Risk Assessment Document
For
Laminar Air Flow
Equipment ID: PR/0

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RISK ASSESSMENT FOR LAMINAR AIR FLOW

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

The risk analysis is carried out for Laminar Air Flow consisting of the following main components:

- Supply HEPA filter module
- Pre filter module
- Main Cabinet
- Fluorescent Light

Laminar air flow is designed for “Grade A” (ISO 4.8) requirements as per ISO 14644-1. Filtration of air is arranged through pre filters, and HEPA filter. Desired pressure and velocity of air can be controlled by setting of damper or other provision for getting uniform laminarity. On/Off switches control the equipment for blower and lights are provided.

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

Most of the possible risk concerning the operation of the Laminar Air Flow 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.
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.

Level	Descriptor	Example detail description
		• Proper supporting documentation not provided. • Major effect on personnel health

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

Qualitative risk analysis matrix – level of risk

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

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

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

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

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

7 Risk Assessment

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

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

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

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

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

Column 5 : **Justification:** Provide justification for declaring both Yes/ No for GMP impact in column 4.

Column 6 : For the risk **other than of GMP impact**, write that what is/ are the type of risks e.g. EHS, operational, etc.

Column 7 : **Justification:** Provide justification for considering the risk.

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Column 8	:	**Risk level:** Determine the risk level as High, Medium or low based on the impact.
Column 9	:	**Risk Control:** It is further divided into the following three sections:
Column 9a	:	**Mitigation Method:** Write the risk mitigation strategy as considered in the design.
Column 9b	:	**Residual risk level:** After the risk mitigation what is the residual risk level, whether it is Acceptable, Low or Medium.
Column 9c	:	**Test document:** Write the test point where the risk mitigation strategy will be verified.
Column 10	:	**Status of RA:** Mention the status of the Risk assessment point i.e. whether it is ‘Closed” or “Open”, after the execution/ approval of the Test document.

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S. No (1)	Process steps/component (2)	Risk (3)	GMP Risk Yes/No (4)	Justification (5)	Other Risk type (6)	Justification (7)	Risk Level (8)	Risk Control (9)			Status of RA (10)
								Mitigation Method (9a)	Residual risk level (9b)	Verification (9c)	
Process											
1.	Working space	Insufficient space for Performing the activity	Yes	Adequate space for the operation is a GMP requirement to conduct error free operation	Operational	Difficult for activity	Medium	The size of the LAF shall be adequate for Performing the relevant activity.	Acceptable	IQ	
2.	Operation under LAF	Viable and non viable particles in the air flow	Yes	The viable and non viable particles will contaminate the product/ object in the working space.	No	No	High	The airflow will be through terminal HEPA filter (EU14, efficiency 99.997%).	Acceptable	IQ	
3.	Lighting	Visibility inside work space is poor	Yes	Visibility for critical operation is a GMP requirement	Operational	No or Insufficient light may lead to difficulty during the activity	Medium	• Fluorescent lights shall be provided for adequate visibility with ON/OFF switch for control. • Adequate level of light (lux level >400) shall be provided for working space.	Acceptable	IQ	
4.	Blower running	Continues running of the blower	No	No impact on the product	Operational	Continues running of the blower shall cause lot of power loss and may damage the blower.	Medium	• The ON/OFF switch shall be provided for controlling the blower operation. • LED indicators for the motor operation shall be provided.	Acceptable	IQ	

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5.	Air flow	• The air flow from HEPA inside LAF is not laminar. • Abnormal flow rate of the air.	Yes	Can create turbulence of air leading to increase in particulate matter.	Yes	High flow rate leads to HEPA filter damage.	High	• No undue obstruction should be present in the route of clean air through HEPA filter. • The air velocity shall be controlled by damper or any other provision to maintain the CFM at working level for uniform laminarity. • The velocity of the air through filter should be controlled and set at 90 fpm ± 20%.	Acceptable	IQ & OQ	
6.	Air Supply	Air Quality failure	Yes	Particle laden air	No	NA	High	• Supply of filtered air via 5 micron pre-filter followed by 0.3 micron HEPA filter. • Pre-Filter should be detachable for periodic cleaning. • SOP: Regular monitoring of the nonviable particle in laminar air flow.	Acceptable	IQ, OQ & SOP	
7.	Air Supply	Failure of Filters	Yes	Admission of contaminated air in to the LAF	No	NA	High	• Filter Integrity Test to be carried-out regularly. • SOP: Requalification of LAF to include integrity testing of HEPA filter	Acceptable	OQ & SOP	
8.	HEPA Filter	Choking of HEPA filter	Yes	The required flow for the laminarity may not be achieved.	No	NA	High	Magnehelic gauge to measure and indicate the differential pressure across HEPA filter shall be provided.	Acceptable	IQ/OQ	

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9.	Hygiene zone	Area under LAF does not meet specified hygiene class parameters	Yes	Equipment will not be suitable for operation	No	NA	High	• Qualification of the equipment hygiene class is to be done. • LAF cleaning and monitoring is to be done.	Acceptable	OQ & PQ	
10.	Recovery time	Immediate activity just after start up	Yes	There are chances of improper removal of initial particle contamination from the inside work area. This may lead to contamination of the article from the air.	No	NA	High	Before the activity to be taken the equipment shall allowed to run continuously for a set period of time. The limit shall be established during qualification.	Acceptable	PQ & SOP	
11.	Filter integrity testing of HEPA filter	No provision for carrying out the integrity test for the HEPA filter	Yes	The integrity test of the HEPA filters is essential requirement to confirm the proper functioning of HEPA filters and to ensure quality of air	No	NA	High	The port for monitoring of upstream concentration of PAO during filter integrity shall be provided in the equipment.	Acceptable	IQ & OQ	
12.	Joint sealing	Joints are not sealed	Yes	It will allow accumulation of particles which may lead to contamination	No	NA	High	Proper sealing over the joints shall be provided.	Acceptable	IQ	
13.	HEPA filter placement	Chances of formation of dead space due to inadequate placement of HEPA filters.	Yes	Laminar air flow may get disturbed.	No	NA	Medium	Proper placement of HEPA filter should be considered to attain minimum dead space.	Acceptable	IQ & OQ	

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Cleaning											
14.	Cleaning	Cleaning of the Pre-filter not possible	Yes	The required flow of air cannot be achieved due to chocking of the pre-filters.	Operational	Frequent changes of the pre-filters shall be required	High	The pre-filters used at the return shall be detached easily and shall be cleaned easily.	Acceptable	IQ	
15.	Cleaning	Cleaning of filter not possible	Yes	It may lead to cross contamination	No	NA	High	Easily detachable and cleanable return filters will be installed.	Acceptable	IQ	
16.	Cleaning	Cleaning of external part not possible	Yes	Cleaning is a basic GMP requirement	No	NA	High	The external part of the equipment shall be designed for manual cleaning	Acceptable	IQ	
17.	Welding joints	Weld joints not ground properly	Yes	Uneven and improperly ground weld joints will form a space for dust accumulation.	No	NA	High	All weld shall be grounded to smooth finish	Acceptable	IQ	
18.	Material of construction	The surface is not compatible with the clean room	Yes	May lead to the product and environment contamination	No	NA	High	All metallic non product contact surfaces shall be constructed of 304 grade stainless steel or better.	Acceptable	IQ	

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19.	Finishing	External finish is not proper	Yes	May lead to improper cleaning of the surface which will lead to contamination.	No	NA	High	All external surface finish shall be smooth finish.	Acceptable	IQ	
Maintenance											
20.	Pre Filters and HEPA filter	The removal of pre-filters and HEPA filters is not possible	Yes	Pre-filters needs to be regularly cleaned. HEPA filters needs to be replaced in case of any damage.	No	NA	High	The equipment should have a side access panel for easy servicing or removal of pre filter and HEPA filter.	Acceptable	IQ	
21.	Maintenance	Malfunctions due to worn parts	Yes	Basic GMP requirement	No	NA	Medium	Machine shall be easy to maintain.	Acceptable	IQ	
Safety											
22.	Noise level	More noise is produced by the equipment during the operation.	No	No impact on the product.	EHS	High noise may cause deafness and anxiety.	Medium	Noise level shall be below 75 db at a distance of 1 m from the LAF.	Acceptable	OQ	
23.	Moving parts	Moving & rotating parts are not covered.	No	NA	EHS	Accident can take place	High	All moving & rotating parts to be covered.	Low	IQ	

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24.	HEPA filters, pre-filter and electrical sockets	During cleaning HEPA filter, pre-filter and electrical sockets are not protected from water	Yes	This is a special requirement for these components to protect from water.	Operational	Components or component performance is not compatible with water.	High	• SOP: Precaution to be taken during cleaning. • Protective grills for HEPA and Pre-filter	Acceptable	IQ & SOP	
25.	Power Failure	Power failure	Yes	Can lead to contamination of the material being tested.	No	NA	High	• On power failure equipment should come in fail safe condition & on recovery of the power failure the equipment shall retain the condition. • UPS supply should be provided for continuous operation.	Acceptable	IQ & OQ	
26.	Measuring Instruments	Measuring instruments not suitable	Yes	Improper measurements	No	NA	High	• Measuring Instruments must have a suitable measuring range. • Measuring Instruments must have appropriate accuracy.	Acceptable	IQ & OQ	
27.	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 should be calibrated (full loop calibration). • Measuring instruments should be suitable for re-calibration	Acceptable	IQ & OQ	

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28.	GMP relevant measurement instruments	Instruments cannot be dismounted	Yes	Defective instruments must be dismounted for exchange and calibration	No	NA	High	• Mounting of instruments must give the possibility for dismounting and replacement • Constructional solution: easy access for re-calibration activities shall be given.	Acceptable	IQ	
Documentation											
29.	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, trouble shooting & maintenance related activities.	Acceptable	OQ & SOP	
30.	User	Operation SOP does not contain proper information and user may operate system	Yes	User may make a wrong decision.	No	NA	High	• System operation SOP must be reviewed with all aspects and approved. • Vendor shall provide execution support to the user to complete all stages of the qualification report.	Acceptable	OQ	

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31.	Documentation	Technical documentation from vendor not adequate	Yes	Adequate technical documentation is basic GMP requirement	No	NA	High	• Vendor documentation shall comprise: - Material certificates - DQ, IQ & OQ protocols - O & M manuals - Bought out components manuals - Spare parts list - Functional design specification - Filter Certificates • Drawings - P&I-diagram - Electrical diagrams - GA diagram • Calibration certificates of measuring instruments.	Acceptable	IQ	

8 Summary & Conclusion

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

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

9 Abbreviations

EU-GMP	:	European – Good Manufacturing Practice
EHS	:	Environment Health Safety
GMP	:	Good Manufacturing Practice
PAO	:	Poly Alfa Olefin
HEPA	:	High Efficiency particulate Air
LAF	:	Laminar Air Flow
RA	:	Risk Assessment
NMT	:	Not More Than
SOP	:	Standard Operating Procedure
SS	:	Stainless Steel
Ra	:	Roughness Average
CFR	:	Code of Federal Regulations
UPS	:	Uninterrupted Power Supply
CE	:	Conformité Européene
db	:	Decibel
FS	:	Functional Specification
IQ	:	Installation Qualification
OQ	:	Operational Qualification
PQ	:	Performance Qualification
O&M	:	Operation and Maintenance
GA	:	General Arrangement
IPSI	:	Integrated Project Services International, New Delhi

10 Revision History

Date	Revision	Reason for Revision
	00	New Document