratings can be customized as long as they are well defined, documented and applied consistently. 'Severity" is a ranking number associated with the most serious effect for a given failure mode, based on the criteria from a severity scale. Attachment-II provides examples of severity ratings.

Step 5: Identify cause(s) of the failure mode - For each mode of failure, causes should be identified. These causes can be design deficiencies that result in performance failures, or induce manufacturing errors. A "cause" is the specific reason for the failure, preferably found by asking “why” until the root cause is determined.

Cause should be taken to the level of failure mechanism. If a cause occurs, the corresponding failure mode occurs.

Step 6: Determine Probability of Occurrence - This step involves determining or estimating the probability that a given cause or failure mode will occur. The probability of occurrence can be determined from field data or history of previous products. If this information is not available, a subjective rating should be made based on the experience and knowledge of the cross-functional experts. As with a numeric severity rating, a numeric probability of occurrence rating can be used in calculating the RPN.

Attachment -III provides an example of a numeric ranking.

Step 7: Identify Controls (Prevention) - The controls that are currently in place that either prevent or detect the cause of the failure mode should be identified.

Preventative controls either eliminate the cause or reduce the rate of occurrence.

Controls that detect the cause allow for corrective action while controls that detect failure allow for interception of the product before it reaches subsequent operations or the customer.

Step 8: Determine Effectiveness of Current Controls (Detection) - The control effectiveness rating estimates how well the cause or failure mode can be prevented or detected. If more than one control is used for a given cause or failure mode, an effectiveness rating should be given to the group of controls. Control effectiveness ratings can be customized provided the guidelines as previously outlined for seventy and occurrence are followed. Attachment -IV provides example ratings.

Step 9: Calculate Risk Priority Number (RPN) - "RPN" is a numerical ranking of the risk of each potential failure mode/cause, made up of the arithmetic product of the three elements: severity of the effect, likelihood of occurrence of the cause, and likelihood of detection of the cause. The RPN is an optional step that can be used to help prioritize failure modes for action. It should be calculated for each failure mode by multiplying the numerical ratings of the severity, probability of occurrence and the probability of detection (effectiveness of detection controls) (RPN=S x 0 x D). In general, the failure modes that have the greatest RPN should receive priority for corrective action. The RPN should not firmly dictate priority as some failure modes may warrant immediate action although their RPN may not rank among the highest.

RPN = Severity (Effects) x Occurrence (Cause) x Detection (Control)

RPN Limitations: RPN has a number of limitations and is not a perfect representation of the risk associated with a failure mode and associated cause.

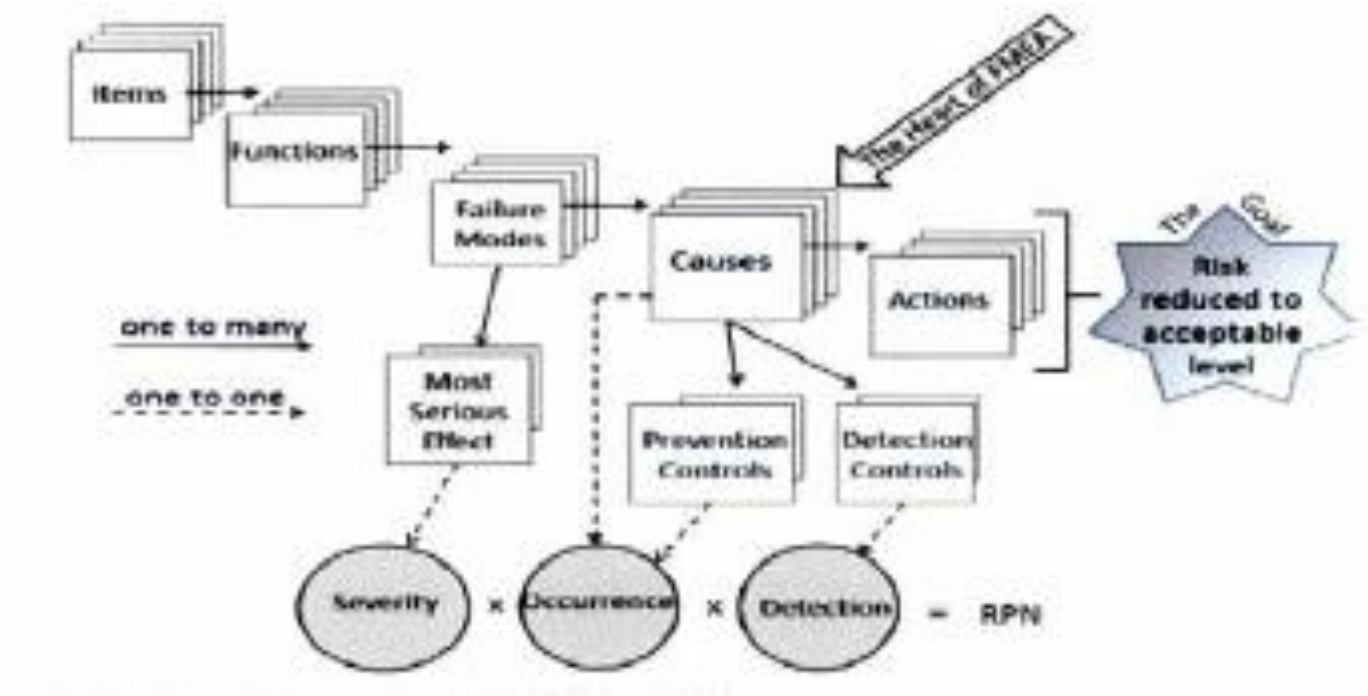
Practitioners using RPN should be aware of the inherent limitations and take measures to be sure product and process risks are properly characterized and addressed.

i. It is subjective, not objective
ii. The potential values of RPN are not continuous
iii. The Detection scale has its own limitations
iv. There are many duplicate RPN values, representing different combinations of Severity, occurrence and detection rankings.
v. The practice of using RPN thresholds is not advised.

Step 10: Determine recommended actions to reduce risk of failure mode-

"Recommended actions' are the tasks recommended by the FMEA team to reduce or eliminate the risk associated with potential causes of failure. They should consider existing controls, relative importance (prioritization) of the issue, and the cost and effectiveness of the corrective action. There can be many recommended actions for each cause. In practice, it usually takes more than one, and sometimes many actions to address high risk issues. The FMEA team must adequately address all high severity as well as high-RPN issues. (In the FMEA worksheet, "Actions Taken" is the specific action that is implemented to reduce risk to an acceptable level. It should correlate to the specific recommended action, and is assessed as to effectiveness by a revised severity, occurrence, detection ranking, and corresponding revised RPN.)

The Logical Relationship between FMEA Elements



7.3.6.13 **Selecting the Right FMEA Activity:**

7.3.6.13.1 Activity should be select when a certain level of risk can be effectively addressed by the FMEA procedure.

7.3.6.13.2 Following important criteria should be used for selecting FMEA Activity but not limited:

- New technology.
- New designs where risk is a concern.
- New applications of existing technology.

- Potential for safety issues.
- History of significant field problems.
- Potential for important regulation issues.
- Mission Critical applications.
- Supplier Capability.

7.3.6.13.3 The risk criteria should be assessed on a variable scale for the items being considered for FMEAs. Preliminary Risk Assessment criteria can be tailored to the unique needs of requirements.

7.3.6.13.4 **Timing Criteria for FMEAs:**

7.3.6.13.4.1 FMEAs should be done early in the product development process, where design and process changes can be most easily implemented.

7.3.6.13.4.2 System FMEA should be started as soon as the system configuration is determined and completed before the system configuration freeze-date.

7.3.6.13.4.3 Design FMEAs should be started as soon as the design concept is determined and completed before the design freeze date.

7.3.6.13.4.4 Process FMEAs should be started as soon as the manufacturing or assembly process is determined at the concept level, and completed before the manufacturing or assembly process freeze date.

7.3.6.14 **Preparing for FMEA Activity:**

7.3.6.14.1 Each selected FMEA Activity requires thorough preparation. The following can be the high level preparation tasks. Each of these tasks should be done thoroughly.

Short cutting FMEA preparation time will significantly increase the amount of time to do FMEAs and jeopardize quality of results.

- Determine the scope of the FMEA Activity.
- Make the scope visible and get consensus on boundaries (such as FMEA Block Diagram or Process Flow diagram).
- Assemble the right FMEA team (not done by one or two people).
- Establish ground rules and assumptions.
- Gather information.
- Prepare for the FMEA meetings.

7.3.6.14.2 Selecting the right FMEA team is necessary for getting high quality results. FMEA is a cross-functional team activity.

7.3.6.14.3 Core team for a FMEA Activity should include subject matter experts (SME) representation from Engineering, Manufacturing, Formulation & development and Quality. Checklist should be included.

7.3.6.15 **Applying Lessons Learned and Quality Objectives:**

7.3.6.15.1Following should be the leading factors that make for effective FMEAs (quality objectives). Common FMEA mistakes converted into Quality Objectives.

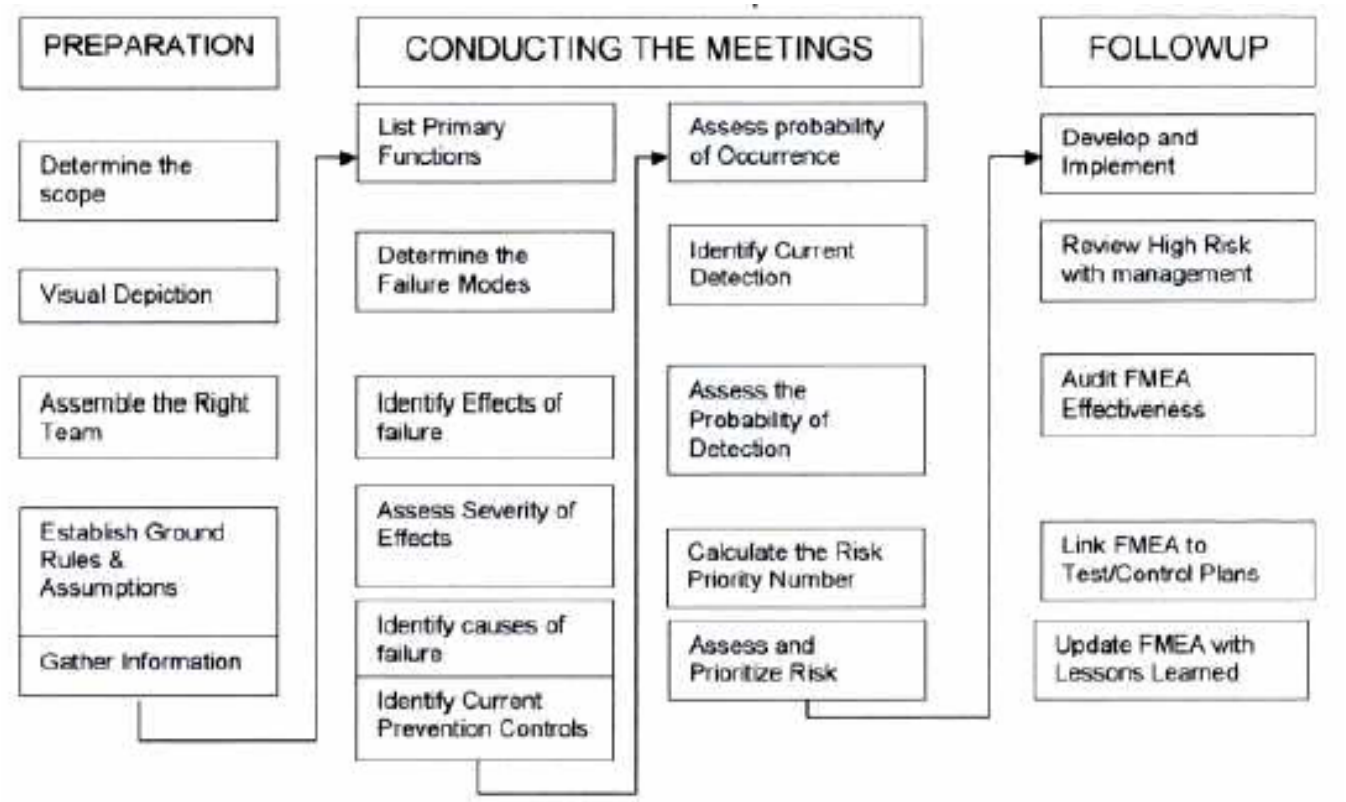
- **Design Improvement —** FMEA should drives product design or process Improvement as the primary objective.
- **High Risk Failure Modes —** FMEA should address all high risk failure modes and execution plans.
- Design verification Plan or process Control Plan considers the failure modes from the FMEA.
- **Interfaces —** FMEA scope should include integration and interface failure modes in both block diagram and analysis.
- **Lesson Learned-** FMEA should consider all major lesson learned (such as high warranty campaign etc.) as input to failure mode identification.
- **Level of Detail-** FMEA should provide the correct level of detail in order to get root causes and effective actions.
- **Timing-** FMEA should be completed during the window of opportunity" It should be most effectively influence the product or process design.
- **Team-** The right people should be adequately trained in the procedure and participate on the FMEA team throughout the analysis.
- **Documentation-** FMEA document should be completely filled out "by supporting raw data" including "Action taken" and final risk assessment.
- **Time Usage- FMEA** team should use an effective and efficient use of time with a value added result.

7.3.6.16 **Providing Excellent FMEA Facilitation:**

7.3.6.16.1 FMEA facilitation is a different subject than FMEA methodology. To be successful, FMEA leaders need to develop expert facilitation skills, including brainstorming, encouraging participation, active listening, controlling discussion, making decisions, conflict management, managing level of detail, managing time, and unleashing team creativity. Good facilitation is essential to prevention of high-risk problems without wasting time.

7.3.6.16.2 A FMEA Roadmap is outlined as under:

FMEA Roadmap



7.3.6.16.3 Key elements of this process include management support for strategy and resources, well-defined roles and responsibilities, management review of high risk issues on an ongoing basis, FMEA quality audits, execution of FMEA recommended actions, and a feedback loop to incorporate lessons learned.

7.3.6.17 **Implementing an Effective FMEA Process:**

7.3.6.17.1FMEA process's key elements should be considered but not limited i.e. good strategy, resources, well-defined roles and responsibilities, FMEA quality audits, execution of FMEA recommended actions, feedback loop to incorporate lessons learned and management review of high risk issues on an ongoing basis.

7.3.6.17.2FMEA process can be integrated with other processes or stand alone to provide effective reviews of high risk failure modes and recommended actions, and mandates attendance of expert FMEA team members.

7.3.6.18 **Rationale for Ranking Scale:**

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Severity Rating

Effect	SEVERITY of Effect	Ranking
Hazardous without warning	Very high severity ranking when a potential failure mode affects safe system operation without warning	**10**
Hazardous with warning	Very high severity ranking when a potential failure mode affects safe system operation with warning	**9**
Very High	System inoperable with destructive failure without compromising safety	**8**
High	System inoperable with equipment damage.	**7**
Moderate	System inoperable with minor damage.	**6**
Low	System inoperable without damage.	**5**
Very Low	System operable with significant degradation **of** performance.	**4**
Minor	System operable with some degradation **of** performance.	**3**
Very Minor	System operable with minimal interference.	**2**
None	No effect	**1**

Probability of Occurrence Rating

Probability	Failure Prob.	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**

Detection Rating

Detection	Likelihood of DETECTION by Design Control	Ranking
Absolute Uncertainty	Design control cannot detect potential cause /mechanism and subsequent failure mode	**10**
Very Remote	Very remote chance the design control will detect potential cause/mechanism and subsequent failure mode	**9**
Remote	Remote chance the design control will detect potential cause /mechanism and subsequent failure mode	**8**
Very Low	Very low chance the design control will detect potential cause/ mechanism and subsequent failure mode	**7**
Low	Low chance the design control will detect potential cause/ mechanism and subsequent failure mode	**6**
Moderate	Moderate chance the design control will detect potential cause/ mechanism and subsequent failure mode	**5**
Moderately High	Moderately High chance the design control will detect potential cause/mechanism and subsequent failure mode	**4**
High	High chance the design control will detect potential cause/ mechanism and subsequent failure mode	**3**
Very High	Very high chance the design control will detect potential cause/ mechanism and subsequent failure mode	**2**
Almost Certain	Design control will detect potential cause/mechanism and subsequent failure mode	**1**

7.3.6.19 **FMEA Case Study: QRM in Pharma Dispensing Area:**

The dispensing area is considered one of the most important units in the production line since the production begins here. If there is any mistake in this unit, the end products can be adversely affected in terms of quality and safety for use. The cross contamination on the starting materials or any error on active pharmaceutical ingredients (API's) can easily make end product become counterfeit or substandard or adulterated or substandard or adulterated.

The main tasks of the dispensing unit are to receive starling materials from the warehouse, to weigh and transfer to the production line.

However, one can imagine that there will be several steps within the main process that needs to be done. Each of steps may use equipment and require human to operate. Thus, failure modes due to equipment malfunction or human error can occur and effect(s) will be ensued. As a result, inadequate products may inadvertently be produced.

Based on potential quality risk identification there can be five different types of counterfeit or

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Sub standard or adulterated or substandard or adulterated mechanism i.e.

i. No active ingredient

ii. Low levels of active ingredient

iii. Poor quality drugs

iv. Wrong ingredients

v. Wrong packaging or source

Potential risks should be managed FMEA basically requires the identification of the following basic information. It is composed of item(s), function(s), failure(s), effect(s) of failure, cause(s) of failure, current control (s), recommended action (s), and other relevant details.

In this case study two types of FMEA i.e. Design (equipment) & Process (human operation) will be done. The fundamental steps of this FMEA study to select the component(s) or process(s) shall be analyzed and identify failure modes of the selected ones.

The immediate effects and final effect of the failure mode together with the severity of the final effect shall be identified. Then the potential causes of that failure mode as well as the probability of occurrence shall be determined.

(A) Failure Modes Analysis of Design (Equipment): The main equipment most affecting quality of starting materials can be identified into two items i.e. weighing scale and HVAC system.

The weighing scale is used to weigh starting materials to the right amount based on the said ingredient. The position, accuracy and performance of the weighing scale are very crucial factors attributing to the wrong ingredient which is one of the categories in counterfeit or substandard or adulterated drug. The failure modes in weighing scale are wrong reading in two conditions. One is due to scale at incorrect position. The other is load cell malfunction.

The HVAC system is of crucial importance in controlled environments. The quality of starting materials also depends upon the performance of HVAC system. As a consequence, the poor quality drugs may be produced, if the system is not properly controlled or it is malfunction.

Therefore, the HVAC system will be taken into account in failure modes analysis. The analysis of failure modes of weighing scale and HVAC system is tabulated in Table -1.

(B) Failure Modes Analysis of Processes (Human Operation):

In this case there are a total of eight possible failure modes. (a) wrong delivery of starting materials to dispensing area, (b) wrong delivery of starting materials to dispensing booth (c) incorrect data entry (d) dispense incorrect type, quantity, lot number of raw materials (e) label wrongly on weighed starling materials

pack (f) mix up of weighed materials (g) mix up of bundle with bulk pack ***(h)*** stain remaining at return grille. The analysis of failure modes of process is tabulated in Table II.

Criticality Assessment of Failure Modes Effect:

Once the failure modes analysis is completed, the criticality assessment of the effects of these modes is followed by recommended actions and effectiveness check of actions taken.

The actions to reduce the adverse effect must be established and implemented. Each of the high criticality failure modes with high RPN value should be mitigated on priority basis followed by low RPN value failure mode.

(I) Case of Failure Modes Analysis of Design (Equipment) - High RPN value failure mode is related to HVAC system — The problem of uncontrolled pressure receives high magnitude in Criticality matrix. This problem jeopardizes the cleanliness of the classified area and it is very crucial. Thus, mitigation actions must be established. One of the main reasons that this failure mode that deserves attention is that the door at air lock room is the only entrance of starting materials to dispensing area.

These facilities tend to malfunction and can cause problems. Likewise the hinges of the door at air lock room tend to dislocate and are not able to position the door at the right angle. Thus, the door is uneven due to heavy use. The recommendation is to request dispensing personal constantly observe the pressure gauge. The preventive maintenance of air lock door must be included in CAPA (corrective and preventive actions) of the factory. Moreover, an alarm system when pressure drops is highly recommended.

(II) Case of Failure Modes Analysis of Process (Human Operation) - A number of risks occurring during transferring of starting materials from receiving area to dispensing room, the controlled clean room may ***be*** due to congestion of starting materials, unsystematic procedure, and/or human blunder. Although, checking stations are designed along the processes, no mistake is still better than detecting it.

These types of problems can be easily prevented by many ways. FEFO/ FIFO organization of the items will present lot number mix-up. Colour labels for visual check can help reduce materials mix-up and speed up sorting and grouping of materials onto the pallet.

Data logging error due to human is considered one of the potential risks and must be prevented.

Although data is just information not exactly involved to the physical product, confusion and traceability is prime importance to the quality assurance. This influences recall procedure, CAPA activity. QMS (quality management system), and so on.

Incorrect labeling after weighing starting materials in weighing booth is considered serious. This leads to misuse of weighed materials and leads to counterfeit or substandard or adulterated drug.

Continuous improvement using ECRS (Eliminate, Combine, Rearrange, and Simplify) technique should be implemented to prevent this risk. For example, weighed materials must immediately labeled to prevent wrong labeling. Standard operation procedure (SOP) should be revised to attain best practice.

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Table- I

Design FMEA Process											Action Results				
Item and Function	**Potential Failure Modes**	**Potential Effect(s) of failures**	**Severity**	**Potential Cause()) of failures**	**Occurrence**	**Current Controls**	**Detection**	**RPN**	**Recommended action**	**Responsibility and target completion date**	**Action taken**	**Severity**	**Occurrence**	**Detection**	**RPN**
Step (1)	**Step (2)**	**Step (3)**	**Step (4)**	**Step (5)**	**Step (6)**	**Step (7)**	**Step (8)**	**Step (9)**	**Step (10)**						
Scale and Weight	Incorrect reading	Wrong weight of starting materials	4	Scale not in the Correct position	2	Self- check before use	7	56	Adoption of do — check mechanism	Dept. head	Procedure implemented	4	2	2	16
Scale and Weight	Incorrect reading	Incorrect weight of starting materials	4	Load cell error	2	Calibration every 3 month and Daily s elf Check	7	56	Adoption of do — check mechanism	Dept. head	Procedure implemented	4	2	2	16
HVAC system	Humidity uncontrolled	Too much moisture in materials	3	Dehumidifier malfunction	3	Calibration and MDR Main Distribution Board, control	5	45	Temp. & RH recording before start of operation	Dept. head	Procedure implemented	3	2	1	8
HVAC system	Temperature uncontrolled	Materials spoiled	3	Compressed electronics breakdown	1	Annual preventive maintenance	3	9	As risk came out *minor* & Is acceptable						
HVAC system	Pressure uncontrolled	Unclean room	4	MU breakdown or door problem	3	Annual Calibration	7	84	Door redesign & PM of AHU d Mann system	HOD and Engg. Dept.		4	3	1	12

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Table- II

Process FMEA Process											Action Results				
Item and Function	**Potential Failure Modes**	**Potential Effect(s) of failures**	**Severity**	**Potential Cause()) of failures**	**Occurrence**	**Current controls**	**Detection**	**RPN**	**Recommended action**	**Responsibility and target completion date**	**Action taken**	**Severity**	**Occurrence**	**Detection**	**RPN**
Step (1)	**Step (2)**	**Step (3)**	**Step (4)**	**Step (5)**	**Step (6)**	**Step (7)**	**Step (8)**	**Step (9)**	**Step (10)**						
Transfer starting material from unclassified area to classified/ dispensing area	Wrong delivery starting material to classified/ dispensing area	Delay the schedule	2	Human Error	3	Checked by operator in dispensing area	7	42	Before weighing material shall be verified by supervisor and QA person	HOD and section in-charge	Procedure implemented	2	3	1	6
Transfer starting material from classified area to dispensing booth	Wrong delivery starting material to dispensing booth/ Receive wrong Lot No. of starting materials	Weigh wrong starting materials/ starting materials mixing Lot No.	4	Human Error	3	Checked by operator	7	84	Design queue for starting material Visual check	HOD and section in-charge	Procedure implemented	2	3	1	6
Data logging	Entry incorrect data	Non traceability problem and incorrect data being use	4	Human Error	4	Checked by Foreman or Pharmacist	7	112	Encoder & decoder i.e. barcode system	HOD & Engg.	Procedure implemented	4	2	2	16
Dispense bulk Pack of starting materials	Dispense incorrect type, quantity, Lot No. of	Wrong ingredients/ starting materials mixing Lot No.	4	Human Error	2	N/A	7	56	Before weighing material shall be verified by	HOD & Section In-charge	Procedure implemented	4	2	1	8

	starting materials								supervisor and OA person						
Labeling	Wrong label on weighed starting materials pack	Wrong ingredients	4	Human Error	3	check by Foreman or Pharmacist	7	84	barcode system for data entry	HOD Engg.	Procedure implemented	4	3	1	12
Sortation	Mix up of weighed 9 Materials	Wrong ingredients	3	Human Error	3	check before execute to bundle	7	63	Before weighing material shall be verified by supervisor	HOD & Section In-charge	Procedure implemented	3	3	1	9
Placing of bundle	Mix up of bundle with bulk pack	Wrong ingredients	3	Human Error	3	N/A	7	63	Before weighing material shall be verified by supervisor	HOD & Section In-charge	Procedure implemented	3	3	1	9
Cleaning return Grille	Strain remaining at return Ole	Poor Quality	4	Improper cleaning	2	SOP and Training	7	56	After cleaning check by supervisor	HOD & Section In-charge	Procedure implemented	4	2	2	16

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7.3.6.20 **FMEA Documentation:**

7.3.6.20.1 All documentation related to the FMEA activities should completed in a defined reasonable time frame.

7.3.6.20.2 Documents should have traceability and accessibility to relevant staff, reviewers or Regulatory Reviewers.

7.3.6.20.3 All documentation related to the FMEA activities should be maintained in accordance with site document & data control procedures.

7.3.6.20.4Prior to implementation, any introduction of a new method or process, proposed change to an existing method or process or any investigation of a method or process failure should be documented using proper risk management assessments and change control procedures.

7.3.7 **Fish Bone Diagrams or Ishikawa Diagram**

7.3.7.1 The fishbone diagram is an analysis tool that provides a systematic way of looking at effects and the causes that create or contribute to those effects. Because of the function of the fishbone diagram, it is also referred to as a cause-and-effect diagram.

7.3.7.2 A cause-and-effect diagram can help identify the reasons why a process goes out of control. Often the fishbone diagram can be used to summarize the results of a brainstorming session, identifying the causes of a specified undesirable outcome. It helps to identify root cause(s) and ensures a common understanding of the causes.

7.3.7.3 Following are the steps for constructing and analyzing a Cause-and-Effect Diagram (Fish bone) as outlined under

Step 1 - Identify and clearly define the outcome or effect to be analyzed. Formulate the problem and write it in a box on the right side of the diagram. Everyone must clearly understand the nature of the problem and the process/product being discussed. If everyone is not clear on the purpose of the session, the session will not resolve the problem. In this step the following rules should be applied:

(i) Decide on the effect to be examined. Effects are stated as particular quality characteristics, problems resulting from work, planning objectives, and the like.

(ii) Use Operational Definitions. Develop an Operational Definition of the effect to ensure that it is clearly understood.

(iii) Remember, an effect may be positive (an objective) or negative (a problem), depending upon the issue that's being discussed.

Step 2 - Use a chart pack positioned so that everyone can see it, draw the spine and create the effect box.

Draw a horizontal arrow pointing to the right. This is the spine.

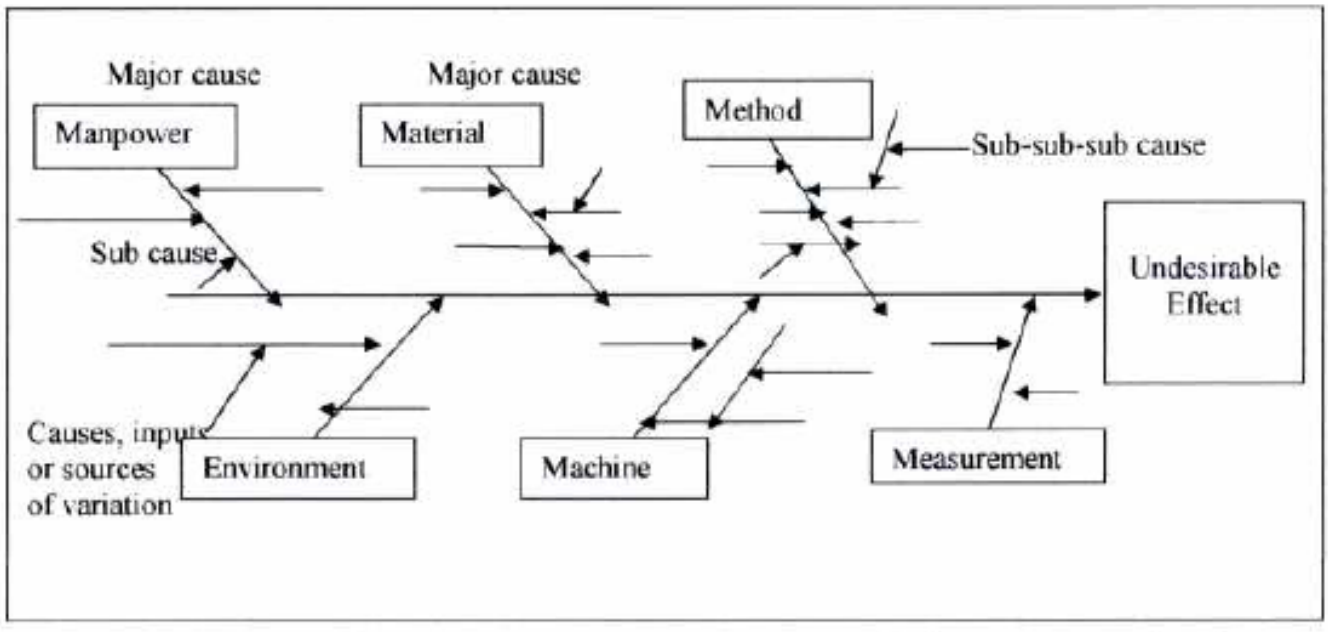
(ii) To the right of the arrow, write a brief description of the effect or outcome which results from the process.

(iii) Draw a box around the description of the effect.

Step 3 - Identify the main cause(s) contributing to the effect being studied. These are the labels for the major branches of the diagram and become categories under which to list the many causes related to those categories Establish the major causes, or categories, under which other possible causes will be listed. Use category labels that make sense for the diagram being created.

(ii) Write the main categories the team has selected to the left of the effect box, some above the spine and some below it.

(iii) Draw a box around each category label and use a diagonal line to form a branch connecting the box to the spine.



Step 4 - For each major branch, identify other specific factors which may be the causes of the effect.

(i) Identify as many causes or factors as possible and attach them as sub branches of the major branches.

Fill in detail for each cause. If a minor cause applies to more than one major cause, list it under both.

Step 5 - Identify increasingly more detailed levels of causes and continue organizing them under related causes or categories. This can be done by asking a series of why questions. It required to break the diagram into

smaller diagrams if one branch has too many sub branches. Any main *cause* (3Ms and P, 4Ps, or a category you have named) can be reworded into an *effect.*

Step 6 - Analyse the diagram. Analysis helps to identify causes that warrant further investigation. Since Cause-and-Effect Diagrams identifies only Possible Causes, use of Pareto Chart can help determine the cause to focus on first.

(i) Look at the "balance" of the diagram, checking for comparable levels of detail for most of the categories.

A thick cluster of items in one area may indicate a *need* for further study.

A main category having only a few specific causes may indicate a need for further identification of causes.

(ii) If several major branches have only a few sub branches, combine them under a single category.

MO Look for causes that appear repeatedly. These ***may*** represent root causes.

(iv) Look for what can be measured in each cause so it can be quantify the effects of any changes you make.

7.3.7.4 Refer Attachment- XI to categorize and brain storm the main causes such as Man power, Machine, Material, Method, Measurement and Environment and take Corrective and preventive action (CAPA) as per SOP titled "CAPA (Corrective and Preventive Action) handling procedure" based on the severity of the identified causes.

7.3.7.5 **Benefit of Fishbone Diagram:**

7.3.7.5.1 Used to explore potential causes **(5 M's & 1E)** that can result in undesirable effect (UDE).

(1) Man Power- Skill, knowledge, competency and attitude, Adequacy of supervision & support, Clarity about job role, Experience, training, Shift in which the activity was done, Conducive work environment, Availability of tools / equipment etc.

(2) Machine- Age of equipment or machine, Maintenance history, was machine operating correctly, Machine capability, Operating parameters, Recent changes etc.

(3) Material- Change in Source of material, Change in process, Age of material v/s stability, Test results at incoming stage / re-test, Material packing. Storage condition, Correctness of Quantity, Quality trends etc.

(4) Method- Is the process well defined, Critical control points, Adequacy of control parameters, Robustness of the process, Process capability, Recent changes if any, Deviations in execution, Trend analysis of process parameters, Safety mechanisms & challenges etc.

(5) Environment - Control of Environmental conditions (Temp / RH), Impact of environmental conditions on the processes, Impact of environmental conditions on the materials, etc.

(6) Measurement (Method of Analysis/procedure)- Method validation- Specificity & robustness, Analyst training, Equipment calibration, Standards used, Frequency of inspection, Other analysis done along with the failing batch, Execution of methodology etc.

7.3.7.5.2 Helps determine root cause(s).

7.3.7.5.3 Encourages group participation.

7.3.7.5.4 Uses an orderly, easy-to-read format to diagram cause and effect relationships.

7.3.7.5.5 Indicates possible causes of variation.

7.3.7.5.6 Increases knowledge of the process by helping everyone to learn more about the factors at work and how they relate.

7.3.7.5.7 Identifies areas for collecting data.

7.3.8 **5 Why analysis:**

7.3.8.1 Shall be used in case of incident involving human factors and obvious errors.

7.3.8.2 It is simple to use, statistical analysis is not required, recognized tool to help identify root cause and helps to determine the relationship between different root causes of a problem.

7.3.8.3 Write down the specific problem as per Attachment-X.

7.3.8.4 Ask why the problem happened and write down the answer below the problem.

7.3.8.5 If the answer written in first instance doesn't identify the root cause of the problem, then again repeat the question why and again write down the answer. Repeat this exercise until the investigation team is in agreement that the root cause is identified.

7.3.8.6 This tool can be used individually or as a part of the fish bone diagram.

8.0 REVISION HISTORY

Version No.	00	Effective Date	
Details of revision: New SOP Prepared			

DECODING PHARMA

QUALITY ASSURANCE DEPARTMENT

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Attachment –I

RISK MANAGEMENT CHECKLIST

Equipment/ Instrument/ Process/System/Area/Product Name:

Code No.: _____ Reference Document No. : _____

S.No.	Parameters/Description	Remarks (√ or X or N/A)	Comments
1.	Availability of Approval User requirement specification /Functional Specification /Technical specification and /or Design Specifications		
2.	Availability of Purchase order		
3.	Operating Manual		
4.	General Arrangement (GA) drawing		
5.	Electrical Wring Diagram		
6.	Supplier test certificates of installed critical instruments, filters, gauges etc.		
7.	Availability of Qualification documents		
8.	Proper installation of all identified Components / sub - components		
9.	Connectivity of computer system (If any) with equipment / control panel.		
10.	Completion of area qualification		
11.	Completion of air handling system qualification		
12.	Completion of water qualification.		
13.	Availability of certificates of material of construction of all products.		
14.	Availability of SOP and their training		
15.	Proper connection of all required supporting utilities like power supply, compressed air, purified water , steam, hot water, chilled water, etc.		
16.	Availability of equipment sequential log		

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Attachment –I Continued…

S. No.	Parameters/Description	Remarks (√ or X or N/A)	Comments
1.	Updation of Preventive Maintenance Schedule		
2.	Calibration of all identified critical instruments with calibration status label		
3.	Utilization of calibrated master critical instrument during qualification / verification I monitoring		
4.	Verification of key functionally before interlocks / alarm verification		
5.	PLC screen print verification with all level password challenges		
6.	Verification of critical parameters like speed flow rate, air velocity etc.		
7.	Availability of interlocks / alarm with respect to GxP risk.		
8.	Availability of interlocks / alarm with respect to safety.		
9.	Verification of all interlocks / alarm / safety features provided in equipment.		
10.	Approval of qualification documents before starting of respective qualification activities		
11.	Successful Fitter integrity testing of installed HEPA filters and incorporation in schedule for next filter integrity testing		
12.	Sufficient space for man and material movement in area		
13.	Proper identification of area / location		
14.	Area is classified as per requirement		
15.	Equipment is identified with name, identification no		
16.	All qualification activities are performed as per pre approval qualified documents		

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Attachment –I Continued…

S.No.	Parameters/Description	Remarks (√ or X or N/A)	Comments
1.	All executed qualification documents are approved before utilization of equipment /system /quality		
2.	SOP shall be available at work place before utilization of machine		
3.	Proper cleaning of equipment and area after completion of all qualification activities		

* Note: If parameter / description complies then put '√', if does not comply then put 'X' and if not applicable, then write 'N/A' in remarks column and write comments (if any) in column of comment.

Risk Evaluation (If any):
Risk Reduction:
Risk Acceptance:

Department	Quality Assurance	Production	Engineering
Sign/Date			
Name			

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Attachment-II

RISK ASSESSMENT MODEL

Equipment/Instrument/Process/System/Area/Product Name:	**Location :**
Equipment/Instrument/Process/System/Area/Product Name Code No.:	
Reference	

S.No.	Unwanted events	Severity (1 to 10)*	Cause / Process failure	Existing Controls	Occurrence (1 to 10)*	Detection (1 to 10)*	RPR (RPN)	Risk Accepted (Yes/ NO)	Risk Mitigation/ Risk Control
(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)

Done By :	**Checked By:**

***L = low, M = Medium and H= High**

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Attachment - III

RISK ASSESSMENT REPORT

Equipment/Instrument/Process/System/Area/Product Name:

Code No.:

Reference Document No.:

1.	**Objective & Scope:** Description of the problem and scope of the study
2.	**Responsible Personnel:** Describe the name & department of the personnel involved in the study and responsibilities assigned to individual. (Ensure, the team has adequate training on the subject and their training records are accessible. It's advisable to put copy of training document along with QRM report. Also, involving a person with statistical background is always helpful)
3.	**Methodology for Risk Assessment:** Define the tools used for the study, data collection including CPP & CQA, background information, and data evaluation methods
4.	**Risk Assessment:** **Risk Identification:** Based on data/information, identification of risk shall be elaborated. **Risk Analysis:** Elaborate and justify, how the risk is analyzed and its significance to the problem being studied. **Risk Evaluation:** Elaborate comparison of the risk with acceptance criteria.
5.	**Risk Control Strategy** **Risk Reduction:** Proposal Elaborate Quality Risk Mitigation , avoidance or elimination plan **Risk Acceptance Criteria:** Depending on chosen tool (s), acceptance criteria shall be elaborated. **Risk Acceptance:** Justify the impact and acceptance/rejection of the risk after implementation of proposed risk control strategy **Risk Review Plan:** Elaborate the data/information being reviewed as part of proposed risk control strategy, periodicity for the review, documentation of such periodic reviews, effectiveness checks and communication to site management.
6.	**Documentation:** Elaborate the list of documents referred during QRA and retain them along with the report **Attachment:** If any
7.	**Management Notification:** The report signed by Site Management shall be considered as management notification. Alternate communication evidence, along with the report, shall also be acceptable.

Prepared by
Sign/Date

Reviewed by
Sign/Date

Approved by
Sign/Date

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Attachment - IV

FAILURE MODES & EFFECT ANALYSIS WORKSHEET

Equipment/ Instrument/ Process/ System/ Area/ Product Name: **Code No.:**	**FMEA ID No.:**
FMEA Team:	**FMEA Date:**

FMEA Process:											**Action Results**				
Item and Function	**Potential Failure Modes**	**Potential Effect(s) of failures**	**Severity**	**Potential Cause(s) of failures**	**Occurrence**	**Current controls**	**Detection**	**RPN**	**Recommended action**	**Responsibility and target taken completion date**	**Action taken**	**Seventy**	**Occurrence**	**Detection**	**RPN**
Step (1)	**Step (2)**	**Step (3)**	**Step (4)**	**Step (5)**	**Step (6)**	**Step (7)**	**Step (8)**	**Step (9)**	**Step (10)**						

Prepared by
Sign/Date

Reviewed by
Sign/Date

Approved by
Sign/Date

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Attachment-V

SEVERITY RATINGS

Category (Product/Process)	Criteria Severity of effect on Product	Criteria Severity of effect on Process	Scale Ranking
Failure to meet Safety or Regulatory requirements	Potential failure mode affects safe operation or regulatory requirements	Potential safety related effect on machine or assembly operator without warning	10
	Potential failure mode affects safe operation or regulatory requirements	Potential safety related effect on machine or assembly operator with warning	9
	Loss of primary function	>50% of product may need to be scrapped line shut down	8
	Degradation of primary function	<50% of production run may need to be scrapped / Decreased line speed	7
Loss or Degradation of Secondary function / Rework out of station	Loss of secondary function	>50% of production run may need to be re worked offline	6
	Degradation of secondary function	<50% of production run may need to be re worked offline	5
Annoyance / Re work in station	Item operable but with annoyance noticed by >75% of customer	>50% of production run may need to be re worked in station	4
	Item operable but with annoyance noticed by 50% of customer	<50% of production run may need to be re worked in station	3
	Item operable but with annoyance noticed by <25% of customer	Slight inconvenience to operation & operator	2
No effect	No noticeable effect	No noticeable effect	1

Attachment-V Continued…

Effect	Severity of Effect	Scale Ranking
Hazardous without Warning	Very high severity ranking when a potential failure mode affects safe system operation without warning. Unsafe operation without warning before failure or non-conformance with government regulations. Risk of injury or Fatality	10
Hazardous with warning	Very high severity ranking when a potential failure mode affects safe system operation with warning. Unsafe operation with warning before failure or non-conformance with government regulations Risk of injury or fatality.	`9
Very High	System inoperable with destructive failure without compromising safety. Loss of primary function renders product inoperable. Intolerable effects apparent to customer. May violate non safety related governmental regulations Repairs lengthy and costly.	8
High	System inoperable with equipment damage. Product is operable at reduced level of performance. High degree of customer dissatisfaction.	7
Moderate	System inoperable with minor damage. Products operable, however comfort or convenience items are inoperable.	6
Low	System inoperable without damage. Product is operable, however performance of comfort or Convenience items is reduced.	5
Very Low	System operable with significant degradation of performance. Effect recognized by most customers.	4
Minor	System operable with some degradation of performance. Average customer will notice effect	3
Very Minor	System operable with minimal interference A few customers may notice effect and may be annoyed.	2
None	No effect. Effect will be undetected by customer or regarded as insignificant.	1

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Attachment -VI

PROBABILITY OF OCCURRENCE RATINGS

Likelihood of Failure	Criteria: Occurrence of Cause	Criteria: Occurrence of Cause (Incident per Item)	% of Occurrence	Scale Ranking
Very high (Relatively consistent Failure)	New technology/new Design with no history.	>100 per Thousands item >1 in 10.	50%	10
	Failure inevitable with new design, new application or change or change in operating conditions	50 per Thousands item 1 in 20	33%	9
High (Repeated Failure)	Failure likelihood with new design, new application or change or change in operating conditions	20 per Thousands item 1 in 50	12.5%	8
	Failure uncertain with new design, new application or change or change in operating conditions	10 per Thousands item 1 in 100	5%	7
Moderate	Frequent Failure associated with similar Design & Design testing	5 per Thousands item 1 in 200	1.25%	6
	Occasional Failure associated with similar Design & Design testing	2 per Thousands item 1 in 500	0.25%	5
	Isolate Failure associated with similar Design & Design testing	1 per Thousands item 1 in 1000	0.05%	4
Low (Few Failures)	Only Isolate Failure associated with almost identical Design & Design testing	0.5 per Thousands item1 in 2000	≤ 0.01%	3
	No observed Failure associated with almost identical Design & Design testing	0.1 per Thousands item 1 in 10000	≤ 0.001%	2
Very Low (Unlikely)	Failure is eliminated through Preventive control	<0.01 per Thousands item 1 in 100,000	≤ 0.0001%	1

Attachment –VII

CONTROL EFFECTIVENESS (DETECTION) RATINGS

Opportunity for Detection	Likelihood of Detection	Criteria: Likelihood of Detection by Process control	Scale Ranking
No Detection Opportunity	Almost Impossible	No current process control, cannot detect or is not analyzed	10
Not Likely to Detect at any Stage	Very Remote	Failure mode/cause is not easily detected	9
Problem Detecting Post Processing	Remote	Failure mode detection post processing operator visual/ tactile/ audible means	8
Problem Detecting at Source	Very Low	Failure mode detection in station by operator-visual/ tactile/ audible means	7
Problem Detecting Post Processing	Low	Failure mode detection post processing by operator-use of variable gauging	6
Problem Detecting at Source	Moderate	Failure mode detection in station by operator-use of variable gauging or automated control	5
Problem Detecting Post Processing	Moderately High	Failure mode detection post processing by automated controls; lock part to prevent further processing	4
Problem Detecting at Source	High	Failure mode detection in station by automated controls; automatically lock part in station	3
Problem Prevention	Very High	Failure mode detection in station by automated controls; prevent discrepant part from being made	2
Detection N/A; Error Prevention	Almost Certain	Failure mode/ cause prevention as a result of fixture design, machine design, or part design	1

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Attachment –VIII

FMEA: RATING SCALE & RPN RESULT ACTION

Rating	Severity of Effect	Likelihood of occurrence	Ability to Detect
10	Lose customer	Very high : Failure is almost inevitable	Cannot detect
9	Serious impact on customer's business or process		Very remote chance of detection
8	major inconvenience to customer	High Repeated failures	Remote *chance* of detection
7	major defect noticed by some customers		Very low chance of detection
6	major defect noticed by most customers	Moderate : Occasional failures	Low chance of detection
5	major defect noticed by discriminating customers		Moderate chance of detection
4	Minor defect noticed by some customers		Moderate High chance of detection
3	Minor defect noticed by most customers	Low : Relatively few feline	high chance of detection
2	Minor defect noticed by discriminating customers		Very High *chance* of detection
1	No effect	Remote : Failure is unlikely	Almost certain detection

RPN: RESULTS AND ACTIONS

Severity	Occurrence	Detection	RPN	Result	Action
1	1	1	1	Ideal Situation	No Action
1	1	10	10	Assured Mastery	No Action
10	1	1	10	Failure does not reach user	No Action
10	1	10	100	Failure reaches user	Address controls
1	10	1	10	Frequent failures detectable, costly	Process improvement
1	10	10	100	Frequent failures, reaches user	Improve Detection first, then process improvement
10	10	1	100	Frequent failures with major impact	Immediate process Improvement
10	10	10	1000	Big trouble	All hands on deck!!

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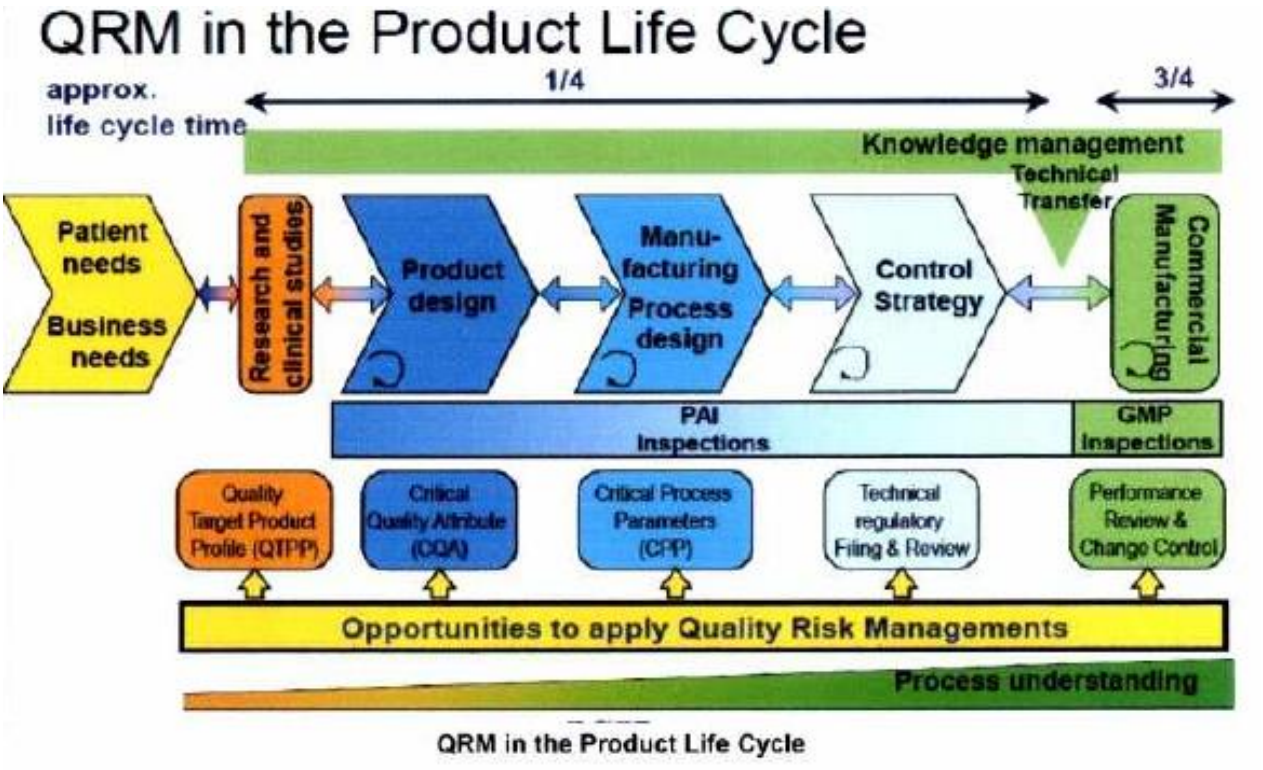
Attachment –IX



QRM in the Product Life Cycle

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Attachment- X

5 WHY ANALYSIS

Reference Document No.:		**Date:**	
Team members name:			

Problem:
Why?
Answer:
Why?
Answer:
Why?
Answer:
Why?
Answer:
Why?
Answer:

Conclusion:

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Post approval:

Functional area	Name	Designation	Signature	Date
PERFORMED BY				
Team Members				
APPROVED BY				
QA Head				
Plant Head				

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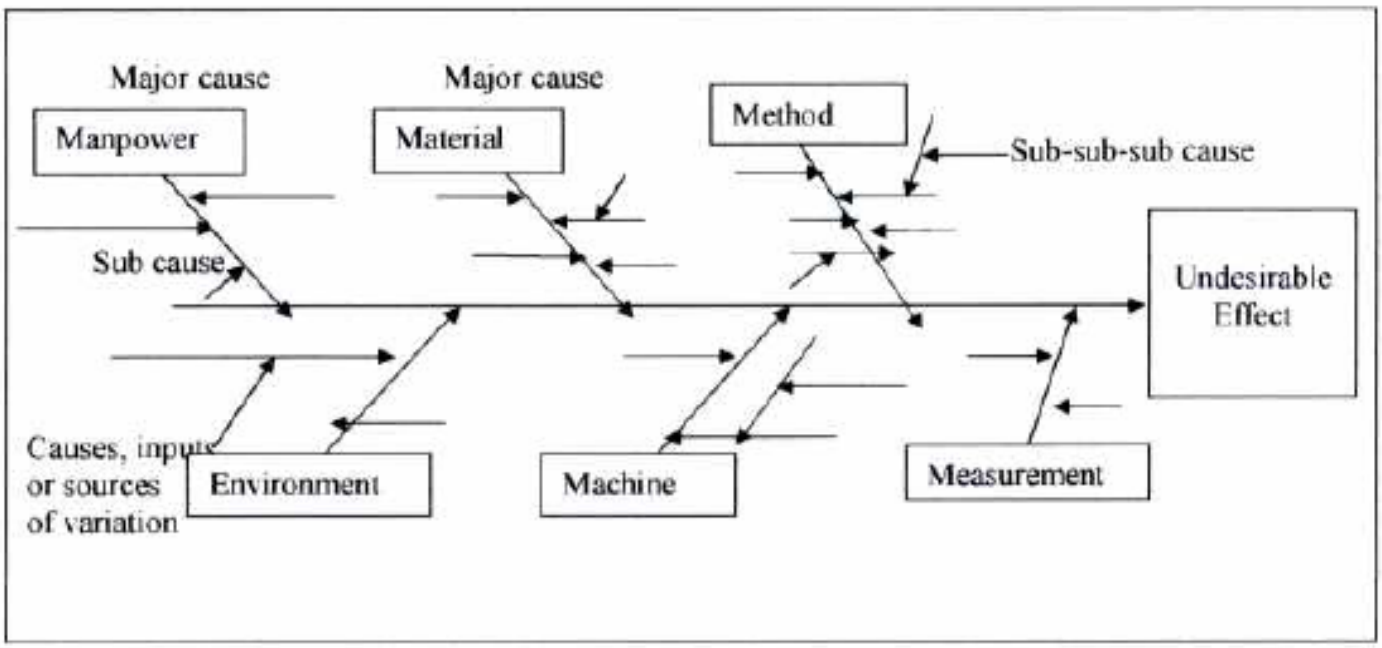
Attachment- XI

ROOT CAUSE ANALYSIS BY FISH BONE DIAGRAM

Reference Document No.:		**Date:**	
Team members name:			



Attachment –XI…….. Continued

Post approval:

Functional area	Name	Designation	Signature	Date
PERFORMED BY				
Team Members				
APPROVED BY				
QA Head				
Plant Head				