RISK ASSESSMENT DOCUMENT FOR BLISTER PACKING MACHINE

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1.0 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.

2.0 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.

3.0 Reference Documents/Drawings

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

4.0 Equipment/ System Description

This risk assessment is conducted for a blister packing machine consisting of the following main components:

Blister packing machine is employed for secondary packing of Ampoules. Ampoules are fed into the hoppers of the blister packing machine manually. The hopper would be equipped with view glass to check the product levels. The foils or PVC/PVDC film roll are loaded onto the respective rollers in the equipment. By the means of heat and/or vacuum blisters are formed in the foil which are later on filled with ampoules from hopper, then appropriate Aluminium foil is sealed by means of heat and pressure on the web carrying ampoules then web is cut into predefined format to produce definite blister pack.

PLC Control system is rendered to regulate all critical parameters and generate alarm in case of variations from the set parameters. The blistered ampoules shall be collated manually and conveyed to the packing line for the further action.

In this GMP risk analysis all critical components of the Blister packing machine, 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 handling/operation of the blister packing machine has been considered in this RA document.

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5.0 Participants

Name	Designation/Department	Signature/Date

6.0 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 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 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. • 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.

7.0 Risk Assessment

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

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

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

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

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

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

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

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

Column 8 : **Risk level:** Determine the risk level as High, Medium or low based on the impact.

Column 9 : **Risk Control:** It is further divided into the following three sections:

Column 9a : **Mitigation Method:** Write the risk mitigation strategy as considered in the design.

Column 9b : **Residual risk level:** After the risk mitigation what is the residual risk level, whether it is Acceptable, Low or Medium.

Column 9c : **Test document:** Write the test point where the risk mitigation strategy will be verified.

Column 10 : **Status of RA:** Mention the status of the Risk assessment point i.e. whether it is ‘Closed” or “Open”, after the execution/ approval of the Test document.

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Charging											
1.	Charging Conveyor	Vials/ampoules are not available on charging conveyor	Yes	Empty blisters or blisters with missed ampoules/vials may be produced.	Operational	Product loss	Medium	• View glass shall be provided for assessing the product presence on the conveyor. • Alarm shall be generated in case of low or no vials/ampoules available on charging conveyor with machine stoppage.	Acceptable	IQ & OQ	
2.	Feeding of ampoules/vials	Feed rate cannot be controlled	No	Does not impact quality of the product	Operational	Uncontrolled feeding of product will lead to frequent breakdown and loss of productivity.	Medium	Feed rate should be controlled with control of vibration intensity and sensor should be placed to maintain the level of ampoules/vials in the distribution plate.	Acceptable	IQ & OQ	
Process											

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3.	Change parts	Provision for change parts is not provided.	No	Does not affect the quality of the product	Operational	Blister packing of ampoules of different sizes and in variable blister format is not feasible.	Medium	Machine should be provided with required change parts to pack the ampoules in desired format.	Acceptable	IQ	
4.	Process control	Process parameters such as machine speed, sealing temperature, forming temperature, pressure, vacuum etc. cannot be monitored and controlled.	Yes	Operation cannot be run in control.	No	NA	High	Process parameters will be displayed and control by PLC/HMI.	Acceptable	IQ & OQ	

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5.	In-process control	Blisters with empty pocket are found with the good blisters	Yes	It will produce incorrect blister quantity leading to market complaint.	No	NA	High	Non fill detection (NFD) system shall be installed to the machine.	Acceptable	IQ & OQ	
6.	In-process control	Over-printing is incorrect or illegible.	Yes	Incorrect or illegible printed matter will mislead the patient, lead to market complaint.	No	NA	High	• Checking of printed matter and over-printed matter will be done initially and intermittently during entire operation with online camera system. • SOP shall be prepared for In process Checking.	Acceptable	OQ & SOP	
7.	Lubricant System	Lubricant migrates into product	Yes	It will cause contamination	No	NA	High	• Lubrication system must be leak proof. • Food grade lubricant shall be used.	Acceptable	OQ	

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8.	Foil dispensing station	Absence of foil cannot be assessed	No	Does not affect the quality of the product	Operational	Machine will run without foil leading to breakdown.	Low	• Foil detection sensor to be considered in the design. • Alarm shall be generated with stoppage of machine in case of absence of foil.	Acceptable	IQ & OQ	
9.	Overprinting	Overprinting is not feasible	Yes	Batch identity cannot be overprinted.	No	NA	High	Provision for overprinting unit to be considered in the design.	Acceptable	IQ & OQ	
10.	Blister cutting	Blisters are cut with undesired printed matter.	Yes	Product may be produced with incomplete information.	No	NA	High	Finished blisters will be checked intermittently during operation as per In process check SOPs.	Acceptable	OQ & SOP	
11.	Blister counting	Blister output cannot be assessed.	Yes	Yield cannot be monitored.	No	NA	Medium	Blister counter to be considered in the design	Acceptable	IQ & OQ	
Discharge											

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12.	Blister collation	Blisters cannot be collated	Yes	Unarranged discharge of blister will lead to punctured blister.	No	NA	Medium	Blister collator with compatibility to blister format shall be considered.	Acceptable	IQ & OQ	
13.	Reject blister discharge	Rejected blisters are mixed with good blisters.	Yes	Blisters with empty pocket may go with good blisters lead to market complaint.	No	NA	Medium	Rejected blister chute should be provided with rejection confirmation system. It will be attached to the rejection box.	Acceptable	IQ & OQ	
Equipment Construction											

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14.	Material of Construction	▪ Surface and construction of the machine is not compatible to product. ▪ Material reacts with cleaning media like PW, IPA etc.	Yes	It will lead to product contamination due to corrosion	No	NA	High	▪ All product contact metallic surfaces should be of SS 316 or better. ▪ All welds and joints shall be ground finish; metallic surface will have no crevices. ▪ Non Contact surfaces should be SS304 with external surface matt finish.	Acceptable	IQ	
15.	Polymeric materials	• Polymeric materials are not compatible with product. • Polymeric material not replaceable.	Yes	May lead to product contamination.	No	NA	High	• Gaskets coming in direct / indirect contact surfaces should be made up of food grade polymeric materials only and are high temperature and pressure resistant. • The easy change of gaskets should be possible.	Acceptable	IQ	

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16.	Welding Joints	Uneven and improperly ground weld joints will form a space for dust accumulation	Yes	Weld joints not grounded properly and are not passivated.	No	NA	High	All welds shall be ground finished and properly passivated.	Acceptable	IQ	
17.	Finishing	Accumulation of dust, particles on internal surfaces; possibility of microbial growth and hence product contamination.	Yes	Internal surface finish of contact parts is not proper	No	NA	High	• All internal metallic surface should be electro-polished with ≤ 0.8 µm Ra. • External surface should be free from sharp edges, corners, crevices etc., all metallic external surface shall be matt finished with ≤ 1.0µm Ra, 180 Grit. • Test certificate for the same shall be provided by the vendor.	Acceptable	IQ	

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18.	Joints	Leaking joints may lead to contamination of product.	Yes	Joints are not air tight. Suitable gaskets are not provided or are not replaceable.	No	NA	High	Suitable gaskets should be provided for air tight triclover connection and should be easily replaceable.	Acceptable	IQ	
Cleaning											

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19.	Cleaning	Difficult cleaning	Yes	Accumulation of particles, contamination of clean room possible	No	NA	High	• Design of the equipment should enhance cleaning feasibility by providing minimum sharp corners, minimum crevices & smooth finished surface. • Parts which are required for cleaning are provided with quick fixing arrangement. • All bolts, nuts on the exterior part of equipment are provided with cap head or cap nut.	Acceptable	IQ	

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20.	Cleaning	Labeling of components/ media inappropriate	Yes	Prerequisite for qualification & maintenance	No	NA	Medium	• Unique identity number / flow direction must be on components / media, operator panel, etc. (e.g. according to P&ID) • Labels affixed on the equipment should be heat resistant. • All labelling in English language and according to project standard.	Acceptable	IQ	
Control System											
21.	PLC / Control system	Process parameters are not controlled automatically.	Yes	Possibility of human error leads to a process which is not validated	No	Na	High	• The equipment shall control & detect failure mode automatically. • The System shall be PLC based and fully automatic.	Acceptable	IQ & OQ	

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22.	PLC / Control system	Process / process status not visible for operating personnel.	Yes	Operating personnel must have knowledge on the process status	No	NA	High	MMI shall be provided with adequate display and clean room suitable key board for operation and entering process parameters.	Acceptable	IQ	
23.	PLC / Control system	Display language not identified.	Yes	Pre-requisite for the GMP compliant operation	No	NA	High	The language on the display of MMI should be English language only.	Acceptable	OQ	
24.	PLC / Control system	Recorder failure	Yes	Basis GMP requirement (incomplete / no documentation)	No	NA	High	• Data backup for process data must be foreseen . • Diagnostic function test to be a part of qualification activity.	Acceptable	OQ	

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25.	PLC / Control system	Monitoring/recording and documentation of GMP relevant data not possible	Yes	Basic GMP requirement	No	NA	High	• It should be possible to monitor/record GMP relevant data • Batch records / print outs to be defined. • Printout facility should be available with fade proof prints.	Acceptable	OQ	
26.	PLC / Control system	Control system does not detect failures and generate alarms	Yes	Process optimization and validation is not possible	No	NA	High	Failure of set parameters gets indicated and printed as alarms and machine stops.	Acceptable	OQ	

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27.	PLC / Control system	Power failure / emergency stop	Yes	Process out of specification	EHS	May lead to some accident	High	• Operator settings unchanged and restored after emergency stop / power failure; • Alarm message; • Machine must not start automatically without operator intervention after incident • UPS supply should be provided for the control system. • SOP for 'Maintenance and operation of Blister Packing Machine'.	Acceptable	OQ & SOP	

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28.	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	

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29.	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	
30.	PLC / Control system	Parameter settings not identified universally	Yes	Basic GMP requirement	No	NA	High	Parameters settings should be in numeric only.	Acceptable	OQ	
31.	PLC / Control system	Time measurement works incorrect	Yes	Process insufficient	No	NA	High	• PLC Clock verification • SOP “calibration and maintenance” • Time synchronisation of system	Acceptable	OQ & SOP	

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32.	PLC / Control system	No protection of PLC against manipulation & changes.	Yes	Basic GMP requirement.	No	NA	High	Minimum 3 level password protections should be provided. ➢ Level 1: for operator settable parameters. ➢ Level 2: for editing cycle parameters. ➢ Level 3: for admin/ engineering level setting.	Acceptable	OQ	
Measuring Instruments											
33.	Measuring Instruments	Measuring Instruments not suitable	Yes	Improper measurements	No	NA	High	• Measuring Instruments must have a suitable measuring range. • Operational range of Measuring Instruments > equipment working range. • Measuring Instruments must have appropriate accuracy.	Acceptable	IQ	

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34.	Measuring instruments	Measuring instruments not calibrated	Yes	Non calibrated measuring instruments may lead to false machine functions	No	NA	High	• Measuring instruments should be calibrated, traceable to national or international standards. ▪ Re-calibration of instruments should be possible.	Acceptable	IQ	
35.	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	
Maintenance											

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36.	Maintenance	Malfunctions due to worn parts	Yes	Basic GMP requirement	No	NA	High	• Equipment shall be easy to maintain. • Preventive maintenance procedure should be available. • Vendor to provide special tools for maintenance. • The unit must contain necessary protection devices to ensure that the equipment & the article remain in a safe condition.	Acceptable	IQ & SOP	
Environment & Safety											
37.	Electrical system	Electrical systems are not verified for safety	No	It will not affect the quality of product.	EHS	May lead to an accident	Medium	All electrical systems shall be tested for safety and shall be provided with safety markings e.g. C.E. marking.	Acceptable	IQ	

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38.	Noise level	Noise level liberated by the system is high.	No	It will not affect the final quality of product.	EHS	Heavy noise will cause problems to the service persons	Medium	The noise liberated by the system shall not be more than 75 db from 1m from the system.	Acceptable	OQ	
39.	Emergency stop	Instantaneous stopping of the equipment not possible	No	Does not have any impact on quality of the product	EHS	Emergency stop function is required for equipment, personnel and product protection	High	Emergency stop with alarm to be installed on accessible area.	Acceptable	IQ & OQ	
Documentation											

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RISK ASSESSMENT FOR BLISTER PACKING MACHINE

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)	
40.	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	
41.	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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								Mitigation Method (9a)	Residual risk level (9b)	Verification (9c)	
42.	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	

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								Mitigation Method (9a)	Residual risk level (9b)	Verification (9c)	
43.	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 • Operation and maintenance instructions • Spare parts list • Operating manual of bought out components • Functional design specification • List of failure indications • HMI functions with screen shots • Drawings • P&I-diagrams • Electrical diagrams • GA diagram • Calibration certificates of measuring instruments.	Acceptable	IQ	

8.0 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. Blister Packing 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".*

9.0 Abbreviations

EU-GMP	:	European – Good Manufacturing Practice
EHS	:	Environment Health Safety
GMP	:	Good Manufacturing Practice
RA	:	Risk Assessment
NMT	:	Not More Than
SOP	:	Standard Operating Procedure
SS	:	Stainless Steel
Ra	:	Roughness Average
P&ID	:	Process/ Piping & Instrumentation Diagram
PLC	:	Programmable Logic Controller
MMI	:	Man Machine Interface
CFR	:	Code of Federal Regulations
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

10.0 Revision History

Date	Revision	Reason for Revision
	00	New Document