Risk Assessment Document
For
Cartonator

Table of Contents

RISK ASSESSMENT FOR CARTONATOR

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 a cartonator consisting of the following main components:
The machine should be suitable to insert vials and leaflets into the carton. On line product feeding and detecting, leaflet fold (1-4folds) and feeding, leaflet detecting, carton opening and forming, products and leaflet pushing into carton, printing or embossing batch number, sealing carton with tuck-in. Automatically reject lacking of leaflet or product with online check weighing machine. Automatic detection of unique Pharma code assigned to leaflets & cartons and rejection of mix ups.
PLC control system to regulate all critical parameters and generate alarm in case of variations from the set parameters.

In this GMP risk analysis all critical components of the cartonator, 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 cartonator 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 ASSESSMENT FOR CARTONATOR

- 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.

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  This document applies the risk management principles to identify the risks associated with the design, Construction and operational features of the proposed sterile formulation facility.
  The objectives of this risk assessment are to:
  • Review the design around a structured methodology
  • Identify the failure modes and associated risks
  • Check if the proposed control measures are adequate
  • Identify recommendations to obtain a more acceptable risk level if required

RISK ASSESSMENT FOR CARTONATOR

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”.

RISK ASSESSMENT FOR CARTONATOR

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 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.

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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)	
Charging											
1.	Vial feeding	Product is not available at in feed.	Yes	Carton without product may processes with leaflet only. Empty running of machine.	Productivity loss	This will increase the reworking & market complainant	High	• Sensor shall be provided at infeed to detect the presence of products. • Machine should stop with alarm in case of no product available at infeed.	Acceptable	IQ & OQ	
2.	Vial feeding	Vials may get damaged during feeding.	Yes	Products will lose its aesthetic look, identity and integrity.	Productivity loss	Damaged vials may cause machine breakdown.	High	Cartonator to be designed in such a way so as to provide smooth shift of vials.	Acceptable	OQ	
3.	Carton feeding	Cartons in the carton feeder are exhausted.	No	NA	Productivity loss	More rejection due to unavailability of carton	High	Sensor, alarm and interlocking system will be installed in the machine so as to provide continuous supply of cartons and to avoid empty run.	Acceptable	IQ & OQ	
4.	Literature feeder	Absence of literature in the carton feeder.	Yes	Finish packs may go without literature	No	NA	High	• Senor shall be provided at leaflet dispensing to detect the presence of leaflet/literature. • Carton without literature should be rejected wit alarm.	Low	IQ & OQ	
5.	Literature feeder	Literature is not properly folded at the time of insertion in the carton.	Yes	• Literature may damage during insertion. • Incomplete information to the user.	No	NA	High	Cartonator machine should be designed in such a way so as to provide smooth processing of literatures inside the carton.	Acceptable	IQ & OQ	
Process											

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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)
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6.	Vial & leaflet packing	Improper packing of vials & leaflet inside the carton.	Yes	Improper packing of carton may lead to productivity loss & market complaint.	No	NA	High	• All part of the system feedings, carton making, leaflet insert, carton printing, carton flap closing system should have adjustable speed and be synchronized to assure maximal production capacity. • If all product components are not present or correctly identified the system should not feed a carton.	Acceptable	IQ & OQ	
7.	Carton	Incorrect carton is fed	Yes	Identity of the pack will differ.	No	NA	High	• Sensor shall be provided to monitor the presence of carton prior to loading • Open carton flaps are to be detected and automatically rejected.	Acceptable	IQ & OQ	
8.	Literature	Incorrect literature is fed	It will lead to deliver incorrect information to the customer	No	No	NA	High	Pharma code / bar code reader system will be installed and interlocked with the machine and generate alarm	Acceptable	IQ & OQ	
9.	Carton coding	Incorrect, illegible coding on the cartons	Yes	Identity identification of the carton cannot be assured	No	NA	High	In-process checking as per SOP for manual checking of carton coding to be developed.	Acceptable	OQ & SOP	
10.	Carton packing	Empty cartons may pack.	Yes	Empty carton will lead to market complaint	No	NA	High	Non-fill detection and rejection system shall be provided.	Acceptable	IQ & OQ	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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11.	Product size	Equipment not suitable for different size of products.	No	No impact on product quality.	Operational	Different vial sizes may not be processed with same equipment.	Medium	▪ Equipment shall be suitable for packing of different sizes of products by changing format (change) parts. ▪ Change parts for different product size shall be provided by vendor, along with the equipment.	Acceptable	IQ	
Discharge											
12.	Carton discharge	Rejected cartons may mix with good cartons.	Yes	Incorrect pack to be rejected will be mixed with good packs and lead to market complaints.	Productivity	It will trigger re-working	High	Unit shall be designed not to allow rejected cartons to go with good cartons. SOP will be developed to handle line rejection. Carton counter should be provided.	Acceptable	IQ & OQ	
13.	Carton	Cartons get damaged in the carton carrier	Yes	Pack will loose its aesthetic look and identity	Productivity	It will trigger re-working	High	Conveyor or carrier belts will be designed so that it will not affect the carton quantity.	Acceptable	IQ & OQ	
Equipment Construction											
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	Process blistering has certain physical-chemical characteristics, which may be effected due to non compatible materials.	No	NA	High	▪ All product contact metallic surfaces should be of SS 304 or better. ▪ All welds and joints shall be ground finish; metallic surface will have no crevices.	Acceptable	IQ	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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15.	Polymeric materials	• Polymeric materials are not compatible with product. • Polymeric material not replaceable.	Yes	May lead to clean room 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. • Vendor to provide MOC certificates for the same.	Acceptable	IQ	
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 as well as clean room 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	
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											

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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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	
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	
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	HMI shall be provided with adequate display and clean room suitable key board for operation and entering process parameters.	Acceptable	IQ	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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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.	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 (electronic recording, 21 CFR part 11 compliant). • Diagnostic function test to be a part of qualification activity.	Acceptable	OQ	
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 (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	
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	
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 cartonator'.	Acceptable	OQ & SOP	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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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	
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	ceptable	OQ & SOP	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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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	
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											

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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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	
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	
40.	Compressed air	Insufficient/ No pressure	Yes	Equipment operation will be disturbed	No	NA	High	Pressure gauge/ Pressure switch shall be provided at compressed air inlet to monitor & control compressed air pressure along with alarm provision in case of low pressure.	Acceptable	IQ & OQ	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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)
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41.	Vacuum	Insufficient/ No vacuum	Yes	Equipment operation will be disturbed	No	NA	High	Vacuum gauge/ switch shall be provided to monitor & control vacuum along with alarm provision in case of low or no vcuum.	Acceptable	IQ & OQ	
Documentation											
42.	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	
43.	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	
44.	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	

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

RISK ASSESSMENT FOR CARTONATOR

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45.	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 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. cartonator.
- 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
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
HMI	:	Human 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 Revision History

Date	Revision	Reason for Revision
	00	New Document