PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

FAILURE MODE EFFECT ANALYSIS FOR MANUFACTURING VESSELS

Sr. No.	Item/ Function	Potential Failure Mode (Failure Mode)	Potential Effect of Failure (Effect)	Potential Cause/ Mechanism of Failure	Current Control	Reference	S	O	D	Risk Priority Number (S*O*D)	Recommend-ended Actions (if any)	Post Risk			
												S	O	D	RPN S*O
1.	Vessel Capacity	Insufficient space for mixing of product solution	➢ Adequate space for the operation is a GMP requirement to conduct error free operation	➢ .	➢ The vessel capacity should be suitable for processing suitable batch size as per requirement										
2.	Vessel	Equipment is not suitable for operation in clean room environments	Equipment may contaminate clean room environment	➢	• The Equipment design should not have any negative influence on the clean room conditions, does not emit/ shed any particles. • Equipment should have proper housing for components. • Minimization of surfaces, connections, media supply in clean room.										
3.	Vessel	Vessel cannot be drained completely	Contamination of product due to previous product/ cleaning agent.	➢	• Dead legs shall be less than 1.5D. • Valve connections used shall be of sanitary design. • Proper slope shall be provided at the bottom towards the outlet valve to ensure complete drainage. • Flush bottom valve shall be provided at the outlet to ensure complete drainage.										

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4.	Vessel	Leakage in vessel	➢ **Contamination of system / product possible**	➢	• Vessel hydrotest report to be provided by the vendor. • An automated process for pressure hold test to be provisioned for checking integrity of the vessel. • A pressure transmitter and gauge should be provisioned on the vessel for monitoring of vessel pressure along with alarm provision in case pressure hold test fails. • 100% Boroscopy for Shell & 10% Boroscopy for jacket shall be performed. ➢ **Boroscopy Report should be available.**										
5.	Vessel	Closure of vessel, nozzle connections not tight/ leak proof.	➢ **Contamination of system / product possible.**	➢	• Design of vessels: closure of vessel, nozzle connections shall be reproducible and tight, independent from operator. • Suitable gasket should be provided for ensuring leak proof closure. ➢ **Connections should be of sanitary design.**										

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6.	Vessel	Reaction of product with atmospheric oxygen.	Products manufactured inside vessel are oxidizable, product degradation.	➢	• A Nitrogen sparger tube shall be provided for sparging of nitrogen inside product solution during manufacturing. • Pneumatic valves are installed on the inlet and outlet of nitrogen line for controlling the flow of nitrogen gas.										
7.	Vessel	Product quality could not be checked	In-process checking of product quality is a basic GMP requirement. Product may not be of required quality.	➢	Offline pH measurement shall be performed as per respective SOP.										
8.	Vessel	A jacket with utility connection is not provided.	➢ **Specific condition required for the product solution preparation could not be provided**	➢	• Vessel should be provided with a jacket around the shell with inlet and outlet nozzles for connecting utilities such as chilled water, cooling water and plant steam. ➢ **All connections should be of sanitary design and chilled water and plant steam lines should be insulated.**										
9.	Vessel	Insulation is not provided/ not proper	The required temperature for product mixing may not be maintained.	• Will lead to heat losses to environment. ➢ **The outside surface would be too hot risking operator safety**	Proper insulation should be provided around the jacket with SS 304 cladding for clean room suitability.										

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10.	Vessel	Mixing of product not possible	Homogenous product solution may not be prepared. Shall affect product quality.	➢	Bottom mounted magnetic mixer should be provided for homogenous mixing of the product solution.										
11.	Vessel	Amount of the product solution to be prepared could not be monitored or controlled.	Product solution could not be prepared as per specification	➢	• Load cells should be installed beneath the leg support of vessel for monitoring of amount of WFI (for product solution). • Alarm should be provided when the required level of WFI (for product solution) is added inside vessel. • Pneumatic zero dead leg valves should be installed on the WFI inlet line to the tank, which would automatically close when required amount of WFI (for product solution) has been filled inside vessel. • Overflow capacity of the vessel should be atleast 5% more than the working capacity.										
12.	Vessel	No sight and light glass provided. Viewing of product level inside vessel not possible.	Need for inspection & monitoring of product inside the vessel.	➢	Sight Glass & Light Glass should be provided in the vessel.										

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13.	Sight and Light Glass	Non- sanitary type	Connected to the manufacturing vessel. May lead to product contamination.	➢	Sight glass & Light glass should be of sanitary design.										
14.	Nozzle height	Nozzle connection height is too long.	Air pockets may be created at nozzles connections during SIP.	➢	The height of nozzles should be minimized and kept preferably at <1.5D.										
15.	Sampling	Sampling of product solution for in-process testing not possible.	Basic requirement for in-process testing.	➢	Sanitary sampling valve should be provided at the side wall of vessel for sampling of product solution.										
16.	Vessel	Product temperature inside vessel/ vessel temperature during SIP could not be monitored.	Product may not be processed as per specification. SIP not possible.	➢	• Temperature sensor cum controller should be provided for monitoring of product temperature or SIP temperature inside vessel. • Alarm provision in case low/ high temperature during product mixing or SIP.										
17.	Vessel	Breathing nozzle is in direct contact with atmospheric air.	➢ Environmental contamination of product solution from breathing nozzle	➢	➢ **Manufacturing vessel should be provided with hydrophobic type of sterilizable grade vent filter (porosity – 0.2 µm) with SS housing.**										

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18.	Magnetic Mixer	Malfunctioning of magnetic mixer.	Will effect homogenous mixing of product.	➢	Alarm feature should be provided in case of malfunctioning of mixers.										
19.	Magnetic Mixer	• Particle emission from mixers. • Product contact parts of mixers are not compatible with product	Product contamination.	➢	• Product contacts surfaces shall be made up of SS 316L grade stainless steel. • All connections are of sanitary design.										
20.	Magnetic Mixer	Mixing at different speeds is not possible.	Different speeds may be required for different products.	➢	• VFD should be provided to automatically control the speed of the mixer as per product requirement. • Speed of the mixer could be set in the control system.										
21.	Load Cell	Malfunctioning of the Load cells	Improper sensing of product level inside the vessel.	➢	• Load cells should be installed for monitoring and controlling product level and shall be calibrated. • Alarm provision in case of malfunctioning. • Load cell to be calibrated routinely as per SOP. • SOP for preventive maintenance,										

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22.	Vent Filter	• Filter choking/ leakage. • Filter integrity test not possible.	Risk of contamination of product inside vessel.	➢	• Pressure transmitter/ gauge/ switch should be installed on the vent filter to monitor differential pressure across filter. • Alarm provision in case differential pressure goes out of limit. • Filter could be removed and integrity could be performed • Filter integrity test at regular intervals. • SOP's: Filter tests; Maintenance										
23.	Vent Filter	Filter may be damaged during SIP or efficiency may decrease.	Risk of contamination of product inside vessel.	➢	• Sterilizable grade filters (porosity – 0.2 µm) should be installed on the Compressed air inlet line to vessel. • Filter Integrity procedure should be defined in respective SOP.										
24.	Vent Filter	Affected by the high temp. During the process	Filter efficiency will decrease leading to further contamination of the products under process.	➢	• High temp. Resistant filters should be used. • Temperature sensor should be provided to monitor temperature during SIP process. • Filter integrity test shall be performed at frequent intervals as per SOP.										

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25.	Vent Filter	No SIP of filter and filter housing possible	Contamination of equipment or product possible	➢	• SIP of filter and filter housing has to be made possible, automatic sterilization cycle including monitoring and recording of temperature. • Alarm provision in case of low/ high temperature during SIP.										
26.	Vent Filter	Filter housing drain ability is not sufficient	Filter must be dry, microbiological contamination	➢	The filter housing should be self draining type.										
27.	Vent Filter	Wrong cartridge material for sterile filters	Damage / blockage of filter possible	➢	• Types of filter cartridges should be defined. • Filter certificates have to be available. • Frequency of filter integrity testing shall be deified in SOP.										
28.	Vent Filter	Non Resistant to excess pressure of the supply utilities.	Damaged filter leads to inefficient sterilization process	➢	• High pressure resistant filters shall be used. • A pressure gauge/ transmitter should be provided for the filters, to monitor & control the pressure across the filters.										

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29.	Product Discharge	The design of the vessel outlet valve not appropriate.	➢ Product could not be discharged completely	➢	• Flush bottom outlet valve with zero dead leg should be provided at the bottom of the vessel. • Nitrogen/compressed air pressure shall be applied to transfer the product from the vessel. • Provision for centrifugal pump with flow switch should be available. ➢ **Alarm shall be provided when the transfer of product if complete.**										
30.	Product Discharge	Nitrogen gas used for product transfer is not sterile.	➢ May contaminate the product.	➢	➢ **Sterilizable grade filter (porosity – 0.2 µm) should be provided at Nitrogen gas inlet line before vessel.**										

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31.	MOC	Internal surface/ contact parts are not compatible with the product solution.	➢ May lead to product contamination	➢	• All Metallic critical contact parts (vessel, nozzles, flanges, pipelines, valves, sampling point etc.) as well as contact parts of instruments etc. should be made of SS 316L grade stainless steel. • Interconnecting pipelines should be electro polished & orbitally welded. • Contact parts of all instruments, level sensors, valves, pumps etc, should be made up of SS 316 grade stainless steel or better. ➢ **Supporting structures should be made of SS 304 or better.**										
32.	Polymeric materials	• Polymeric materials are not compatible with product. • Polymeric material not replaceable.	➢	May lead to product contamination	• Gaskets and O-rings coming in direct / indirect contact surfaces should be made up of food grade polymeric materials only and are high temperature and pressure resistant. • The easy change of gaskets should be possible. • Vendor to provide MOC certificates for the same.										

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33.	Welding Joints	Uneven and improperly ground weld joints will form a space for dust accumulation	➢	Weld joints not grounded properly and are not passivated.	• All welds shall be ground finished and properly passivated and orbital welding should be done. • Welding to be done using high purity argon gas. • 100% Boroscopy for Shell & 10% Boroscopy for jacket shall be performed. • Boroscopy Report should be available.										
34.	Finishing	Accumulation of dust, particles on internal surfaces; possibility of microbial growth and hence product contamination.	Internal surface finish of contact parts is not proper	➢	• All internal metallic surface should be electro-polished with ≤ 0.8 µm Ra. • External surface should be free from sharp edges, corners, crevices etc., all metallic external surface shall be matt finished with ≤ 1.0µm Ra, 180 Grit. • Test certificate for the same shall be provided by the vendor.										
35.	Joints	Leaking joints may lead to contamination of product.	Joints are not air tight. Suitable gaskets are not provided or are not replaceable.	➢	Suitable gaskets should be provided for air tight triclover connection and should be easily replaceable.										

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36.	Cleaning	Difficult cleaning	Accumulation of particles, contamination of clean room possible	➢	• Design of the vessel should enhance cleaning feasibility by providing minimum sharp corners, minimum crevices & smooth finished surface. • Parts which are required for cleaning are provided with quick fixing arrangement. • All bolts, nuts on the exterior part of equipment are provided with cap head or cap nut.										
37.	Cleaning	Inefficient cleaning process	Contamination of product possible	➢	• An automated CIP process should be provided for efficient cleaning so as to minimize the contamination risk. • CIP Procedure should be conductivity & time Based. • Procedure shall be verified at the time of cleaning validation.										
38.	Cleaning	No provision of recirculation of cleaning media	Cleaning process may not be efficient.	➢	A discharge pump should be provided at the vessel outlet for recirculating cleaning media.										

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39.	Cleaning	Malfunctioning of discharge pump; pump overload	CIP process would be affected	➢	• Alarm should be provided for discharge pump overload. • A flow switch should be provided at the pump inlet/suction line to prevent pump from dry running in case of no media.										
40.	Cleaning	Determination of CIP end point not possible.	CIP process not proper or validated	➢	• Conductivity sensor should be provided on the tank drain line for monitoring conductivity of cleaning media during CIP. • Conductivity level required after CIP process could be set in the control system. • Alarm provision in case CIP process end requirement not met.										
41.	Cleaning	Cleaning media could not reach to all parts of the vessel.	Cleaning not uniform inside vessel. Product contamination possible.	➢	• Spray balls (with 360° reach) should be provisioned inside the vessel on the CIP media inlet line, so as to reach every part of the vessel. • CIP functionality test to be done during qualification.										
42.	Cleaning	Particle accumulation inside spray ball; not of sanitary design	Could lead to product contamination.	➢	Static spray ball of sanitary design should be installed inside the vessel for CIP process.										

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43.	Cleaning	CIP cycle time not controlled / measured	Vessel not cleaned/ washed properly due to cycle time too short.	➢	• CIP process should have settable parameters. • Different recipes should be available for different vessel sizes.										
44.	Cleaning	Compressed air pressure too low	Equipment's operation will be disturbed.	➢	• Pressure switch/ gauge along with pressure regulator should be provided for control and monitoring of compressed air pressure. • Alarm provided if pressure low.										
45.	Cleaning	Final rinsing step is not with hot WFI.	Insufficient removal of contaminants from the vessel. Inefficient cleaning success; product contamination.	➢	Final cleaning step should be designed with hot WFI.										
46.	Cleaning	Slope of cleaning media piping too low	Pipelines cannot be drained completely, Insufficient cleaning, Risk of contamination / microbial growth in piping possible	➢	• Dead legs, air pockets, should be minimized (preferred 1.5D); dead volume minimised valves. • Drains should be located at the deepest points. • Inclination to vessel or drain points (>1:100).										

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47.	Cleaning	Labeling of components/ media inappropriate	Prerequisite for qualification & maintenance	➢	• Unique identity number / flow direction must be on components / media, operator panel, etc. (e.g. according to P&ID) • Labels affixed on the equipment should be heat resistant. • All labelling in English language and according to project standard.										
48.	SIP process	SIP of vessel not possible.	Possibility of microbial growth inside vessel; product contamination	➢	• A suitable SIP process should be provided in the PLC for effective sterilization of the manufacturing vessel and interconnecting pipelines. • Pure Steam supply should be provisioned to the vessel for heating during SIP. • Temperature sensor should be provided inside the manufacturing vessel and on the condensate drain lines to monitor temperature during SIP process. • Vessel should be insulated to prevent loss of heat during SIP. ➢ **Alarm should be provisioned in case of High/ low temperature during SIP process.**										

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49.	SIP process	SIP of the vent filter and housing not possible.	Contamination of vessel due to non-sterile vent filter	➢	• Provision for SIP of filter and filter housing should be provided. • Temperature sensor should be provided on the filter housing condensate line to monitor temperature during SIP process. • Alarm should be provisioned in case of High/ low temperature during SIP process.										
50.	SIP process	CIP & SIP of sampling valve not possible.	Contaminated sampling valve; chances of false results	➢	• Provision for CIP and SIP of sampling valve should be provided. • Pure Steam supply should be provisioned to the sampling valve for heating during SIP. • Temperature sensor should be provided on the sampling valve condensate line to monitor temperature during SIP process. • Alarm should be provisioned in case of High/ low temperature during SIP process.										

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51.	SIP process	• Possibility of human error leads to a CIP or SIP procedure which is not validated. • CIP & SIP process parameters are not controlled automatically	CIP & SIP process parameters are not controlled automatically	➢	• CIP & SIP process should be performed by an automatically controlled system. • Suitable PLC control should be considered										
52.	SIP Process	Contamination of vessel after completion of SIP process; contamination of already sterilized vessel and its components.	Positive pressure not maintained after completion of SIP process.	➢	• A positive supply of sterile Nitrogen gas/ compressed air should be maintained after the completion of SIP process to prevent ingress of any contaminated air after sterilization has completed. • Alarm provision should be provided in case of low/ no pressure of nitrogen/ compressed air.										
53.	SIP Process	Low/ Overshoot temperature during Sterilization hold	SIP process out of validated procedure.	➢	Alarm provision should be provided in case temperature goes out of limit during sterilization hold.										
54.	PLC / Control system	Process parameters are not controlled automatically.	Possibility of human error leads to a process which is not validated	➢	• The equipment shall control & detect failure mode automatically. • The System shall be PLC based and fully automatic.										

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55.	PLC / Control system	Process / process status not visible for operating personnel.	Operating personnel must have knowledge on the process status	➢	MMI shall be provided with adequate display and clean room suitable key board for operation and entering process parameters.										
56.	PLC / Control system	Display language not identified.	Pre-requisite for the GMP compliant operation	➢	The language on the display of MMI should be English language only.										
57.	PLC / Control system	Recorder failure	Basis GMP requirement (incomplete / no documentation)	➢	• Data backup for process data must be foreseen (electronic recording, 21 CFR part 11 compliant). • Diagnostic function test to be a part of qualification activity.										
58.	PLC / Control system	Monitoring/recordi ng and documentation of GMP relevant data not possible	Basic GMP requirement	➢	• It should be possible to monitor/record GMP relevant data (e.g. recorder with compliance to GAMP 5 / 21 CFR, Part 11 etc.) • Batch records / print outs to be defined. • Printout facility should be available with fade proof prints.										
59.	PLC / Control system	Control system does not detect failures and generate alarms	Process optimization and validation is not possible	➢	Failure of set parameters gets indicated and printed as alarms and machine stops.										

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60.	PLC / Control system PLC / Control system	Power failure / emergency stop	Process out of specification	➢ SOP for Cleaning & sanitization not followed. ➢ Working personnel lack of adequate knowledge.	• Operator settings unchanged and restored after emergency stop / power failure; • Alarm message; • Machine must not start automatically without operator intervention after incident • UPS supply should be provided for the control system. • SOP for 'Maintenance and operation of Compounding vessel'.	SOP	4	1	1	4 Low category & Risk Accepted	Adequate procedure no recommendation required.	NA	NA	NA	NA
		➢ Status parameters not clear	Process for the particular product at particular stage can't be regulated easily.	➢ WFI not meet its predetermined specification. ➢ Sampling & testing of WFI not done on correct manner.	• Status parameters should remain displayed at each process stage. • The flow of the process shall be provided with the help of arrows. • Alarm should also be visualized along with the fault displayed.	SOP	4	3	1	12 Low category & Risk Accepted	Adequate procedure no recommendation required.	NA	NA	NA	NA
	PLC / Control system PLC / Control system PLC / Control system	Malfunction	Correct function basic requirement for GMP-compliant operation	➢ Sensitivity of temperature indicator controller & Temperature sensors may failed	• Supplier analysis (quality management system for software and control system hardware development) • Input/ Output test implementation in qualification activities • The system must contain all necessary protection devices to ensure that the equipment and article remain in safe condition.	SOP	3	3	1	9 Low category & Risk Accepted	Adequate procedure no recommendation required.	NA	NA	NA	NA

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		➢ Parameter settings not identified universally	Basic GMP requirement	➢ Due to invisible marking on dipstick and/or untrained operator perform batch manufacturing.	Parameters settings should be in numeric only.	SOP	3	3	1	9 Low category & Risk Accepted	Adequate procedure no recommendation required.	NA	NA	NA	NA
		➢ Time measurement works incorrect	Process insufficient	➢ There can be a mechanical problem (in heater or chiller)	• PLC Clock verification • SOP "calibration and maintenance" • Time synchronisation of system	SOP	3	2	1	6 Low category & Risk Accepted	Adequate procedure no recommendation required.	NA	NA	NA	NA
	PLC / Control system	No protection of PLC against manipulation & changes.	Basic GMP requirement.	➢ Online monitoring for cleaning of product line not available ➢ Cleaning process of transfer line interrupted. ➢ Cleaning of transfer line not followed as per SOP. ➢ No proper procedure for cleaning of transfer line.	Minimum 3 level password protections should be provided. ➢ Level 1: for operator settable parameters. ➢ Level 2: for editing cycle parameters. ➢ Level 3: for admin/ engineering level setting.	SOP	4	3	1	12 Low category & Risk Accepted	Adequate procedure no recommendation required.	NA	NA	NA	NA

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	Measuring Instruments	Measuring Instruments not suitable	Improper measurements	➢	• Measuring Instruments must have a suitable measuring range. • Operational range of Measuring Instruments > equipment working range. • Measuring Instruments must have appropriate accuracy.										
	Measuring instruments	Measuring instruments not calibrated	Non calibrated measuring instruments may lead to false machine functions	➢	• Measuring instruments should be calibrated, traceable to national or international standards. ▪ Re-calibration of instruments should be possible.										
		➢	➢	➢	➢										
61.	Pure Steam	High pure steam pressure	Does not impact the quality of product.	Environmental & operator safety hazards	• Sanitary pressure regulated valve and safety relief valve shall be installed on pure steam line. • Alarm provision.										
62.	Compounding vessel	High emission of heat	Disturb room temperature and relative humidity.	Environment & Personnel safety hazards	• Proper insulation and outside temperature should not be more than 45 ºC. • SS 304 cladding should be provisioned for insulation. • Insulation material should be resin bounded Glass wool/ Rock wool.										

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Sr. No.	Item/ Function	Potential Failure Mode (Failure Mode)	Potential Effect of Failure (Effect)	Potential Cause/ Mechanism of Failure	Current Control	Reference	S	O	D	Risk Priority Number (S*O*D)	Recommend-ended Actions (if any)	Post Risk			
												S	O	D	RPN S*O
63.	Skid Piping (Steam & Product transfer line)	High emission of heat	➢ Disturb room temperature and relative humidity	➢	• Proper insulation and outside temperature should not be more than 45 ºC. • SS 304 cladding should be Provisioned for insulation. • Insulation material should be Zote form or other suitable type for clean room. ➢ Insulation should be No shredding type.										
64.	User	Unauthorized person tries to start/stop the system	➢ Untrained persons may damage the system or product quality may be affected	➢	• System should not start without password. • Key-switch should be provided for system power up. OR ➢ Physical entry to equipment room is restricted.										
		➢ Faulty operation & maintenance	➢ SOPs are basic GMP-requirement	➢	• All end-users have to be trained on SOPs • Training of SOPs has to be documented. • Training on the job of end users by vendor ➢ Training on operation, setting parameters, trouble shooting & maintenance related activities.										
		➢ Operation SOP does not contain proper information and user may operate system	➢ User may make a wrong decision.	➢	• System operation SOP must be reviewed with all aspects and approved. ➢ Vendor shall provide execution support to the user to complete all stages of the qualification report.										

Where: S=Severity; O=Occurrence Probability; D=Detection; Risk category 1-25 RPN is Low risk, 26-50 RPN is Medium Risk, 51-125 RPN is High Risk.

FAILURE MODE EFFECT ANALYSIS FOR MANUFACTURING VESSELS

Name of Facility/Equipment/Utility/System/Activity/Procedure/Unit Operation : Manufacturing Vessel		Date:	
S. No.	**Recommended Action**	**Responsible Person**	**Target Date of Completion**
1.	NA	NA	NA
2.	NA	NA	NA

CAPA:
If required, mention CAPA No.:

Quality Risk Management Team			**Reviewed By Head Production Sign & Date**	**Approved By Head QA Sign & Date**
Name	**Department**	**Sign & Date**		

QUALITY RISK ASSESSEMENT AND MITIGATION SUMMARY REPORT

Name of Facility/Equipment/Utility/System/Activity/Procedure/Unit Operation : Manufacturing Vessel

Verification of Action Plan: NA

Remarks (if any): The entire above failure mode and their Severity, Occurrence, Detection rating done and RPN No. is found between 1-25. Hence Risk is detected as low which is acceptable.

Verified By
QA
Sign & Date

Approved By
Head QA
Sign & Date