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QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR PROCESS PREPARATION AND 5-ALA STAGE 1

FMEA: Process Preparation & 5-ALA Stage 1

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	Comments/Recommendations
1	**Materials**							
1.1	**Key Starting Material (Levulinic Acid)**							
1.1.1	Inconsistent product quality	a) Unqualified supplier (trader) & (unknown) manufacturer b) Insufficient defined KSM manufacturing process	a. Supplier qualification program for KSM manufacturer b. Technical package	5 5	5 5	4 4	100 100	The manufacturer qualified based on sample performance. The Q sore of the yearly evaluation is 100%. The audit has been performed final Intermediate/API Impurity profile to high; low stage yield
1.1.2	Impurity profile changes due to biological/ synthetic manufacturing process	Additional by-products/ degradation products	Technical package	5	5	3	75	QAA with the supplier including CC aspects
1.1.3	Undetected SM impurities; low assay	Wrong / insufficient specification	Starting Material test methods as per R&D information and manufacturer COA	6	4	4	96	Stress conditions to verify the selectivity of the selected test method; Validation needed
1.1.4	High heavy metal / metal impurity profile	Unknown process ingredients such as metal catalysts	Manufacturer technical information sheet	5	5	4	100	Heavy metal check e.g. during initial manufacturer/product

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1.1.5	Material losses	Incomplete charging due to physical characteristics e.g. solid (electrostatic), liquid, gas	a) Material charging by trained manpower. b) The hoppers are available for charging the materials in the reactors	3	3	3	27	The Hazardous material training shall be provided as per MSDS
1.1.6	High impurity profile	Wrong transport & storage conditions (degradation)	a)Manufacturer information (stability); CoA / label indication verified by warehouse b) QC perform the sampling and testing C) The warehouse facility available to store the material as per Recommendation	5	5	3	75	If there is damaged in seal label and shortage of material. Manufacturer shall be informed. The material falling to specification shall be rejected
1.2	**Further stage 1 ingredients/Solvents**							
1.2.1	Inconsistent product quality	a) Unqualified supplier (trader) & (unknown) manufacturer b) Insufficient defined	Supplier qualification program for manufacturer Technical solvent grade	5	5	4	100	The all the manufactured are identified and material precaured only from approved vendors only

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		manufacturing process						
1.2.2	Undetected impurities; low assay	wrong / insufficient specification	e.g. GC/HS methods	5	5	4	100	Solvents are segregated by GC/HS methods. The methods are validated MDC could contain e.g. class one solvents
1.2.3	High residual solvent profile	Tanker cross-contamination due to improper tanker cleaning	Cleaning certificate and visually inspected by qualified QC personnel.	6	4	4	96	Solvents unloaded after the satisfactory inspection
1.2.4	High residual solvent profile incl. impurities	Recovered solvent distillation process incomplete Solvent recovery specification insufficient Non-defined recovering cycles (generations) mix-up of solvents from other stages / processes	No recovered used in the manufacturing of 5-ALA stahle 1st					
1.2.5	High heavy metal / metal impurity profile	Unknown process ingredients such as metal catalysts	Vendors are qualified. The certificate are used by manufacturer	5	5	3	75	All the solvents used in stage 1st comply to specification
1.2.6	Exceeded MAC (maximum concentration value)	Use of Hazard materials (e.g. Bromine)	The Bromine is charged in the glass vessel. The bromination had been	5	4	4	80	No incident has been reported during the manufacturing of 5-ala stage 1st.

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			performed in closed system under the PPE and trained manpower					
1.3.	**Stage I Intermediate (Methyl-5-Bromolevuniate)**							
1.3.1	Undetected Intermediate impurities; low assay, unexpected by-products	Wrong/insufficient Intermediate I specification	a) Specification consider the assay ,impurity b) Sampling performed by trained staff c) Manufacturing performed under the supervision of technical staff	4	4	3	48	All batches comply to specification. No deviation has been observed during manufacturing, sampling and testing.
1.3.2	High impurity profile	Wrong intermediate storage (degradation)	a) Storage condition is mentioned in BPR b) The list of material stored displayed c) Option of 2nd check	5	4	3	60	Since the stage 1st is insitu and used as such for stage 2nd manufacturing
2	**Machinery & Premises**							
2.1	**Dispensing equipment**							
2.1.1	Incorrect weighing of the	Out of Calibration; maintenance overdue, wrong	a)Daily verification of	5	4	3	60	No deviation has been observed during the

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	Balances	placement	weight b) Preventive maintenance as per schedule c) Calibration be formed once in three months					weighing of material
2.1.2	Contamination due to Laminar flow unit	Insufficient air supply due to a. filter replacement overdue b. pressure device defect c. maintenance overdue	a)The reverse laminar system qualified once in six month. b)RLAF run 15 minutes before start the activity. C) after every activity the RLAF cleaned	5	4	4	100	The qualification of RLAF comply to the specification.
2.2	**Reactor**							
2.2.1	High foreign particle concentration	a. Non-inert reactor inner coating b. broken inner coating	a) only SS -316 and glass coated qualified reactors are used.	4	5	3	60	Only qualified reactors are used for 5-ALA manufacturing
2.2.2	Material loss	a. Damaged manhole	a)Visual inspection	4	4	3	48	All the batches are taken after the visual

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		b. Leaking charge-pipe connections c. Wrong pipe connection d.	b) Identified lines c) Second check					inspection and in the presence checker.
2.2.3	High impurity profile	a) Wrongly connected pipe(s) b) Incorrect temperature and/or pressure due to calibration c) Incorrect vacuum – pump failure	a) All the gauges are calibrated as per schedule b) Temperature and vacuum are recorded in batch production record c) System of deviation is in place	4	4	4	64	Since all the lines are identified. The temperature, pressure and vacuum gauges are calibrated. No deviation had been observed.
2.3.	**Centrifuge**							
2.3.1	Low yield	Broken centrifuge bag	a) The double centrifuge bags used b) Bags are checked before and after use.	4	5	5	100	Since yield of all the batches as per range. There is no damage in centrifuge bags reported.
2.3.2	High impurity profile	Multipurpose used bags; Insufficient bag cleaning; batch to batch carryover	a) After each batch bags are replaced. b) The fresh bags are kept at designated place.	4	4	4	64	Bags may be used for more than one batches based on evaluation of quality.

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2.4	**Pipe work**							
2.4.1	High foreign particle concentration	a) Unclean pipework (metal pieces, material wearing) b) Porous sealing	SS-316	3	5	4	60	Permanent installed pipes
2.4.2	Material loss	a) Leaking pipework b) incorrect welding's c) dead legs	a)Argon welding b) discharge by gravity	4	7	4	112	
2.4.3	High unknown impurity profile	a) Additive extraction from flexible (plastic) hoses b) Multipurpose used hoses (cleaning, inner film) c) Batch to batch carry overs of degradation	The equipments are cleaned as per batch production recorded after every batch through pipe line.	5	4	3	60	Batch to batch carry over reduced by batch to batch cleaning
2.5	**Rooms**							
2.5.1	High impurity profile	Storage rooms not qualified e.g. too hot	a) All the storage rooms are qualified.	5	4	5	100	The probes are fitted at the hottest spot.

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			b) The temperature recording performed daily					
3	**Methods**							
3.1	**Dispensing**							
3.1.1	Too high/low material weighting	Wrong calibration (overdue, calibration range)	All the balances in calibration and range					All the materials dispensed in warehouse under RLAF. 2nd check is in production to verify the quantity and tags.
3.1.1.1	Key Starting Material		The key raw material dispensing performed in the warehouse. Then weight verified at production.	5	5	4	100	
3.1.1.2	Solid ingredients		The raw material dispensing performed in the warehouse. Then weight verified at production.	5	5	4	100	
3.1.1.3	Solvents		The drums solvents are dispensed by dispensing pump	6	6	3	108	
3.1.2		Cross-contamination due to improper cleaning						Seen during inspection

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3.2	**Reaction 1 & work-up**							
3.2.1	High impurity profile	Charging while a 2nd product is charged as well Layer separation	a) Trained manpower b) The classified area separated from unclassified area	5	4	3	60	The activity of layer separation only performed by trained manpower only.
3.2.2	Material loss	Layer separation not clearly detected, safety extra volume discarded	a) Inspection lamp for layer separation. b) Separation in the presence of 2nd checker c) estimate of layer as per calibration chart	5	5	3	75	
3.2.3	High inorganic impurities	Salt carryover due to not proper layer separation	) Inspection lamp for layer separation. b) Separation in the presence of 2nd checker c) estimate of layer as per calibration chart	5	5	3	75	
3.3	**Distillation & Crystallisation**							
3.2.1	Impurity Material loss	Training	Batch production records and trained manpower	5	4	5	100	

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3.4	**Centrifugation**							
3.4.1	Low yield High impurity profile	Training, Maintenance	The shut down maintenance performed yearly. Preventive maintenance once in three month. All the operation performed as per SOP and BPR	5	5	3	75	
3.5	**Transfer LPA1 to Pilot plant**							
3.5.1	Material loss Cross contamination	Awareness, lose drum rings	The material is packed in double polybags. Twist and tied. Then material put into dedicated HDPE drum. The Drum is locked by metallic ring.	5	5	3	75	
4	**Provisions**							
4.1	**Personnel Qualification**							
4.1.1	GMP failure Loss of yield and quality	Awareness,slacness, lack of knowledge	Training, evaluation and retraining.	5	4	5	100	Only trained and qualified personnel performed the activity of manufacturing, testing and releasing
4.2	**Documentation**							

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4.2.1	Batch production records	Awareness,Knowledge	Training, evaluation	5	4	5	100	Batches are taken as per approved BPR issued from QA.Three batches are considered for validation. Training provided after mastering the BPR.
	Validation	Awareness, Knowledge	Training, evaluation	5	4	5	100	
4.2.2	Standard operating procedures and standard testing procedure	awareness, Knowledge	Training, evaluation	5	4	5	100	

Please note:

This document provides our ideas for a Risk Assessment for 5-ALA resulting from a first “brainstorming” based on the available process information and the impressions from inspection of the site. The above given list of potential risks raises no claim to be complete or fully appropriate. It shall be regarded as a guidance and collection of ideas in order to – maybe – amend your risk assessment.