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RISK ASSESSMENT FOR PROCESS VALIDATION

1. **Risk Assessment Tool– Failure Mode effect Analysis (FMEA)**
   Risk Identification

S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
1.	Equipments (Reactors and Centrifuge)	Equipment Selection Equipment Qualification Man hole Opening & Closing Awareness Equipment Malfunctioning Power failure	Product Failure GMP Violation Contamination Deviation Impact on Conversion of reaction Yield Loss	Qualified equipments are used in production of stage 1st of 5-ALA.Awarness provide through training and preventive maintenance records verified. Equipments history checked no malfunctioning was found. The equipments used in 5-ALA stage Ist are glass lined reactor and SS reactor and centrifuge. The Glass lined reactor was used in bromination.The reactor is suitable for reaction as justified according the process

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
2.	Process	Technology transfer Product stability Product knowledge Analytical method validation	Product validation Stability Filling Customer commitment Business impact Campaign failure	5-ALA stage 1st was develop in R&D. The R&D batches are kept on Holding Time Study. Based on ROS and process package development batches are taken batches were comply with the Specification After development batches evolution of quality and yield performed. Based on success of development batches the validation batches had been taken. All the batches comply with the specification. Based on R&D lab batches, Development batches and validation batches it is concluded that process is robust.

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
3.	Raw Materials	Vendor Sampling Testing and specification Awareness Material handling and storage	Quality Product Failure GMP Violation Conversion of reaction Yield	Awareness regarding sampling, testing and handling of raw material provided. Material procured from approved vendors. Vendors were qualified as per SOP on vendor management. Raw materials are tested as per approved specification. Only approved raw materials are used in manufacturing of 5 ALA stage 1st.MSDS was followed for handling, sampling and storage of raw materials. Batches are taken as per Approved BPRs. All the in process parameter comply with specification. All the batches of stage 1st comply with the specification. Yield of all the batches was within range. Based on the yield, quality, in process check, good laboratory practices and cGMP. it is concluded that the raw materials are of good quality and handled sampled and tested appropriately.

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
4	Process Parameters and In process Checks	Awareness Written Procedure Selection of Equipments Raw Materials Sampling & Handling	Deviation Product Failure Yield Contamination	All the batches are taken as per approved BPR's.inprocess checks are defined in BPR's. Sampling and testing performed as per specification. Critical parameters were performed as per BPR's and Checked by Shift Incharge. All the critical process parameters are identified as per process package of Product indentified in BPR marked as Bell. Based on In process check Critical parameters controlling on all the batches. Quality and quality are within limit.

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
5.	Intermediate	Sampling, Testing Material handling and storage	Contamination Yield and Quality	Stage -1st Intermediate of 5-ALA sampled and tested as per specification. All the batches were stored below 25°C. Stage 1st Intermediate packages in double bag further keep in HDP container having metallic ring and tag. Material was handled by trained staff using PPE.

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
6.	Impurities	Raw Material Awareness Equipment's Selection Batch size Analytical Procedure	Product Failure Product Contamination Deviation Yield and Quality	Structure elucidation had been performed at R&D. Analytical procedure are developed and apply. On all R&D Batches. Based on R & D Batches technology and Method Transferred of 5-ALA for Commercial Scale. All the batches comply with impurity profile by GC. Awareness provided before starting the campaign. Equipments are selected keeping in observation of Impurities generation and heating cooling impact. Based on Evaluation of quality and yield data all the batches of 5-ALA Stage -1st That batches are taken in suitable equipments under the supervision of trained man power

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S.No.	Failure Mode {What can go wrong}	Potential cause of Failure	What are the Consequences	Justification
	Risk Identification			
7.	Extraneous Matter	Inappropriate door Opening &Closing Non Availability of Standard Procedure for cleanliness verification of entering person	Raw Material Packing Material Equipment Surface Floor & Walls of the facility	Stage 1st of 5-ALA Manufactured in LBA Block. All the raw material charged using PPE. Before charging of batch equipment surfaced is cleaned. The Floor and Walls of the facility are good condition. Inappropriate door opening & Closing give a chance for the Extraneous Matter incursion inside the facility which there after can move into the Material flow line And results into contamination.

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Risk Analysis:

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**
1.	Equipments (Reactors and Centrifuge)	Equipment Selection Equipment Qualification Man hole Opening & Closing Awareness Equipment Malfunctioning Power failure	Product Failure GMP Violation Contamination Deviation Impact on Conversion of reaction Yield Loss	Qualified equipments (DQ,IQ,OQ,PQ) Preventive Maintenance of Equipments Training to concerned persons Work order system to rectify any breakdown of equipments	4	6	2	RPN = 4X6X2 = 48

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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**
2.	Process	Technology transfer Product stability Product knowledge Analytical method validation	Product validation Stability Filling Customer commitment Business impact Campaign failure	Tecchnology transfer documents are provided from R& D to plant Trained Operators w.r.t process Method Validated				

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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**
03	Raw Materials	Vendor Sampling Testing and specification Awareness Material handling and storage	Quality Product Failure GMP Violation Conversion of reaction Yield	SOP for dispensing of material (Ref……) Provision of PPEs SOP for cleaning of scoop and scrapers Trained Operators Procedure for the destruction floor sweep material (Ref……) Separate De-dusting facility are provided for both raw materials & packing materials MSDS are available w.r.t materials				

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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.	Process Parameters and In process Checks	Awareness Written Procedure Selection of Equipments Raw Materials Sampling & Handling	Deviation Product Failure Yield Contamination	Process design for filtration to prevent Extraneous matter incursion in the API like particle,rust etc (Ref Manufacturing BPRs) Procedural control to check the Layer sepration by visual inspection by sight glass & verification through BPR				

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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**
5.	Intermediate	Sampling, Testing Material handling and storage	Contamination Yield and Quality	Specification & STP are provided to analyst Trained analyst				
6.	Impurities	Raw Material Awareness Equipment's Selection Batch size Analytical Procedure	Product Failure Product Contamination Deviation Yield and Quality	Specification & STP are provided to analyst Qualified Instrument are Method Validation are provided to analyst Provision of PPEs Trained analyst				

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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**
7.	Extraneous Matter	Inappropriate door Opening &Closing Non Availability of Standard Procedure for cleanliness verification of entering person	Raw Material Packing Material Equipment Surface Floor & Walls of the facility	Work order system to rectify the failure of door functioning Air curtains are installed on the entry doors for the plants The SOP to verify personnel hygienic which allows verification through checklist for cleanliness for the operating persons				

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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.	Equipments (Reactors and Centrifuge)	Equipment Selection Equipment Qualification Man hole Opening & Closing Awareness Equipment Malfunctioning Power failure	Qualified equipments (DQ,IQ,OQ,PQ) Preventive Maintenance of Equipments Training to concerned persons Work order system to rectify any breakdown of equipments					Since the Existing design control keep the risk at acceptable level Still there is a scope of additional Design control				

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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	Process	Technology transfer Product stability Product knowledge Analytical method validation	Tecchnology transfer documents are provided from R& D to plant Trained Operators w.r.t process Method Validated					Since the Existing design control keep the risk at acceptable level Still there is a scope of additional Design control				

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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											
03	Raw Materials	Vendor Sampling Testing and specification Awareness Material handling and storage	SOP for dispensing of material (Ref.) Provision of PPEs SOP for cleaning of scoop and scrapers Trained Operators Procedure for the destruction floor sweep material (Ref.) Separate De-dusting facility are provided for both raw materials & packing materials MSDS are available w.r.t materials					Since the Existing design control keep the risk at acceptable level Still there is a scope of additional Design control				

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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.	Process Parameters and In process Checks	Awareness Written Procedure Selection of Equipments Raw Materials Sampling & Handling	Process design for filtration to prevent Extraneous matter incursion in the API like particle,rust etc (Ref Manufacturing BPRs) Procedural control to check the Layer separation by visual inspection by sight glass & verification through BPR					Since the Existing design control keep the risk at acceptable level Still there is a scope of additional Design control				

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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.	Intermediate	Sampling, Testing Material handling and storage	Specification & STP are provided to analyst Trained analyst					Since the Existing design control keep the risk at acceptable level Still there is a scope of additional Design control				

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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											
6.	Impurities	Raw Material Awareness Equipment's Selection Batch size Analytical Procedure	Specification & STP are provided to analyst Qualified Instrument are Method Validation are provided to analyst Provision of PPEs Trained analyst					Since the Existing design control keep the risk at acceptable level Still there is a scope of additional Design control				

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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											
7.	Extraneous Matter	Inappropriate door Opening &Closing Non Availability of Standard Procedure for cleanliness verification of entering person	Work order system to rectify the failure of door functioning Air curtains are installed on the entry doors for the plants The SOP to verify personnel hygienic which allows verification through checklist for cleanliness for the operating persons					Since the Existing design control keep the risk at acceptable level so no additional Design control required Layout Display for the Man & Material Movement in the plant				

RISK ASSESSMENT FOR PROCESS VALIDATION

3. Acceptance criteria

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

4. 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. Summary and Conclusion

The risk associated with each Failure mode lies in between the range 0<RPN<100 after going through risk mitigation and reduction process

Hence it meets the acceptance criteria for risk acceptance

6. References:

1. Risk Management Master Plan
2. ICH Q9

7. Annexure:

Annexure No.	Annexure Title	Page No's
1.	List of Reference Documents	02

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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