RISK ASSESSMENT
& MITIGATION
FOR
CEFIXIME TRIHYDRATE

Location: …….
Product: Cefixime Trihydrate

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QUALITY ASSURANCE DEPARTMENT

Risk Assessment and Mitigation

for the manufacturing process of Cefixime Trihydrate product

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1.0 Report Approval

This is a specific report for Risk assessment for the manufacturing process of Cefixime Trihydrate in Block.

Prepared By:

Name	Designation	Department	Signature	Date

Checked By:

Name	Designation	Department	Signature	Date

Approved By:

Name	Designation	Department	Signature	Date

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2.0 Overview

2.1 Objective:

The Objective of this report is to describe in detail about the decision taken by adopting a systematic process for the assessment, control, communication and review of risk associated with manufacturing process of Cefixime Trihydrate in ……

2.2 Purpose and Scope

The purpose of this report is to outline a scientific and practical approach for decision making process by applying a suitable tool of risk assessment covering all aspects of risk associated with manufacturing process of Cefixime Trihydrate in ……...

2.3 Risk Assessment Team

- Quality Assurance Executive/Officer/Manager
- Production Executive/Officer/Manager

2.4 Responsibility

S.No.	Department	Designation	Responsibility
1.	Production	Executive/Officer/ Manager	Facilitate to Identify, analyse and evaluate the risk Execute the risk mitigation exercise Compile the supporting data
2.	Quality Assurance	Executive/Officer/ Manager	Review & approval of Risk Assessment document. Identify, analyse and evaluate the risk Review the supporting documents.

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3.0 Introduction

Risk analysis for the manufacturing process of Cefixime Trihydrate, shall be done by considering the below mentioned factors

- The Risk Impact on the Process
- The Risk impact on the Product Quality
- The Risk impact on the environment
- The Risk impact on the person
- The Risk impact on the regulatory compliance

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4.0 Quality Risk Management Process

Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. Its consists Identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards

Quality risk assessment begins with a well defined problem description or risk question.

For risk assessment process three fundamental questions are considered

— What might go wrong?

— What is likely hood **(Occurrence)** it will go wrong?

— What are the consequences **(Severity)?**

- **Risk Identification**

  Risk Identification is systematic use of information to identify hazards referring to risk questions or problem description. Information may include historical data theoretical analysis, informed opinions and concerns of stakeholders. risk Identification will be conducted by reviewing the types of events that might occur in both normal and unusual situations. This may be done by challenging the normal presumptions, and considering the possibilities of unanticipated situations. For each risk event, the underlying (root) cause should be determined that will create the potential risk occurrence.

  Risk Identification addresses the “what might go wrong” question including identifying the possible consequences. This provides the basis for the further steps in quality risk management process.

- **Risk Analysis**

  Risk analysis is the estimation of risk associated with the identified hazards.

  It is the quantitative or qualitative process of linking the likelihood of occurrence and severity of harm and sometime the detectability of harm is also consider during estimation of risk.

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- **Risk Evaluation**

  Risk Evaluation compares the identified and analyzed risk against the given risk criteria. Risk evaluation considers the strength of evidence for all three of fundamental questions.

  Risks are ranked by scoring various criteria with appropriate numerical ratings, adding to scores to determine the overall score of each risk, and sorting the risks into descending order based on each score. A risk scoring threshold is established, over which risks must be mitigated using adequate design and/ or process controls that will protect the system. Those risks that fall below the threshold are either unmitigated or scheduled for later mitigation. An additional threshold or characteristic of risk can be used to determine the differentiation of non- mitigation versus postponed mitigation.

- **Risk Control**

  Risk control includes decision making to reduce or mitigate risk. The purpose of risk control is to reduce the risk to the acceptance level

  The risk control is done by considering the following question

  — Is the risk above an acceptable level?

  — What can be done to reduce or eliminate risk?

  — What is appropriate balance among benefits, risks and resources?

  — Are new risk is introduced as a result identified risk being controlled?

- **Risk Reduction**

  Risk reduction focuses on processes the mitigation or avoidance of quality risk when it exceeds the acceptable level. Risk reduction includes action taken to mitigate the severity, occurrence or probability of harm and the processes that improve the detectability of harm. It is the part of risk control strategy and involves

  — Engineering Control

  — Procedural Control

  — Manual control etc.

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5.0 Risk Assessment for the manufacturing process of cefixime Trihydrate

5.1 Risk Assessment Legend

A. Severity

Ranking	Effect	Criteria
10	Hazardous	Hazardous effect without warning. Safety related. Regulatory non-compliant.
9	Serious	Potential hazardous effect. Able to stop without mishap. Regulatory compliance in jeopardy.
8	Extreme	Item inoperable but safe. Customer very dissatisfied.
7	Major	Performance severely affected but functional and safe. Customer dissatisfied.
6	Significant	Performance degraded but operable and safe. Non-vital part inoperable. Customer experiences discomfort.
5	Moderate	Performance moderately affected. Fault on non-vital part requires repair. Customer experiences some dissatisfaction.
4	Minor	Minor effect on performance. Fault does not require repair. Non-vital fault always noticed. Customer experiences minor nuisance.
3	Slight	Slight effect on performance. Non-vital fault notice most of the time. Customer is slightly annoyed.
2	Very Slight	Very slight effect on performance. Non-vital fault may be noticed. Customer is not annoyed.
1	None	No effect.

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B. Probability or Occurrence

Ranking	Possible Failure	Probability of Failure
10	≥ 1 in 2	Almost certain.
9	1 in 3	Very high.
8	1 in 8	High.
7	1 in 20	Moderately high.
6	1 in 80	Medium
5	1 in 400	Low
4	1 in 2,000	Slight
3	1 in 15,000	Very slight.
2	1 in 150,000	Remote.
1	1 in 1,500,000	Almost impossible.

C. Detection

Ranking	Detection	Likelihood of Detection by design control
10	Absolute Uncertainty	No design control or design control will not detect potential cause.
9	Very Remote	Very remote chance design control will detect potential cause.
8	Remote	Remote chance design control will detect potential cause.
7	Very Low	Very low chance design control will detect potential cause.
6	Low	Low chance design control will detect potential cause.
5	Moderate	Moderate chance design control will detect potential cause.
4	Moderately High	Moderately high chance design control will detect potential cause.
3	High	High chance design control will detect potential cause.
2	Very High	Very high chance design control will detect potential
1	Almost Certain	Almost certain that the design control will detect potential cause.

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5.2 Risk Assessment Tool– Failure Mode effect Analysis (FMEA)

5.2.1 Risk Identification

S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
1.	Cleaning process	Non availability of approved cleaning procedure for equipments In appropriate cleaning procedure	All the mentioned potential causes for the failure of cleaning process will result in poor performance of cleaning Which ultimately leads to product contamination due to residue carryover in the next product	The non availability or inappropriate cleaning procedure for the equipments can leads to confusion among the persons responsible for cleaning the equipment So its mandatory to establish a cleaning procedure for the equipments used for Cefixime manufacturing.

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
2.	Manufacturing Operation	Operators may not be trained for the approved cleaning procedure	All the mentioned potential causes for the failure of Manufacturing operation will result in poor performance of product.	The established and well lay down approved manufacturing procedure will not give anticipated results unless and until the operators /Chemists are not trained properly for its execution to reduce mistakes and errors
		Unit operation of the equipments is not feasible as mentioned in the defined procedure.	Which ultimately leads to product quality and yield issue.	Unit operation as defined in the SOP for the Equipments operation must be followed.
		PPE,s and other provisions required to perform the manufacturing operations are not provided.	Any incident/accident may be happen any time.	Using of the PPEs as per the requirement for safety and effectiveness should be incorporated BPRs.
		Lack of awareness for the MSDS of raw materials using for manufacturing of Cefixime.	All the mentioned potential causes for the failure of Manufacturing operation will result in poor performance of product in terms of yield and quality.	MSDS must be available & training of concern persons helps to reduce any unwanted accidents, deviations while executing the unit operations.
		Precautionary measures are not defined which are required as 1. In process control 2. Critical operation 3. Supervision		All precautionary measures should be defined in BPR & to be followed strictly for the manufacturing of Cefixime.

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
3.	Manufacturing Process	Manufacturing process is not well defined & supported by R&D. GMP is not followed. SOPs are not available. Commercial production is started without process validation.	Product quality, Stability & yield consistency may vary batch to batch.	Manufacturing process first developed in R&D by performing several experiments. After successful R&D trial, process must be transferred in plant by written documents. Before starting commercial production, SOP's for critical operations must be available and Process validation activity should performed.
4.	Material Handling & storage	Raw materials as well as Product handling & storage requirements are not fulfilled.	Product quality will not stable as desired	All raw materials, intermediates and finished goods must be stored as per the requirement. Handling of raw material /finished good must be followed as per the lay down procedures. Temperature sensitive raw material must be stored in cold room at 2-8 deg.
5.	Equipments & facility	Adequate and Qualified equipment's are not available for the different stages of Cefixime. Facility is also not available as per the requirement.	Consistent Product quality and yield will not be achieved.	Before commercial activity Equipments must be qualified as Design Qualification and Install qualification. SOPs must be available for operation of Equipments, as Reactor, Sparkler filter, Centrifuge. Dryer, Sifter Micronizer.

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
6.	Utility	Utility is not adequate to achieve desired temperature for performing unit operation.	Product quality and yield consistency will not be achieved, resulting in unplanned deviations in the process.	To maintain time and temperature required as per the process, it is necessary to have utility of desired capacity.
7.	HVAC System	HVAC system not available for critical stages / processing	Failure of HVAC system will lead to the rise in temp & differential pressure of particular area resulting degradation of product and possibility of cross contamination.	HVAC system must required for product quality and stability. It should be available in Finished product operations as in Crystallization, Centrifuging, Dying and Powder processing area.
8.	Water system	Water system is not meeting the specification	Quality of product will not maintain as per the specification	Water quality used for the manufacturing of API must be as per the FDA guidelines & system also should be qualified.
9.	Documentations	All the critical steps are not defined in the BPR. The in process limits is not defined appropriately in the BPR. BPRs are not approved before the actual execution	All the mentioned potential causes will not give rise to good documentation practices Which is results in Regulatory non compliance Customers dis satisfactions.	The principals of Good documentation practices not only helps to govern an effective quality management system but also reduce the various observations during the regulatory and customer services by eradicating ambiguity. Providing clear and correct instructions Proper flow of process, procedures in a well setup of organizational structure

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5.2.2 Risk Analysis

S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	Existing Design Control	Severity	Probability	Detection	Risk Priority Number
				(S)	(P)	(D)	RPN=S x P x D
	Risk Analysis						Risk valuation
1.	Cleaning process	Non availability of approved cleaning procedure for equipments Inappropriate cleaning procedure	Approved and appropriate procedure. Applicability is ensured as cleaning procedure is same for regulatory and domestic process.	7	3	3	=7×3×3=63

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	Existing Design Control	Severity	Probability	Detection	Risk Priority Number
				(S)	(P)	(D)	RPN=S x P x D
	Risk Analysis						**Risk evaluation**
2.	Manufacturing Operation	Operators may not be trained for the approved cleaning procedure Unit operation of the equipments is not feasible as mentioned in the defined procedure. PPE,s and other provisions required to perform the manufacturing operations are not provided. Lack of awareness for the MSDS of raw materials using for manufacturing of Cefixime. Precautionary measures are not defined which are required as In process control Critical operation Supervision	All operators are trained for Batch operations as per written procedure. Equipments are dedicated for all unit operations as per requirement. PPE's and other provisions required to perform the cleaning operations are provided. Nose mask, hand gloves safety goggles etc. MSDS are available for all raw materials. BPR incorporated all precautionary steps to be followed during batch operations. BPR specified all critical operation, in process control. All operation and critical parameters supervision is performed by Shift in charge.	9	3	3	=9×3×3=81

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	Existing Design Control	Severity	Probability	Detection	Risk Priority Number
				(S)	(P)	(D)	RPN=S x P x D
	Risk Analysis						**Risk evaluation**
3.	Manufacturing Process	Manufacturing process is not well defined & supported by R&D. GMP is not followed. SOPs is not available. Commercial production is started without process validation.	Manufacturing Process is well defined & supported by R&D. SOPs are available for and operators are trained accordingly to process the batch. . Manufacturing process is Validated and Commercial production started after process validation. During Manufacturing GMP is following as per guidelines.	7	2	3	=7×2×3=42
4.	Material Handling & storage	Raw materials as well as Product handling & storage requirements are not fulfilled.	Raw materials are stored as per product temperature requirement. Critical storage requirement (2-8 ºC) is also fulfilled. Solvents are stored in dedicated tanks handled in closed pipelines.	7	2	2	=7×2×2=28
5	Equipments & facility	Adequate and Qualified equipments are not available for the different stages of Cefixime. Facility is also not available as per the requirement.	Adequate and Qualified equipments are available for the different stages of Cefixime. Dedicated production Facility is available as per the requirement.	7	2	3	=7×2×2=42

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	Existing Design Control	Severity	Probability	Detection	Risk Priority Number
				(S)	(P)	(D)	RPN=S x P x D
	Risk Analysis						**Risk evaluation**
6	Utility	Utility is not adequate to achieve desired temperature for performing unit operation.	Utility is designed adequately to achieve desired temperature for performing unit operation.	7	2	2	=7×2×2=28
7	HVAC System	HVAC system not available for critical stages / processing.	HVAC system is available for critical stages as Powder processing activity where temperature less than 25 deg and differential pressure is maintained specifically. HVAC system pre and HEPA filter, its periodically validation is performed.	7	2	3	=7×2×3=42
8	Water system	Water system is not meeting the specification	Water system available as Purified water for Intermediate stages and Purified water with Ultra filtration for Finished goods stage . Water system is validated system meeting all specification as per ICH guidelines requirement.	7	3	2	=7×3×2=42

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9	Documentation	All the critical steps are not defined in the BPR. The In process limits is not defined appropriately in the BPR. BPRs are not approved before the actual execution	All the critical steps and in process control are defined in the BPR. The In process limits are defined appropriately in the BPR. Master BPR is approved by QA . Before starting batch BPR is issued by QA and completely filled BPR is submitted in QA. So totally controlled documentation by QA. Equipment's occupancy, Periodic equipments cleaning, temperature & pressure records. Facility daily cleaning record, Raw material dispensing record and other related documents are issued & controlled by QA.	7	2	2	=7×2×2=28

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5.2.3 Risk Reduction or Mitigation

S. No.	Failure Mode {What can go wrong}	Existing Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number RPN	Additional Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number (RPN)
	Risk Mitigation										
1.	Cleaning Process	Approved and appropriate procedure. Applicability is ensured as cleaning procedure is same for regulatory and domestic process.	7	3	3	=7×3×3= 63	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	3	3	=7×3×3= 63

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2.	Manufacturing Operation	All operators are trained for Batch operations as per written procedure.Equipment's are dedicated for all unit operations as per requirement. PPE's and other provisions required to perform the cleaning operations are provided. Nose mask, hand gloves safety goggles etc. MSDS are available for all raw materials. BPR incorporated all precautionary steps to be followed during batch operations. BPR specified all critical operation, in process control. All operation supervision is performed by Shift in charge.	9	3	3	=9×3×3= 81	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	9	3	3	=9×3×3= 81

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S. No.	Failure Mode {What can go wrong}	Existing Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number (RPN)	Additional Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number (RPN)
	Risk Mitigation										
3.	Manufacturing Process	Manufacturing Process is well defined and documentary supported by R&D. SOPs are available for and operators are trained accordingly to process the batch. . Manufacturing process is Validated and Commercial production started after process validation. During Manufacturing GMP is following as per guidelines.	7	2	3	=7×2×3= 42	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	2	3	=7×2×3= 42
4.	Material Handling & storage	Raw materials are stored as per product temperature requirement. Critical storage requirement (2-8 ° C) is also fulfilled. Solvents are stored in dedicated tanks handled in closed pipelines.	7	2	2	=7×2×2= 28	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	2	2	=7×2×2= 28

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5	Equipments & facility	Adequate and Qualified equipments are available for the different stages of Cefixime. Dedicated production Facility is available as per the requirement.	7	2	3	=7×2×3= 42	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	2	3	=7×2×3= 42

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S. No.	Failure Mode {What can go wrong}	Existing Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number (RPN)	Additional Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number (RPN)
	Risk Mitigation										
6.	Utility	Utility is designed adequately to achieve desired temperature for performing unit operation.	7	2	2	=7×2×2= 28	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	2	2	=7×2×2 =28
7.	HVAC System	HVAC system is available for critical stages as Powder processing activity where temperature less than 25ºC and differential pressure is maintained specifically. HVAC system pre and HEPA filter, it's periodically validation is performed.	7	2	3	=7×2×3= 42	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	2	3	=7×2×3 =42

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S. No.	Failure Mode {What can go wrong}	Existing Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number (RPN)	Additional Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number (RPN)
	Risk Mitigation										
8.	Water system	Water system available as Purified water for Intermediate stages and Purified water with Ultra filtration for Finished goods stage .Water system is validated system meeting all specification as per ICH guidelines requirement.	7	3	2	=7×3×2= 42	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	3	2	=7×3×2= 42
9.	Documentation	All the critical steps and in process control are defined in the BPR. The In process limits are defined appropriately in the BPR. Master BPR is approved by QA .Before starting batch BPR is issued by QA and completely filled BPR is submitted in QA. So totally controlled documentation by QA. Equipment's occupancy, Periodic equipment's cleaning, temperature & pressure records. Facility daily cleaning record, Raw material dispensing record and other related documents are issued & controlled by QA.	7	2	2	=7×2×2= 28	Since the existing design control made the risk at the acceptable level of risk, so no any additional design control is required.	7	2	2	=7×2×2= 28

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3.0 Acceptance Criteria

The Risk Priority Number shall be within the range 0<RPN<125

4.0 Risk Control Strategy

S.No.	Risk Priority Number	Risk Decision	Risk control strategy
1.	0<RPN<125	Risk Acceptable	No control is required
2.	125<RPN<500	Risk Reduction	Additional Procedural Control
			Manual Control
			Documentary Evidence
3.	500<RPN<1000	Risk Reduction	Rugged Procedural control
			Additional Manual Control
			Auditing
			Engineering controls (if Possible)

5.0 Summary

S.No.	Failure Mode	Risk Priority Number	Risk Decision
1.	Cleaning Process	63	Risk Acceptable
2.	Manufacturing Operation	81	Risk Acceptable
3.	Manufacturing Process	42	Risk Acceptable
4.	Material handling & storage	28	Risk Acceptable
5.	Equipments & facility	42	Risk Acceptable
6.	Utility	28	Risk Acceptable
7.	HVAC	42	Risk Acceptable
8.	Water system	42	Risk Acceptable
9.	Documentation	42	Risk Acceptable

6.0 Conclusion

The risk associated with each Failure mode lies in between the range 0<RPN<125 after going through risk mitigation and reduction process

Hence it meets the acceptance criteria for risk acceptance

On the basis of Risk assessment process using FMEA tool it is concluded that the Manufacturing procedure of **Cefixime Trihydrate** in Block is associated with minimum risk.

7.0 References:

1. Risk Management Master Plan
2. ICH Q9