Risk Assessment Document

For

Ampoule Filling & Sealing Machine

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RISK ASSESSMENT FOR AMPOULE FILLING & SEALING 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 Ampoule Filling & Sealing Machine which shall consist of the following main components:

S. No.	Description	Purpose
1	In feed buffer Table	To feed ampoules for filling machine from depyrogenation tunnel.
2	Filling Machine and sealing	Filling of solution in ampoules and sealing

Machine should have all operation automatic with minimum manual intervention. Buffer table should have been provisioned for attachment with out-feed system of tunnel so that smooth transfer of ampoules takes place from tunnel to buffer table with interlocking.

Filling volume should be précised and can be controlled without breaking ampoules, touching any contact part of machine as well as process.

Sealing should be done by the gas burner provided with a hot suction system. The exhaust shall have the HEPA filter.

All operation should take place in aseptic area or laser system under laminar air-flow (grade A zone) with background of grade B.

The complete Ampoule Filling & Sealing machine along with the infeed and out feed transfer system shall be installed under oRABs (optional) system with Grade A classification.

Most of the possible risk concerning the handling/ operation of the Ampoule Filling & Sealing 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.
  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.

- 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.

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.

Level	Descriptor	Example detail description
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 procedure

Column 4 : Verify that whether risk have **GMP impact** in terms of Yes/ No.

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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	:	**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.	Ampoule size	Equipment is not suitable for different size of ampoules	No	No impact on product quality	Operational	Different ampoule sizes may not be processed with same equipment.	Medium	Filling machine is suitable for filling & sealing of different sizes of ampoules by changing format (change) parts.	Low	DQ	Change parts for different ampoule size with marking provided by vendor, along with the equipment, as per requirement.	Low	IQ & OQ	
2.	Ampoule transport	Overturned/ fallen ampoules on the infeed conveyor belt.	Yes	Ampoule jamming, ampoule damage or breakage may take place. Continuous filling operation will effected.	No	NA	High	The design of the system ensures proper positioning and transfer of ampoules via a conveyor belt with SS side guides.	Low	DQ	• Overturned ampoules should not enter in the conveyor. • Functionality shall be checked during qualification activities.	Low	IQ & OQ	
3.	Transfer of Ampoules	Improper positioning of ampoules 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 ampoules are transferred and positioned properly below the filling needles at filling station.	Low	DQ	Functionality shall be checked during qualification activities.	Low	OQ	

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4.	Transfer of ampoules from tunnel to filling station	Depyrogenated ampoules travel through unclean (unclassified) environment	Yes	Particle contamination of ampoule; micro-biological contamination possible	Operational	Product loss	High	The transfer of ampoules, filling & sealing is performed under unidirectional air flow unit (Grade A).	Low	DQ	Classification level shall be verified 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 shall be 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 Ampoules	Ampoules minimum load on the infeed buffer table	Yes	No ampoules supplied to the ampoule filling machine; product spillage.	Operational	Product loss	High	Ampoules minimum load detection sensor is installed on the infeed buffer table to detect the low accumulation of ampoules along with alarm provision.	Low	DQ	Machine should go into standby mode in case of low ampoules at infeed buffer table.	Low	IQ & OQ	

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Process														
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.	Operational	Product loss	High	All the connections to the buffer tank are performed under Grade A conditions.	Low	DQ	Classification level shall be verified and qualified during qualification	Low	IQ & OQ	
8.	Filling & sealing	Filling & Sealing carried out under unclean environment.	Yes	Grade A and unidirectional airflow is requirement for performing aseptic filling & sealing process.	No	NA	High	Unidirectional Air Flow system (Grade A) is provided over complete filling & sealing 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 shall be provided for filling machine.	Low	DQ	The suitability of the materials shall be proven by certificate/ manufacturers declarations	Low	IQ	

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10.	Dosing pumps	Incorrect product dosing in ampoules	Yes	Inefficient filling of ampoules may leads to wrong dosage.	Operational	Ampoule with incorrect product dose shall be rejected from market	High	The rotary piston pump and peristaltic pump design is appropriate and ensures that required amount of product is filled inside ampoules.	Medium	DQ	Rotary piston pump & peristaltic pump movement shall be synchronized with the transport movement before filling.	Low	IQ & OQ	
11.	Product transfer line from buffer tank to filling needle	Product contact parts of equipment cannot be sterilized	Yes	Contamination of sterile product may possible.	EHS	Health safety risk to consumers.	High	Product contact parts of equipment are removable /fixed type and sterilizable grade and could sustain steam sterilizable for validated time.	Low	DQ	The suitability of the materials shall be proven by certificate/ manufacturers declarations & shall be verified during qualification studies	Low	IQ & OQ	
12.	Dosing	Different range of filling volume could not be achieved.	Yes	Incorrect dosage may leads to market recall	No	NA	High	Different rotary piston pump sets are provided by vendor for different range of filling volume, to ensure accurate volume.	Medium	DQ	Fill volume set point adjustment should be possible through equipment control system.	Low	IQ & OQ	

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13.	Filling	Presence of headspace oxygen	Yes	Chance of product degradation; microbial contamination due to presence of air.	No	NA	High	Provision for Pre and post nitrogen (or other suitable pharmaceutical gas) purging is included in the design based on applicable products.	Medium	DQ	Control system should be able to set the pre and post nitrogen purging time and the pressure for the same.	Low	IQ & OQ	
14.	Nitrogen Gas Purging	Low Flow of nitrogen	Yes	Purging of ampoules cannot be performed	No	NA	High	▪ Provision of flow meters for monitoring the gas flow along with alarm system. ▪ Pressure switch/ Regulator is installed at the supply line.	Low	DQ	Alarm provision shall be provided in case of low/ no pressure of nitrogen gas.	Low	IQ & OQ	
15.	Nitrogen 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 gas flow line so as to regulate the purging gas flow, as per requirement.	Low	DQ	Alarm shall be provided in case of high pressure gas.	Low	IQ & OQ	

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16.	Nitrogen Gas Purging	Nitrogen gas quality failure.	Yes	Particle and microbial contamination of ampoules may leads to product failure	No	NA	High	Provision of sterilizing grade filter (0.2 μm) on the nitrogen/ pharmaceutical gas line before pre-purging and post purging station.	Low	DQ	▪ Nitrogen 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 gas quality at regular interval	Low	IQ, OQ & SOP	
17.	Filling	Filling speed could not be adjusted or maintained.	Yes	Variation in output	Yes	Time loss	Mediu m	Counters are placed at infeed and out feed to count number of filled ampoules.	Low	DQ	The equipment control system shall be suitable to adjust & maintain the rate of ampoule filling (number of ampoules/ minute).	Low	IQ & OQ	
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 ampoules.	No	NA	High	Product level sensor is provided to monitor the product level inside the buffer tank.	Medium	DQ	In case of low level of product inside buffer tank, alarm should be generated and filling should stop.	Low	IQ, OQ & SOP	

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19.	Filling	Filling accuracy not proper.	Yes	Ampoules without constant fill volume shall be filled may leads to reject.	Operational	Product loss	High	Manual Check weighing system (Tare weight & Gross weight) is provided to check fills weight and ensures fill volume accuracy.	Low	DQ	▪ Dosing pump shall be appropriately design to maintain filling accuracy of ±0.5% of set volume. • Filling volume accuracy shall be verified during qualification.	Low	IQ & OQ	
20.	Filling	Ampoules with incorrect fill volume get discharged to the downstream equipment.	Yes	Ampoules with incorrect fill volume may be processed further.	No	NA	High	Manual Weighing system is provided to separate and reject ampoules with fill volume out of range.	Low	DQ	Functionality shall be verified during execution of qualification studies.	Low	OQ	

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21.	Filling	Position of the filling needles could not be adjusted.	Yes	▪ Spillage of product may possible. ▪ Generation of air bubbles due to gap between needle and ampoule surface, which might lead to product contaminatio n.	No	NA	High	Machine is suitable for filling of different sizes of ampoules by adjusting height of the filling needle automatically as per different ampoule size with different set of dosing pump & needle.	Low	DQ	Filling needle height shall be adjustable based on different format parts, so as to be close to the ampoule mouth.	Low	IQ & OQ	
22.	Filling	Filling starts without ampoule at filling station	Yes	Possible contamination of clean room, filling machine and product due to spillage	Operational	Yield loss	High	▪ No Ampoule-No filling function is provided in the system. ▪ Sensor is installed before filling station to check and assure the presence of ampoules.	Low	DQ	Functionality shall be verified during execution of qualification studies.	Low	OQ	

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23.	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. ▪ Back suction provision for filling needles is provided in the control system to prevent dripping.	Low	DQ	Functionality shall be verified during execution of qualification studies.	Low	OQ	
24.	Sealing	Improper flow of LPG	Yes	Improper sealing of ampoule due to insufficient LPG supply	No	NA	High	Flow regulator is installed on LPG inlet line along with alarm provision in case of low flow of supplied LPG.	Low	DQ	Provision shall be provided to stop Machine manually in case of insufficient flow of the LPG.	Low	IQ & OQ	
Discharge Output														

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25.	Out feed	Maximum accumulation at out feed.	Yes	Ampoule filing machine operation may continue leading to accumulation of ampoules, which may lead to ampoule breakage.	No	NA	High	▪ Out feed occupancy sensor is provided. ▪ Ampoule filling & sealing machine will stop in case of full capacity at out feed.	Low	DQ	Functionality shall be verified during execution of qualification studies.	Low	IQ & OQ	
Filters														
26.	Filter (Nitrogen gas line)	No provision for sterile filtration of nitrogen gas.	Yes	Basic requirement. Product contamination possible.	No	NA	High	Hydrophobic, Sterilizable grade filter (0.2 micron) shall is provided at the terminals of Nitrogen gas line on filling machine.	Low	DQ	Functionality shall be verified during execution of qualification studies.	Low	IQ	
27.	Filter (Nitrogen gas line)	Filter leakage.	Yes	Filter leakage may lead to product contamination.	No	NA	High	NA	High	NA	Filter integrity testing shall be performed at regular intervals as per SOP	Low	OQ & SOP	

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28.	Filter (Nitrogen gas line)	Filter integrity test not 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	OQ & SOP	
Equipment Construction- Internal Surface														
29.	Metallic components in direct contact with Ampoules/ filling media/ compressed air	The material may not be suitable; may contaminate the product.	Yes	MOC not resistant - Interaction with product & media 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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30.	Polymeric materials	Polymeric materials are not compatible and are not replaceable	Yes	Shall lead to contamination of Ampoules.	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	
31.	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 performed, wherever possible.	Low	DQ	Weld reports/ certificate/ declaration have to be provided by vendor.	Low	IQ	
32.	Metallic contact parts.	Internal surface finishing insufficient	Yes	May lead to improper cleaning of the surface which will lead to microbial growth hence Ampoule 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	
Equipment Construction- External Surface														

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33.	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	
34.	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														
35.	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	

RISK ASSESSMENT FOR AMPOULE FILLING & SEALING 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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36.	Labeling of components	Labeling of components/ media inappropriate	Yes	Prerequisite for qualification &maintenance	No	NA	Medium	Unique identity number/ flow direction is provided on components/ media, operator panel, etc. (e.g. according to P&ID).	Low	DQ	• Labels affixed on the equipment should be heat resistant. • All labelling shall be done in English language and according to P&ID	Low	IQ	
PLC/ Control System														
37.	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	
38.	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 Touch screen for operation and entering process parameters.	Low	DQ	NA	Low	IQ	
39.	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	
40.	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	

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41.	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	
42.	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.	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	
43.	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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44.	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 Ampoule filling & sealing 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	
45.	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	
46.	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	

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47.	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	
48.	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	
49.	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														

RISK ASSESSMENT FOR AMPOULE FILLING & SEALING MACHINE

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50.	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	
51.	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	
52.	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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53.	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	
54.	Conveyor main drive	Conveyor main drive overload	Yes	Filling and sealing process may be affected	No	NA	High	Alarm provision in case of conveyor main drive overload.	Low	DQ	Preventive maintenance of motors shall be carried out at regular intervals as per SOP.	Low	OQ & SOP	
55.	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 Ampoules are provided with quick-fit arrangement.	Low	DQ	The change parts should be identified by non-erasable marking.	Low	IQ & OQ	
Environment & Safety														

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56.	Electrical system	• Electrical systems are not verified for safety. • Earthing not provided for equipment.	No	It will not affect the filling process	EHS	May lead to an accident	Mediu m	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	
57.	Emergenc y 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	
58.	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	
59.	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 & sealing station is covered with a protective, removable acrylic covering.	Low	DQ	All moving & electrical parts shall be covered properly.	Low	IQ & OQ	

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60.	Hygiene Conditions	Non-Viable and Viable particle count monitoring not possible.	Yes	Basic GMP requirement for Grade A environment.	No	NA	High	▪ Non-viable particle count locations are provided in the filling machine. ▪ 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 in LAF flow. ▪ Monitoring of particles (viable/ non-viable) shall be performed during qualification. ▪ Routine microbiological monitoring shall be performed as per SOP.	Low	IQ, OQ & SOP	
61.	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 ampoules.	No	NA	High	Uniform unidirectional flow will be maintained from the LAF up to the working area inside oRABs.	Medium	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	OQ	

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62.	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 & Sealing machine and on its infeed and discharge side.	Medium	DQ	▪ Machine shall stop in case of any LAF failure. ▪ Alarm provision shall be provided in case LAF fails/ stops	Low	OQ	
63.	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 & SOP	

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64.	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 filter is provided. ▪ Downstream monitoring of HEPA filter is also possible.	Low	DQ	Verification of functionality shall be checked during qualification studies.	Low	IQ & OQ	
65.	LAF (over Filling & discharge conveyor)	Choking/ Damage of Pre-filter	No	HEPA filter is present in the downstream	Operational	Particulate matter load directly on the HEPA filter, may lead to frequent replacement of HEPA filter.	Medium	Differential pressure switch/ gauge is provided for indicating choking or leakage of pre-filters with alarm provision in case of high or low DP.	Low	DQ	Pre-filters shall also be cleaned regularly as per SOP.	Low	IQ & SOP	
66.	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 are 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.	Low	DQ	Alarm provision shall also be provided for the same.	Low	IQ & OQ	

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67.	Equipment access doors	Service access door may be opened during process.	No	No impact on process	EHS	Operator safety risk, as machine's moving parts shall be operating.	Mediu m	Security switches/ sensors are provided at the service access doors along with interlock feature i.e. machine should stop immediately if service doors are opened.	Low	DQ	Alarm provision shall also be provided for the same.	Low	IQ & OQ	
68.	Compress ed air	Insufficient 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	Verification shall be performed at the time of qualification studies	Low	IQ & OQ	
Documentation														
69.	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	

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70.	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	
71.	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	

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72.	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. Ampoule filling & Sealing 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
SIP	:	Sterilization in place
COA	:	Certificate of Analysis
LAF	:	Laminar Air Flow
LPG	:	Liquified Petroleum Gas
oRABs	:	Open Restricted Access Barrier System
GMP	:	Good Manufacturing Practice
DP	:	Differential Pressure
HEPA	:	High Efficiency Particulate Air
RA	:	Risk Assessment
VFD	:	Variable Frequency Drive
SOP	:	Standard Operating Procedure
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
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