| | ACCENT PHARMACEUTICALS & DIAGNOSTICS<br>FOREST ROAD SOLAN H.P(INDIA)<br>CORPORATE QUALITY ASSURANCE<br>BATCH PACKING RECORD | |
|---|---|---|

| | | | |
|---|---|---|---|
| **PRODUCT NAME** | **CHANGE CONTROL** | | |
| **BPR No.** | **APD/QAD/CCC** | **REVISION NO.** | **NA** |
| **BPR SUPERSEDES NO.** | **NA** | **EFFECTIVE DATE** | **15/06/2024** |
| **BATCH NO.** | **S** | **BATCH SIZE** | **S** |



## 1.0 OBJECTIVE:

To provide a procedure for Risk Management by Failure Mode, Effects and Criticality Analysis.

## 2.0 SCOPE:

Applicable to different aspects of pharmaceutical quality like development, manufacturing, testing, distribution, inspection and submission/review processes throughout the life cycle of drug substance, drug products including equipment, facilities, system, raw material, solvents, packaging, labeling and manufacturing operations which are likely to affect the product or process and any other activity which is directly or indirectly affecting product quality of Accent Pharmaceuticals & Diagnostics, forest road, Solan Himachal Pradesh (India).

## 3.0 RESPONSIBILITY:

| Designation | Responsibilities |
|---|---|
| Head – QA / Designee | ➢ Responsible for coordinating quality risk management across various functions and departments of the organization.<br>➢ Formation of FMEA team and team leader.<br>➢ Responsible to review, evaluate, advice and approve FMEA and corrective action and preventive action generated by FMEA team. |
| FMEA Team | ➢ Identifying all potential failures with respect to equipment, facilities, manufacturing process, packing, system and personnel including pertinent assumption identifying the potential for risk.<br>➢ Preparation of action plan in case of higher RPN and risk communication to Unit QA head and Unit head.<br>➢ Assessing the adequacy of existing control measures.<br>➢ Specify timelines, deliverables and appropriate level of decision making for the risk management process. |

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| Designation | Responsibilities |
|---|---|
| | ➢ Specify timelines, deliverables and appropriate level of decision making for the risk management process<br>➢ Performing periodic risk assessment. |

**4.0 ACCOUNTABILITY:**

Head QA

**5.0 PROCEDURE:**

**5.1 Definitions**

**5.1.1 Failure Mode:** Different ways that a process or sub-process can fail to provide the anticipated result.

**5.1.2 Failure mode, effects and critically analysis (FMEA):** A systematic method of identifying and preventing product and process problems.

**5.1.3 Harm:** Damage to health, including the damage that can occur from loss of product quality or availability.



**5.1.4 Hazard:** The potential source of harm

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

**5.1.6 Risk:** Combination of the probability of occurrence of harm and severity of that harm.

**5.1.7 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 evaluate on of risk associated with exposure to those hazards

**5.1.8 Risk control:** Actions implementing risk and risk management between the decision maker and other stakeholders.

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

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

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

**5.1.12 Quality risk management:** A systematic use of information to identity potential sources of harm (hazards) referring to the risk question or problem description.

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

**5.1.14 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.

**5.1.15 Risk Priority Number (RPN):** The risk priority number, or RPN, is a numeric assessment of risk assigned to a process, or steps in a process, as part of failure mode, effects and criticality analysis (FMEA). Each failure mode gets a numeric score that quantifies likelihood of occurrence, likelihood and detection and severity of impact. The product of these three scores is the Risk Priority Number (RPN) for that failure mode. RPN: severity rating x occurrence rating x detection rating.



**5.1.16 Severity:** Measure of the possible consequences of the hazard.

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

**5.2 Health, Safety and Environment:** Issues pertaining to Health, Safety and Environment should be given due consideration while carrying out risk assessment.

**5.3 Procedure:**

**5.3.1** Risk to product quality, patient safety and company reputation should be controlled through the implementation of robust quality management system and good manufacturing practices. These should include management controls, validation, internal audits and risk assessment.

**5.3.2** Two primary principles of Quality Risk Management are:

**5.3.2.1** The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and

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**5.3.2.2** The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

**5.3.2** Quality risk management is a systematic process for the assessment, control communication and review of risks to the quality of the drug products across the product lifecycle. It can be applied both proactively and retrospectively.

**5.3.3** The scope of quality risk management is limitless, following are a few examples which include but are not limited to

**5.3.3.1** Equipment and facility design.

**5.3.3.2** Equipment and facility qualification.

**5.3.3.3** Change management.

**5.3.3.4** Deviations

**5.3.3.5** Validations/revalidations etc.

**5.3.3.6** Change control

**5.3.3.7** Market complaint

**5.3.3.8** Product recall

**5.3.3.9** Failure investigation



**5.3.3.10** During analysis the following points should be considered wherever possible:

**5.3.3.10.1** Potential hazards in relation to materials and ingredients

**5.3.3.10.2** Physical characteristics and composition of the product

**5.3.3.10.3** Processing procedures

**5.3.3.10.4** Microbial limits, where ever applicable

**5.3.3.10.5** Premises

**5.3.3.10.6** Equipments

**5.3.3.10.7** Packaging

**5.3.3.10.8** Sanitation and hygiene

**5.3.3.10.9** Personnel

**5.3.3.10.10** Risk of explosions

**5.3.3.10.11** Mix – ups

**5.3.3.10.12** Storage conditions of raw materials

**5.3.3.10.13** Material safety data sheet. (MSDS)

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**5.3.3.10.14** Storage conditions of in process material

**5.4 Failure mode, effects and criticality analysis:**

**5.4.1** FMEA methodically breaks down the analysis of complex process into manageable steps. The FMEA is a formalized, systematic and analytical approach to failure, prevention. It can identify places where additional preventive actions might be appropriate to minimize risk.

**5.4.2** The aim of FMEA is:-

**5.4.2.1** To create an awareness of potential failures.

**5.4.2.2** Establish a baseline for process knowledge and process effects.

**5.4.2.3** Identify, analyse and ultimately prevent potential failures as well as their effects and causes.

**5.4.2.4** Define measures aimed at preventing and identifying (i.e. investigating) potential Causes of failure and to monitor and demonstrate the effectiveness of such measures.



**5.4.2.5** Application of FMEA methodology helps quality controlling by specifying test parameters for any remaining risks to the product or process. FMEA is suitable for developing knowledge databases and therefore, helps in preventing recurring failures.

**5.4.3** In conducting FMEA, the basic steps are:

**5.4.3.1** Identify the process to be examined.

**5.4.3.2** Justification should be provided for selecting the item / equipment/ process/ Product/ system / facility for FMEA as per Annexure.

**5.4.3.3** From FMEA team and assign team leader, The Team should essentially include QA representative and other members from Production, Engineering, QC, Stores as applicable based on the topic under consideration. They should be experienced, acquainted with the subject and have adequate training on risk assessment.

**5.4.3.4** Explain the methodology to the team.

**5.4.3.5** Prepare a flow chart or detailed process flow of the process under analysis. All Steps in the process should be included.

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**5.4.3.6** FMEA number should be issued by Quality Assurance as follows:
FMEA/XX/SUBJECT/YYY/RR
Where
FMEA- Failure mode, effects and criticality analysis.
XX- Last two digits of the year in which FMEA is conducted
SUBJECT- Name of item/ Equipment/Process/Product/System/Facility
YYY- Serial Number Starting from 001
RR- Version number starting from 01

**5.4.3.7** Log of FMEA should be maintained as per respective Annexure with quality Assurance.

**5.4.3.8** List down the functions and malfunctions of product/process/system/item.

**5.4.3.9** Designate which of the steps in the process constitute "Functions" and identify elements of variation in equipment, methods, materials, control and measurement.

**5.4.3.10** Determine which functions represent potential "Failure Modes" or points of potential failure. Determine the worst potential "Effect" or consequences of each of the failure modes.



**5.4.3.11** Determine the contributory Factors" for each failure mode.

**5.4.3.12** Identify any "controls'' in the process. Controls are components of the process which
(a) reduce the likelihood of a contributory factor or a failure mode,
(b) reduce the severity of an effect, or
(c) detect the occurrence of a Failure Mode or.
Contributory Factor before it leads to the adverse outcome (effect)

| Rank | Likely hood of occurrence | Description |
|---|---|---|
| 1 | Remote | Failure is unlikely |
| 2 | Low | Relatively few failures |

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| | | |
|---|---|---|
| 3 | | |
| 4 | Moderate | Occasional failure. |
| 5 | | |
| 6 | | |
| 7 | High | Repeated failures |
| 8 | | |
| 9 | Very high | Failure is almost certain. |
| 10 | | |

**5.4.3.15 Assessment of detection:**

| Rank | Detectability | Description |
|---|---|---|
| 1 | Very high | Will be detected prior to releasing of the batch or by control available at place. |
| 2 | | |
| 3 | High | Very likely can be detected prior to final release. |
| 4 | | |
| 5 | Moderate | May detect prior to final release. |
| 6 | | |
| 7 | Low | The control may not detect a potential problem. |
| 8 | | |
| 9 | Very low | Undetectable until failure occurs in the field. |
| 10 | | |



**5.4.3.16** The probability of detection is assessed by giving the ranking number. 1 to 10 ranking represents the decreasing detectability. (Very high to very low). While giving the ranking in the scale the following grading should be considered as a guideline.

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Examples of control measures are: Standard Operating Procedures, BMR, BPR, Validation, In-process controls, alarm systems and training programs.

**5.4.3.13 Assessment of severity :**

Severity is assessed by giving the ranking number. 1 to 10 ranking represents increasing severity (Minor to very high). While giving the ranking in the scale the following grading should be considered as a guideline.

| Rank | severity | Description |
|---|---|---|
| | | |
| 1 | Minor | Unreasonable to expect that the minor nature of this failure would cause any real effect on the product quality, GMP non compliance and patient safety. |
| 2 | Low | Nature of the failure might cause only slight issue in the product quality or patient safety. |
| 3 | | |
| 4 | Moderate | Failure causes customer dissatisfaction. Customer is made uncomfortable or is annoyed by the failure. |
| 5 | | |
| 6 | | |
| 7 | High | High degree of customer dissatisfaction due to the nature of failure. Could cause product non compliance or patient's safety. |
| 8 | | |
| 9 | Very high | The failure affects patient's safety and non compliance with Government regulation. |
| 10 | | |



**5.4.3.14 Assessment of likely hood of occurrence/ Probability:** Likely hood of occurrence is assessed by giving the ranking number. 1 to 10 ranking represents increasing probability (Remote to Very high). While giving the ranking in the scale the following grading should be considered as a guideline.

**5.4.3.17Note:**

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- Prepare scale table for each FMEA study individually for severity occurrence and detection.
- Available control measures in the process of risk assessment should be challenged by FMEA team prior to determining the likelihood of occurrence.
- Historical data like maintenance record, complaints, deviations and other applicable records should be reviewed for assigning risk rating i.e. severity, occurrence and detection of individual potential failure mode.

**5.4.3.18 Risk categories**

Based on the analysis risk assessments are divided into three categories

- High risk
- Medium risk
- Low risk

➢ **High risk**: This is associated with equipment that comes in direct contact with product and its failure leads to product failure.



➢ **Medium risk**: This is associated with equipment that may have a direct impact on product quality and its failure may lead to product failure.

➢ **Low risk:** This is associated with equipment that may have some impact on a products quality attributes, but may not lead to product failure or may not lead to product loss. Assess risk likelihood and severity of the impact and its detection

**5.4.3.19** The RPN determines the criticality of the failure mode and helps to determine whether the risk of failure should be accepted (No action may be required for the potential failure), controlled (take action to enhance detection or reduce the risk of the potential failure) or eliminated (prevent the potential failure).

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**5.4.3.20** FMEA should be used to analyze the current process and evaluate the potential impact of change under consideration. For example: New equipment/process, major modification, Calculate the estimated RPN each time you consider a change to the process, to evaluate the impact of the change. If RPN is high, then priority should be given to such items and based on the current control measures. Priority should also be given to items with high severity rate.

**5.4.3.14** **Risk priority number (RPN) :** overall risk of the process step is evaluated by combining individual risk values that is by multiplying severity, probability and detectability. The multiplication gives risk priority number.

**5.4.3.15** Based on a mid score 5 for each of the above parameters, the acceptable risk limit given as 125 (5x5x5).

**5.4.3.16** Any Failure Mode with a RPN in excess of 125 is considered unacceptable and should be avoided or mitigated.



**5.4.3.17** As a safer practice, risk mitigation action is taken for any RPN values in excess of 90 in this exercise.

**5.4.3.18** Depending on RPN rating, following decision should be made.

**5.4.3.19** Depending on the type of failure, appropriate action plan should be implemented to control reduce the occurrence to an acceptable level, if not, detection system should be improved.

**5.4.3.20** **Note :**

- For RPN rating ≤ 25, no action plan is required. However, for the improvement. Purpose, action plan can be proposed for RPN rating ≤25, if required.
- Action plan is required if any of individual Severity and occurrence is high (even if RPN is within Acceptance criteria.)
- Considering acceptance criteria, detailed action plans should be drawn with responsibility and target completion date. The effectiveness of these action