Risk Assessment Document

Lyophilizer

Equipment ID: ……

Revision index

Revision	Date	Reason for revision
00		

Table of Contents

RISK ANALYSIS FOR LYOPHILIZER

RISK ANALYSIS FOR LYOPHILIZER

1.0 Approval Signature

This document is prepared by the Validation team of the .....for the project "Integrated Sterile Bulk and Formulations Facility" of ....., under the authority of Unit Head & QA Head. Hence this document before being effective shall be approved by the Unit Head & QA Head.

PREPARED BY		
NAME/FUNCTIONAL AREA	**DESIGNATION**	**SIGNATURE/DATE**
Validation & QA		
CHECKED BY		
NAME/FUNCTIONAL AREA	**DESIGNATION**	**SIGNATURE/DATE**
Validation & QA		
Production		
Engineering		
Quality Assurance		
APPROVED BY		
NAME/FUNCTIONAL AREA	**DESIGNATION**	**SIGNATURE/DATE**
Unit – Head		
Quality Assurance – Head		

RISK ANALYSIS FOR LYOPHILIZER

2.0 Introduction:

According to the definition, given in Annex 15, 20 of the EU-GMP-Guide and ICH Q9, a risk assessment is a method to assess and characterise 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 analyses are performed as basic GMP/EHS-Risk assessment, which shall help to identify important GMP/EHS-requirements.

3.0 Aim of the Risk Analysis:

At the very basic stage of design the risk assessment is 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 and EHS parameters will be identified and assessed for the risk if not considered in the design or requirements.
The Risk assessment report is produced to provide the documented evidence that design concepts or requirement are complete in considering all GMP and EHS risks.

4.0 Reference Documents

S.No.	Document Title	Document Number
1.	Validation master plan	
2.	Project validation plan	

RISK ANALYSIS FOR LYOPHILIZER

5.0 System Description

This risk assessment is conducted for the Lyophilizer consisting of the following main components:

S.No.	Description	Purpose
1.	Chamber with chamber door	Chamber provides the closed system used for proper Lyophilization of the product.
2.	Product shelves	Provides the proper surface area for the vials to be lyophilized.
3.	Heat exchange system	Consist of coils which contain coolant used for the transfer of temperature to the product.
4.	Ice condenser	Helps in changing the solidified ice to gaseous form to remove the water from the product.
5.	Refrigeration system	Used for freezing of the product.
6.	Vacuum system	Removes out the mist formed due to condensation of liquid to ice. Helps in formation of dry power.

In this GMP risk assessment all critical components of the Lyophilizer, based on the technical details, are listed and rated according to their influence of the product quality, EHS and operational requirements.

RISK ANALYSIS FOR LYOPHILIZER

6.0 Participants

Name (block letters)	Function	Signature

7.0 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:**

  It 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:**

  It 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.

This document applies the risk management principles to identify the risks associated with the design, construction and operational features of any equipment, which is going to be procured and installed in the facility.

7.1 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 MOC of the product contact part 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 product contact materials for equipment and containers (eg. Selection of SS grade, gaskets, lubricants etc.)
- Risks related to appropriate utilities and their control (eg. Steam, gases, power source, compressed air etc.)
- Risks related to calibration/ preventive maintenance
- Risks related to protection the environment and health & safety of personnel.
- Risks related to cleaning & sterilization
- Risks related to control system of the equipment
- Risks related to product loss

7.2 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".

RISK ANALYSIS FOR LYOPHILIZER

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. • 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.

RISK ANALYSIS FOR LYOPHILIZER

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.

RISK ANALYSIS FOR LYOPHILIZER

8.0 Risk Analysis

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

Column 1:	**Serial number** of Risk analysis item.
Column 2:	**Process step/Component**: Identify the process step or component associated with the risk.
Column 3:	**Risk**: Identify the type of risk associated with the process or component.
Column 4:	**GMP Risk:** Verify that whether risk have **GMP impact.**
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 what is the type of risks e.g. EHS, Operational.
Column 7:	**Justification**: Provide justification for considering any risk.
Column 8:	**Risk level** Determine the Risk level as High, Medium or low based on the impact.
Column 9:	**Risk Control:** It is further divided into following three sections
Column 9a:	**Mitigation Method**: Write the risk mitigation strategy as considered in 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:	**Verification**: Write the test point where the risk mitigation strategy will be verified.

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
A) Design										
1.	Refrigeration system	Insufficient capacity	Yes	Condenser cooling requirement can't meet	No	NA	High	• Compressor shall be provided with suitable capacity.	Acceptable	IQ
2.	Shelf system	Insufficient Space	Yes	Cannot meet the batch size requirement	No	NA	High	• Self dimensions and total shelf area must be considered	Acceptable	IQ
3.	Condenser	Insufficient capacity	Yes	Condenser is fails to collect sufficient evolving water molecules during primary & secondary drying phase	No	NA	High	• Total condenser capacity should to be considered • P&ID should to be provided	Acceptable	IQ
4.	Clean-ability of outer chamber at loading/ unloading side	Chances for Contaminations in clean room	Yes	Surface of the equipment may encourage dust accumulation / microbial growth	No	NA	High	• The design must ensure easy clean-ability by providing smooth surface finishes **(Ra)** and round edges.	Acceptable	IQ

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
5.	CIP/SIP system	Insufficient space for cleaning inner chamber	Yes	Manual cleaning is not possible	No	NA	High	• CIP/SIP cycle should consider.	Acceptable	OQ
B) Charging										
6.	Sub Door/Pizza Door	• Leakage from door. • Manually door lock	Yes	• Chance of leakage during cycle • Manual operation may increase chance of contamination	No	NA	High	• Dual Gasket for safety and protection to be provided • Automatic door locking devises to be considered	Acceptable	IQ/OQ
7.	Loading vials	Manual handling of vials	Yes	• Vial may fall resulting in Product spillage • Clean room contamination	No	NA	High	• Lyo Loading system shall be considered • Loading /Unload SOP shall be adopted, which shall ensure proper handling of the vials	Acceptable	IQ / SOP

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
8.	Chamber	Low/ High chamber temperature during process	Yes	Temperature less/ more than operating range may result in out of specification	No	NA	High	• T type Temperature • sensor shall be provided • Alarm will indicate if out of range	Acceptable	IQ/OQ
9.	Chamber	Low/ High chamber pressure/vacuum during process	Yes	Low/ High chamber pressure cause damage to the vials	Operational	Low pressure may result in improper process	High	• Pressure transducer shall be provided with suitable operating range • Alarm will indicate if out of range	Acceptable	IQ/OQ
10.	Shelves	Temperature is not uniform at different shelves	Yes	Freeze drying will not be proper and lead to product damage.	No	NA	High	• T type Temperature sensor shall be provided in each shelf • Shelf uniformity test to be considerd done.	Acceptable	IQ/OQ
11.	Condenser chamber	Coils may leak	Yes	Coolant leakage from coil may result in contaminated product.	No	NA	Low	• Temperature and pressure sensor shall be provided within the chamber • Alarm to be provide	Acceptable	IQ/OQ/ OQ

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
								for over load •Leak testing shall be performed.		
12.	Freezing	Incomplete freezing of vials during process	Yes	Silicon oil level low	No	NA	High	•Oil Level indicator to be provided with expansion tank •Provision to be provided for Control, monitor and record Process parameter in SCADA	Acceptable	IQ
13.	Rate and Holding with respect to temperature/ time	Required temperature not reaching in specific time.	Yes	Process out of specification	No	NA	High	•Provision to be provided to optimize All phage of freeze drying cycle	Acceptable	OQ
14.	Ice condenser	Condensation capacity insufficient	Yes	Freeze drying cannot be performed appropriately	No	NA	High	•Condensation capacity shall be considered •Malfunction of cooling shall be alarmed •Process validation with worst case	Acceptable	IQ/OQ/ PQ

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
								loading scheme		
15.	Ice condenser	Low/ High Condenser pressure	Yes	High pressure may cause damage to the vials	Operational	Low pressure may result in improper process	High	•Pressure transducer shall be provided to monitor, indicate & control •Alarm to be in corporate	Acceptable	IQ/OQ
16.	Evacuation / primary drying / secondary drying	Closed isolation valve	Yes	Transfer of sublimate not possible; Damage of product	No	NA	Medium	•Malfunction of isolation valve shall be alarmed •Relevant SOP shall be adopted, which shall ensure proper Operating procedure	Acceptable	OQ/SOP

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
17.	Drying with vacuum	Required vacuum level will not achieved	Yes	Process requirement	No	NA	High	• Efficiency of vacuum to be checked • Pressure control test to be performed • Alarm in case of process parameter failure. • Provision for optimise the vacuum level in Process validation with worst case loading scheme along	Acceptable	OQOQ/ OQ/PQ
18.	Nitrogen backfill	low pressure	Yes	Contamination of product can occur	No	NA	High	• **Pressure regulator** to be provide to monitor nitrogen flow	Acceptable	IQ
19.	Stoppering of vials	Manual stoppering after Lyophilization	Yes	chance of contamination	No	NA	High	• Automated stoppering after Lyophilization shall be considered	Acceptable	OQ
20.	Sterilisation of the freeze	Incorrect temperature/	Yes	Sterilisation out of validated	No	NA	High	• SOP should be establish	Acceptable	OQ/OQ/ PQ

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
	dryer	pressure measurement		procedure				• Alarm to be considered to monitor process failure • Empty chamber heat distribution study to be performed		
21.	Sterilisation of the freeze dryer (Moist steam)	Wrong programs / sequences for sterilisation (SIP)	Yes	Sterilisation out of validated procedure; microbiological contamination possible	Operational	Process hold up may result in loss of productivity	High	• Sterilization parameters have to be controlled monitored and recorded in SCADA	Acceptable	OQ
22.	Aeration	Filter integrity fail	Yes	Microbiological contamination possible	No	NA	High	• SOP for Filter integrity test shall be defined	Acceptable	OQ
23.	Door/ Seal	Door can be opened during operation	Yes	Incomplete Process	Operational	Process hold up may result in loss of productivity	High	• Interlock of door during cycle to prevents process interruption • Malfunction of door interlock shall be alarmed.	Acceptable	OQ/OQ

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
24.	Door/ Seal	Sealing is damaged	Yes	Product contamination	Operational	Process hold up may result in loss of productivity	High	• SOP for leak test should to be establish	Acceptable	OQ
25.	Vacuum pump (dry pump)	Oil suck-back in case of power failure	Yes	No	NA	Contamination of pump oil by water vapour possible	High	• Constructional solution; e.g. automatically closing anti suck-back safety valves • Power failure shall be alarmed	Acceptable	OQ/OQ
26.	Vacuum pump (dry pump)	Malfunction of pump	Yes	Lyophilization process out of specification	Operational	Process hold up may result in loss of productivity	High	Malfunction of pump shall be alarmed.	Acceptable	OQ
27.	Vacuum control valve	Malfunction of valve	Yes	damage of product	Operational	Process hold up may result in loss of productivity	High	Malfunction of valve shall be alarmed.	Acceptable	OQ
28.	Booster Pump	Malfunction of pump	Yes	Required pressure not achieved	Operational	Process hold up may result in loss of productivity.	High	Malfunction of pump shall be alarmed.	Acceptable	OQ

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
29.	Isolation valve (chamber-condenser)	Malfunction of valve	*Yes*	Pressure rise test not possible; contamination of chamber possible	Operational	Process hold up may result in loss of productivity	High	• Malfunction of valve shall be alarmed. • SOP for preventive maintenance to be provided	Acceptable	OQ/SOP
30.	Sterile filter (Air / N2)	Wrong filter (e.g. material, size, type, etc.)	Yes	Viable and non-viable particles contamination of freeze dryer	No	NA	High	• Sterile grade 0.22mm hydrophobic filters	Acceptable	IQ
31.	Sterile filter (Air / N2)	Low/ High pressure	No	NA	Operational	• Low pressure may result in improper process • High pressure may cause damage the filter	High	• Pressure transducer shall be provided to monitor, indicate and control the pressure • Alarm need to be considered	Acceptable	OQ/OQ

C) Discharge

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
32.	Discharging of outputs	Manual handling of vials	Yes	• Vial may fall resulting in • Product spillage • Clean room contamination	No	NA		• Auto unloading shall be considered • Relevant SOP shall be adopted, which shall ensure proper handling of the vials.	Acceptable	OQ
D) Control system										
33.	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 equipment shall control & detect failure mode automatically. • The System shall be PLC based and fully automatic.	Acceptable	IQ/ OQ
34.	Human machine Interface	Process / process status not visible for operating personnel	Yes	Operating personnel must have knowledge on the process status	No	NA	High	Machine shall be fitted with adequate display and clean room suitable key board for operation.	Acceptable	IQ/ OQ
35.	Human machine Interface	Display language not identified.	Yes	Pre-requisite for the GMP compliant operation	No	NA	High	The language on the display of HMI should be English language only.	Acceptable	OQ

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
36.	Human machine Interface	Recorder failure	Yes	Basis GMP requirement (incomplete / no documentation)	No	NA	High	• Data backup for process data must be foreseen (electronic recording, 21 CFR part 11 compliant). • Diagnostic function test to be a part of qualification activity.	Acceptable	IQ/ OQ
37.	Human machine Interface	Monitoring/ recording and documentation of GMP relevant data not possible	Yes	Basic GMP requirement	No	NA	High	• It should be possible to monitor/record GMP relevant data (e.g. recorder with compliance to GAMP 5 / 21 CFR, Part 11 etc.) • Batch records / print outs to be defined. • Printout facility should be available with fade proof prints.	Acceptable	OQ
38.	PLC / Control system	Control system does not detect failures and generate alarms	Yes	Process optimization and validation is not possible	No	NA	High	Failure of set parameters gets indicated as alarms and machine stops.	Acceptable	OQ
39.	PLC / Control system	Control system is not suitable to select process/operational parameter for process control	Yes	Most of the Washing cycle steps require Process Control.	No	NA	High	Verification during qualification	Acceptable	OQ

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
40.	Power	Power failure / emergency stop	Yes	Data loss	Safety	Unsafe if start automatically on restoration of power	High	▪ Operator settings unchanged and restored after emergency stop / power failure ▪ Alarm message ▪ On power failure equipment should come to rest to protect operator, equipment itself & the product (vials). ▪ Machine must not start automatically without operator activity after incident ▪ SOP for 'Maintenance and operation of the machine'	Acceptable	OQ/ SOP
41.	PLC / Control system	Status parameters not clear	Yes	Process for the particular product at particular stage can't be regulated easily.	No	NA	High	• Status parameters should remain displayed at each process stage. • The flow of the process shall be provided with the help of arrows. • Alarm should also be visualized along with the fault displayed.	Acceptable	OQ

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
42.	PLC / Control system	Malfunction	Yes	Correct function basic requirement for GMP-compliant operation	No	NA	High	• Supplier analysis (quality management system for software and control system hardware development) • Input/ Output test implementation in qualification activities • The system must contain all necessary protection devices to ensure that the equipment and article remain in safe condition.	Acceptable	OQ
43.	Accessibility to PLC	Parameter settings not identified universally	Yes	Basic GMP requirement	No	NA	High	Parameters settings should be in numeric only.	Acceptable	OQ
44.	PLC / Control system	Time measurement works incorrect	Yes	Process insufficient	No	NA	High	• PLC Clock verification • SOP “calibration and maintenance” • Time synchronisation of system	Acceptable	OQ

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
45.	PLC / Control system	No protection of PLC against manipulation & changes.	Yes	Basic GMP requirement.	No	NA	High	• 3 level password protections should be provided. ➢ Level 1: for operator settable parameters. ➢ Level 2: for editing cycle parameters. ➢ Level 3: for admin level parameter setting.	Acceptable	OQ
E) Material of Construction										
46.	Material of construction	Material not suitable	Yes	Leads to contamination	No	NA	High	• Metallic critical contact surfaces & critical utility pipelines should be constructed of 316L grade stainless steel or better with internal mirror surface finish < 0.5µm Ra and external surface finish < 1.2µm Ra, matte finish. • All non contact parts should be constructed of SS304 or better grade • MOC certificate shall be provided for contact parts	Acceptable	IQ
47.	Polymeric materials	Polymeric materials are not compatible and are not replaceable	Yes	Shall lead to water contamination	No	NA	High	• Gaskets (shall be high temperature & pressure resistant) and O-rings coming in	Acceptable	IQ

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
								direct / indirect contact surfaces shall be made up of food grade polymeric materials only. • The easy change of gaskets must be possible. • Vendor shall provide the certificate for food grade polymeric material.		
48.	Welding Joints	Weld joints not ground properly and are not passivated	Yes	Uneven and improperly ground weld joints will form a space for dust accumulation	No	NA	High	All welds shall be ground finished to ≤1.2 µm Ra and properly passivated and orbital welding should be done.	Acceptable	IQ
49.	Finishing	Internal finish is not proper	Yes	May lead to improper cleaning of the surface which will lead to microbial growth hence vial contamination	No	NA	High	• All internal metallic surfaces shall be mirror polished with ≤0.5 µm Ra. • Vendor to provide test certificate for surface finish.	Acceptable	IQ
50.	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 shall be provided for air tight connection which shall be replaceable. • Quick release Tri-clover joints are recommended.	Acceptable	IQ

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
51.	Lubricant	Material of lubricant not suitable	Yes	Leads to contamination	No	NA	High	• Lubricant used in the equipment shall be food grade • Design shall ensure lubricant used in the equipment must not come in contact with potential product contact • Food grade certificate shall be provided for lubricant .	Acceptable	IQ
F) Safety										
52.	Electricity	Power recovery is not warned	No	NA	EHS	Staff protection	High	Equipment should start with human intervention only. After regain of power the equipment should start from the step it stopped.	Acceptable	OQ
53.	Control system	Overload for all pumps, drives and belts	No	NA	No	NA	High	Machine should stop with alarm.	Acceptable	OQ
54.	Notification of alarms	Failure of utility supply is not indicated	Yes	Process parameters may get disturbed	EHS	Product/ machine safety	High	Various utilities supply should be interlocked and indicated by alarm.	Acceptable	OQ

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
55.	Noise level	More noise is produced by the equipment during the operation	No	NA	EHS	High noise may cause deafness and anxiety	Medium	Noise level shall be below 75 dB at a distance of 1 m from the equipment.	Acceptable	OQ
56.	Moving parts & wiring	Moving parts & wiring are not covered	No	NA	EHS	Accident can take place	Medium	All moving parts & wiring to be covered, door and interlocked Motors should be of reliable make Proper earthing of the equipment	Acceptable	IQ
G) MEASURING INSTRUMENTS										
57.	Measuring instruments	Measuring instruments not suitable	Yes	Improper measurements	No	NA	High	• Measuring instruments must have a suitable measuring range. • Operational range of measuring instruments > instrument working range. • They must have appropriate accuracy.	Acceptable	IQ

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
58.	GMP relevant measuring instruments	Measuring instruments cannot be dismounted	Yes	Defective instruments must be dismounted for exchange and calibration	No	NA	High	• Mounting of instruments must give the possibility for dismounting and replacement • Constructional solution: easy access for calibration activities shall be given	Acceptable	IQ
59.	Measuring instruments	• Instruments not calibrated. • Re-calibration is not possible	Yes	Non calibrated instruments may lead to false machine functions	No	NA	High	• Measuring instruments should be calibrated, traceable to national or international standards. • Re-calibration of instruments should be possible.	Acceptable	IQ/ OQ
H) Documentation										
60.	User	Faulty operation & maintenance	Yes	SOPs are basic GMP-requirement	No	NA	High	• All end-users have to be trained on SOPs • Training of SOPs has to be documented • Training on the job of end users by vendor. • Training on operation, setting parameters, trouble shooting & maintenance related activities.	Acceptable	OQ & SOP

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ANALYSIS FOR LYOPHILIZER

S.No	Process steps/ component	Risk	GMP Risk Yes/No	Justification	Other Risk type	Justification	Risk Level	Risk control		
								Mitigation Method	Residual Risk Level	Verification
61.	User	Unauthorized person tries to start/stop the system	Yes	Untrained persons may damage the system or product quality may be affected	No	NA	High	▪ System should not start without password. ▪ Key-switch should be provided for system power up. OR ▪ Physical entry to equipment room is restricted.	Acceptable	IQ & OQ
62.	User	Operation SOP does not contain proper information and user may operate system	Yes	User may make a wrong decision.	No	NA	High	• System operation SOP must be reviewed with all aspects and approved. • Vendor shall provide execution support to the user to complete all stages of the qualification report.	Acceptable	OQ
63.	User	Operation SOP does not contain proper information and user may operate system	Yes	User may make a wrong decision.	No	NA	High	• System operation SOP must be reviewed with all aspects and approved. • Vendor shall provide execution support to the user to complete all stages of the qualification report.	Acceptable	OQ

RISK ANALYSIS FOR LYOPHILIZER

9.0 Summary and Conclusion

- The Risk analysis is performed to establish the design parameters of the equipment so as to meet the desired performance of the equipment i.e. Lyophilizer
- The critical risks pertaining 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 SOP's, are also possible measures for special GMP-risks. The availability of these SOP's will be checked during the performance of the OQ.
- The risks where conceptual procedures shall be employed, standard operating procedures (SOP's), Preventive maintenance schedules, Certificates and related documents indicated as mitigation procedures shall be ensured at respective test points.

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

10.0 Abbreviations and Definitions

Acronym	Definition
GMP	Good manufacturing practices
EHS	Environment health and safety
GMP	Good manufacturing practice
IQ	Installation Qualification
DQ	Design Qualification
OQ	Operational Qualification
PQ	Performance Qualification
PVP	Project Validation Plan
UV	Ultra Violet
MOC	Material of construction
DPB	Dynamic Pass Box
HEPA	High Efficiency Particulate Air
LAF	Laminar Air Flow
LPG	Liquefied Petroleum Gas

RISK ANALYSIS FOR LYOPHILIZER

Acronym	Definition
LYO	Lyophilizer
db	Decibel
SOP	Standard Operating Procedure
MOC	Material Of Construction
URS	User Requirement Specification