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Research Article for understanding systematic approach to achieve quality standards by Quality Risk Management as per ICH Q9

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Abstract -*To lay down a Standard Operating Procedure to provide systematic approach to achieve quality standards by assessing, controlling, communicating and reviewing risks related to products, equipment's, utilities, facility, QMS (i.e.Change control, deviation, OOS, OOT, Market complaint, Self-inspection QA analytical review etc.), GMP computer systems and environment.*

Key Words:*RISK PRIORITY NUMBER, KEY QUALITY RISK MANAGEMENT, RISK ASSESSMENT, RISK ACCEPTANCE, RISK CONTROL.*

1. INTRODUCTION

QRM approach is applicable to various aspects of the pharmaceutical manufacturing including products life cycle, facilities, equipment's, utilities and pharmaceutical quality system Quality risk management shall be applicable for following (but not limited to);

- ***Integrated quality management***
  - *Documentation*
  - *SOP*
  - *Training and education*
  - *Quality defects*
  - *Complaint*
  - *Trend*
  - *Deviation*
  - *Investigation*
  - *OOS/OOT/OOC result*
  - *CAPA effectiveness failure etc.*
  - *Auditing / Inspection*
  - *Periodic review (e.g. PQR, environment monitoring data)*
  - *Change management / change control*
  - *Continual improvement*
- ***Regulatory operations***
  - *Inspection and assessment activities*
- ***Development***
- ***Facilities, equipment and utilities***
  - *Design of facility / equipment*
  - *Hygiene aspects in facilities*
  - *Qualification of facility/equipment/utilities*
  - *Cleaning of equipment and environmental control*
  - *Contamination*
  - *Cross contamination*
  - *Calibration/preventive maintenance*
  - *Computer systems and computer controlled equipment (hardware and software)*
- ***Materials management***
  - *Assessment and evaluation of suppliers and contract manufacturers*
  - *Starting material*
  - *Use of materials*
  - *Storage, and transport conditions*
- ***Production***
  - *Validation*
  - *In-process sampling and testing*
  - *Production planning*
  - *Manufacturing process*
- ***Laboratory control and stability studies***
  - *Retest period / expiration date*
- ***Packaging and labeling***
  - *Design of packages*
  - *Selection of container closure system*
- *DEFINITION(S)*
  - *Harm: Damage to health, including the damage that can occur from loss of product quality or availability.*
  - *HHazard: The potential source of harm.*
  - *Severity: A measure of the possible consequences of a hazard.*
  - *Occurrence: The likelihood that the cause of the failure will happen, resulting in harm to the patient.*
  - *Detectability: The ability to discover or determine the existence, presence, or fact of a hazard.*
  - *Risk: The combination of the probability of occurrence of harm and the severity of that harm.*
  - *Quality: The degree to which a set of inherent properties of a product, system or process fulfils requirements.*

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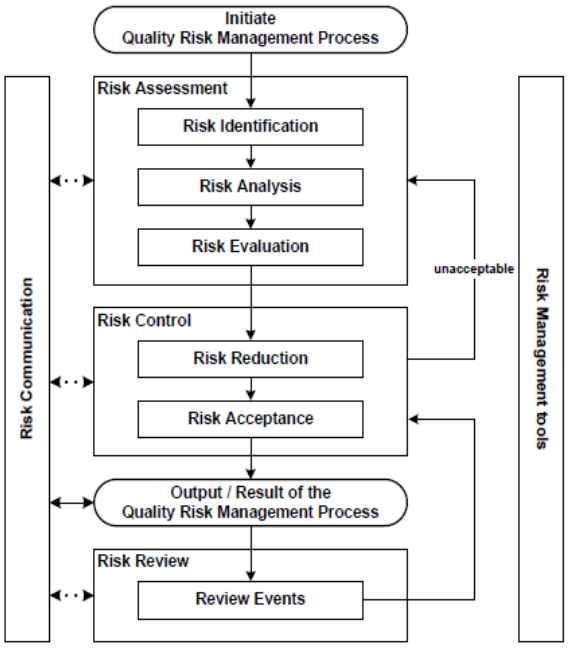
- *Quality Risk Management: A systematic process for the assessment, control, monitoring, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.*
- *Risk Identification: The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description*
- *Risk Analysis: The estimation of the risk associated with the identified hazards.*
- *Risk Evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.*
- *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.*
- *Risk Reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm.*
- *Risk Acceptance: The decision to accept risk.*
- *Risk Control: Actions implementing risk management decisions*
- *Risk Review: Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.*
- *Decision Maker: Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.*
- *Risk communication: The sharing of information about risk and risk management between the decision maker and other stakeholders.*
- *Failure Mode Effects Analysis (FMEA): Failure modes and effects analysis is a step-by-step approach for identifying all possible failures in a design, a manufacturing or assembly process, or a product or service. "Failure mode" means 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. "Effects analysis" refers to studying the consequences of those failures.*
- *Risk Priority Number (RPN): A numeric assessment of risk assigned to a process, or steps in a process, as part of FMEA. Each failure mode gets a numerical score that quantifies the probability of occurrence, probability of detection and severity of impact. The product of these three scores is the RPN for that failure mode. (RPN = severity rating × occurrence rating × detection rating).*
- *Product Life Cycle: All phases in the life of the product from the initial development through marketing until the product's discontinuation.*
- *Vertical Impact Assessment: Impact assessment to evaluate the impact of non-conformity on the same lot/ process/ equipment/ system/ area.*
- *Horizontal Impact Assessment: Impact assessment to evaluate the impact of non-conformity on the other lots of same product or other similar processes/equipment/ system/area to avoid the same non-conformity.*

2. Tools& TECHNIQUES FOR RISK ASSESSMENT

Risk Assessment Team is responsible for the evaluation of critical parameters involved; team shall identify the process, systems, equipment or utility under risk, based on proper justification and risk associated with them.

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.

Quality Risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the product across the product life cycle. Quality risk management process consists of following steps.



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2.1 Riskassessment: *Risk assessment is defined as a systematic approach for identifying, describing, quantifying and evaluation for the risks associated with process, action and events.*

Risk assessment shall be carried out by using following tools

Note: A single tool or set of tools can be used based on the situation in which the quality risk management procedure is used.

2.2 Basic risk management facilitation methods

The simple techniques that are to be used to structure risk management by organizing data and facilitating decision-making are- Flowcharts, Gap Analysis, Process Mapping, Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

2.2.1 Failure Mode Effects Analysis (FMEA).

FMEA provides an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

2.2.2 Failure Mode, Effects and Criticality Analysis (FMECA).

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

2.2.3 Fault Tree Analysis (FTA).

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. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

2.2.4 Hazard Analysis and Critical Control Points (HACCP).

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products. HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. 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.

HACCP consists of the following seven steps:
Conduct a hazard analysis and identify preventive measures for each step of the process.
Determine the critical control points.
Establish critical limits.
Establish a system to monitor the critical control points.
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 the HACCP system is working effectively.
Establish a record-keeping system.

2.2.5 Preliminary Hazard Analysis (PHA)

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. 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.

Risk assessment study may be planned (in case of new product, equipment, GMP computer system, and utilities) or unplanned (in case of deviation, OOS, Change control, product recall etc.)

Risk assessment consists of following steps.

- *Risk identification*
- *Risk analysis*
- *Risk evaluation*

In order to manage the risk assessment in a fair and stable manner, a Risk assessment team is formed by the initiator and verified by QA. This Risk assessment team comprises of members from concerned

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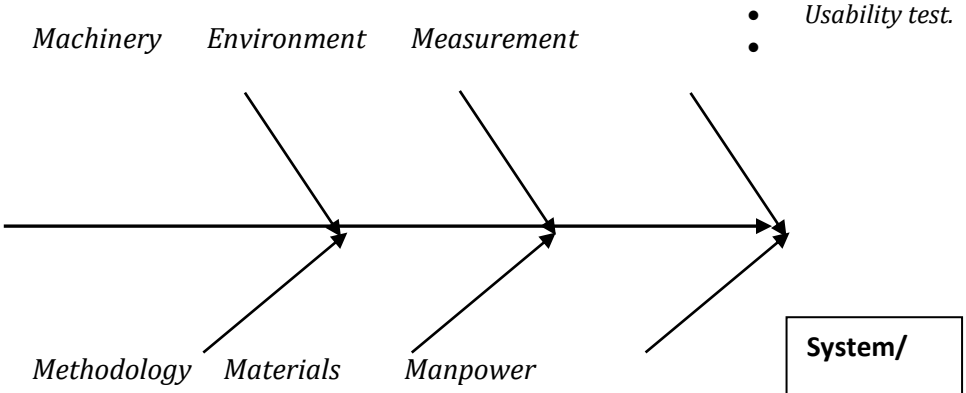
department and influenced by the proposed risk assessment.
Example - Risk assessment team for risk assessment of new equipment of production department shall comprise of members from QA, P&E, and Production department. In the same way Risk assessment team for risk assessment of new product inclusion in facility shall comprise of members from QA, P&E, FR&D, Warehouse, QC, IT and Production department.

2.3 *Risk Identification:* *Risk assessment team identifies risks/Potential failure modes associated with a system/Product through brainstorming, by considering historical failures, and also by considering below mentioned questions.*
What might go wrong? 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.
What is the likelihood (probability) it will 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.

- *What are the consequences (severity)? Compare the identified and analyzed risk against given risk criteria considering the probability, detectability and severity*

Ishikawa fish bone diagram can also be used for identification of different failure modes or point of failure mode associated with a product/system.



Ischikawa Fish BoneDiagram

- *The functions and malfunctions of process/system/equipment etc. are listed down*
- *Determine which functions represent potential "Failure modes" or point of potential failure and record.*
- *Determine the worst potential "Effect" or consequences of each of the failure modes.*
- *Manual error is not considered as failure in risk assessment.*
- *Determine the "Contributory factor" for each failure mode.*
- *Identify any "Control measures" in the process. Controls are components of the process which-*
- *Reduce the likelihood of a contributory factor or a failure mode.*
- *Reduce the severity of an effect.*
- *Detect the occurrence of a failure mode or contributory factor before it leads to the unfavorable result (Effect).*
- *Examples of some measures are – SOP, BMR/BPR, In-process checks, alarm system, etc.*

2.4 *Risk analysis:* *Risk analysis is the estimation of the risk associated with the identified hazards. Risk assessment team ranks the Severity, Occurrence and Detection factors by using the below mentioned scale parameters.*
The approach shall include:

- *The initiating event or circumstance that can lead to the failure.*
- *The context and sequence of events that could lead to failure.*
- *The likelihood of arising such situations.*
- *The nature of potential failure.*
- *Based on the nature of study, additional information / data can also be referred, but not limited to the following:*
- *Published Standards.*
- *Scientific technical data.*
- *Historical data.*
- *Usability test.*
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- *Clinical evidences – Knowledge from literature, product literature, IND/NDA data or any such source.*
- *Outcome of investigations.*
- *Expert opinion.*
- *Supplier's knowledge.*
- *External quality assessment.*
- *Risk Evaluation*

2.5 *Risk evaluation:* *The risk evaluation could be of two categories:*

- *Quantitative Risk management*
- *Qualitative Risk management*

Quantitative Risk Management:

- *Risk evaluation compares the identified and analyzed riskagainst given risk criteria. Risk evaluations consider the strength of evidence for all the three fundamental questions used for risk assessment. Depending on RPN (Risk priority number) values following points have to be considered for risk evaluation:*
- *Failure shall not be accepted if RPN (risk priority number) is not within specified acceptance level.*
- *Depending on the type of failure, corrective and preventive action shall be taken in order to reduce the occurrence to an acceptable level or method of detection should be improved.*
- *If failure is critical, it shall be totally eliminated or brought to the acceptance level.*
- *The "RPN" valuealso determines the criticality of the failure mode and helps determine whether the risk of failure should be accepted or need to be control.*
- *Priority shall be given to items with high-risk priority number (RPN).*
- *Calculate the Risk priority number (RPN = SxPxD) which is multiplication of below three factors.*
- *Severity (S): What will be the effect or impact.*
- *Probability (P): How often you think type of failure could occur*
- *Detection (D): What controls or measures are in place that would increase your chances of detecting this failure.*

Ranking	*PROBABILITY OF OCCURRENCE*
10	*Almost Certain*
7	*Likely (Moderately High)*
4	*Unlikely (Slight)*
1	*Almost never*

Ranking	*DETECTION*
10	*Undetectable(Impossible to detect)*
7	*Slight (Presence of a single system of detection which is not 100% reliable.)*
4	*Moderately High (Single system of detection that is 100% reliable.)*
1	*Almost certain (System of multiple and independent automatic detection tools that is 100% reliable.)*

- *Scoring for S, P and D shall be done on a scale of 10 i.e. 1,4,7,10 [1 is considered as least risk to no risk and 10 as highest risk. The possible score in this range can range from 1 (1 x 1 x 1) to 1000 (10 x 10 x 10)]. If required, the scale can be expanded within 1 – 10.*

Acceptance Criteria (Risk Acceptability Decision):

S. No.	*RPN Rating*	*RPN Category*	*Action Status*
01.	*≥ 76*	*Critical*	*CAPA Required*
02.	*51 to 75*	*Major*	*CAPA Required*
03.	*26 to 50*	*Moderate*	*CAPA Required*
04.	*Up to 25*	*Minor*	*Not applicable*

- *Note: Action plan is also required if any of individual score of Severity, Probability and Detection is high i.e. more than 4 (even if RPN is within acceptance criteria).*
- *Caution should be used when prioritizing risks or areas for remediation on just the RPN number. For example, a process step that has 10 for severity, 10 for occurrence and 1 for detection does not really have the same level of risk as a process step that has 10 for severity, 1 for occurrence and 10 for detection although they both have the same RPN. In such cases appropriate action should be taken to reduce risk as per this policy. The second example provided, puts the patient at a higher risk. Patient safety is always of utmost importance.*

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Qualitative Risk Management:

Probability

Magnitude	***Numerical Value assigned***	***Criterion***
Low	*1*	*Occurrence would be rare*
Medium	*2*	*Occurrence would be possible*
High	*3*	*Occurrence would be almost certain*

Severity

Magnitude	***Numerical Value***	***Criterion***
Low	*1*	• *Highly unlikely that use of product will cause an adverse health consequence.* • *Few minor observations / comments.*
Medium	*2*	• *Use of product may cause temporary or medically reversible adverse health consequences* • *Major observations or regulatory warning letter. Repeated and/or multiple minor observations.*
High	*3*	• *Use of product will cause a serious health consequence.* • *Consent decree, product seizure, regulatory-imposed cessation of operations*

Risk Classification	***Probability***		
Severity	***Low***	***Medium***	***High***
High	*2 (Level 2)*	*3 (Level 3)*	*3 (Level 3)*
Medium	*1 (Level 1)*	*2 (Level 2)*	*3 (Level 3)*
Low	*1 (Level 1)*	*1 (Level 1)*	*2 (Level 2)*

Probability of Detection

Magnitude	***Numerical Value assigned***	***Criterion***
High	*1*	*System of multiple and independent automatic detection tools or a single system of detection that is 100% reliable*
Medium	*2*	*Presence of a single system of detection which is not 100% reliable.*
Low	*3*	*Undetectable*

Criteria for Evaluating System Specific Risks

Risk Priority	***Probability of Detection***		
Risk Classification	***High***	***Medium***	***Low***
3	*Medium Priority*	*High Priority*	*High Priority*
2	*Low Priority*	*Medium Priority*	*High Priority*
1	*Low Priority*	*Low Priority*	*Medium Priority*

Guidance for selection of the Risk Assessment approach:

Type of RA	***Purpose (But not limited to)***
Quantitative Risk assessment	*New product introduction, Process change / modification, Procedure/Document change Equipment/product transfer, Facility/utility modification*

Type of RA	*Purpose (But not limited to)*
	FMECA performed as part of QMS document *Deviation, Investigation, Complaint OOS, OOT and OOC*
Qualitative Risk assessment	*Can be used for above mentioned cases where qualitative assessment only is needed or when any vendor shared the Qualitative risk assessment as a part of Qualification of any equipment and instrument.*

2.6 Risk control: *Risk control includes decision making to reduce and/or accept risks. If the risk analyzed exceeds the risk criteria than risk control measures are required. On the basis of risk evaluation risk assessment team recommends action plan(s) for risk reduction. The effectiveness of these plans has to be reviewed.*

Risk control includes decision making to reduce and/or accept risks. Risk control shall focus on:

- *Is the risk above acceptance level?*
- *What can be done to reduce or eliminate risk?*
- *What is appropriate balance among benefits, risks and patient safety?*
- *Any new risk is being introduces as a result of control of identified risk?*

Risk control shall be continued throughout the lifecycle of process.

2.7 Risk reduction:*Plan quality risk mitigation, avoidance or elimination with a focus on the severity and/or detectability followed by probability of the harm.*

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 patient safety.

The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks.Hence in such case revisit the risk management to identify and evaluate any possible change in risk after implementing a risk reduction process.

Appropriate CAPA (Corrective actions & Preventive actions) must be defined and its effectiveness must be evaluated as part of risk reduction process. Appropriate approach must be selected for pre-mitigation and post-mitigation plan for risk reduction.

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

- *Elimination:Completely eliminate the risk. There may be practical limitation to the extent to which this may be achieved.*
- *Substitution: Replace the high cause of risk with low or no risk alternate.*
- *Reduction: Reduce potential of risk through additional controls, alarms, dedicated/ closed systems.*
- *Administrative Controls: SOP, QMS, spatial arrangement, flow of materials and personnel, segregation, training, behaviors, cultural controls, redundancies.*
- *Personnel Protective Equipment (PPE)*

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

In the event residual risk remains, a determination shall be made to accept this residual risk or following actions shall be considered.

Modify the process to reduce the risk to an acceptable level (This usually involves modifications which will decrease the probability of occurrence).

Enhance the method of detection to increase the likelihood of detecting the issue.

Employ a new process that has an acceptable level of risk.

Communicate the risk level to the management for further consideration.

It shall be demonstrated and documented that the residual risk is suitably managed and controlled to an acceptable level.

2.9 Risk communication: *Risk communication is the sharing of information about risk and risk management, between the members of risk assessment team and concerned departments.*

2.10 Risk review:*Process of continuous review of risk management and its efficiency is called as risk review. The review performed in the below mentioned cases, may either prove the risk management is correct or need further improvement.*

- *Review of initial risk management may be initiated in following instances (but not limited to):*
- *As a part of failure investigation like Complaint/Deviation/OOS/OOT/OOC/ CAPA effectiveness failure etc.*
- *When new risks are identified as a result of increased process knowledge.*

- *As a change control measure that is part of change control program.*
- *Upon implementation of process changes.*

3. CONCLUSIONS

- *Risk Assessment Team concludes all the activities of risk assessment and prepares the risk assessment reporIf different approach is to be applied; then the risk assessment shall be done through the approved protocol. Trending of the risks will be done annually based on the source and categorization that is critical, major, moderate and minor.*

4.0 ABBREVIATIONS

The abbreviations used are:

- *No. / NO. / no.- Number*
- *QA & RA- Quality assurance and Regulatory affairs*
- *Sr. No.- Serial number*
- *SOP-Standard operating procedure*
- *NA- Not applicable*
- *F R & D- Formulations research and development*
- *i.e.- That is*
- *Sr. No.- Serial number*
- *QC- Quality control*
- *P & E- Projects and engineering*
- *CAPA - Corrective Action and preventive action*
- *QMS - Quality management system*
- *RPN - Risk priority number*
- *FMECA - Failure mode, effects and criticality analysis*
- *OOS -Out Of Specification*
- *GMP - Good Manufacturing Practice*
- *BMR - Batch Manufacturing Record*
- *BPR - Batch Packing Record*
- *RPN - Risk Priority Number*
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4.0REFERENCES

[1] *ICH Q9. Guidance on Quality Risk Assessment*