RISK ASSESSMENT & MITIGATION FOR USES OF UNDER TEST BETA-NAPHTHOL COMPLEX IN CEFACLOR BATCHES

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Risk Assessment and Mitigation
for Uses of Under Test Beta-Naphthol Complex in Cefaclor Batches

REPORT Contents

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1. Report Approval:

This is a specific report for Risk assessment and Mitigation for Uses of Under test Beta-Naphthol Complex in Cefaclor Batches.

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. 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 for Uses of Under test B-Naphthol Complex in Cefaclor Batches at ……

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 for Uses of Under test B-Naphthol Complex in Cefaclor Batches at ……

2.3 Risk Assessment Team

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

2.4 Responsibility

S.No.	Department	Designation	Responsibility
1.	**Quality Control**	Executive/Officer/ Manager	Preparation of Report To Provide and compile the all relevant information/Analytical trends that are required while undergoing Risk assessment process for for Uses of Under test B-Naphthol Complex in Cefaclor Batches.
2.	**Production**	Executive/Officer/ Manager	Review of report To Provide the all relevant information that is required while undergoing Risk assessment process.
3.	**Quality Assurance**	Executive/Officer/ Manager	Review of Report To review all the Procedural controls To perform impact evaluation on the quality of product Final approval of report By head quality Assurance.

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3. Introduction:

Risk analysis for Uses of Under test B-Naphthol Complex in Cefaclor Batches, at ……..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 regulatory compliance

4. 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.

- **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.

5.0 Risk Assessment for Uses of Under test B-Naphthol Complex in Cefaclor Batches

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 Rates	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 cause.

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.	**Instrument Design**	Power fluctuation	Instrument failure	Continuous power supply is required for the efficient analyses of the samples.
		Maintenance and Calibration of Auto - Titrator	Malfunctioning of Auto - Titrator	If instrument is not maintained and calibrated at the required interval of time then it will result in malfunctioning that will have adverse impact on analysis

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
2.	**Provisions and Procedures**	Non availability or in appropriate standard operating procedure for instrument.	Malfunctioning of Auto - Titrator	Well designed approved Standard operating procedure gives sequential instructions for functioning of Auto – Titrator.
		Non availability or in appropriate standard testing procedure for analysis.	Result in non compliance and inappropriate testing which ultimately result in poor quality of product	Well designed approved Standard testing procedure provides well designed instructions for the analytical parameters to meet the objective of analysis
		Analyst Not trained for the instrument operation and testing procedure.	Increase the chances of mistakes and errors. Malpractice of the instrument and inappropriate testing which ultimately result in poor quality of product	Training removes confuse and a well trained and qualified analysts avoid mistakes and errors
3.	**Environmental conditions required for instrument operation**	Non availability or in appropriate controls for the environmental conditions specified for instrument operation	Malfunctioning of Auto - Titrator Instrument is designed to work in an environment of < 25ºC.	If controls are not specified for Environmental conditions required to operate Auto - Titrator then it will be difficult to prevent malfunctioning of the Auto -Titrator

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
4.	**Testing & release procedure of intermediates**	Inadequate procedure may lead to non compliance	cGMP Non-compliance and product failure	Adequate and effective procedure should be in place to comply the cGMP requirements and to meet the product quality.
5.	**Impact on F.G Quality**	Beta-naphthol complex having B. No…… used in Cefaclor batchs without testing i.e. B.No. ……..	Usage of under test RM/intermediate may lead to product failure and noncompliance.	To evaluate the risk on product quality risk analysis performed.
6	**Personnel**	Lack of Awareness between QC Person and production	cGMP Non compliance	Manufacturing personal neither confirmed the results from QC nor was it intimated by QC person about delay in the analysis.

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5.2.2 Risk Analysis

S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Existing Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number RPN=S x P x D
	Risk Analysis							**Risk valuation**
1.	**Instrument Design**	Power fluctuation	Instrument failure	UPS power supply is provided	9	2	5	=9 x 2 x 5=90
		Maintenance and Calibration of Auto -Titrator	Malfunctioning of Auto Titrator Instrument failure	The instrument is calibrated on quarterly basis and record is maintained	9	2	2	=9 x 2 x 2= 36

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Existing Design Control	Severity (S)	Probability (P)	Detection (D)	Risk Priority Number RPN=S x P x D
	Risk Analysis							**Risk valuation**
2.	**Provisions and Procedures**	Non availability or in appropriate standard operating procedure for instrument	Malfunctioning of Auto - Titrator	Approved SOP for Auto - Titrator is in place **(ref. QC……..)**	9	2	2	=9 x 2 x 2=36
		Non availability or in appropriate standard testing procedure for analysis	Result in non compliance and inappropriate water testing which ultimately result in poor quality of product	Approved STP for Auto - Titrator analyzer to analyze assay of Beta-Naphthol complex of cefaclor is in place **(ref. ……..)**	9	2	2	=9 x 2 x 2=36
		Analyst Not trained for the instrument operation and testing procedure	Increase the chances of mistakes and errors. Malpractice of the instrument and inappropriate water testing which ultimately result in poor quality of product	Analyst is trained and qualified for the operation of Auto - Titrator	9	2	2	=9 x 2 x 2=36

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3.	**Environmental conditions**	Non availability or in appropriate controls for the environmental conditions specified for instrument operation	Malfunctioning of Auto - Titrator	Instrument is designed to work in an environment of < 25ºC. SOP on temperature monitoring in QC department is in place. Temp.is recorded "**Thrice a Day**"	9	2	2	=9 x 2 x 2=36

S. No.	**Failure Mode {What can go wrong}**	**Potential cause of Failure**	**What are the Consequences**	**Existing Design Control**	**Severity**	**Probability**	**Detection**	**Risk Priority Number**
					(S)	**(P)**	**(D)**	**RPN=S x P x D**
	Risk Analysis							**Risk valuation**
4.	**Testing & release procedure of intermediates**	Procedure used for the testing and release of intermediates having limited control on system due to that under test beta naphthol complex used without testing.	cGMP Non compliance	As per SOP, production personnel shall send the ARF and sample to QC and QC chemist shall perform the analysis and fill the results in production copy of ARF and production personnel will collect the same from QC.	9	6	6	=9x 6 x 6=324

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<table>
<tr>
<td>5.</td>
<td>Impact on FG Quality</td>
<td>Beta-naphthol complex having B. No. …….. used without testing in Cefaclor B. No……</td>
<td>cGMP Non compliance</td>
<td>Analysis of beta-naphthol B. No. …….. could not be performed in time due to malfunctioning of Autotitator. Batchs were analyzed later and meets the predefined specification limit.
<table>
<tr><th>B. No.</th><th>Assay (NLT- 70.0%)</th></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
</table>
Yield and quality data of the Cefaclor blend B. No. ……. are reviewed and found well within specified limit.</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>=9 ×1 × 2 = 18</td>
</tr>
</table>

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Existing Design Control	Severity	Probabilit..	Detection	Risk Priority Number
					(S)	(P)	(D)	RPN=S x P x D
	Risk Analysis							Risk valuation
6.	**Personnel**	Lack of Awareness	cGMP Non compliance	On- job Training SOP No. HR-…… is in place	9	2	5	= 9 ×2 × 5 = 90

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5.2.3 Risk Reduction or Mitigation

S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	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.	**Instrument Design**	Power fluctuation	UPS power supply is provided	9	2	5	90	Design control keep the risk at acceptable level so no additional Design control Is required Further in case of Malfunctioning of Auto - Titrator	9	2	5	= 90
		Maintenance and Calibration of Auto - Titrator	Quarterly maintenance agreement is established, record is maintained.The instrument is calibrated on quarterly bases and record is maintained	9	2	2	36		9	2	2	= 36

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	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											
2.	**Provisions and Procedures**	Non availability or in appropriate standard operating procedure for instrument	Approved SOP for TOC analyzer is in place (ref. QC……)	9	2	2	36	Since the Existing design control keep the risk at acceptable level so no additional Design control Is required	9	2	2	= 36
		Non availability or in appropriate standard testing procedure for water analysis	Approved STP for Auto - Titrator QC…… to analyze the purity (ref …….)	9	2	2	36		9	2	2	= 36
		Analyst Not trained for the instrument operation and testing procedure	Analyst is trained and qualified for the operation of Auto - Titrator (QC……)	9	2	2	36		9	2	2	= 36
3.	**Environmental conditions**	Non availability or in appropriate controls for the environmental conditions specified for instrument operation	Instrument is designed to work in an environment of < 25 ° C	9	2	2	36		9	2	2	= 36

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	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											
4.	Testing & release procedure of intermediates	Procedure used for the testing and release of intermediates having limited control on system due to that under test beta naphthol complex used without testing.	As per SOP no QC……. production personnel shall send the ARF and sample to QC and QC chemist shall perform the analysis and fill the results in production copy of ARF and production personnel will collect the same from QC.	9	6	6	=9x6 x 6 = 324	Procedural control is required in the form Supervisory control for the verification to Issued approved labels by QC to Production after approval of Intermediates. i.e. SOP on testing and Release of intermediate has been revised to incorporate affixing of approved/rejected labels on containers of intermediates	9	2	2	= 36

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S. No.	Failure Mode {What can go wrong}	Potential cause of Failure	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												
5.	**Impact on F.G Quality**	Beta-naphthol complex having B. No. …… used in Cefaclor batchs without testing i.e. B.No. ……	Analysis of beta-naphthol B. No. …… could not be performed in time due to malfunctioning of Autotitator. Batches were analyzed later and meets the predefined specification limit. **B. No.** | **Assay (NLT 70.0%)** Yield and quality data of the Cefaclor blend B. No. …… reviewed and found well within specified limit.	9	1	2	= 18	No additional Design Control is required	9	1	2	= 18
6	**Personnel**	cGMP Non compliance	On- job Training	9	2	5	= 90	As it is identified as human error, retraining has been imparted to QC and production personnel's.	9	2	2	= 36

6.0 Acceptance criteria

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

7.0 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)

8.0 Summary and 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 there is no impact on product quality, Cefaclor B. No……. shall be dispatched to regular customer.

9.0 References:

1. Risk Management Master Plan
2. ICH Q9

10.0 Annexure:

Annexure No.	Annexure Title	Pages
01	List of Reference Documents	

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Annexure – 01

List of Reference Documents

Facility:	
Location:	
No. of Pages:	

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List of Reference documents

S.No.	Document Title	Document No
1.	SOP on Operation & Calibration of Auto - Titrator Apparatus (……)	
2.	Specification: Beta-Naphthol Complex of Cefaclor	
3.	STP: Assay of beta Naphthol Complex of Cefaclor	
4.	SOP on testing and Release of intermediate (Draft Copy attached)	
5.	Trend data analysis of Beta-Naphthhol complex for Year of ……	
6.	Quality data comparison of Cefaclor	