RISK ASSESSMENT FOR HOLDING VESSEL

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1 Introduction

According to the definition, given in Annex 15 to the EU-GMP-Guide, a Risk Assessment is a method to assess and characterize the critical parameters in the functionality of an equipment or process. Therefore, risk assessment is a key element in the qualification and validation approach.

In the project context, risk assessment for the equipment is performed as basic GMP/ EHS-Risk Assessment, which shall help to identify important GMP/ EHS-requirements.

2 Aim of Risk Assessment

At the very basic stage of design the Risk Assessment is carried out to verify that all features are taken into consideration to avoid the risk of failure of critical GMP and EHS parameter in the equipment.

During study, all GMP, EHS and operational parameters will be identified and assessed for the risk, appropriate mitigation will be proposed and verification point will be identified and defined.

The Risk Assessment report is produced to provide the documented evidence that design concepts or requirement are complete in considering all GMP, EHS and operational risks.

3 Reference Documents/ Drawings

S.No.	Document Title	Document Number
1.	Validation master plan	

4 Equipment/ System Description

This risk assessment is conducted for a holding vessel consisting of the following main components:

- Vessel with cylindrical flanged top dish and welded bottom dish.
- Jacket on shell with SS 304 spirals
- Nozzles
- Vent filter
- Light glass with assembly
- Sight glass assembly
- Pressure relief valve
- Port on shell for pH & DO sensor etc
- Sampling valve
- Flush bottom valve
- Variable frequency drive
- Vessel mounted RIO Panel
- Legs Supports
- Spray Ball
- J Tube

- Load cell
- Nitrogen Sparger tube
- Pressure Gauge

Most of the possible risk concerning the handling/operation of the holding vessel has been considered in this RA document.

5 Participants

Name	Designation/ Department	Signature/ Date

6 Risk Management Process

A typical Risk management process consists of following steps:

- Risk Assessment:
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation

- Risk Control
  - Risk Reduction
  - Risk Acceptance

- Result of Risk management processes
- Risk Review

- Risk Assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
  Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description.
  Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harm.

  Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluation considers the strength of evidence for all three of the fundamental questions.
  The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of range of risk. In case of qualitative description the risk is expressed using descriptors such as “high”, “medium” or “low”.

- Risk control includes decision making to reduce and/ or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used of risk control should be proportional to the significance of the risk.

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm.
Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified.

- The output/ result of the quality risk management process should be appropriately communicated and documented.
- Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.
- The output/ results of the risk management process should be reviewed to take into account new knowledge and experience.

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This document applies the risk management principles to identify the risks associated with the design, Construction and operational features of the proposed sterile formulation facility.
The objectives of this risk assessment are to:
• Review the design around a structured methodology
• Identify the failure modes and associated risks
• Check if the proposed control measures are adequate
• Identify recommendations to obtain a more acceptable risk level if required

6.1 Identifying GMP risk

Identification of Risk associated with the equipment, is generally based on prior experience and the concerns of the participants of risk assessment document.

The risks identified are categorized as “GMP risk” or “Non-GMP risk”.

GMP is defined as “the practices which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.”

Thus, GMP covers all aspects of the manufacturing process: defined manufacturing process; validated critical manufacturing steps; suitable premises, storage, transport; qualified and trained production and quality control personnel; adequate laboratory facilities; approved written procedures and instructions; records to show all steps of defined procedures have been taken; full traceability of a product through batch records and distribution records; and systems for recall and investigation of complaints.

Thus those risks which might have a direct or indirect impact on the quality of the product are classified as “GMP risk”. Also, those risks which might result in regulatory guidelines non-compliance are also classified as “GMP risk”.
For example: The Hygiene level of the manufacturing areas has a direct impact on the quality of the Product. Thus, it is classified as GMP risk.
The “Non GMP” risks include risks related to EHS, operational and other non-critical hazards.

Following types of risks are mainly identified during risk assessment process:

- Risk related to hygiene level of the manufacturing and supporting areas
- Risks related to appropriate utilities and their control (eg. power source, compressed air etc.)
- Risks related to calibration/ preventive maintenance
- Risks related to protection of the environment and health & safety of personnel.
- Risks related to cleaning & sterilization
- Risks related to unidirectional flow of the material
- Risks related to cross contamination of the products
- Risks related to entry and exit of personnel and material.
- Risks related to all the environment features of the manufacturing areas.
- Risks related to requirement of particular rooms for different activities.
- Risks related to environment health and safety of personnel.

6.2 RISK ANALYSIS & EVALUATION

The risk analysis is performed using a qualitative basis of approach.

Qualitative analysis uses word form or descriptive scales to describe the magnitude of potential consequences/ impact and the likelihood that those consequences will occur.

The qualitative measures of likelihood includes descriptors like “Unlikely”, “Possible” and “Likely”, whereas the qualitative measures of consequence/ impact includes descriptors like “Minor”, “Moderate” and “Major”.

Qualitative measures of likelihood

Level	Descriptor	Example detail description
1	Unlikely	May occur at some time
2	Possible	Might occur at some time
3	Likely	Will probably occur in most circumstances

Qualitative measures of consequence/ impact

Level	Descriptor	Example detail description
1	Minor	• No impact on the product quality or outcome of the equipment. • Features required for easing equipment operation.
2	Moderate	• No direct impact on product quality/ outcome of equipment. However may indirectly affect the product quality. • Minor effect on personnel health • Used in the initial stage of operation, however it may

Level	Descriptor	Example detail description
		affect the final output but those are not used for final release of output. • Effect on environment such as clean room.
3	Major	• Features having direct impact on product quality/ outcome of equipment like contact parts MOC, Surface finish, Control system, Process air quality etc. • Failure could lead to regulatory non-compliance. • Loss/ damage to equipment or its critical sub-components • Critical instruments not calibrated or not of desired range or accuracy. • Proper supporting documentation not provided. • Major effect on personnel health

Based on the above parameters of likelihood and consequence a qualitative risk analysis matrix is prepared to identify the overall Level of Risk, as mentioned in table below.

Qualitative risk analysis matrix – level of risk

Likelihood	Consequences/ Impact		
	1 – Minor	2 – Moderate	3 – Major
1 (Unlikely)	Low	Medium	High
2 (Possible)	Low	Medium	High
3 (Likely)	Medium	High	High

The final Risk level shall thus be described using descriptors such as “Low”, “Medium” & “High”, where each descriptor implies the following meaning:

Low – Risk can be accepted or ignored. These do not affect the final quality of the equipment/ system and it can be managed by routine procedures and are unlikely to need specific application of resources.

Medium – Risk required ongoing monitoring and review, to ensure level of risk does not increase. Otherwise managed by routine procedures.

High – Action plans must be developed, with clear assignments of individual responsibilities and timeframes.

7 Risk Assessment

In the following section a table is produced for the risk assessment. The significance or instruction for each column is described in the following paragraph.

Column 1 : **Serial number** of the Risk assessment item

Column 2 : **Process step/ Component**: Identify the process step or component associated with the risk.

Column 3 : **Risks:** Identify the type of risk associated with the process or component

Column 4	:	Verify that whether risk have **GMP impact** in terms of Yes/ No.
Column 5	:	**Justification:** Provide justification for declaring both Yes/ No for GMP impact in column 4.
Column 6	:	For the risk **other than of GMP impact**, write that what is/ are the type of risks e.g. EHS, operational, etc.
Column 7	:	**Justification:** Provide justification for considering the risk.
Column 8	:	**Risk level:** Determine the risk level as High, Medium or low based on the impact.
Column 9	:	**Risk Control:** It is further divided into the following three sections:
Column 9a	:	**Mitigation Method:** Write the risk mitigation strategy as considered in the design.
Column 9b	:	**Residual risk level:** After the risk mitigation what is the residual risk level, whether it is Acceptable, Low or Medium.
Column 9c	:	**Test document:** Write the test point where the risk mitigation strategy will be verified.
Column 10	:	**Status of RA:** Mention the status of the Risk assessment point i.e. whether it is ‘Closed” or “Open”, after the execution/ approval of the Test document.

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General Design of Vessel											
1.	Vessel Capacity	Insufficient space for holding of product solution	Yes	Adequate space for the operation is a GMP requirement to conduct error free operation.	Operational	Batch size will reduced	Medium	The vessel capacity should be suitable for processing suitable batch size as per requirement.	Acceptable	IQ	
2.	Vessel	Equipment is not suitable for operation in clean room environments	Yes	May cause contamination of the product and the environment.	No	NA	High	• 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.	Acceptable	IQ	
3.	Vessel	Vessel cannot be drained completely	Yes	Contamination of product due to previous product/ cleaning agent.	No	NA	High	• 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.	Acceptable	IQ	

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4.	Vessel	Leakage in vessel	Yes	Contamination of system / product possible.	Operational	Product loss	High	• 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.	Acceptable	IQ & OQ	
5.	Vessel	Closure of vessel, nozzle connections not tight/ leak proof.	Yes	Contamination of system / product possible.	Operational	Product loss	High	• 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. • Pressure leak test shall be performed before SIP.	Acceptable	IQ	

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6.	Vessel	A jacket with utility connection is not provided.	Yes	Specific condition required for the product solution could not be provided.	No	NA	High	• 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.	Acceptable	IQ	
7.	Vessel	Insulation not provided/ not proper	Yes	The required temperature for product may not be maintained.	EHS	• Will lead to heat losses to environment. • The outside surface would be too hot risking operator safety.	High	Proper insulation should be provided around the jacket with SS 304 cladding for clean room suitability.	Acceptable	IQ	

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8.	Vessel	Amount of product solution transferred could not be monitored or controlled.	Yes	Product solution could not be monitored as per requirement	No	NA	Medium	• Load cells should be installed beneath the leg support of vessel for monitoring of amount of product solution. • Pneumatic zero dead leg valves should be installed on the product inlet line to the tank, which would automatically close when required amount of product solution has been transferred inside vessel. • Overflow capacity of the vessel should be atleast 5% more than the working capacity.	Acceptable	IQ & OQ	
9.	Vessel	No sight and light glass provided. Viewing of product level inside vessel not possible.	Yes	Need for inspection & monitoring of product inside the vessel.	No	NA	Medium	Sight Glass & Light Glass should be provided in the vessel.	Acceptable	IQ	
10.	Sight and Light Glass	Non- sanitary type	Yes	Connected to the manufacturing vessel. May lead to product contamination.	No	NA	High	Sight glass & Light glass should be of sanitary design.	Acceptable	IQ	

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11.	Nozzle height	Nozzle connection height is too long.	Yes	Air pockets may be created at nozzles connections during SIP.	No	NA	High	The height of nozzles should be minimized and kept preferably at <1.5D.	Acceptable	IQ	
12.	Vessel	Product temperature inside vessel/ vessel temperature during SIP could not be monitored.	Yes	Product may not be maintained as per specification. SIP not possible.	No	NA	High	• Temperature sensor cum controller should be provided for monitoring of product temperature or SIP temperature inside vessel. • Alarm provision in case low/ high temperature of product or during SIP.	Acceptable	IQ & OQ	
13.	Vessel	Breathing nozzle is in direct contact with atmospheric air.	Yes	Environmental contamination of product solution from breathing nozzle.	No	NA	High	Holding vessel should be provided with hydrophobic type of Sterilizable grade vent filter (porosity – 0.2 µm) with SS housing.	Acceptable	IQ	
14.	Load Cell	Malfunctioning of the Load cells	Yes	Improper sensing of product level inside the vessel.	No	NA	High	• 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,	Acceptable	IQ, OQ & SOP	

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15.	Vent Filter	• Filter choking/ leakage. • Filter integrity test not possible.	Yes	Risk of contamination of product inside vessel.	No	NA	High	• 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.	Acceptable	IQ, OQ & SOP	
16.	Vent Filter	Filter may be damaged during SIP or efficiency may decrease.	Yes	Risk of contamination of product inside vessel.	No	NA	High	Sterilizable grade filters (porosity – 0.2 µm) should be installed on the Compressed air inlet line to vessel.	Acceptable	IQ	
17.	Vent Filter	Affected by the high temp. During the process	Yes	Filter efficiency will decrease leading to further contamination of the products under process.	No	NA	High	• 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 interval as per SOP.	Acceptable	IQ & SOP	

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18.	Vent Filter	No SIP of filter and filter housing possible	Yes	Contamination of equipment or product possible	No	NA	High	• 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.	Acceptable	OQ	
19.	Vent Filter	Filter housing drain ability is not sufficient	Yes	Filter must be dry, If not dry it may lead to microbiological contamination	No	NA	High	The filter housing should be self draining type.	Acceptable	IQ	
20.	Vent Filter	Wrong cartridge material for sterile filters	Yes	Damage / blockage of filter possible	No	NA	High	• Types of filter cartridges should be defined. • Filter certificates have to be available.	Acceptable	IQ	
21.	Vent Filter	Non Resistant to excess pressure of the supply utilities.	Yes	Damaged filter leads to inefficient sterilization process	No	NA	High	• 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.	Acceptable	IQ	

Discharging of Output

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22.	Product Discharge	The design of the vessel outlet valve not appropriate.	Yes	Product could not be discharged completely	No	NA	High	• 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.	Acceptable	IQ & OQ	
23.	Product Discharge	Nitrogen gas used for product transfer is not sterile.	Yes	May contaminate the product.	No	NA	High	Sterilizable grade filter (porosity – 0.2 µm) should be provided at Nitrogen gas inlet line before vessel.	Acceptable	IQ	
Equipment Construction											

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24.	MOC	Internal surface/ contact parts are not compatible with the product solution.	Yes	May lead to product contamination	No	NA	High	• 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.	Acceptable	IQ	
25.	Polymeric materials	• Polymeric materials are not compatible with product. • Polymeric material not replaceable.	Yes	May lead to product contamination	No	NA	High	• 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.	Acceptable	IQ	

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26.	Welding Joints	Uneven and improperly ground weld joints will form a space for dust accumulation	Yes	Weld joints not grounded properly and are not passivated.	No	NA	High	• 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.	Acceptable	IQ	
27.	Finishing	Accumulation of dust, particles on internal surfaces; possibility of microbial growth and hence product contamination.	Yes	Internal surface finish of contact parts is not proper	No	NA	High	• 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.	Acceptable	IQ	
28.	Joints	Leaking joints may lead to contamination of product.	Yes	Joints are not air tight. Suitable gaskets are not provided or are not replaceable	No	NA	High	Suitable gaskets should be provided for air tight triclover connection and should be easily replaceable.	Acceptable	IQ	
CIP Process											

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29.	Cleaning	Difficult cleaning	Yes	Accumulation of particles, contamination of clean room possible.	No	NA	High	• 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 dome nut.	Acceptable	IQ	
30.	Cleaning	Inefficient cleaning process	Yes	Contamination of product possible	No	NA	High	• 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.	Acceptable	OQ & Cleaning Validation	
31.	Cleaning	No provision of recirculation of cleaning media	Yes	Cleaning process may not be efficient.	Operational	Loss of cleaning media	High	A discharge pump should be provided at the vessel outlet for recirculating cleaning media.	Acceptable	IQ	

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32.	Cleaning	Malfunctioning of discharge pump; pump overload	Yes	CIP process would be affected	No	NA	High	• 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.	Acceptable	IQ & OQ	
33.	Cleaning	Determination of CIP end point not possible.	Yes	CIP process not proper or validated	No	NA	High	• Conductivity sensor should be provided on the 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.	Acceptable	IQ & OQ	
34.	Cleaning	Cleaning media could not reach to all parts of the vessel.	Yes	Cleaning not uniform inside vessel. Product contamination possible.	No	NA	High	• 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.	Acceptable	IQ & OQ	

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35.	Cleaning	Particle accumulation inside spray ball; not of sanitary design	Yes	Could lead to product contamination.	No	NA	High	Static spray ball of sanitary design should be installed inside the vessel for CIP process.	Acceptable	IQ	
36.	Cleaning	CIP cycle time not controlled / measured	Yes	Vessel not cleaned/ washed properly due to cycle time too short.	No	NA	High	• CIP process should have settable parameters. • Different recipes should be available for different vessel sizes.	Acceptable	OQ	
37.	Cleaning	Compressed air pressure too low	Yes	Equipment's operation will be disturbed.	No	NA	High	• Pressure switch/ gauge along with pressure regulator should be provided for control and monitoring of compressed air pressure. • Alarm provided if pressure low.	Acceptable	IQ & OQ	
38.	Cleaning	Final rinsing step is not with hot WFI.	Yes	Insufficient removal of contaminants from the vessel. Inefficient cleaning success; product contamination.	No	NA	High	Final cleaning step should be designed with hot WFI.	Acceptable	OQ	

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39.	Cleaning	Slope of cleaning media piping too low.	Yes	• Pipelines cannot be drained completely. • Insufficient cleaning. • Risk of contamination / microbial growth in piping possible	No	NA	High	• 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).	Acceptable	IQ	
40.	Cleaning	Labeling of components/ media inappropriate	Yes	Prerequisite for qualification & maintenance	No	NA	Medium	• 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.	Acceptable	IQ	
SIP Process											

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41.	SIP process	SIP of vessel not possible.	Yes	Possibility of microbial growth inside vessel; product contamination	No	NA	High	• A suitable SIP process should be provided in the PLC for effective sterilization of the holding vessel and interconnecting pipelines. • Pure Steam supply should be provisioned to the vessel for heating during SIP. • Temperature sensor should be provided inside the holding 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.	Acceptable	IQ & OQ	

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42.	SIP process	SIP of the vent filter and housing not possible.	Yes	Contamination of vessel due to non-sterile vent filter	No	NA	High	• 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.	Acceptable	IQ & OQ	
43.	SIP process	Possibility of human error leads to a CIP or SIP procedure which is not validated	Yes	CIP & SIP process parameters are not controlled automatically	No	NA	High	• CIP & SIP process should be performed by an automatically controlled system. • Suitable PLC control should be considered	Acceptable	OQ	
44.	SIP Process	Contamination of vessel after completion of SIP process; contamination of already sterilized vessel and its components.	Yes	Positive pressure not maintained after completion of SIP process.	No	NA	High	• A positive supply of sterile Nitrogen gas 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.	Acceptable	OQ	

RISK ASSESSMENT FOR HOLDING VESSEL

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								Mitigation Method (9a)	Residual risk level (9b)	Verification (9c)	
45.	SIP Process	Low/ Overshoot temperature during Sterilization hold	Yes	SIP process out of validated procedure.	No	NA	High	Alarm provision should be provided in case temperature goes out of limit during sterilization hold.	Acceptable	OQ	
46.	CIP & SIP Process	CIP & SIP process parameters are not controlled automatically.	Yes	Possibility of human error leads to a CIP or SIP procedure which is not validated.	No	NA	High	• CIP & SIP process should be performed by an automatically controlled system. • Suitable PLC control should be considered.	Acceptable	OQ	
Control System											
47.	PLC / Control system	Process parameters are not controlled automatically.	Yes	Possibility of human error leads to a process which is not validated	No	Na	High	• The equipment shall control & detect failure mode automatically. • The System shall be PLC based and fully automatic.	Acceptable	IQ & OQ	
48.	PLC / Control system	Process / process status not visible for operating personnel.	Yes	Operating personnel must have knowledge on the process status	No	NA	High	MMI shall be provided with adequate display and clean room suitable key board for operation and entering process parameters.	Acceptable	IQ	
49.	PLC / Control system	Display language not identified.	Yes	Pre-requisite for the GMP compliant operation	No	NA	High	The language on the display of MMI should be English language only.	Acceptable	OQ	

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50.	PLC / Control system	Recorder failure	Yes	Basis GMP requirement (incomplete / no documentation)	No	NA	High	• 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.	Acceptable	OQ	
51.	PLC / Control system	Monitoring/recording and documentation of GMP relevant data not possible	Yes	Basic GMP requirement	No	NA	High	• 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.	Acceptable	OQ	
52.	PLC / Control system	Control system does not detect failures and generate alarms	Yes	Process optimization and validation is not possible	No	NA	High	Failure of set parameters gets indicated and printed as alarms and machine stops.	Acceptable	OQ	
53.	PLC / Control system	Power failure / emergency stop	Yes	Process out of specification	EHS	May lead to some accident	High	• 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 holding vessel'.	Acceptable	OQ & SOP	

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54.	PLC / Control system	Status parameters not clear	Yes	Process for the particular product at particular stage can't be regulated easily.	No	NA	High	• 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.	Acceptable	OQ	
55.	PLC / Control system	Malfunction	Yes	Correct function basic requirement for GMP-compliant operation	No	NA	High	• 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.	Acceptable	OQ	
56.	PLC / Control system	Parameter settings not identified universally	Yes	Basic GMP requirement	No	NA	High	Parameters settings should be in numeric only.	Acceptable	OQ	
57.	PLC / Control system	Time measurement works incorrect.	Yes	Process insufficient	No	NA	High	• PLC Clock verification • SOP "calibration and maintenance" • Time synchronisation of system	Acceptable	OQ & SOP	

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58.	PLC / Control system	No protection of PLC against manipulation & changes.	Yes	Basic GMP requirement.	No	NA	High	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.	Acceptable	OQ	
Measuring Instrument											
59.	Measuring Instruments	Measuring Instruments not suitable	Yes	Improper measurements	No	NA	High	▪ Measuring Instruments must have a suitable measuring range. ▪ Operational range of Measuring Instruments > equipment working range. ▪ Measuring Instruments must have appropriate accuracy.	Acceptable	IQ	
60.	Measuring instruments	Measuring instruments not calibrated	Yes	Non calibrated measuring instruments may lead to false machine functions	No	NA	High	● Measuring instruments should be calibrated, traceable to national or international standards. ▪ Re-calibration of instruments should be possible.	Acceptable	IQ	
61.	GMP relevant measurement instruments	Instruments cannot be dismounted	Yes	Defective instruments must be dismounted for exchange and calibration	No	NA	High	▪ Mounting of instruments must give the possibility for dismounting and replacement ▪ Constructional solution: easy access for re-calibration activities shall be given.	Acceptable	IQ	

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Maintenance											
62.	Maintenance	Malfunctions due to worn parts	Yes	Basic GMP requirement	No	NA	High	▪ Vessel shall be easy to maintain. ▪ Preventive maintenance procedure should be available. ▪ Vendor to provide special tools for maintenance. ▪ The unit must contain necessary protection devices to ensure that the equipment & the article remain in a safe condition.	Acceptable	IQ & SOP	
Environment & Safety											
63.	Electrical system	Electrical systems are not verified for safety	No	It will not affect the quality of product.	EHS	May lead to an accident	Medium	All electrical systems shall be tested for safety and shall be provided with safety markings e.g. C.E. marking.	Acceptable	IQ	
64.	Noise level	Noise level liberated by the system is high.	No	It will not affect the final quality of product.	EHS	Heavy noise will cause problems to the service persons	Medium	The noise liberated by the system shall not be more than 75 db from 1m from the system.	Acceptable	OQ	
65.	Emergency stop	Instantaneous stopping of the equipment not possible	No	Does not have any impact on quality of the product	EHS	Emergency stop function is required for equipment, personnel and product protection	High	Emergency stop with alarm to be installed on accessible area.	Acceptable	IQ & OQ	

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66.	Heating inside vessel during SIP	Excess heating & Excess pressure	No	Does not have any impact on quality of the product.	EHS	Environmental & operator safety hazards.	Medium	▪ Temperature & Pressure limit for the resistance of the vessel should be defined & feeded. ▪ Warning stickers on all hot surfaces must be provided to protect personnel, product and equipment. ▪ Elevated temp. & pressure should be alarmed leading to the opening of the safety valve of chamber & jacket.	Acceptable	IQ & OQ	
67.	Pure Steam	High pure steam pressure	No	Does not impact the quality of product.	Safety & Operational	Environmental & operator safety hazards	High	• Sanitary pressure regulated valve and safety relief valve shall be installed on pure steam line. • Alarm provision shall be provided.	Acceptable	IQ & OQ	
68.	Holding vessel	High emission of heat	Yes	Disturb room temperature and relative humidity.	EHS	Environment & Personnel safety hazards	High	▪ 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.	Acceptable	IQ	

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69.	Skid Piping (Steam & Product transfer line)	High emission of heat	Yes	Disturb room temperature and relative humidity.	EHS	Environment & Personnel safety hazards	High	• 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 Non-shredding type.	Acceptable	IQ	
Documentation											
70.	User	Faulty operation & maintenance	Yes	SOPs are basic GMP-requirement	No	NA	High	▪ 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.	Acceptable	OQ & SOP	
71.	User	Operation SOP does not contain proper information and user may operate system	Yes	User may make a wrong decision.	No	NA	High	▪ 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.	Acceptable	OQ	

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72.	User	Unauthorized person tries to start/stop the system	Yes	Untrained persons may damage the system or product quality may be affected	No	NA	High	• System should not start without password. • Key-switch should be provided for system power up. OR • Physical entry to equipment room is restricted.	Acceptable	IQ & OQ	
73.	Documentation	Technical documentation from vendor not adequate	Yes	Adequate technical documentation is basic GMP requirement	No	NA	High	• Vendor documentation shall comprise: - Material certificates - DQ, IQ & OQ protocols - O & M manuals - Bought out components manuals - Spare parts list - Welding report - Hydrotest certificate - Functional design specification - List of failure indications - Surface finish test reports - HMI functions with screen shots • Drawings - P&I-diagram - Electrical diagrams - GA diagram • Calibration certificates of measuring instruments	Acceptable	IQ	

8 Summary & Conclusion

- The Risk Assessment was performed to establish the design parameters of the equipment so as to meet the desired performance of the equipment i.e. holding Vessel.
- The critical risks pertained to GMP and other than GMP, were analyzed with justification and mitigation procedures.
- For each recognized GMP-risk and other than GMP risks, necessary measures are defined. Organizational measures, like SOPs, are also possible measures for special GMP-risks. The availability of these SOPs will be checked during the performance of the OQ.
- The risks where conceptual procedures shall be employed, standard operating procedures (SOPs), Preventive maintenance schedules, Certificates and related documents indicated as mitigation procedures shall be ensured at respective test points

*"It is concluded that the **Risk Assessment** performed for the equipment will prevent the risk of failures of critical parameters during, design commissioning, installation, operation and performance of the equipment".*

9 Abbreviations

EU-GMP	:	European – Good Manufacturing Practice
EHS	:	Environment Health Safety
GMP	:	Good Manufacturing Practice
PTFE	:	Polytetrafluoroethylene
SIP	:	Sterilization in place
RA	:	Risk Assessment
NMT	:	Not More Than
SOP	:	Standard Operating Procedure
SS	:	Stainless Steel
Ra	:	Roughness Average
P&ID	:	Process/ Piping & Instrumentation Diagram
PLC	:	Programmable Logic Controller
MMI	:	Man Machine Interface
CFR	:	Code of Federal Regulations
CIP	:	Cleaning In Place
UPS	:	Uninterrupted Power Supply
CE	:	Conformité Européene
db	:	Decibel
FS	:	Functional Specification
IQ	:	Installation Qualification
OQ	:	Operational Qualification
PQ	:	Performance Qualification
O&M	:	Operation and Maintenance
GA	:	General Arrangement
IPSI	:	Integrated Project Services International, New Delhi

10 Revision History

Date	Revision	Reason for Revision
	00	New Document