Risk Assessment Document
For
Vial Filling & Stoppering Machine

RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

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RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

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 Vial Filling & Stoppering Machine which shall consist of the following main components:

The Vial Filling & Stoppering machine shall be an automatic machine with preferably 8 different stations to fill 8 vials at a time and stoppering the filled vials.

The sterilized and depyrogenated vials shall be transported from the upstream depyrogenation tunnel into the filling and stoppering machine via infeed turn table, infeed transfer system and star wheels.

From the infeed star wheel the vials shall be handed over to infeed conveyor, which shall transport the vials through the filling and stoppering machine.

IPC tare weighing and gross weighing stations with star wheels shall be provided before and after filling, for checking weight of product filled. Pre and post –gassing station for vials shall also be provided before and after filling.

At the filling station, the vials shall be filled with required volume of product solution, using rotary piston pumps. After IPC gross weighing station, the vials shall be transported via the conveying system to the stopper inserting station. At the stopper inserting station the vials shall be inserted with stoppers and the stoppers shall be pressed down. The machine shall be suitable for both type of stoppering i.e. half stoppering (for products to be lyophilized) and full stoppering (for liquid filled product). During stopper inserting also, the vials shall be gassed with inert gas. The vials shall then be checked for stopper presence. Faulty detected vials shall be rejected in the reject station via reject star wheel.

The machine discharge shall consist of a discharge conveyor and two discharge turn round discs. At the machine discharge there shall be two possibilities for the downstream vial transport:

- Transport for vials with liquid product via conveyor to Vial sealing machine.
- Transport for vials with liquid product to freeze dryer (FD) via conveyor to Automatic Loading-Unloading System.

Most of the possible risk concerning the handling/ operation of the Vial Filling & Stoppering Machine 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.

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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 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.

Level	Descriptor	Example detail description
		• 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 procedure

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.

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Column 8	:	**Risk level:** Determine the risk level as High, Medium or low based on the impact.
Column 9	:	**Existing 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	:	**Proposed Additional Risk control measure:** Write the additional risk control measures which needs to be taken in case the existing risk control measures are insufficient to bring the residual risk level to low
Column 11	:	**Revised Residual Risk level:** After the additional risk mitigation what is the residual risk level i.e. Low, Medium or High
Column 12	:	**Mitigation Proposal:** Write the reference document where the additional risk mitigation strategy shall be verified i.e. reference number of CAPA/ Change Control, any new SOP or IQ, OQ or PQ addendum
Column 13	:	**Status of RA**: Mention the status of RA whether it is open or closed

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Input & Charging														
1.	Vial size	Equipment not suitable for different size of vials	No	No impact on product quality	Operational	Different vial sizes may not be processed with same equipment.	Medium	Equipment is suitable for filling & stoppering of different sizes of vials by changing format (change) parts.	Low	DQ	▪ Change parts for different vial size shall be provided by vendor, along with the equipment, as per requirement. ▪ Functionality shall be checked during qualification studies.	Low	IQ & OQ	

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2.	Transfer of vials	Overturned/ fallen vials on the infeed conveyor belt.	Yes	Vial jamming, vial damage or rupture may take place	No	NA	High	▪ Mechanical ejection system is provided at infeed turn table for removal of overturned/ fallen vials. ▪ Infeed star wheel is provided after infeed turn table. Overturn/ fallen vials on star wheel will result in jamming and machine stoppage.	Low	DQ	▪ Speed of the infeed turn table shall be controlled through control system through VFD, to stop the jerk & allow smooth flow, preventing vials from overturning/ falling. ▪ Transfer system shall be designed in a way to prevent falling of vials entering infeed conveyor.	Low	IQ & OQ	
3.	Transfer of Vials	Improper positioning of vials during transfer to filling station.	Yes	Filling shall not be proper; product spillage may occur.	Operational	Product loss	High	The design of the system ensures that individual vials are transferred and positioned properly below the filling needles at filling station.	Low	DQ	Functionality shall be checked during qualification studies.	Low	OQ	

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4.	Transfer of vials from tunnel to filling station	Depyrogenated vials travel through unclean (unclassified) environment	Yes	Particle contamination of vial; micro-biological contamination possible	No	NA	High	The transfer of vials is performed under unidirectional air flow unit (Grade A).	Low	DQ	Classification level shall be verified and qualified during qualification.	Low	IQ & OQ	
5.	Transfer of product	Contamination of product while transfer from holding vessel.	Yes	Product failure	No	NA	High	The product transfer is through a closed system wherein sterile product shall be transferred using either peristaltic pump or through Nitrogen gas pressure, from holding vessel to buffer tank (placed on filling machine), through sterilizable grade filter (0.2 µm), whenever applicable.	Low	DQ	The complete transfer system shall be sterilized routinely through autoclave/ SIP, before every batch, as per SOP.	Low	IQ & OQ	
6.	Transfer of Vials	Vials minimum load on the infeed turn table	Yes	No vials supplied to the vial filling machine; product spillage.	Operational	Product loss	High	Vials minimum load detection sensor is provided on the infeed turn table to detect the low accumulation of vials along with alarm provision.	Low	DQ	Machine should go into standby mode in case of low vials at infeed turn table.	Low	IQ & OQ	
Process														

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7.	Transfer of product from holding vessel to buffer tank (on filling machine)	Connection of transfer line to buffer tank not in Grade A environment.	Yes	Particle contamination of product; micro-biological contamination possible	No	NA	High	All the connections to the buffer tank is performed under Grade A conditions.	Low	DQ	Classification level shall be verified and qualified during qualification	Low	IQ & OQ	
8.	Filling & stoppering	Filling & Stoppering carried out under unclean environment.	Yes	Grade A and unidirectional airflow is requirement for performing aseptic filling & stoppering process.	No	NA	High	Unidirectional Air Flow system (Grade A) is provided over complete filling & stoppering machine.	Low	DQ	Classification level shall be verified and qualified during qualification.	Low	IQ & OQ	
9.	Ceramic Piston pump and needles	Material reacts with the products	Yes	Contamination of sterile product.	No	NA	High	Ceramic piston pumps & needles are provided for filling machine.	Low	DQ	▪ Functionality shall be checked during qualification studies. ▪ Sterilization shall be performed as per respective SOPs.	Low	IQ, OQ & SOP	

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10.	Dosing pumps	Incorrect product dosing in pumps	Yes	Inefficient filling; leading to wrong dosage.	Operational	Vial with incorrect product amount shall be rejected; Product loss	High	▪ The system performs priming of the piston pumps before filling to remove any air bubbles, which may lead to incorrect filling. ▪ The system performs teaching of peristaltic pump system before filling to ensure proper fill volume.	Low	DQ	▪ Rotary piston pump & peristaltic pump (if applicable) movement shall be synchronized with the transport movement before filling ▪ The rotary piston pump and peristaltic pump design shall be appropriate and ensure that required amount of product is filled inside vials.	Low	IQ, OQ & PQ	

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11.	Product transfer line from buffer tank to filling needle	Product contact parts of equipment contaminated; cannot be sterilized	Yes	Contamination of sterile product.	EHS	Health safety risk to consumers.	High	All product contact parts of equipment are removable type and sterilizable grade and could sustain steam sterilizable for validated time.	Low	DQ	▪ Functionality shall be checked during qualification studies. ▪ Sterilization shall be performed as per respective SOPs.	Low	IQ, OQ & SOP	
12.	Dosing	▪ Automatic change in fill volume not possible. ▪ Different range of filling volume could not be achieved.	Yes	Incorrect dosage; different quantity of fill volume as per available vial sizes not possible.	No	NA	High	Different rotary piston pump sets are provided by vendor for different range of filling volume, to ensure accurate volume.	Low	DQ	Fill volume set point adjustment should be possible through control system.	Low	IQ & OQ	
13.	Filling	Presence of headspace oxygen	Yes	Chance of product degradation; microbial contamination due to presence of air.	No	NA	High	Pre and post nitrogen (or other suitable pharmaceutical gas) purging is included in the design based on applicable products.	Low	DQ	Control system should be able to set the pre and post nitrogen purging time and the pressure for the same.	Low	OQ	

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14.	Nitrogen/ Pharmaceutical Gas Purging	Low/ No Flow	Yes	Purging cannot be performed; filling out of validated procedure.	No	NA	High	▪ Pressure switch/ Regulator is provided at the supply line. ▪ Alarm provision is provided in case of low/ no pressure.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
15.	Nitrogen/ Pharmaceutical Gas Purging	Purging pressure too high/ cannot be adjusted.	Yes	Chances of product spillage in case of too high pressure.	No	NA	High	▪ Flow regulator is provided on nitrogen/ pharmaceutical gas flow line so as to regulate the purging gas flow, as per requirement. ▪ Alarm is provided in case of high pressure gas.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	

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16.	Nitrogen/ Pharmaceutical Gas Purging	Nitrogen/ Pharmaceutical gas quality failure	Yes	Particle contamination of vials	No	NA	High	▪ Provision of sterilizing grade filter (0.2 µm) on the nitrogen/ pharmaceutical gas line before pre-purging and post purging station. ▪ Sampling provision is provided for filtered nitrogen/ pharmaceutical gas after filters.	Medium	DQ	▪ Nitrogen/ pharmaceutical gas supply to the equipment shall be qualified or COA should be available for purity (in case cylinders are used). ▪ SOP: Monitoring and testing of Nitrogen/ pharmaceutical gas quality at regular interval.	Low	IQ , OQ & SOP	

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17.	Filling	Filling speed could not be adjusted or maintained.	Yes	Variation in output	Yes	Time loss	Medium	Counters are placed at infeed and out feed to count number of filled vials.	Low	DQ	▪ Functionality shall be checked during execution of qualification studies. ▪ The equipment control system shall be suitable to adjust & maintain the rate of vial filling (number of vials/ minute).	Low	IQ & OQ	

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18.	Filling	Product level in the buffer tank could not be monitored	Yes	Low level or no product inside buffer tank may produce wrong fill in vials.	No	NA	High	▪ Load cell (or any other suitable provision) is provided for monitoring product solution level inside buffer tank. ▪ In case of low level of product inside buffer tank, alarm is generated and filling will stop.	Low	DQ	▪ Calibration of load cells shall be performed routinely as per SOP. ▪ In case product level is below required level, the inlet valve shall open and product from holding vessel should be transferred automatically to buffer tank.	Low	IQ , OQ & SOP	

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19.	Filling	Filling accuracy not proper.	Yes	Product vials without constant fill volume shall be filled.	Operational	Product loss	High	▪ Check weighing system) is installed before and after filling to check fill weight and ensure fill volume accuracy. ▪ Vials will pass through check-weighing system (on frequency basis as per requirement), so as to ensure proper fill volume.	Medium	DQ	▪ Filling volume accuracy shall be verified during qualification. ▪ Dosing pump shall be appropriately design to maintain filling accuracy of ±0.5% of set volume.	Low	IQ, OQ & PQ	
20.	Filling	Check-weighing system may not indicate proper weight of vials due to high static load of vials.	Yes	Incorrect fill volume result shall be provided; good vials shall be rejected.	Operational	Yield Loss	High	The check-weighing station is separate from the main conveyor by star wheels.	Low	DQ	Routine calibration of check-weighing system shall be performed as per SOP.	Low	IQ & SOP	
21.	Filling	Vials with incorrect fill volume get discharged to the downstream equipment.	Yes	Vials with incorrect fill volume may be processed further.	No	NA	High	Auto-rejection system is provided after filling & stoppering station to separate and reject vials with fill volume out of range, along with alarm provision.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	

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22.	Filling	Check-weighing system is not working/ malfunctioning	Yes	Improper filled vials may not be rejected and may be processed.	No	NA	High	Alarm shall be generated in case any of the check-weighing system (Tare & gross weighing) is not working.	Medium	DQ	▪ Verification of check-weighing system during qualification. ▪ Routine calibration of check-weighing system shall be performed as per SOP.	Low	OQ & SOP	
23.	Filling	Design of rotary piston pump & needle not suitable for the product.	Yes	Filling not appropriate; blockage of needle.	No	NA	High	The design of the rotary piston pump and needle is based on the nature of the product .i.e. density, viscosity, frothiness and diameter of aperture of vial.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	OQ	

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24.	Filling	Position of the filling needles could not be adjusted.	Yes	▪ Spillage of product possible. ▪ Generation of air bubbles due to gap between needle and vial surface, which might lead to product contaminatio n.	Operational	The machine may not be suitable for different size of vials.	High	▪ Filling needle height is adjustable based on different format parts, so as to be close to the vial mouth. ▪ Machine is suitable for filling of different sizes of vials by adjusting height of the filling needle automatically as per different vial size.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
25.	Filling	Vial not present on filling station	Yes	Contamination of filling machine with product due to spillage.	Operational	Yield loss	High	▪ No Vial-No filling function is provided in the system. ▪ Sensor is provided before filling station to check and assure the presence of vials.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
26.	Filling	Dripping of products from filling needles	Yes	Contamination of filling machine and product loss	No	NA	High	The design viz., the SS rotary piston pump/ peristaltic pump and needles movement ensures that no dripping takes place after filling.	Low	DQ	Back suction provision for filling needles should be provided in the control system to prevent dripping.	Low	OQ	

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27.	Stoppering	Sterility failure of stoppers	Yes	Contamination of filled product	No	NA	High	▪ Charging of stoppers to feeding hopper is performed under LAF (Grade A). ▪ Transfer of stopper from hopper to vibratory bowl and transfer chute is performed under Grade A environment.	Low	DQ	▪ Classification level shall be verified during qualification. • SOP should mention procedure for transfer of sterile stoppers.	Low	IQ, OQ & SOP	
28.	Stoppering	No stopper in bowl	Yes	Vial will not be stoppered	No	NA	High	▪ Sensor is provided to monitor level of bungs in vibratory bowl. ▪ In case of low level in bowl, bungs from hopper will transfer automatically to bowl.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
29.	Stoppering	Low level of stopper at chute/ track	Yes	Vial will not be stoppered	No	NA	High	▪ Sensor is provided on stopper track (s) for detecting minimum level of stoppers. ▪ Alarm will provide in case of low level, along with machine stoppage.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	

RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

S. No. (1)	Process steps/ Component (2)	Risk (3)	GMP Risk Yes/ No	Justification	Other Risk type	Justification	Risk Level	Existing Risk Control			Proposed Additional Risk control measure (Mandatory for risk having Residual Risk Level as Medium or high)	Revised Residual Risk level	Mitigation Proposal (Mention either CAPA/ Change Control reference number, SOP, IQ, OQ or PQ)	Status of RA
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30.	Stoppering	No vial at stoppering station	Yes	Stoppers shall be spilled inside the filling area.	No	NA	High	▪ No vial- no stoppering system is provided. ▪ Sensor is provided to check presence of stoppers on vials after stoppering station.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
31.	Stoppering	Stoppering machine not suitable for all kind of stopper e.g. lyo stopper.	Yes	Machine is not suitable for operation for vials for Lyophilization.	No	NA	High	Machine is suitable for all sizes and kind of stoppers i.e. 20 mm and 13 mm, normal stopper and lyo stopper	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
32.	Stoppering	Machine not suitable for different type of stoppering i.e. half stoppering or full stoppering	Yes	Lyophilized vials could not be processed	No	NA	High	The machine is suitable for performing both type of stoppering i.e. half stoppering or full stoppering.	Low	DQ	The same could be set easily in the control system	Low	OQ	
33.	Stoppering	Incorrect presentation of stoppers at stoppering station	Yes	Incorrect stoppering of vials	No	NA	High	Provision of vibrating bowl feeder accompanied with feeding track and pick & place for correct presentation of stoppers at stoppering station.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	

RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

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34.	Stoppering	Low vacuum	Yes	Stoppering activity shall be impacted.	No	NA	High	▪ Pressure switch/ regulator is provided on vacuum supply line. ▪ Low vacuum will be alarmed.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
35.	Stoppering	Vial without stopper may move ahead in the process.	Yes	Improper sealing/ lyophilization	No	NA	High	▪ Sensor is provided to sense the presence of stopper after stoppering station. ▪ Vials without stopper is bypassed to the different route and rejected.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
36.	Stoppering	Stoppering station height not adjustable.	Yes	Improper bunging for different size of vials.	No	NA	High	Provision for adjusting the bunging height level is provided as per vial size.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	OQ	
37.	Utility	Inadequate or low pressure of compressed air	Yes	Process may be affected	No	NA	High	Pressure switch/ transmitter is provided on compressed air inlet line along with alarm provision in case of low pressure.	Medium	DQ	Machine shall stop in case of insufficient pressure of the compressed air.	Low	IQ & OQ	
Discharge														

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38.	Transfer to downstream equipment	Filled & stoppered vials are exposed to environmental air during transfer to sealing machine or lyophilizer Auto Loading-Unloading system.	Yes	Contamination of product filled vials may occur.	No	NA	High	The vials are transferred through online conveyor to the Lyophilizer collection unit or Sealing machine under LAF (Grade A) environment.	Medium	DQ	Classification level shall be verified and qualified during qualification.	Low	IQ & OQ	
39.	Transfer of filled and stoppered vials	Vials get stuck in the discharge wheel/ guide.	Yes	Damage of vials	Operational	Product loss due to damage of filled vials.	High	▪ The discharge wheel/ guide is designed in a way to avoid vials from getting stuck. ▪ The discharge wheel movement is sync with the main filling machine movement.	Low	DQ	Vial jamming should lead to an alarm, leading to immediate stopping of machine.	Low	OQ	
40.	Filling and Transfer to downstream equipment	Unidirectional air flow/ Laminarity not maintained under LAF during filling or during transfer of vials to sealing machine or lyophilizer collection unit.	Yes	Turbulent flow may increase particulate count and contaminate product.	No	NA	High	oRABs or Transparent safety glass/ acrylic doors is provided (up to working level height) over the entire filling and discharge line to sealing and lyophilizer collection unit to maintain laminarity.	Low	DQ	Air flow study shall be conducted to demonstrate laminarity.	Low	IQ & OQ	

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41.	Outfeed	Maximum accumulation at out feed.	Yes	Vial filing machine operation may continue leading to accumulation of vials, which may lead to vial breakage.	No	NA	High	Out feed occupancy sensor shall be provided.	Low	DQ	Vial filling & stoppering machine shall stop in case of full capacity at out feed.	Low	IQ & OQ	
42.	Discharge	Online conveying of stoppered product vials to lyophilizer collection unit or sealing machine (as per requirement) is not possible.	Yes	Chances of contamination of product filed vials due to operator handling/	No	NA	High	▪ Online conveying system is provided at discharge side, so as to transfer the filled vial under Grade A environment to either lyophilizer collection unit or to Sealing machine as per requirement. ▪ Automatic lyo loading-unloading system unit is provided at the end of conveyor for collection of vials to be loaded to lyophilizer.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
Filters														

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43.	Filter (Nitrogen, Vacuum, Pharmaceutical gases line)	No sterile filters, filter test failure	Yes	Basic requirement. Product contamination possible.	No	NA	High	Hydrophobic, sterilizable grade filter (0.2 micron) is provided at the terminals of Nitrogen/ vacuum/ Pharmaceutical gas line of filling machine.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
44.	Filter (Nitrogen, Vacuum, Pharmaceutical gases line)	No filter test possible	Yes	Filter integrity could not be verified; in case of leakage may lead to product contamination	No	NA	High	Online & offline integrity testing of the filters is possible.	Low	DQ	Filter integrity testing shall be performed at regular intervals as per SOP.	Low	DQ	
Equipment Construction- Internal Surface														
45.	Metallic components in direct contact with vials/ product media/ compressed air	The material may not be suitable; may contaminate Vials during or after filling.	Yes	MOC not resistant - Interaction with product solution possible	No	NA	High	• Metallic critical contact surfaces is constructed of 316 grade stainless steel or better, electro polished, orbitally welded. • Supporting structure and non-contact parts shall be made up of SS 304 or better.	Low	DQ	The suitability of the materials shall be proven by certificate/ manufacturers declarations	Low	IQ	

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46.	Polymeric materials	Polymeric materials are not compatible and are not replaceable	Yes	Shall lead to contamination of Vials.	No	NA	High	Gaskets and O-rings coming in direct/ indirect contact surfaces is made up of food grade polymeric materials only and shall be high temperature and pressure resistant.	Low	DQ	• Food grade polymeric material certificate/ declaration have to be provided by vendor • The easy change of gaskets should be possible.	Low	IQ	
47.	Welding Joints	Weld joints not grounded properly and are not passivated	Yes	Uneven and improperly ground weld joints will form a space for dust accumulation.	No	Na	High	All welds are ground finished and properly passivated and orbital welding is to be performed, wherever possible.	Low	DQ	Weld reports/ certificate/ declaration have to be provided by vendor.	Low	IQ	
48.	Metallic contact parts.	Internal surface finishing insufficient	Yes	May lead to improper cleaning of the surface which will lead to microbial growth hence Vial contamination	No	NA	High	Internal surface is constructed of 316 grade stainless steel or better, electro polished, orbitally welded.	Low	DQ	The suitability of the materials & roughness, Ra ≤ 0.8 µm shall be proven by certificate/ manufacturers declarations.	Low	IQ	

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49.	Joints	Joints are leaking	Yes	May lead to contamination of water which may finally lead to contamination of Vial.	Operational	Water may spill in the clean room.	High	• Suitable gaskets are provided for air tight connection and which are replaceable. • Quick release Tri-clover joints are provided in design.	Low	DQ	NA	Low	IQ	
Equipment Construction- External Surface														
50.	Surface	External surface of equipment is not suitable	Yes	May lead to the clean room contamination	No	NA	Medium	Supporting structures and frames installed inside clean rooms are made up of SS 304 or better grade stainless steel.	Low	DQ	The suitability of the materials shall be proven by certificate/ manufacturers declarations.	Low	IQ	
51.	Finishing	External finish of equipment is not proper.	Yes	May lead to the microbial growth	No	NA	Medium	NA	Medium	NA	External surface should be free from sharp edges, corners, crevices etc., all metallic external surface shall be matt or mirror finished.	Low	IQ	
Cleaning														

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52.	Cleaning	Difficult cleaning	Yes	Accumulation of particles, contamination of clean room possible	No	NA	High	All bolts, nuts on the exterior part of equipment is made as per clean room design, for e.g. provided with dome nuts, etc.	Medium	DQ	• Parts which are required for cleaning shall be provided with quick fixing arrangement • The design of the complete equipment shall ensure adequate clean ability (smooth, SS 316 or better surface).	Low	IQ	
53.	Labeling of components	Labeling of components/ media inappropriate	Yes	Prerequisite for qualification &maintenance	No	NA	Mediu m	Unique identity number/ flow direction is provided on components/ media, operator panel, etc. (e.g. according to P&ID).	Low	DQ	All labelling shall be done in English language and according to P&ID	Low	IQ	
PLC/ Control System														
54.	Process automation	Process parameters are not controlled automatically.	Yes	Possibility of human error leads to a process which is not validated	No	NA	High	The System is PLC based and fully automatic.	Low	DQ	The equipment shall control & detect failure mode automatically.	Low	IQ & OQ	

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55.	Man-machine Interface	Process / process status not visible for operating personnel.	Yes	Operating personnel must have knowledge on the process status	No	NA	High	MMI is provided with adequate display and clean room suitable key board/Touch screen for operation and entering process parameters.	Low	DQ	NA	Low	IQ	
56.	Man-machine Interface	Display language not identified.	Yes	Pre-requisite for the GMP compliant operation	No	NA	High	.NA	High	NA	The language on the display of MMI shall be English language	Low	OQ	
57.	Man-machine Interface	Monitoring of GMP relevant data not possible	Yes	Basic GMP requirement	No	NA	High	Printout facility is available with fade proof prints.	Medium	DQ	Monitoring of GMP relevant data should be possible	Low	OQ	
58.	Man-machine Interface	Recorder failure	Yes	Basic GMP requirement; Critical process parameters & batch report might not be saved and printed.	No	NA	High	Data backup for process data is provided (electronic recording, 21 CFR part 11 compliant).	Medium	DQ	• Diagnostic function test for the same shall be carried out as part of qualification activity. • Routine backup for process data shall be performed as per SOP.	Low	OQ, PLC Validation & SOP	

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59.	PLC/ Control system	Control system does not detect failures and generate alarms	Yes	Process optimization and validation is not possible	No	NA	High	Alarm is provided in case of any critical instrument/ sensor not working properly, loss of communication or broken wire.	Medium	DQ	• Batch records / print outs shall be defined during qualification. • Failure of set parameters should get indicated as alarms and necessary interlocks should be in place.	Low	OQ	
60.	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 are remaining displayed at each process stage. • Alarm is visualized along with the fault displayed.	Low	DQ	Verification shall be performed at the time of qualification activities.	Low	OQ	

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61.	PLC / Control system	Power failure/ emergency stop	Yes	Process out of specification	Safety	Unsafe if start automatically on restoration of power	High	• Alarm message; • On power failure equipment comes to rest to protect operator, equipment itself & the articles. • Machine is not start automatically without operator intervention after incident.	Medium	DQ	• SOP for "Operation and Maintenance of Vial Filling & Stoppering machine" should mention action to be taken in case of power failure. • Operator settings shall remain unchanged and restored after emergency stop/ power failure. • Provision of UPS to the control system.	Low	IQ, OQ & SOP	

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62.	PLC / Control system	Malfunction of control system	Yes	Correct function of control system is a basic requirement for GMP-compliant operation	No	NA	High	The equipment contains all necessary protection devices to ensure that the equipment and article remain in safe condition.	Medium	DQ	• Input/ Output test implementation during qualification activities • Control system software backup should be provided by the vendor.	Low	OQ	
63.	Accessibility to PLC	Parameter settings not identified universally	Yes	Basic GMP requirement	No	NA	High	NA	High	DQ	Parameters settings shall be in numeric only.	Low	OQ	
64.	PLC / Control system	Time measurement works incorrect	Yes	Process cannot be carried out using validated parameters.	No	NA	High	NA	High	NA	• Time verification of the system clock shall be performed at frequent intervals as per SOP. • PLC Clock verification shall be performed during qualification.	Low	OQ & SOP	

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65.	PLC / Control system	No protection of PLC against manipulation & changes.	Yes	Basic GMP requirement.	No	NA	High	Minimum 3 level password protections is provided for the system. ➢ Level 1: Operator ➢ Level 2: Supervisor ➢ Level 3: Admin/ Manager	Low	DQ	• All users shall be provided with unique passwords. • System shall allow only authorized users to access system and change parameters.	Low	OQ	
66.	PLC/ Control System	Wrong programs (Not appropriate for the designated process)	Yes	Process out of specification	No	NA	High	PLC/System is equipped with different number of programs, dedicated for different container sizes.	Low	DQ	• Verification of correct program, set values during qualification. • List of all process relevant parameters including related, programmed limits shall be described in SOP.	Low	OQ, PQ & SOP	
Measuring Instruments														

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67.	Measuring Instruments	Measuring instruments not suitable	Yes	Improper measurements	No	NA	High	• Measuring Instruments installed have suitable measuring range. • Measuring Instruments have appropriate accuracy.	Low	DQ	Operational range of Measuring Instruments > equipment's working range.	Low	IQ & OQ	
68.	Measuring instruments	Measuring instruments not calibrated and not suitable for re-calibration	Yes	Non calibrated measuring instruments may lead to false machine functions	No	NA	High	• Measuring instruments are calibrated, traceable to national or international standards. • Re-calibration of instruments is possible.	Low	DQ	Test certificate shall be verified during execution of qualification studies	Low	IQ & OQ	
69.	GMP relevant measurement instruments	Instruments cannot be dismounted	Yes	Defective instruments must be dismounted for exchange and calibration	No	NA	High	NA	Low	NA	• Mounting of instruments should give the possibility for dismounting and replacement • Constructional solution: easy access for re-calibration activities shall be provided.	Low	IQ	
Maintenance														

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70.	Maintenance	Malfunctions due to worn parts	Yes	Basic GMP requirement	No	NA	High	Preventive maintenance procedure is provided by the vendor.	Low	DQ	• The unit should contain necessary protection devices to ensure that the equipment & the article remain in a safe condition. • Preventive maintenance SOP shall be prepared • Machine shall be easy to maintain.	Low	IQ & SOP	
71.	Star wheels & Main drive	Star wheels & main drive overload	Yes	Filling process may be affected	No	NA	High	Alarm is provisioned in case of star wheels and main drive overload.	Low	DQ	Preventive maintenance of star wheels and motors shall be carried out at regular intervals as per SOP.	Low	OQ & SOP	

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72.	Change parts	Difficult maintenance & time consuming change-over	No	NA	Operational	Improper maintenance & time consuming change-over will affect the quality & productivity of the product	Medium	• Full access to the machine is provided for changing parts. • Limited number of change parts is be provided leading to efficient change-over. • Change parts for different size of vials are provided with quick-fit arrangement.	Low	DQ	The change parts should be identified by non-erasable marking.	Low	IQ & OQ	
Environment & Safety														
73.	Electrical system	• Electrical systems are not verified for safety. • Earthing not provided for equipment.	No	It will not affect the sterilization process	EHS	May lead to an accident	Medium	NA	Medium	NA	• All electrical systems shall be tested for safety and shall be provided with safety markings e.g. C.E. marking. • Electrical parts shall be covered. Proper earthing shall be provided for the equipment.	Low	IQ	

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74.	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 shall is installed on accessible area, along with alarm provision.	Low	DQ	Verification shall be performed at the time of qualification activities.	Low	IQ & OQ	
75.	Noise level	More noise is produced by the equipment during the operation.	No	Does not have any impact on quality of the product	EHS	High noise may cause deafness and anxiety	Medium	Noise level is below 75 db at a distance of 1 m from the equipment.	Low	DQ	Verification shall be performed at the time of qualification activities.	Low	OQ	
76.	Moving & electrical parts	Moving & electrical parts are not covered.	No	Does not have any impact on quality of the product	EHS	Operator safety	Medium	The main filling & stoppering machine is covered with oRABs system with glass/ acrylic door having glove ports for operation.	Low	DQ	All moving & electrical parts shall be covered properly.	Low	IQ & OQ	

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77.	Hygiene Conditions	Non-Viable and Viable particle count monitoring not possible.	Yes	Basic GMP requirement for Grade A environment.	No	NA	High	Equipment has arrangement for installing online particle counters.	Medium	DQ	▪ Position for settle plates next to critical positions shall be provided and location shall ensure that there is no disturbance. ▪ Non-viable particle count locations shall also be provided. ▪ Monitoring of particles (viable/ non-viable) shall be performed during qualification. ▪ Routine microbiological monitoring shall be performed as per SOP.	Low	IQ , OQ & SOP	

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78.	LAF (over Filling & discharge conveyor)	The air flow from LAF is not uniform or is turbulent.	Yes	Turbulent or insufficient flow may lead to particulate contamination of the product inside vials.	No	NA	High	Uniform unidirectional flow is maintained from the LAF up to the working area inside oRABs.	Low	DQ	▪ A uniform air velocity of 90 fpm ± 20% shall be maintained at the working level inside oRABs. ▪ Air velocity and smoke study shall be carried out during qualification for verification of the same.	Low	IQ & OQ	
79.	LAF (over Filling & discharge conveyor)	LAF fails/ Stops	Yes	Contamination of product is possible if machine is in operation.	No	NA	High	Machine operation is interlocked with LAF's operation, which are mounted on top of the entire filling & Stoppering machine and on its infeed and discharge side.	Low	DQ	▪ Machine shall stop in case of any LAF failure. ▪ Alarm provision shall be provided in case LAF fails/ stops.	Low	IQ & OQ	

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S. No. (1)	Process steps/ Component (2)	Risk (3)	GMP Risk Yes/ No	Justification	Other Risk type	Justification	Risk Level	Existing Risk Control			Proposed Additional Risk control measure (Mandatory for risk having Residual Risk Level as Medium or high)	Revised Residual Risk level	Mitigation Proposal (Mention either CAPA/ Change Control reference number, SOP, IQ, OQ or PQ)	Status of RA
								Risk Control	Residual risk level	Reference Document				
80.	LAF (over Filling & discharge conveyor)	HEPA Filter leakage/ Choking	Yes	In case of leakage may lead to product contamination.	No	NA	High	▪ Pre-filter is installed at the upstream of HEPA filters to prevent direct load of particles on HEPA filter ▪ Differential pressure switch/ transmitter is provided to monitor pressure across all HEPA filters of LAF, along with alarm in case of high or low DP.	Low	DQ	Integrity test of HEPA filters shall be performed during qualification and routinely as per SOP.	Low	IQ & OQ	
81.	LAF (over Filling & discharge conveyor)	HEPA filters integrity cannot be performed.	Yes	Integrity checking is a GMP requirement to check efficiency of HEPA filters.	No	NA	High	▪ Provision for injecting and monitoring PAO at the time of integrity testing of the filters is available. ▪ Downstream monitoring of HEPA filter is also possible.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	

RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

S. No. (1)	Process steps/ Component (2)	Risk (3)	GMP Risk Yes/ No	Justification	Other Risk type	Justification	Risk Level	Existing Risk Control			Proposed Additional Risk control measure (Mandatory for risk having Residual Risk Level as Medium or high)	Revised Residual Risk level	Mitigation Proposal (Mention either CAPA/ Change Control reference number, SOP, IQ, OQ or PQ)	Status of RA
								Risk Control	Residual risk level	Reference Document				
82.	oRABs access doors	oRABs access door may be opened during process.	Yes	Chances of product contamination by direct handling of operators.	EHS	Operator safety risk	High	▪ Security switches/ sensors is provided at the access doors with interlock feature with the operation of machine i.e. machine should stop immediately if oRABs access doors are opened. ▪ Alarm provision is also provided for the same.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
83.	Compressed air	Insufficient/ No pressure	Yes	Equipment operation will be disturbed	No	NA	High	Pressure gauge/ Pressure switch is provided at compressed air inlet to monitor & control compressed air pressure along with alarm provision in case of low pressure.	Low	DQ	Functionality shall be checked during execution of qualification studies.	Low	IQ & OQ	
Documentation														

RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

S. No. (1)	Process steps/ Component (2)	Risk (3)	GMP Risk Yes/ No	Justification	Other Risk type	Justification	Risk Level	Existing Risk Control			Proposed Additional Risk control measure (Mandatory for risk having Residual Risk Level as Medium or high)	Revised Residual Risk level	Mitigation Proposal (Mention either CAPA/ Change Control reference number, SOP, IQ, OQ or PQ)	Status of RA
								Risk Control	Residual risk level	Reference Document				
84.	User	Faulty operation & maintenance	Yes	SOPs are basic GMP-requirement	No	NA	High	NA	High	NA	▪ 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, trouble shooting & maintenance related activities.	Low	OQ & SOP	
85.	User	Operation SOP does not contain proper information and user may operate system	Yes	User may make a wrong decision.	No	NA	High	NA	Low	DQ	• 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.	Low	OQ & SOP	

RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

S. No. (1)	Process steps/ Component (2)	Risk (3)	GMP Risk Yes/ No	Justification	Other Risk type	Justification	Risk Level	Existing Risk Control			Proposed Additional Risk control measure (Mandatory for risk having Residual Risk Level as Medium or high)	Revised Residual Risk level	Mitigation Proposal (Mention either CAPA/ Change Control reference number, SOP, IQ, OQ or PQ)	Status of RA
								Risk Control	Residual risk level	Reference Document				
86.	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 is not start without password.	Low	DQ	Key switch should be provided for operation of the system	Low	IQ & OQ	

RISK ASSESSMENT FOR VIAL FILLING & STOPPERING MACHINE

S. No. (1)	Process steps/ Component (2)	Risk (3)	GMP Risk Yes/ No	Justification	Other Risk type	Justification	Risk Level	Existing Risk Control			Proposed Additional Risk control measure (Mandatory for risk having Residual Risk Level as Medium or high)	Revised Residual Risk level	Mitigation Proposal (Mention either CAPA/ Change Control reference number, SOP, IQ, OQ or PQ)	Status of RA
								Risk Control	Residual risk level	Reference Document				
87.	Vendor	Technical documentation from vendor not adequate	Yes	Adequate technical documentation is basic GMP requirement	No	NA	High	Following documents is provided by vendor (in English): ▪ DQ/ FS, IQ and OQ documents ▪ Welding certificates/ declaration along with welder qualification certificate. ▪ Material certificates & surface finish reports ▪ O&M manual ▪ Calibration certificates of all instruments ▪ Software backup ▪ Parts list (sufficient details - part no., supplier, type etc.) ▪ Drawings (P&ID, GA, Power wiring etc.). ▪ Certificates of bought out components. ▪ Filter certificates	Low	DQ	Verification of documents shall be performed at the time of qualification activities	Low	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. Vial filling & Stoppering Machine.
- 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
PW	:	Purified Water
RA	:	Risk Assessment
SOP	:	Standard Operating Procedure
AISI	:	American Iron and Steel Institute
Ra	:	Roughness Average
SS	:	Stainless Steel
P&ID	:	Process/ Piping & Instrumentation Diagram
PLC	:	Programmable Logic Controller
MMI	:	Man Machine Interface
CFR	:	Code of Federal Regulations
UPS	:	Uninterrupted Power Supply
CE	:	Conformité Européene
db	:	Decibel
DQ	:	Design Qualification
LAF	:	Laminar Air Flow
oRABs	:	Open Restricted Access Barrier System
DP	:	Differential Pressure
FS	:	Functional Specification
PQ	:	Performance Qualification
O&M	:	Operation and Maintenance
GA	:	General Arrangement

10 Revision History

Date	Revision	Reason for Revision