PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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

To lay down a Procedure for Quality Risk Management.

2.0 SCOPE:

This SOP is Applicable to Quality Risk Management for all Department.

3.0 RESPONSIBILITY:

QA (Officer/ Executive) : Preparation, Distribution, Revision, Retrieval and Destruction of this SOP.

To maintain Risk Assessment Reports.

To maintain Quality Risk Assessment Record with mitigation plans and actions (if any).

To coordinate with concern Plant specific departments for scheduling and execution of Quality Risk Assessment.

QA (Manager): Review, Training and effective implementation of this SOP to all concerned Departments.

Risk Management Team: To Identify, Analyze and Evaluate the Risks/Hazards.

To prepare the Risk Assessment Reports.

4.0 ACCOUNTABILITY:

Head QA: Approval, Authorization, ensure Training and Implementation of this SOP

To ensure coordination with concern plant specific department for scheduling and execution of Quality Risk Assessment.

Approval of Quality Risk Assessment and Mitigation Plan.

To review and evaluate the Risk Assessment Reports.

5.0 DEFINITION:

5.1 **Detectability:** The ability to discover or determine the existence, presence or fact of a Hazard.

5.2 **Harm:** Damage to Health, including the damage that can occur from loss of Product Quality or Availability.

5.3 **Hazards:** The Potential Source of Harm

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5.4 **Product Lifecycle:** All phases in the life of the product from the initial development through marketing until the product's discontinuation.

5.5 **Risk:** The combination of the Probability of Occurrence of Harm and the Severity of that Harm

5.6 **Risk Assessment:** A Systematic Process of Organizing Information to support a risk decision to make 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.

5.7 **Risk Initiation:** Identifying the risk using suitable technique such as Brain Storming Process.

5.8 **Risk Management:** The Systematic Application of Quality Management Policies, Procedure and Practices to tasks of Assessing, Controlling, Communicating and Reviewing Risks.

5.9 **Quality:** The degree to which a set of inherent properties of a Product, System or Process fulfils requirements.

5.10 **Quality Risk Management:** A Systematic Process for the Assessment, Control, Communication and review of risks to the Quality of the Drug (medicinal) Product across the Product Life Style.

5.11 **Quality System:** The sum of all aspects of a System that implement Quality Policy and ensure that Quality Objectives are met.

5.12 **Risk Analysis:** The estimation of the risk associated with the Identified Hazards.

5.13 **Risk Control:** Actions implementing Risk Management Decisions.

5.14 **Risk Mitigation:** Systematic Reduction in the extent of exposure to a Risk and /or the Likelihood of its occurrence. Also termed as Risk Reduction.

5.15 **Risk Reduction:** Actions taken to lessen the Probability of Occurrence of Harm and Severity of that Harm.

5.16 **Risk Evaluation:** The comparison of the Estimated Risk to given risk to given criteria using a Quantitative or Qualitative scale to determine the significance of the risk.

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

5.18 **Risk Communication:** The sharing of information about Risk Management between the Decision Maker and other Stakeholders.

5.19 **Risk Summary / Conclusion:** It is summary Report of Observations / Mitigation which has high Risk with appropriate actions proposed target date and responsible person to reduce the identified risk.

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5.20 **Risk Review Report:** Review or Monitoring of Output/Results of the Risk Management Process considering (if appropriate) new knowledge and experience about the risk.

5.21 **Severity:** A measure of the possible consequences of a Hazard.

5.22 **High Risk:** The Failure of the System or Process that will have direct impact on Product Quality/ Safety/ Purity/ Efficacy.

5.23 **Medium Risk:** The Failure of the System or Process is expected to have Indirect Impact or Incidental Impact on Product Quality/ Safety/ Purity/ Efficacy.

5.24 **Low Risk:** The Failure of the System does not have an Impact on Product Quality/ Safety/ Purity/ Efficacy.

5.25 **Risk Priority Number:** The Risk priority number or RPN is numeric assessment of risk assigned to a process, or steps in a process, as part of failure modes, effects and criticality Analysis. Each failure Mode gets a numeric score that quantifies likelihood of occurrence, likelihood of detection and severity of impact.

5.26 The product of these three scores is the Risk priority Number (RPN) for that failure mode. Severity rating x Occurrence rating x Detection rating

5.27 **Occurrence:** Probability of negative events in a fixed time frame.

5.28 **Failure Modes:** Failure modes mean the ways, or modes, in which something might fail. Failures are any errors or defects, especially ones that affect the customer, and can be potential or actual.

5.29 **Effects Analysis:** Refers to studying the consequences of those failures.

6.0 PROCEDURE:

6.1 Quality Risk involved in Manufacturing of Pharmaceuticals all Dosage Forms, which affects the Safety, Efficacy, Purity, Strength, Identity and Quality of Product at various stages of Manufacturing like Facility / Area / Equipment / Utility / Quality Management System / Activity / Procedure / Unit Operation / Validation / Qualification / Calibration etc.

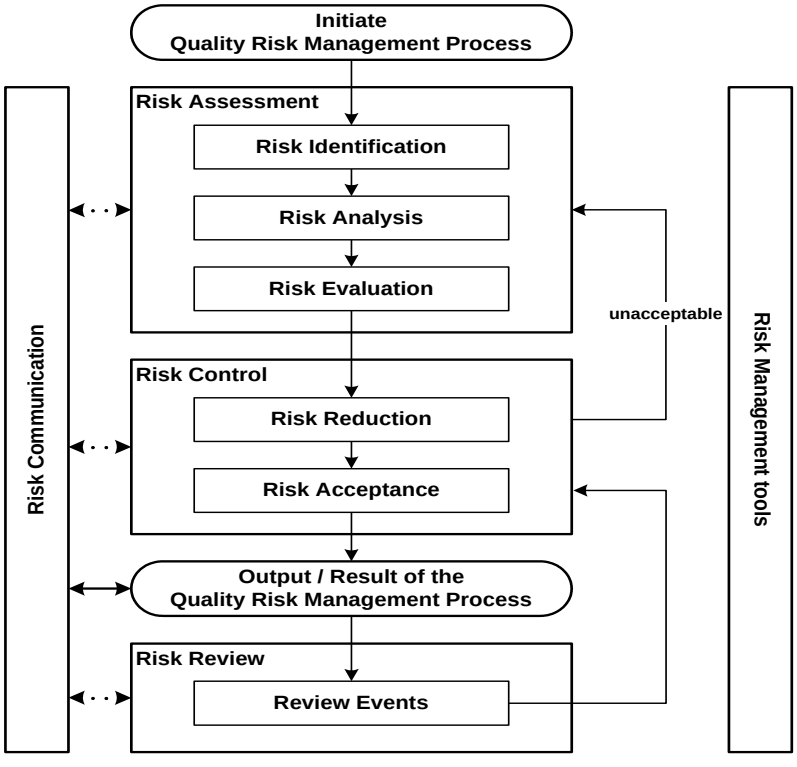
6.2 The evaluation of the risk to quality is based on scientific knowledge and ultimately link to Patient Safety.

6.3 The Level of effort and documentation of the Quality Risk Management Process to be commensurate with Level of Risk.

6.4 Quality Risk Management is a Systematic Process for the Assessment, Control, Communication and review of risks to the Quality of the Drug Product across the Product Lifecycle.

6.5 The emphasis on each component of the framework might differ from case to case but a Robust Process shall be incorporated considering all elements at a level of details that is commensurate with the specific risk.

6.6 An overview of typical Quality Risk Management Process is as given on next page:



"Unacceptable" in the flow charts does not only refer to statutory, legislative or regulatory requirements, but also to the need to revisit the risk assessment process.

Risk Management Process Flow Chart

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6.7 **RISK ASSESSMENT TEAM SELECTION:**

6.7.1 Quality Risk Management Team shall be cross functional Team comprises of expert from different areas such as Quality Assurance, Quality Control, Production, Operations, Warehouse, Engineering, P&A / HR, R&D, Drug Regulatory Affairs etc.

6.7.2 In addition to the above, individuals who are knowledgeable about the Quality Risk Assessment shall also be part of the Team.

6.7.3 Quality Risk Management shall comprise of four members (at least but not limited to) and Head QA or his / her designee shall be the Team Leader.

6.7.4 Quality Risk Management Team members must have at least the following but not limited to:

6.7.5 Educational Qualification: Graduate in Pharmacy, Science, Engineering and other respective Disciplines.

6.7.6 Team Individuals shall be knowledge about the Quality Risk Management Process.

6.7.7 Team Individual shall have a minimum of Five Years' Experience in Pharmaceutical Industry.

6.7.8 Quality Risk Management Team details shall be maintained as per **Annexure-I**, Titled **"Quality Risk Management Team"**.

6.8 **INITIATION / PLANNING OF QUALITY RISK MANAGEMENT PROCESS:**

6.8.1 The scope and study of the initiated Risk Assessment shall be discussed with cross functional team during the planning.

6.8.2 The Risk Management Program shall emphasize more on the risk based approach by considering Safety, Identity, Strength, Purity and Quality.

6.8.3 The Risk to the Product, Personnel and to the Environment shall be taken as order of priority while performing the Risk Assessment.

6.8.4 During Risk Assessment Planning the chances of Mix-ups, Cross Contamination and Containment Methodology shall be evaluated.

6.8.5 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:

6.8.5.1 Clearly identify the process being assessed and what it is attempting to achieve, i.e. what the Harm/Risk is and what the impact could be on the Patient.

6.8.5.2 Assemble background information and/or data on the Potential Hazard, Harm or Human Health Impact relevant to the Risk Assessment;

6.8.5.3 Take full account of current Scientific Knowledge.

6.8.5.4 Use Factual evidence supported by expert assessment to reach conclusions.

6.8.5.5 Do not include any unjustified assumptions.

6.8.5.6 Be conducted by people with experience in the Risk Assessment Process and the process being risk assessed.

6.8.5.7 Identify all reasonably expected risks-simply and clearly along with a Factual Assessment and Mitigation where required.

6.8.5.8 Be documented to an appropriate level and Controlled / Approved.

6.8.5.9 Ultimately be linked to the protection of the Patient.

6.9 QUALITY RISK MANAGEMENT METHODOLOGY:

6.9.1 Quality Risk Management supports a scientific and practical approach to decision making. It provides Documented, Transparent and Reproducible Methods to accomplish steps of Quality Risk Management.

6.9.2 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, Trend and Other Information

6.9.3 Continue the approaches that provide useful information for support of Handling of Complaints, Quality Defects, Deviations and allocation of resources.

6.10 QUALITY RISK MANAGEMENT TOOL:

6.10.1 Basic Risk Management Facilitation Methods:

6.10.1.1 Some of the simple techniques that shall be commonly used to structure Risk Management by organizing data and facilitating decision-making are:

- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

6.10.2 Failure Mode Effects Analysis (FMEA):

6.10.2.1 FMEA provides for an evaluation of Potential Failure Modes for processes and the likely effect on outcomes and / or Product Performance.

6.10.2.2 Once Failure Modes are established, Risk Reduction can be used to Eliminate, Reduce or Control the potential failures.

6.10.2.3 FMEA relies on product and process understanding. FMEA methodically breaks down the Analysis of complex processes into manageable steps.

6.10.2.4 FMEA is a powerful tool for summarizing the important Modes of Failure, Factors causing these failures and the likely effects of these failures.

6.10.2.5 FMEA shall be used to prioritize risks and monitor the effectiveness of risk control activities.

6.10.2.6 FMEA shall be applied to Equipment and Facilities, and might be used to analyze a Manufacturing Operation and its effect on product or process. It identifies Elements / Operations within the system that renders it vulnerable.

6.10.2.7 The output / result of FMEA shall be used as a basis for design or further analysis or to guide Resource Deployment.

6.10.3 **Potential Failure Cause Mechanism:**

6.10.3.1 The cause of a failure mode is a design deficiency or machinery process variation that can be described in terms of something that can be corrected or can be controlled.

6.10.3.2 Identification of causes shall start with those failure modes with the highest severity rating.

6.10.3.3 Review historical test reports, warranty data, concern reports, recalls, field reports, and other applicable documents. Also review surrogate FMEAs. Brainstorm potential cause(s) of each failure mode by asking questions, such as:

What could cause the subsystem to fail in this manner?

What circumstance(s) could cause the subsystem to fail to perform its function?

What can cause the subsystem to fail to deliver it intended function?

6.10.3.4 Identify all first level causes. A first level cause is the immediate cause of the failure mode. It will directly make the failure mode occur. In a Cause and Effect Diagram, it

will be an item on the major fishbone of the diagram. In a Fault Tree Analysis (FTA), it will be the first cause identified below the failure mode.

6.10.4 **Potential Areas of Use(s):**

6.10.4.1 FMEA shall be used to prioritize risks and monitor the effectiveness of risk control activities.

6.10.4.2 FMEA shall be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process.

6.10.4.3 It identifies elements/ operations within the system that render it vulnerable.

6.10.4.4 The output/ results of FMEA shall be used as a basis for design or further analysis or to guide resource deployment.

6.10.5 **Failure Mode, Effects and Criticality Analysis (FMECA):**

6.10.5.1 FMEA shall be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA).

6.10.5.2 In order for such an analysis to be performed, the product or process specifications shall be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

6.10.5.3 **Potential Areas of Use(s):**

6.10.5.3.1 This tool is applicable in the Pharmaceutical Industry shall mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited Quality Risk Management to this application.

6.10.5.3.2 The output of an FMECA is a relative risk “score” for each failure mode, which is used to rank the modes on a relative risk basis.

6.10.6 **Fault Tree Analysis (FTA)**

6.10.6.1 The FTA tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains.

6.10.6.2 The results shall be represented pictorially in the form of a tree of fault modes.

6.10.6.3 At each level in the tree, combinations of fault modes are described with logical operators. FTA relies on the experts' process understanding to identify causal factors.

6.10.6.4 **Potential Areas of Use(s):**

6.10.6.4.1 FTA shall be used to establish the pathway to the root cause of the failure.

6.10.6.4.2 FTA shall be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem).

6.10.6.4.3 Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

6.10.7 **Hazard Analysis and Critical Control Points (HACCP):**

6.10.7.1 HACCP is a Systematic, Proactive, and Preventive Method for assuring Product Quality, Reliability, and Safety.

6.10.7.2 HACCP is a structured approach that applies Technical and Scientific Principles to Analyze, Evaluate, Prevent, and Control the Risk or the Adverse Consequence(s) of Hazard(s) due to the Design, Development, Production, and use of Products.

6.10.7.3 HACCP is most useful when Product and Process understanding is sufficiently comprehensive to support identification of critical control points.

6.10.7.4 The output of a HACCP analysis is a Risk Management Information that facilitates Monitoring of Critical Points not only in the Manufacturing Process but also in other Life Cycle Phases.

6.10.7.5 HACCP consists of the following steps:

Conduct a Hazard Analysis and Identify Preventive Measures for each step of the Process.

Determine the Critical Control Points.

Establish Critical Limits.

Determine the Risk Level on the basis of Severity, Occurrence and Detection.

Establish a System to monitor the Critical Control Points to Reduce Risk to Acceptable Level.

Establish the Corrective Action to be taken when Monitoring indicates that the Critical Control Points are not in a state of Control.

Establish System to verify that HACCP system is working effectively.

Determine the level of Risk after Implementation of Action.

Establish a Record-keeping System.

6.10.7.6 **Potential Areas of Use(s):**

6.10.7.6.1 HACCP shall be used to identify and manage risks associated with physical, chemical and biological hazards including microbiological contamination).

6.10.7.6.2 HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points.

6.10.7.6.3 The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

6.10.8 **Hazard Operability Analysis (HAZOP):**

6.10.8.1 HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions.

6.10.8.2 It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g. No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions.

6.10.8.3 It often uses a team of people with expertise covering the design of the process or product and its application.

6.10.8.4 **Potential Areas of Use(s):**

6.10.8.4.1 HAZOP shall be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products.

6.10.8.4.2 It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards.

6.10.8.4.3 As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

6.10.9 **Preliminary Hazard Analysis (PHA):**

6.10.9.1 PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system.

6.10.9.2 The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result and 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures.

6.10.9.3 **Potential Areas of Use(s)**

6.10.9.3.1 PHA shall be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used.

6.10.9.3.2 It shall be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product.

6.10.9.3.3 PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies.

6.10.9.3.4 Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

6.10.10 **Risk Ranking and Filtering:**

6.10.10.1 Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk.

6.10.10.2 The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk.

6.10.10.3 These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

6.10.10.4 **Potential Areas of Use(s):**

6.10.10.4.1 Risk ranking and filtering shall be used to prioritize manufacturing sites for inspection/audit by regulators or industry.

6.10.10.4.2 Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool.

6.10.10.4.3 Risk ranking shall be useful for management to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

6.10.11 **Supporting Statistical Tools:**

6.10.11.1 Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making.

6.10.11.2 Some principle statistical tools are listed below:

Control Charts, for Example:

Acceptance Control Charts

Control charts with arithmetic average and warning limits

Cumulative sum charts

Shewhart control charts

Weighted moving average

Design of experiments

Histograms

Pareto charts

Process Capability Analysis

6.10.12 Risk Assessment provides for an evaluation of Potential Failure Modes for processes and the likely Effect on outcomes and / or Product Performance.

6.10.13 Once Failure Modes are established, Risk Reduction shall be used to Eliminate, Reduce or Control

the potential failures.

6.10.14 Risk assessment relies on product and process understanding. Risk assessment methodically breaks down the analysis of complex process into manageable steps.

6.10.15 Risk Assessment is a powerful tool for summarizing the important Modes of Failure, Factors Causing these failures and the likely effects of these failures.

6.10.16 Risk Assessment shall be used to prioritize risks and monitor the effectiveness of risk control activities.

6.10.17 Risk Assessment shall be applied to Equipment and Facilities, and be used to assess Manufacturing Operations and its effect on product or process. It identifies Elements / Operations within the System that renders it vulnerable.

6.10.18 The output / result of Risk Assessment shall be used as a basis for design or further analysis or to guide resource deployment.

6.10.19 Following steps to be followed to carry out Risk Assessment by using QRA Tool as shown in **Annexure-V**:

List the Elements/Item/Functions of the System.

List of Potential Failure Modes

Describe the potential effect of the Failure

Determine Failure Severity (S), Occurrence (O) and Detectability (D).

Determine cause(s) of the Failure

Determine risk Level on the basis of S, O, and D.

Check whether the risk is Accepted or not.

Mitigation plan to reduce the Highest Risk upto under acceptance criteria.

6.10.20 When risk is evaluated, a numerical probability shall be used.

6.10.21 Calculate the Risk Priority Number as the multiplication of the risk numbers of

Risk Priority Number = Severity × Occurrence × Detection.

6.10.22 Assessment of Severity, Occurrence and Detection shall be done as given below:

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Severity Ranking:

Severity Effect	Rating
No Effect	1
Minor Effect	2
Moderate Effect	3
Serious Effect	4
Hazardous Effect	5

Likelihood Occurrence Ranking:

Likelihood Occurrence	Rating
Unlikely	1
Very Rare	2
Possible	3
Likely	4
Almost Certain (every time)	5

Detection Ranking:

Likelihood of Detection	Rating
Always Detected	1
Will Detect Failure	2
Might Detect Failure	3
Almost certain not to Detect Failure	4
Lack of Detection Control	5

Note: Pareto Chart with the traditional 20/80% rule to determine which potential cause/mechanism shall be addressed first (as applicable).

1. A Pareto Chart graphically summarizes and displays the relative importance of difference between groups.
2. About 80% of problems are from 20% of the causes.

6.10.23Based on Risk Priority Number (RPN) Risk categorized into three categories as mentioned below:

6.10.23.1 **Acceptance Criteria:**

In case of the calculated RPN rating is greater than 50 those Particular failure are not acceptable.

S.No.	RPN Rating	Category
1.	51 to ≤ 125	High
2.	26 to 50	Medium
3.	Upto25	Low

Rational:

1. ***For RPN rating ≤ 25, No action plan required, however, for the improvement purpose action plan can be proposed for RPN rating ≤ 25, if required.***
2. ***Action plan is required if any of individual Severity and occurrence is high. (Even if RPN is within Acceptance Criteria).***

6.10.23.2 Based on the process criticality and requirements, an acceptable risk priority number shall be fixed to prioritize the risk control measures.

Note: Acceptable level shall depend on control measures parameters and shall be decided on a case-by-case basis.

6.10.23.3 Other appropriate tools, but not limited to like FMEA, FTA, HACCP, HAZOP, PHA, Risk Ranking, supporting statistical tools may be used to arrive at a detailed risk analysis.

6.10.23.4 Risk Level shall be determined on the basis of Severity, Occurrence and Detection Risk Ranking as Low, Medium and High.

6.10.23.5 Risk Level shall be checked whether accepted or not. If accepted, actions shall be recommended to control the risk, where required.

6.10.23.6 After risk analysis process to mitigate the evaluated, team members shall meet to arrive at a formal decision to accept the residual risk.

6.10.23.7 If risk is not accepted, new engineering (e.g. new design) or administrative controls (e.g. New System / Procedures) or process changes with validation through change control shall be

recommended to reduce the risk to the acceptable level.

6.10.23.8 High risk and Medium Risk shall be reduced through mitigation plan and further, Corrective Action and Preventive Action shall be performed as per SOP, Titled **"Corrective Action & Preventive Action (CAPA)"**.

6.10.23.9 Risk Assessment shall be carried out as per format shown in **Annexure-V**.

6.10.23.10 Potential areas of use (s) are following but not limited to:

Material Receipt
Sampling
Analysis
Release
Dispensing
Manufacturing Process
Packing Process
In-process Analysis
Finished Product Analysis
Finished Goods Storage
Dispatch of Finished Product

6.10.24 **RISK ASSESSMENT:**

6.10.24.1 Risk Assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

6.10.24.2 Quality Risk Assessment begins with 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.

6.10.24.3 For clearly defining risk, three fundamental questions are often helpful:

What might go wrong?
What is the likelihood (Probability) it will go wrong?
What are the Consequences (Severity)?

6.10.24.4 **Risk Assessment shall be carried out for (but not limited to):**

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Quality Management System

Facilities, Equipment and Utilities

New Facility, Equipment, Instrument, Utility or Major Modification in Facility Equipment, Instrument and Utility, Transfer of Location.

Production System

For each Manufacturing Process

In-process Sampling and Testing.

6.10.25 **RISK IDENTIFICATION:**

6.10.25.1 Risk shall be identified for working area in his/her respective workplace with the systematic use of information.

6.10.25.2 Risk identification addresses the **"what might go wrong?"** question, including identifying the possible consequences.

6.10.25.3 Risk identification shall be done after elaborate team discussions based on prior knowledge, Historical Data, Theoretical, Literature References and concerns of Stake holders.

6.10.25.4 The Quality Risk Management Team shall discuss and identify the Potential Hazards involved with the points covered in **Point No. 6.6.5.5** by using appropriate tools.

6.10.25.5 Team shall identify the control measures available for each Hazard. For example: in case of Process Flow Charts, Identify Potential Hazard and Control Measures in each step of Flowchart.

6.10.25.6 This provides the basis for further steps in the Quality Risk Management Process.

6.10.26 **RISK ANALYSIS:**

6.10.26.1 Risk Analysis is the estimation of the risk associated with the Identification Hazards.

6.10.26.2 Risk Analysis is the Qualitative or Quantitative Process of Linking the Likelihood of Occurrence and Severity of Harms.

6.10.26.3 Team shall analyze the Risk Linking the Likelihood of Occurrence, Detection and Severity of Harm using Qualitative Descriptor, such as **"High"**, **"Medium"** and **"Low"**.

Relative Risk	Description
High	1. The Failure of the System or Process that will have direct impact on Product Quality/ Safety/ Purity/ Efficacy.. 2. Failure of the System which may result in an inappropriate decision or action related to Product Quality / Safety. 3. There is no other System to check or verify the Product Quality / Safety.
Medium	1. The Failure of the System or Process is expected to have Indirect Impact or Incidental Impact on Product Quality/ Safety/ Purity/ Efficacy. 2. Failure of the System which may result in an inappropriate decision or action related to supporting Process or System that have Direct Impact on Product Quality / Safety.
Low	1. The Failure of the System does not have an Impact on Product Quality/ Safety/ Purity/ Efficacy. 2. Failure of the system may result into changes in Practices, Procedure and SOP Modification etc. with no risk to Product Quality / Safety.

6.10.26.4 Risk shall be Analyzed by setting Occurrence Level based on actual occurrence History of Particular Problem / Failure by referring documents like Deviations, Change Control, Market Complaint, Impact of OOS Result, Review of Reports of Previous Inspection and Follow-up Actions, Review of Report of any samples by Competent Authorities, Risk Record, Environmental Monitoring Records, Sterility Testing Pressure Differentials and Interventions that could potentially impact Batch Quality and Sterility.

6.10.27 **RISK EVALUATIONAND CONTROL:**

6.10.27.1 After Analyzing, the risk shall be evaluated against given Acceptance Criteria/Limits by the Quality Risk Management Team.

6.10.27.2 Risk shall be evaluated by considering the probability of Occurrence, Detectability and

Severity of Harm as per **Annexure-V** covered under Risk Management Tools.

6.10.27.3 Identified Risk pertaining to Product Quality, Quality Management System, Procedures shall be communicated to the relevant Departments including Head Production and Head QA.

6.10.27.4 During Evaluation, Team shall decide the steps to control the risk by considering the following:

- Whether the risk estimated in the Assessment above is in Acceptable Level?
- What can be done to reduce or eliminate the risk?
- What is the appropriate balance among benefits, risk and resources?
- Are new risks introduced due to identified risk being controlled?

6.10.27.5 Effort shall be done to mitigate or avoid the risk by Quality Risk Management Team keeping in mind that the steps taken shall not introduce a new risk.

6.10.27.6 Following points shall be considered during Risk Reduction**:**

- Mitigate the Severity
- Reduce Probability of Harm
- Increase Delectability of Hazards.

6.10.27.7 It is not possible to entirely eliminate the Risk; decision shall be taken to accept the risk assuring to reduce it to acceptable level. This acceptable level shall depend on many parameters and shall be decided on a case to case basis.

6.10.27.8 The Quality Risk Management Team shall identify the Corrective Actions for the identified Failure or Risk, for e.g. in case of Raw Material or Packaging Material does not meet the Compendia Requirement or In- house Specification the Material shall be Rejected.

6.10.27.9 The Quality Risk Management Team shall draw out the conclusion at the end of the Quality Risk Assessment in Relevant as per **Annexure-V**.

6.10.27.10 Risk Assessment Reports as per **Annexure-V** along with supporting documents (if any) shall be forwarded to Head Production. Further same reports shall be forwarded to Head QA for Review and Approval.

6.10.27.11 Once Approved, Quality Risks shall be communicated as per **Annexure-III**, Titled **"Risk Communication"** to the relevant Department Heads to implement the suggested actions to Mitigate/ Avoid Risks. Training shall be given to the Concerned to Mitigate / Avoid Risks.

6.10.27.12 Identified Quality Risks through Risk Assessment shall be logged and tracked as per **Annexure-II**, Titled **"Quality Risk Assessment Log"**.

6.10.27.13 For Supplier / Customers/MAH/ QP / RA shall be communicated for any potential Risk identified during risk assessment.

6.10.27.14 Risk Assessment Report and log shall be maintained by QA.

6.10.28 **RISK REVIEW:**

6.10.28.1Quality Management Process, Risk Management shall be reviewed to take into account new Knowledge and Experience.

6.10.28.2 Once Quality Risk Management Process has been intimated, the process shall be utilized continuously by Quality Risk Management Team, for events that might impact the original Quality Risk Management decision.

6.10.28.3The Quality Risk Management Team shall review and verify for the effectiveness of the Process of Risk Assessment.

6.10.29 **RISK COMMUNICATION:**

6.10.29.1Risk shall be communicated between QRA team and senior management (if required) involved with other functions as per **Annexure-III**.

6.10.30 **INTEGRATION OF QUALITY RISK MANAGEMENT INTO QUALITY SYSTEM:**

6.10.30.1 Quality Risk Management is a process that supports science based and practical decision when integrated in to quality system.

6.10.30.2 Quality Risk Management shall include Systematic Processes designed to coordinate, facilitate and improve Science-based Decision making with respect to risk.

6.10.30.3 Quality Risk Management Process shall be integrated into existing operations and documented appropriately.

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

6.10.30.5 **Documentation**

- To review current documentation
- To determine the desirability of and/or develop the content of SOP, guidelines, etc.

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6.10.30.6 **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 on a periodic assessment of previous training (e.g., its effectiveness).
- To identify the training, experience, qualification and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.

6.10.30.7 **Quality Defects**

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

6.10.30.8 **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 facility
- Robustness of a company'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, Key Personnel
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches)
- Test results of official Control Laboratories

6.10.30.9 **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).

6.10.30.10 **Change Management/Change Control**

- 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 change, e.g., additional testing, requalification, revalidation or communication with regulators.

6.10.30.11 **Continual Improvement**

- To facilitate continual improvement in processes throughout the product life cycle.

6.10.31 **Quality Risk Management as Part of Regulatory Operations:**

6.10.31.1 **Inspection and Assessment Activities**.

- To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity.
- To evaluate the significance of for example, Quality Defects, Potential Recalls and inspectional findings.
- To determine the appropriateness and type of post-inspection regulatory follow-up.
- To evaluate information submitted by industry including pharmaceutical development information.
- To evaluate impact of proposed variations or changes.
- To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT).

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

- To design a quality product and its manufacturing process to consistently deliver the intended performance of the product.

- 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.
- To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials.
- To establish appropriate specifications, identify critical process parameters and establish manufacturing control.
- To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer.
- To make use of the "design space "concept.

6.10.33 **Quality Risk Management as Part of Facilities, Equipment and Utilities:**

6.10.33.1**Design of Facility / Equipment**

- To determine appropriate zones when designing buildings and facilities, (e.g. flow of material and personnel, minimize contamination, pest control measures, prevention of mix-ups, open versus closed equipment, clean rooms versus isolator technologies, dedicated or segregated 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.
- To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts).

6.10.33.2**Hygiene Aspects in Facilities**

- To protect the product 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.

6.10.33.3**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).

6.10.33.4**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.

6.10.33.5**Calibration / Preventive Maintenance**

- To set appropriate calibration and maintenance schedules.

6.10.33.6**Computer Systems and Computer Controlled Equipment**

- To select the design of computer hardware and software (e.g., modular, structured, fault tolerance.
- To determine the extent of validation (e.g., identification of critical performance parameters, selection of requirement and design, code review, the extent of testing and test methods, reliability of electronic records and signatures).

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

6.10.34.1**Assessment and evaluation of suppliers and contract manufacturers**

- To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).
- In case of New / Existing vendor, performance of supplier shall be evaluated for the need of audit/re-audit through Risk Assessment in consideration to Regulatory requirement and criticality of material.

6.10.34.2**Starting Material**

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

6.10.34.3**Use of Materials**

- To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing.
- To determine appropriateness of reprocessing, reworking, use of returned goods.

6.10.34.4**Storage, Logistics and Distribution Conditions**

- To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design).
- To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management).
- To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance).
- To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

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

6.10.35.1**Validation**

- To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods).
- To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation).
- To distinguish between critical and non-critical process steps to facilitate design of a validation study.

6.10.35.2**In-process Sampling & Testing**

- To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control).
- To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

6.10.35.3**Production Planning**

- To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

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

6.10.36.1**Out of Specification Results**

- To identify potential root causes and corrective actions during the investigation of out of specification results.

6.10.36.2**Retest Period / Expiration Date**

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

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

6.10.37.1 **Design of Packages**

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

6.10.37.2 **Selection of container closure system**

- To determine the critical parameters of the container closure system.

6.10.37.3 **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.

6.10.38 **Periodic Risk Review Management:**

6.10.38.1 Risk Management should be an ongoing part of the Quality management process. The Output/results of the risk management process shall be reviewed to take into account new knowledge and experience. Risk review should include reconsideration of risk acceptance decision or new risk reduction measures and to evaluate any possible change in 'risk' after implementation of the previous "Risk reduction measures".

6.10.38.2 Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision. Some cases are mentioned here which can lead to revisiting of Risk assessment.

6.10.38.3 Risk Assessments shall be reviewed for its adequacy whenever there is a change in the Area related to that Activity or any major addition/deletion in Machine / Equipment / Procedure / System / Utility etc. or in case of Introduction of New Product.

6.10.38.4 Risk Assessments shall be reviewed for its adequacy whenever Deviation, Incident, Market Complaints, Recall, OOS etc. observed or as and when required by any customers, regulatory.

6.10.38.5 Quality Risk Assessments review shall be carried out **"Once in two years".**

6.10.38.6 A periodic review frequency of particular Quality Risk Management process can be defined during finalization of the risk assessment.

6.10.38.7 The status of identified risks shall be reviewed after the completion of actions/CAPAs generated from the risk assessment report.

6.10.38.8 Review shall also be performed if actions/CAPAs/change proposal are voided.

6.10.39 **RISK SUMMARY / CONCLUSION:**

6.10.39.1 During the Risk Summary / Conclusion, the Risk Reduction Measures / Actions taken to mitigate the Severity and Probability of Harm shall be reviewed.

6.10.39.2 Once QRA team agreed to Mitigation Measures /actions are completed, the same shall be checked by the Department Head and acknowledge in summary and conclusion report as per format shown in **Annexure-V**.

6.10.40 **NUMBERING SYSTEM OF QUALITY RISK ASSESSMENT:**

6.10.40.1 Risk Assessment Number shall be assigned by the QA and details shall be recorded as per format shown in **Annexure-II.**

6.10.40.2 Quality Risk Assessment Number is consist of an Nine Alphanumerical characters as shown below:

QRA/YY/NNNN

Where,

QRA : Denotes Quality Risk Assessment

/ : separator

YY : denotes Year

NNN : denotes Serial Number start from 001, 002 …..

Example, **QRA/24/001:** Denotes First Quality Risk Assessment Report in year 2024.

6.10.40.3 RiskAssessment shall be performed as per **Annexure-IV**, Titled **"Risk Assessment Flow Chart"**.

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7.0 ABBREVIATION:

EHS	Environment Health & Safety
FMEA	Failure Mode Effect Analysis
FMECA	Failure Mode Effect and Criticality Analysis
FTA	Fault Tree Analysis
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard Operability Analysis
ICH	International Conference on Harmonization
IEC	International Electro technical Commission
ISO	International Organization for Standardization
Ltd.	Limited
No.	Number
OOS	Out of Specification
P&A	Personnel & Administration
Pvt.	Private
QA	Quality Assurance
QRM	Quality Risk Management
R&D	Research & Development
RPN	Risk Priority Number
SOP	Standard Operating Procedure
WHO	World Health Organization

8.0 ANNEXURES:

ANNEXURE No.	ANNEXURE TITLE	FORMAT No.
Annexure-I	Quality Risk Management Team	
Annexure-II	Quality Risk Assessment Log	
Annexure-III	Risk Communication	
Annexure-IV	Risk Assessment Flow Chart	
Annexure-V	Quality Risk Assessment and Mitigation Plan	

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9.0 DISTRIBUTION:

- Master Copy — Quality Assurance Department
- Controlled Copy No. 01 — Head Quality Assurance
- Controlled Copy No. 02 — Head Quality Control
- Controlled Copy No. 03 — Head Production
- Controlled Copy No. 04 — Head Warehouse
- Controlled Copy No. 05 — Head Engineering
- Controlled Copy No. 06 — Head Personnel & Administration and Human Resources
- Controlled Copy No. 07 — Head Information and Technology

10.0 REFERENCES:

- ICH Q9 Quality Risk Management
- WHO Technical Report Series No 908, 2003, Annex 7 Application of Hazard Analysis and Critical Control Point (HACCP) Methodology to Pharmaceuticals.
- AS IEC 61882 Hazard and Operability Analysis (HAZOP Studies) - Application guide.
- Active Pharmaceutical Ingredients Committee (APIC) Supplier Qualification & Management Guideline December 2009.

11.0 REVISION HISTORY:

Revision No.	Change Control No.	Details of Changes	Reason of Changes	Effective Date	Done By
00					

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ANNEXURE-I
Quality Risk Management Team

Year:

S. No.	Name	E. Code	Designation	Department	Qualification	Experience	Remarks

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ANNEXURE-II
Quality Risk Assessment Log

Year:

S. No.	QRA No.	Name of Facility/Area / Equipment /Utility/System / Activity / Procedure / Unit Operation	Dept.	QRA Logged by QA (Sign & Date)	Recommended Action (s) (Yes / No)	CAPA Taken (Yes / No)	Date of Compliance (In case of Recommendation)	Closed By QA (Sign & Date)

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ANNEXURE-III
Risk Communication

Department: **Date:**

Item/ Equipment/Process/Product/System/Facility:

QRA No.:

Scope:

Risk review:

Risk Assessment Conclusion:

Compiled By:	**Reviewed By:**	**Approved By:**
QRA Team	**Head of the Department**	**Head QA**
(Sign & Date)	**(Sign & Date)**	**(Sign & Date)**

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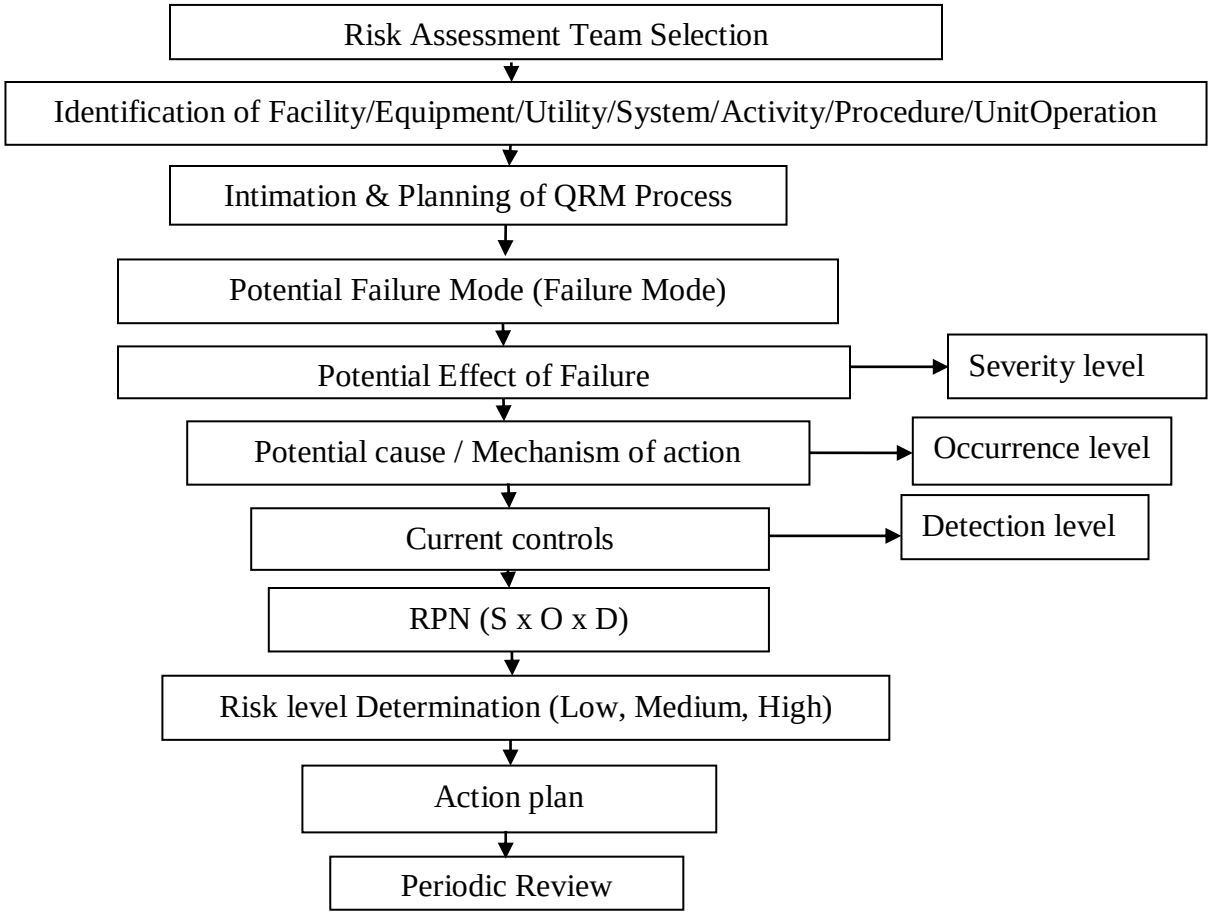
ANNEXURE-IV
Risk Assessment Flow Chart



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ANNEXURE-V
Quality Risk Assessment and Mitigation Plan

QRA No.:

Name of Facility / Equipment / Utility / System/Activity / Procedure / Unit Operation:	Quality Risk Assessment Date:

S. No.	Item / Function	Potential Failure Mode (Failure Mode)	Potential Effect of Failure	Potential Cause/ Mechanism of Failure	Current Control	Reference Document No.	S	O	D	Risk Priority Number (SxOxD)	Recommended Actions (if any)	Post Risk Evaluation			
												S	O	D	RPN SxOxD

Where: S=Severity; O=Occurrence Probability; D=Detection

S.No.	Recommended Action	Responsible Person	Target Date of Completion

CAPA (Required / Not Required):

If required, mention CAPA No.:

Quality Risk Management Team			Reviewed By Concerned Department Head (Sign & Date)	Approved By Head QA (Sign & Date)
Name	Department	Sign & Date		

QUALITY RISK ASSESSEMENT AND MITIGATION SUMMARY REPORT

Name of Facility / Equipment / Utility / System / Activity / Procedure / Unit Operation:	

Verification of Recommended Action:

Remarks (if any):

Verified By
Officer/Executive QA (Sign & Date)

Approved By
Head QA (Sign & Date)