CONTAMINATION CONTROL STRATEGY FOR STERILE PRODUCTS MANUFACTURED IN VIAL LINE (LIQUID)

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1. INTRODUCTION:

1.1 OBJECTIVE:

This document is based on EU Annex 1, which requires to develop a Contamination Control Strategy based on the following principles (quoted from **EU Annex 1**):

"The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial, cellular debris (e.g. Pyrogen /Endotoxin) and Particulate contamination (e.g. glass and other visible and sub-visible particles)."

The elements considered in CCS are listed in EU Annex 1:

i. *Design of both the plant and processes including the associated documentation.*
ii. *Premises and equipment.*
iii. *Personnel.*
iv. *Utilities.*
v. *Raw material controls – including in-process controls.*
vi. *Product containers and closures.*
vii. *Vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers.*
viii. *Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services.*
ix. *Process risk management.*
x. *Process validation.*
xi. *Validation of sterilisation processes.*
xii. *Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination.*
xiii. *Cleaning and disinfection.*
xiv. *Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination.*
xv. *Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools.*
xvi. *Continuous improvement based on information derived from the above.*

"CCS-Document summarizes how our company approached each of the elements and how we maintain the standard to ensure an adequate level of contamination control. This document considers quality risk assessment and the overall approach to managing microorganisms, pyrogens and particulates contamination of products manufactured in the site. It makes reference to relevant documents, in which details are defined and documented. To avoid mismatches; this CCS document does not repeat details provided in other documents".

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CCS main goals are:

To identify the set of controls required to detect and prevent microbial, pyrogen and particulate contamination across the facility and in final product,

Assess the collective effectiveness of all the controls and monitoring measures employed to prevent the risk of contamination across the facility (e.g., utilities, cleaning and disinfection, process validation, facility design, etc.) and in the final product,

Improve the quality system with continuous improvement plans based on the analysis and trending of data gathered through the monitoring measures employed,

Assess the development of the contamination control performance over time through Monthly Quality Meeting.

1.2 SCOPE:

The present document represents the overall risk evaluation associated of potential microbial, pyrogen and particulate contamination in sterile product manufacturing facility Ampoule.

1.3 DEFINITIONS:

Contamination:

The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particulate matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.

Contamination Control Strategy:

A planned set of controls for microorganisms, endotoxin/pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to the active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

2. STRATEGY:

2.1 CCS IMPLEMENTATION METHOD:

The following 3 steps have been followed to establish the **Contamination Control Strategy:**

Environmental scanning and Strategy formulation: Description of the Facility, premises, equipmentdesign and description of the Quality target product profile including description of the production process,

Strategy Implementation: Process Mapping through quality risk assessment allowing to:

Identify risk and source of contamination for both environment and process, Define the critical control point and monitoring related parameters face to each of the risks identified, Statement of risk acceptance based on critical control points/mitigation measures established and new risks quotation,

Strategy Evaluation, consisting of:

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Define / identify any monitoring tools or measures face to each critical control point,
CCS efficiency evaluation by data trending and analysis through monitoring implemented,
Establish a Strategic plan for continuous improvement based on this review.

Note: Process mapping has been done according QRM principles and FMEA method described in SOP.

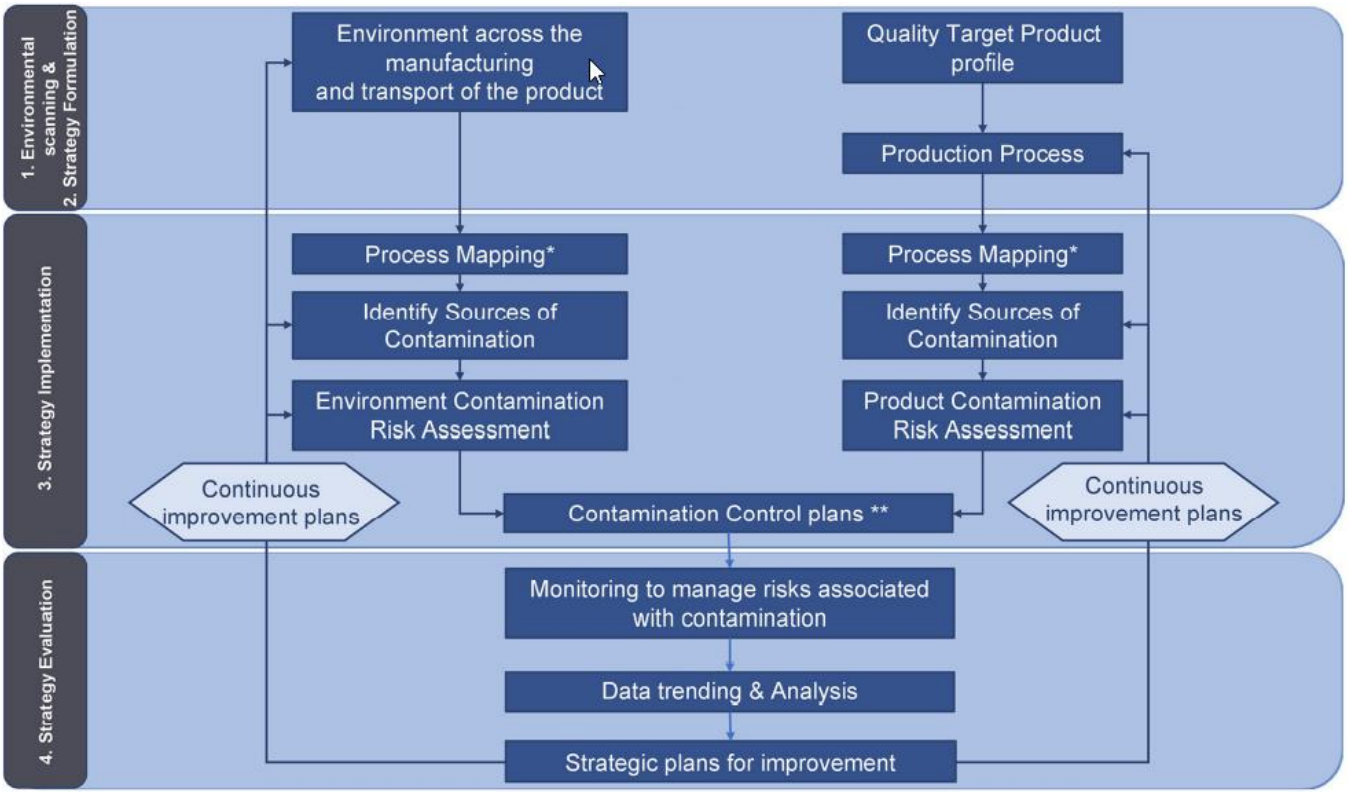

Figure 1: CCS Methodology – ref PDA J Pharm Sci and Tech 2021, 75 445-453

2.2 FACILITY DESIGN:

Sterile product manufacturing facility, including Vial line (Liquid) at. ……, is dedicated for sterile product only. The plant is designed to ensure the process steps are performed in the clean room Grades which are required according to **EU Annex 1**.

Access to the clean room grades is done via separate air-locks for personnel and material.

The following grades are in use for the different manufacturing operations:

Grade A/B - Filling, Sealing and other critical operations eg. Unloading of Sterilized components, holding tank storage,

Grade A/D - Sampling and Dispensing of API/Excipients, dedicated areas for each type of raw material,

Grade A/CNC - Sampling of primary packaging articles,

Grade C - Compounding area, washing and sterilization/Depyrogenation of Vial,

Grade CNC - Decartoning of Vial.

Facility was designed to minimize risk of contamination using:

Adapted flow of material and people,

Adapted system for Air treatment at any process stage,

Adapted Environment Monitoring System (EMS) to guarantee product and materials protection at any process steps through adapted monitoring of temperature, Humidity%, Pressure Differential.

The different corresponding layouts are attached in the appendixes:

Facility Layout ref: ……

Material Movement layout ref: ……

Man, Movement flow layout ref: ……

HVAC layout ref: ……..

AHU Zoning: …….

Pressure Zoning: …….

Pest Control is in place in the whole facility to prevent any external contamination from insects, rodents, etc.
Documentation related to Pest control is SOP this operation is managed by HR.
Pest control is covered by Process mapping, Risk Assessment and Strategy.

2.3 EQUIPMENT DESIGN:

Qualification/validation status corresponds to the target to be achieved, some Qualification & Validation Actions are still on going and followed through project action plan.

Critical process Equipment are as follow, detail and reference for qualification are given in the process mapping:

2.3.1Mixing vessel, transfer line and Holding vessel:

These equipments are fully Qualified as DQ/IQ/OQ and PQ done, and validated CIP/SIP cycles are performed to minimize risk of contamination.

2.3.2Autoclave for Sterilization of articles like Garments, Machine parts and Disinfectants accessories:

This equipment is fully Qualified as DQ/IQ/OQ and PQ done, and corresponding loading patterns are fully validated.

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2.3.3Vial washing machine:

This equipment is fully Qualified as DQ/IQ/OQ and PQ done and washing cycle are fully validated.

2.3.4Ampoule Depyrogenation Tunnel:

This equipment is fully Qualified as DQ/IQ/OQ and PQ done and depyrogenation cycle are fully validated.

2.3.5Filling and sealing Machine:

Restricted Access Barriers Systems (O-RABs) was implemented to minimize risks of contamination: This equipment is fully Qualified as DQ/IQ/OQ and PQ done and designed to minimize aseptic connection and direct intervention to the products.

Filling and sealing machine are fully validated.

2.3.6*Camera based automated visual and leak test detector machine:*

This equipment is fully Qualified as DQ/IQ/OQ and PQ done to guarantee any detection of particles and risk of contamination through lack of integrity.

2.3.7Critical utilities Equipments are as follows:

HVAC systems to maintain Grade A/B/C/D areas classification
Purified Water System,
WFI System,
Pure Steam Generation System,
Nitrogen Gas system,
Compressed Air Gas System.

Refer Appendix 1 for lay-outs.
All these equipment's are fully Qualified as DQ/IQ/OQ and PQ done to minimize risk of contamination.

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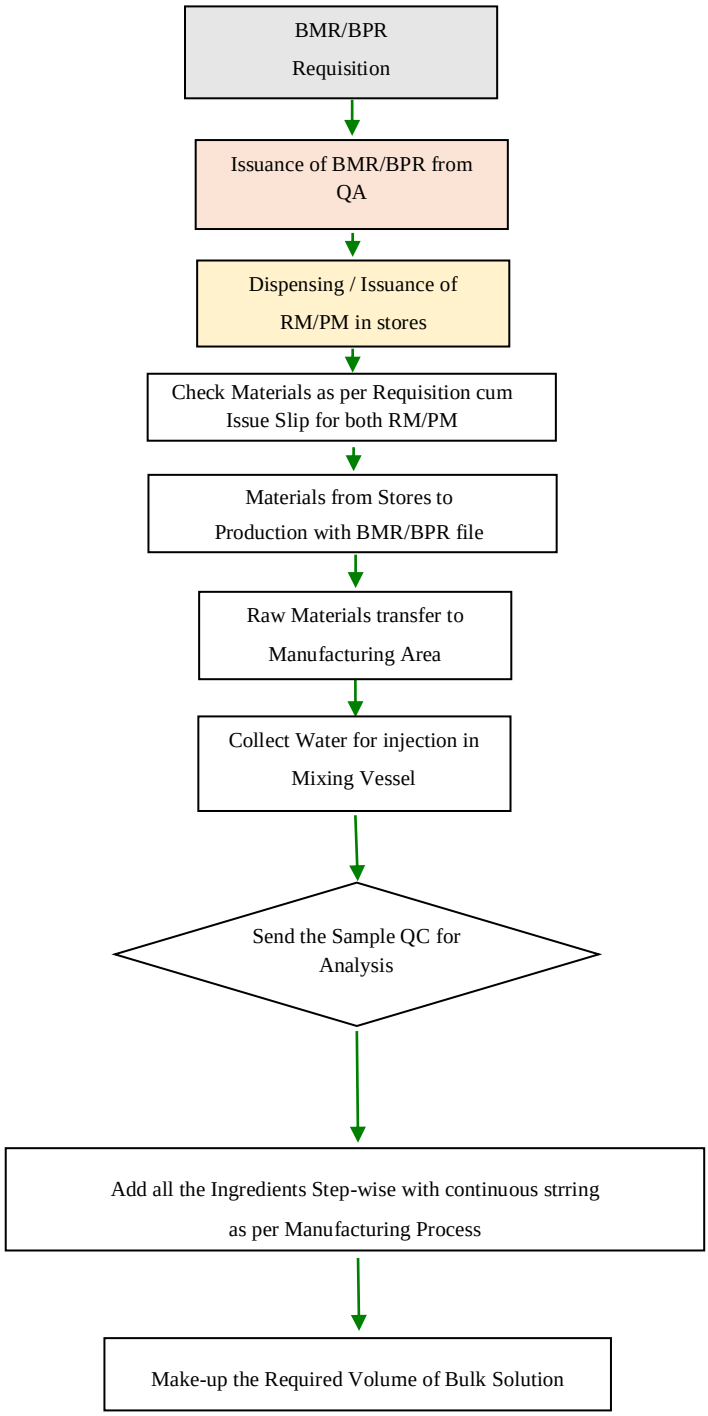
2.4 PROCESS DESIGN:

In Vial line (Liquid) manufacturing processes are carried out in asepsis (product sterilized by filtration through a sterile, sterilizing grade filter with nominal pore size of 0.22 micron).

The Type of products manufactured is Liquid Vial.

Process workflow of Liquid Vial manufactured in Vial line is as follows:



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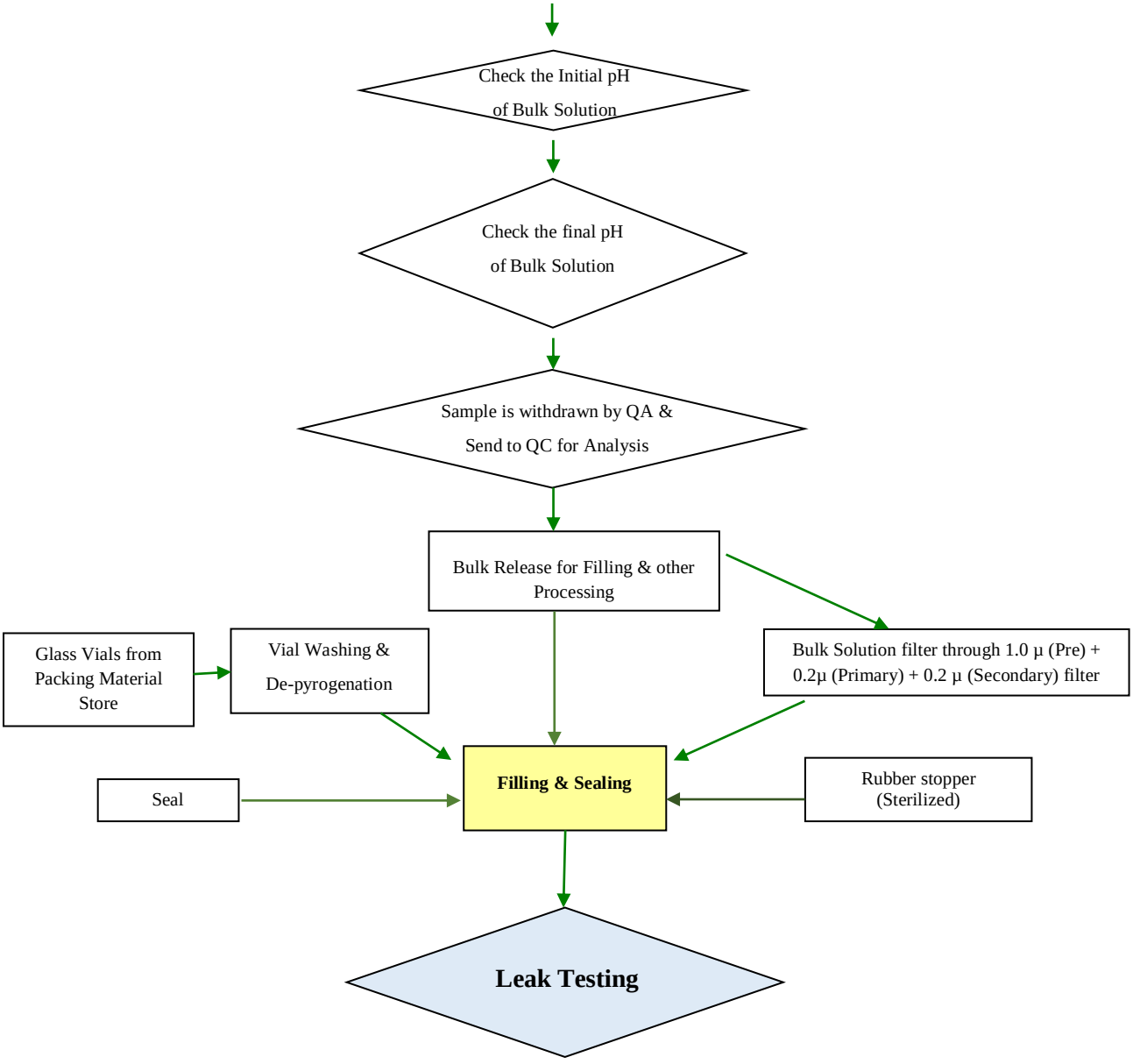

3. PRODUCT QUALITY TARGET PROFILE:

3.1 RAW MATERIALS:

All Approved specification & Standard Test Procedure of Raw materials (Active ingredient, Excipients) prepared as per SOP.

3.2 PRIMARY PACKAGING MATERIAL:

All Approved specification & Standard Test Procedure of Primary packing material prepared as per SOP.

3.3 BULK PRODUCT:

All Approved specification & Standard Test Procedure of Primary packing material prepared as per SOP.

3.4 FINISHED PRODUCT:

All Approved specification & Standard Test Procedure of finished product prepared as per SOP.
Note: *If any impact on microbial, Pyrogen /Endotoxin,*

4 RISK ASSESSMENT:

For the purpose of this document and assess the risks for contamination before and after mitigation measures linked with each critical control points, FMEA (Failure Mode Effects Analysis) Method has been used as analysis tool since it can be applied to equipment and facilities and used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable (ref ICH Q9 Quality Risk Management Annex 1, paragraph I.2).

The individual possible risks that can be associated with sterility and particulates failure have been identified in the following paragraphs as well as the degree of Severity and Probability of Occurrence associated with them.

A team has been defined based on the specific knowledge of all the members in order to realize the present risk assessment, including Production, Quality Control, Engineering and QA expertise.

Method used is as follows:

4.1 RISK IDENTIFICATION:

A sterility failure during the manufacturing of drug products can be associated to the following risks:

- Contaminated product on the market with severe consequences on patient's health,
- Contaminated sterile manufacturing area driving to multiple batches contamination,
- For process Mapping first column is for risk assessment, then potential failure mode, potential cause of failure then RPN calculated for overall risk assessment prior to risk mitigation,
- Then in continuation critical control point risk mitigation, RPN calculated for overall risk assessment after risk mitigation, detail description of documents refer for risk mitigation and final statement about Risk under control.

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4.2 RISK ANALYSIS:

The scoring table provides descriptors for Impact (Severity), Probability (Occurrence/ Frequency), and Detectability.

These are recorded in the relevant columns on the template.

The explanation for each number in the scoring system for Probability/occurrence, Impact/severity and Detectability/detection as well as the RPN threshold ranges are mentioned as below.

These scales and ranges are harmonized (severity, occurrence and detection) and should be used to conduct FMEA exercises.

4.2.1 Severity (S):

Severity is a numerical subjective estimate of how severe the end user will perceive the effect of a failure. In other terms is the measure of the possible consequences of a hazard.

In the present case study, the failure to be considered is the loss of Quality/sterility in the final product. Nevertheless, a loss of confidence in sterility might always have an extremely severe impact on patient's health, being able to cause illness, serious injury, or death.

Severity Rating Scale:

Severity Effect	Rating
No Effect	1
Minor Effect	2
Moderate Effect	3
Serious Effect	4
Hazardous Effect	5

4.2.2 Probability of Occurrence (P):

The probability of occurrence (P) is defined as the correlation between the frequency of the failure mode, within a defined period of time, and the probability that it would result in the occurrence of the Failure mode effect.

Frequency of the failure mode is the frequency of the failure mode considering the relevant activity frequency on the basis of a routine working day (16 working hours - 2 shifts) and an estimation of the occurrence.

Occurrence Rating Scale:

Likelihood Occurrence	Rating
Unlikely	1
Very Rare	2
Possible	3
Likely	4
Almost Certain (every time)	5

Probability of failure mode effect is the probability that the identified failure, independently from the frequency, could cause the effect considered.

4.2.3 Detection:

It is an estimate of the effectiveness of the controls to prevent or detect the cause or failure mode before the failure reaches the customer.

Rating Scale for Detection:

Likelihood of Detection	Rating
Always Detected	1
Will Detect Failure	2
Might Detect Failure	3
Almost certain not to Detect Failure	4
Lack of Detection Control	5

4.3 RISK EVALUATION:

Calculation of Risk (RPN):

The RPN number is used to aid prioritization of actions, the intention is different from the criticality, which is solely linked to patient impact / product quality. The higher the number the greater the risk, and hence the areas where effort should be made to reduce it.

For the calculation of “risk” each factor has a defined meaning used to establish quantification of score. Individual scores of impact/severity, probability/occurrence and detectability/detection are multiplied to calculate the overall RPN (Risk priority number) for each Critical Control Point.

The following formula is used:

RPN = Severity Rating x Probability Rating x Detectability Rating

The lowest risk RPN is 1 (1 x 1 x 1) and for highest risk RPN is 125 (5 x 5 x 5).

Acceptance criteria applied to process mapping and RPN related:
In case of the calculated RPN rating is greater than 50 those Particular failure are not acceptable.

S.No.	RPN Rating	Category
1.	51 to ≤ 125	High
2.	26 to 50	Medium
3.	Upto25	Low

4.4 RISK REDUCTION:

Initial RPN have been calculated for each Potential cause of failure / Type of contamination risk for Viable/Non-Viable/Endotoxin-Pyrogen.

Critical Control point have been identified and described against each potential cause of failure and RPN recalculated based on measures (Design/Procedural/Technical/Organizational) already in place.

According to Acceptance criteria defined in section 4.3, a final statement has been given for each level of risk. When risk was considered as not acceptable, new measures or actions have been decided and collected in a global action plan called 'Process mapping action plan'.

This Action plan is followed on a weekly basis to guarantee that all actions will be implemented to reduce the risk to an acceptable level.
CCS and process mapping linked with will be subject to an update when all actions will be implemented.

5 STRATEGY IMPLEMENTATION:

The strategy implementation consists of executing the strategic plan through the mapping of the Pharmaceutical process, allowing to:

Identify any risk of contamination& contamination sources,

Assess initial risk based on RPN calculation& FMEA method,

Identify each critical control point & measures already in place to control the initial risk calculated,

Assess the residual risk and decide any new measures if this residual risk does not comply with acceptance criteria defined.

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Any new measures or actions decided are detailed in the process mapping and were compiled in a process mapping action plan, giving a Responsibility Owner and due date for each of them.

Beside detailed Process mapping, some global Systems are in place, covering the whole process and allowing to control any source of contamination identified.

These systems, preventive maintenance and training are described and detailed separately.

5.1 PERSONNEL TRAINING:

Personnel is trained in all areas of their responsibilities. More details about the areas and the applicable procedures are provided:

Type of Training	**Reference Document**	
	Title	**SOP No.**
Induction training	Procedure of induction program	-
On job training (OJT)	Training of personnels	-
cGMP-training& External Training	Training of personnels	-
Personnel Hygiene(SOP for Entrance of Production Block)	SOP on procedure for personnel hygiene of personnel	-
Personnel Hygiene and Monitoring (SOP for Entrance of Aseptic Area)	Personnel Hygiene and Monitoring	-
Personnel Qualification	Qualification for the personnel Entering in to Aseptic area	-
Aseptic Behaviour	Procedure for Aseptic Behaviour and Technique	-

5.2 MAINTENANCE PROGRAM:

A maintenance program is in place and followed for each of the critical equipment as described below:

Preventive Maintenance	**Reference Document**	
	Title	**SOP No.**
HVAC	SOP For AHU filters cleaning	-
HVAC	Operation of Air Handling Unit	-
HVAC	SOP for Annual Preventive Maintenance Plan	-
COMPOUNDING VESSELS AND EQUIPMENT	SOP for Annual Preventive Maintenance Plan	-
WASHING MACHINE	SOP for Annual Preventive Maintenance Plan	-
STERILIZATION/DEPYROGENATION TUNNEL	SOP for Annual Preventive Maintenance Plan	-
FILLING MACHINE	SOP for Annual Preventive Maintenance Plan	-
AUTOCLAVE (COMPONENT)	SOP for Annual Preventive Maintenance Plan	-
AUTOMATIC VISUAL INSPECTION & HVLD EQUIPMENT	SOP for Annual Preventive Maintenance Plan	-
QC LAB EQUIPMENT CHEMISTRY	Operation/usage ,calibration & Maintenance of Laboratory instruments & Equipments	-
QC LAB EQUIPMENT MICROBIOLOGY	SOP for Annual Preventive Maintenance Plan	-
WFI EQUIPMENT	SOP for Annual Preventive Maintenance Plan	-
PURE STEAM EQUIPMENT	SOP for Annual Preventive Maintenance Plan	-
COMPRESSED AIR EQUIPMENT	SOP for Annual Preventive Maintenance Plan	-
NITROGEN EQUIPMENT	SOP for Annual Preventive Maintenance Plan	-

5.3 PROCESS MAPPING:

The established process mapping cover all process steps from reception of component to shipping of finished product, released.

This process is divided in 9 parts, as follows:

1. Process step description,
2. Potential Failure Mode,
3. Potential cause of failure and type of contamination identified giving detail if viable, non-viable and/or endotoxin/Pyrogen,
4. Initial RPN calculated based on potential cause of failure identified,
5. Critical Control point risk mitigation describing what measures are in place or should be in place,
6. Recalculated RPN if expected measure is in place against each type of contamination,
7. Site Documentation reference & evidence linked with expected measure – if action decided or ongoing, description and details are given in this part,
8. Type of measure in place or to be in place: Design/Procedural/Organizational/Technical,
9. Action Number if any – when some actions are already covered through the project action plan, details are given (refer to X).

Legend used:

Risk acceptable

Risk not acceptable, Action(s) decided

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S.No.	Process steps	Potential failure mode	Potential cause of failure type of contamination risk (Viable/Non- Viable/ Endotoxin-Pyrogen)	RPN	Critical control point risk mitigation	RPN	Documents / reference/ remark or action	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			1.Raw material may be received from an unapproved vendor. (V/NV/End-Py)		1.Approved vendor list is available, checked by warehouse and dispensing people to ensure the material is received from approved vendor.		Vendor list: API: EXCIPIENTS: SOP describing the check: Warehouse: Dispensing: Records in place:	Procedural	Yes
			2. contaminated or damaged container may be received. (V/NV/End-Py)		2.1 During receiving of material each container checked by warehouse person as per the checklist. If any damage container received it shall be segregated with proper status label and trending with respect to damaged containers.		SOP describing the check: Warehouse: Quality Assurance: Records in place: Warehouse form: Quality Assurance:	Procedural	Yes
					2.2 De-dusting Booth provided to remove the external contamination of the container.		SOP describing the cleaning operation: Warehouse: Records in place: Qualification of de-dusting Booth: DQ: IQ: OQ: PQ:	Procedural Technical Design	Yes
			3-Cold chain products (API) received without any coolant pack or		3. Verification of coolant availability & data logger prints are being verified by		SOP to be revised, to Verified coolant Availability & Data logger	Procedural	NO Action

			temperature excursion during transportation. (V)		QA.		Prints verification add on Checklist.		No-01
			4-Controlled Temperature conditions not maintained during storage (V)		4.1 Checklist Available for Storage of Raw Material 4.2 Continuous temperature monitoring 4.3 daily (EMS) print out of temperature monitoring Not checked by warehouse		4.1 SOP describing the Storage condition of Raw material check: Warehouse: Record in place: Warehouse form: EMS System DQ: 1Q: OQ: Temperature Mannual Recorded as per SOP No: Action : SOP to be revised for daily (EMS) print out of temperature monitoring checked by warehouse & QA	Procedural Technical Design	NO Action - 02
			5. Material may be received without vendor COA. (V/NV/End-Py)		5.COA of all Materials is being obtained from the vendor. verified by QA.		SOP describing the check: Warehouse: Records in place: Warehouse form: Vendor COA of material	Procedural	Yes
			6. Mix-up of material		6.1. Different raw materials stored		Layout:	Procedural	YES

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			during storage. (V/NV/End-Py)		separately on different pallets. 6.2. Storage area separated from production area Adequate space for storage of materials available.		SOP describing the check:		
			7- Storage at improper conditions. (V/NV/End-Py)		7. Continuous temperature monitoring through EMS Temperature monitoring Record in logbook (Manually)		Storage area mapping: Mapping Done at summer conditions, Rainy condition and also done at winter conditions. EMS Qualification DQ: IQ: OQ: Temperature manually recorded as per SOP Action: Action: SOP to be revised for daily (EMS) print out of temperature monitoring checked by warehouse & QA.	Procedural Technical Design	No Action No:03
			8- Staging of material without clear status. (V/NV/End-Py)		8. Material is labelled with Quarantine, Under Test, sampled, Approved & Rejected at different stages & as per the findings/results. Separate Rejected material storage area under lock & key is available.		Handling of rejected raw material SOP No: is describe that key for rejected material is kept by QA	Procedural Design	YES
			9-Using the wrong material		9.BOM QA approved in ERP system Dispensing check		ERP validation: DQ:	Procedural Design	Yes

			(V/NV/End-Py)				IQ: OQ: PQ Protocol: PQ Report: SOP: Manufacturing Batch Record:		
			10-Storage areas cleanliness not maintained (V/NV/End-Py)		10. Area cleaning is being done for area and equipment's as per approved procedure.		SOP: Record:	Procedural	Yes
2.	Component Sampling	Raw materials contamination	11. Unadapted Design		11. Qualified RLAF		Layout:	Technical	Action No
			12. Contamination through analysts (V/NV/End-Py)		12. Protective Clothing is being used during sampling.		SOP for entry in sampling area: 0	Procedural Organization	Yes
			13. Unadapted environment for sampling (V/NV/End-Py)		13 Sampling is being done under RLAF only.		SOP for sampling:	Procedural Technical Design	Yes
			14. Inefficient protection to avoid any contamination (V/NV/End-Py)		14 HVAC qualification performed & H14 HEPA filter provided at terminal stage		Initial classification/qualification DQ: IQ: OQ: PQ:	Procedural Technical Design	Yes

2.	Component Sampling	Raw materials contamination							
			15. Contamination brought through sampling tools (V/NV/End-Py)		15. Dedicated washing area not available for cleaning of used sampling tools. Currently washing of used tools is being done in production unit preparation area (Ist Floor)		SOP for washing: Records in place: Warehouse form: SOP Sampling tools Cleaning validation done Ref No: Actions SOP: not describe where to store cleaned tools	Procedural Technical Design	Action No:05
			16.Mix up between clean and unclean (V/NV/End-Py)		16. Separate areas are not available to keep uncleaned & cleaned tools. SOP to be revise and Risk assessment to be prepare		Layout: Actions	Procedural Design	Action No:06
			17.Unadapted design of the facility for sampling (V/NV/End-Py)		1. Sampling area separate from production area 2 sampling area provided for API & Excipient		Layout:	Procedural Design	Yes
			18. Mix up between materials (V/NV/End-Py)		18. At a time only one material/batch is being sampled.		Actions: SOP: Not describe that at a time only one material/batch is being allowed to sampled.	Procedural Organizational	No Action 7
			19. wrong status of the material (V/NV/End-Py)		19. Proper status label affixed after sampling of material till approval of the material.		SOP for sampling SOP Sampled label: SOP Actions SOP should be updated to describe	Procedural	No Action 8

							that Proper status label is affixed after sampling of material till approval of the material		
2.	Component Sampling	Raw materials contamination	20. Dirtyness of RLAF (V/NV/End-Py)		21. Clear written instructions for RLAF filter cleaning & replacement.		SOP for cleaning: Record: Actions Cleaning validation & disinfection validation done	Procedural	Yes
			21. Lack of grade protection due to power cut (V/NV/End-Py)		21. Clear written down procedure available to handle the situation in case of power failure.		Implement SOP to handle power Failure .	Procedural	No Action No:09
			22. Area and equipment dirtiness (V/NV/End-Py)		22. Area cleaning and sanitization is being done for area and equipment as per approved procedure.		Area cleaning procedure describe: SOP: Record: For RLAF equipment cleaning procedure describe: Record:	Procedural	YES

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			23.Contaminated raw material (V/NV/End-Py)		23. QC Testing of materials for Bioburden + pyrogen		Action: SOP for sampling and analysis shall be revise for the testing with respect to pyrogen and bioburden for API and Excipient both (Done for API, to be implemented for excipients) SOP for ref.	Procedural	No Action 10
		PPM Contamination	24.Contaminated PPM from Vendor (V/NV/End-Py)		24. Sampling and testing during PPQ + Periodic testing to be implemented (Bioburden and Endotoxin)		PPQ Protocol/Report Ref + SOP for periodic testing of Bioburden & endotoxin on PPM	Procedural	No Action 11
			25. Contamination through sampling (V/NV/End-Py)		25.Sampling under LAF, but not qualified: need to qualified as grade D (handling of components)		SOP	Procedural Design	No Action 12
3.	Raw Material Dispensing	Raw materials contamination	26. Unadapted Design for Dispensing (V/NV/End-Py)		26. Qualified RLAF provided to control the contamination. Supporting area of RLAF is Grade D. Required to upgrade as Grade C		Layout:	Design	No Action 13
			27. Contamination through Operators (V/NV/End-Py)		27. Protective clothing is being used during Dispensing		SOP for entry in dispensing area:	Procedural Organizational	Yes

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3.	Raw Material Dispensing	Raw materials contamination	28. Unadapted environment for dispensing (V/NV/End-Py)		28. Dispensing is being done under RLAF only.		SOP for dispensing:	Procedural Technical Design	Yes
			29. Unefficient protection to avoid any contamination (V/NV/End-Py)		29. HVAC qualification performed & H14 HEPA filter provided at terminal stage		Initial classification/qualification DQ: IQ: OQ: PQ:	Procedural Technical Design	Yes
			30. Contamination brought through Dispensing tools (V/NV/End-Py)		30. Dedicated washing area not available for cleaning of used Dispensing tools. Currently washing of used tools is being done in production unit preparation area (Ist Floor)		SOP for washing: Records in place: Warehouse form: SOP Dispensing tools cleaning validation Ref No: SOP describe where to store cleaned tools but Dedicated Area not provided for Cleaned Tools	Procedural Technical Design	No Action 14
			31.Mix up between clean and unclean (V/NV/End-Py)		31. Separate areas are provided to keep uncleaned & cleaned tools.		Action: SOP to describe where to store clean dispensing tools No dedicated Room/ Area provide to store Cleaned & Uncleaned tools	Procedural Design	No Action 15
	Raw Material Dispensing		32.Unadapted design of the facility for Dispensing (V/NV/End-Py)		32.1 Dispensing area separate from production area 32.2 No Dedicated area for API & Excipient Dispensing.		Layout:	Procedural Design	NO Action 16

3.			33. Mix up between materials (V/NV/End-Py)		33. At a time only one material is being dispensed.		SOP describe that at a time only one material is being allowed to be Dispensed.	Procedural Organisational	Yes
			34. wrong status of the material (V/NV/End-Py)		34. Only QC approved verified by QA materials are brought to dispensing area		Action: SOP should be updated to describe that Only QC approved verified by QA materials are brought to dispensing area	Procedural Organisational	No Action 17
			35. Dirtyness of RLAF (V/NV/End-Py)		35. Clear written instructions for RLAF filter cleaning & replacement.		SOP for Filter cleaning: Record: Cleaning Validation & disinfection validation done	Procedural	YES
			36. Lack of grade protection due to power cut (V/NV/End-Py)		36. Clear written down procedure available to handle the situation in case of power failure.		Implement SOP to handle power Failure	Procedural	No Action :18

3.	Raw Material Dispensing	Raw materials contamination	37. Area and equipment dirtiness (V/NV/End-Py)		37. Area cleaning and sanitization is being done for area and equipment as per approved procedure.		Dispensing area cleaning Procedure Described: SOP: Record Format: Dispensing Equipment Cleaning Procedure described: SOP: Record Format:	Procedural	Yes
			38.Particulate contamination through polybags used to store dispensed materials (V/NV/End-Py)		38. Double poly bags used for storage of dispensed API and Excipient after dispensing			Procedural	Yes
			39. Contamination from the bags used to store materials after dispensing (V/NV/End-Py)		39. Polybags Pharmaceutical grade used		Action: SOP to update to include check of pharmaceutical grade for polybags used	Procedural Technical	No Action 19

4.	Transfer dispensed material to solution preparation	Raw materials contamination	40. raw material contamination through transfer (V/NV/End-Py)		40.After dispensing material stored in polybags (double) & Dispensed material Transfer to compounding area with trolleys through Dynamic Pass box. Check of raw materials bags during compounding		Storage in double polybags described in SOP Verification of material in the Batch manufacturing record. Action SOP describing transfer operations and mitigation actions to minimize contamination for transfer to create	Procedural	No Action 20
5. **5.**	Solution preparation Solution preparation	Contamination of Raw materials or solution during compounding Contamination of Raw materials or solution during compounding	41. Compounding or/and holding tank dirtiness (V/NV/End-Py)		41. IQ/OQ for both tanks and validated CIP in place. CIP/SIP validated on holding tank& Compounding tank CIP/SIP in place reviewed through BMR by production and QA		DQ/IQ/OQ of Compounding tanks Ref: DQ: IQ: OQ: Validated CIP/SIP for both tanks CIP/SIP result recorded in BMR Ref. for CIP& SIP Validation on Compounding tank: DQ/IQ/OQ of Holding tanks DQ: IQ: OQ: Ref. for CIP &SIP validation on Holding Tank:	Technical Design	No Action 21

			42.Unadapted Design for Compounding (V/NV/End-Py)		42. Qualified HVAC system provided to control the contamination.		Layout:	Design Technical	Yes
			43. Inefficient protection to avoid any contamination (V/NV/End-Py)		43. HVAC qualification performed & H14 HEPA filter provided at terminal stage		Initial classification/qualification DQ: IQ: OQ: PQ:	Design Technical	Yes
			44. Lack of grade protection due to power cut (V/NV/End-Py)		44. Clear written down procedure available to handle the situation in case of power failure.		Implement SOP to handle power Failure and to be provide AHU interlocking system as higher grade to lower grade.	Procedural	Action No:22
			45.Contamination through Operators (V/NV/End-Py)		45. Protective clothing is being used during compounding. Fresh Garments change every entry in solution preparation area.	72	SOP for entry in Solution preparation area:	Procedural Organisational	Yes
			46.Contamination through WFI used (V/NV/End-Py)		46. Qualified System for WFI production		DQ/IQ/OQ/PQ for WFI system ref: DQ IQ OQ PQ Action Periodic sanitization once a month through pure steam to be validated SOP	Technical Design Procedural	No Action 22
			47.Contamination		47. Qualified system for N2 production		DQ/IQ/OQ/PQ for N2 system ref:	Technical	Yes

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			through N2 used (V/NV/End-Py)		Three 0.2µm filtration are in place, first 0.2 µm in service floor, followed by a second in Compounding area followed by a third one at the point of use Third filter tested for integrity and changed every 25 sterilization Second filter changed every 25 sterilization First filter, changed every 6 months		DQ: IQ: OQ: PQ: SOP for filter management Logbook for filters management	Design Procedural	
			48. Contamination brought through other Compounding equipment: glass cylinder for PH adjustment (V/NV/End-Py)		48. Equipment washed with WFI in component preparation area – dried – packed and stored in compounding area		SOP for washing: Action: small equipment cleaning validation (eg glassware) to be done including holding time validation	Design Procedural	No Action 24
			49 Compounding Area dirtyness (V/NV/End-Py)		49. Cleaning and disinfection		SOP Record: Cleaning Validation: Disinfection validation:	Procedural	
	Solution	Contamination of Raw materials or solution during compounding	50. Compounding solution contaminated (V/NV/End-Py)		50. Double layer 1µm +0.2µm filtration between compounding and holding tank Filter integrity test done before and after filtration Single use filter		SOP for filter integrity BMR Action: Describe in SOP …. that the product filter should be single use for Lidocaine	Technical Design Procedural	No Action 26

5.	preparation								
6.	Ampoules decartonning Ampoules decartonning	Contamination from ampoules Contamination from ampoules	51. Particulates contamination (broken or damaged (NV)		51.Visual inspection after decartonning and before to feed washing machine		SOP: Record: BMR recorded Risk assessment for breakage RA No: ….and SOP for breakage management to be prepared	Procedural	NO
6.			52. Non adapted environment (V/NV/End-Py)		52. Operation performed in CNC area Required to upgrade as Grade D		Action	Design Procedural	Action
			53. Contamination through Operators (V/NV/End-Py)		53. Protective clothing is being used during de cartoning.		SOP:	Procedural Organisational	Yes

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7.	Washing of Ampoules	Contamination from ampoules	54. Particulates contamination (NV)		54. Washing machine qualified and Washing cycle validated Alarms in place to stop the process in case of issue (eg low pressure of WFI or compressed air) Line clearance actions in case of breakage		Qualification of washing machine ref DQ/IQ/OQ/PQ DQ: IQ: OQ: PQ: Risk assessment for breakage RA No: and SOP for breakage management to be prepared.	Technical Design Procedural	Action
			55. Microbial contamination through utilities WFI (V/NV/End-Py)		55. WFI system qualified and 0.2µm filtration in place. Integrity testing once a month Replacement once a Six month		DQ IQ OQ PQ SOP for integrity testing of cartridge filter SOP. SOP for Issuance, Cleaning, usages, handling, replacement & Destruction of Filter SOP	Technical Design Procedural	Yes
			56. Micro contamination through Compressed air (V/NV/End-Py)		56. Compressed air system qualified and 0.2µm filtration in place Integrity testing once a month Replacement once a Six month		DQ/IQ/OQ ref DQ IQ OQ: PQ: SOP for filter management	Technical Design Procedural	Yes

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							Sop For Issuance, Cleaning, usages, handling, replacement & Destruction of Filter SOP		
8.	Ampoules transfer from washing machine to tunnel	Contamination of ampoules	57. Ampoules contaminated through grade C environment (V/NV/End-Py)		57. LAF Not implemented to protect ampoules transfer		Action	Technical Design Procedural	NO
9.	Sterilization & Depyrogenation of Ampoules	Contamination from ampoules	58. microbial and pyrogen contamination (V/NV/End-Py)		58.Tunnel qualified and Depyrogenation cycle validated Alarms in place to stop the process in case of issue (eg low Temperature)		Qualification of Sterilization and Depyrogenation tunnel ref DQ/IQ/OQ/PQ DQ: IQ: OQ: PQ:	Technical Design Procedural	YES

	Sterilization & Depyrogenation of Ampoules	Contamination from ampoules	59. Unadapted environment for Sterilization & Depyrogenation (V/NV/End-Py)		59. Qualified HVAC system provided to control the contamination, grade C		Layout:	Technical Design Procedural	Yes
			60. Lack of grade protection due to powercut (V/NV/End-Py)		60.. Clear written down procedure available to handle the situation in case of power failure.		SOP for power failure shall be prepare EMS Qualification DQ: IQ: OQ:	Procedural	No Action 27
			61.Unefficient protection to avoid any contamination (V/NV/End-Py)		61. HVAC qualification performed & H14 HEPA filter provided at terminal stage		Initial classification/qualification DQ: IQ: OQ: PQ:	Technical Design Procedural	Yes
			62. Washing, Sterilization& Depyrogenation Area dirtyness (V/NV/End-Py)		62. Cleaning and disinfection		SOP: Record: Cleaning & Disinfection validation done	Procedural	No Action 28
			63.Contamination through Operators		63. Protective clothing is being used during washing and Depyrogenation.		SOP	Procedural Organisational	Yes

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			(V/NV/End-Py)						
9.		Contamination from ampoules	64.Particulate contamination (NV)		64.Breakage management		Risk assessment for breakage and SOP for breakage management to be prepared	Procedural	No Action 29
10.	Aseptic filling	Empty or filled ampoules contamination	65. Unadapted Design for Filling (V/NV/End-Py)		65. Qualified HVAC system provided to control the contamination, grade A/B with extended LAF		Layout: SMH/SF/004 AHU Zoning: Air Flow:	Technical Design Procedural	Yes
		Empty or filled ampoules contamination	66. Inefficient protection to avoid any contamination (V/NV/End-Py)		66. HVAC qualification performed & H14 HEPA filter provided at terminal stage		Initial classification/qualification DQ: IQ: OQ:	Technical Design Procedural	Yes

							PQ: EMS System qualified DQ: IQ: OQ:		
10.	Aseptic filling	Empty or filled ampoules contamination	67. Lack of grade protection due to power cut (V/NV/End-Py)		67.Grade A and Grade B AHUs connected with UPS for uninterrupted power supply		EMS System qualified DQ: IQ: OQ: Action: Grade A & B AHUs to be Connected with UPS	Technical Design Procedural	No Action 30
			68. Contamination from grade B environnent (V/NV/End-Py)		68.Open RABS in place Integrity test on gloves at the end of the batch Periodic change (every 80 sterilization cycles) of RABS Gloves RABS gloves vendor approval Aseptic connections minimized		SOP for Handling of filling Machine gloves Risk assessment for Aseptic Connections: Action: Manually Gloves integrity Test performed as per monthly frequency need to revised Integrity test on gloves at the end of the batch, Online gloves integrity tester not Available	Technical Design Procedural	No Action 31
			69. Contamination through		69. Protective clothing is being used during de filling.		SOP for gowning in grade A/B Vendor Qualification, action for	Procedural Organizational	Action 32

10.	Aseptic filling	Empty or filled ampoules contamination	Operators/garment (V/NV/End-Py)		Sterile gowning / secondary gloves / Sterile Googles		strategy evaluation Gowning management: Action: Gowning changed every 4 hours to be described in SOP Garment replacement/Destroyed after 80 cycles: SOP Garment check after washing and sterilization: SOP Action: Frequency of Googles sterilization at every day not describe in SOP Googles Discarded after 50 Cycles:		
			70. Contamination through operators/interventions (V/NV/End-Py)		70. Aseptic Process simulation Risk assessment for aseptic connections QA oversight, interventions check/observation every 3 month Process for disqualification viable and non-viable monitoring performed before machine assembly till end of filling activity.	72	MFT ref / protocol to be given through CCS v2 SOP to be prepared for oversight SOP for assembly to be prepared Process for disqualification:	Procedural Organisational	No
			71 Contamination through materials entered with airlock (V/NV/End-Py)		71. List of critical materials UV cycle validation		Action : List of critical materials to create Protocol and report for UV validation	Procedural Organizational	No Action 33
			72 Contamination through materials/equipment		72. Autoclave validation Unloading in grade A/B under LAF and transfer to the filling line with mobile		Autoclave DQ/IQ/OQ ref DQ :	Technical Design	No Action

10.	Aseptic filling	Empty or filled ampoules contamination	entered with Autoclave after sterilization (V/NV/End-Py)		LAF within grade A No exposure to grade B		IQ : OQ: Autoclave loads validation ref Unloading LAF qualification: Mobile LAF qualification: SOP for unloading and transfer to be prepared Validated holding time after sterilization:	Procedural	
		Contamination of the solution	73.Contamination between holding tank and filling (V/NV/End-Py)		73. 2 capsules 0.2µm filters Integrity test / PUPSIT Single Use filters		Qualification of filter integrity machine : IQ: OQ: SOP for integrity test SOP Action: PUPSIT implementation	Technical Design Procedural	No Action
		Contamination of the solution	74.Contamination through Nitrogen purged in solution (V/NV/End-Py)		74.0.2µm filters for pre and post purging provided, integrity test performed		Qualification of filter integrity machine: IQ: OQ: SOP for integrity test SOP	Technical Design Procedural	Yes
			75.Particulates contamination		75.Breakage management		Risk assessment to be prepared for breakage and SOP to be prepared	Procedural	No Action

			(NV)				for breakage management		29
10.	Aseptic filling	Contamination of the solution	76.Contamination through sealing / lack of integrity (V/NV/End-Py)		76.100% leak test detection by automated VI machine		DQ/IQ/OQ/PQ ref DQ : IQ : OQ : PQ:	Technical Design Procedural	NO
	Aseptic filling		77. Filling area Dirtyness (V/NV/End-Py)		77. Cleaning and disinfection program Fogging daily & After operation Fumigation on a Twice in month		SOP: Record: SOP for Fogging: SOP for fumigation: Action: Fumigation validation Cleaning & Disinfection validation done	Technical Procedural	No Action 36

10.									
11.	Thermal treatment 98-100^{0}C for 30 min		78.Improper heat treatment wrt temperature and time may be happened. (V/End-Py) 79.Without heat treatment partial quantity of product may be transferred to VI (V/End-Py)		78/79 1.Area cleaning is being done for area as per approved procedure. 2.Line clearance shall be done before starting of Thermal treatment cycle. 3.Thermal treatment cycle is validated 98-100^{O}C for 30 min. 4.Check the status label and quantity before starting and after completion of Thermal treatment cycle. 5.Material hold quarantine provided to storage of the material. 6.After Thermal treatment lot wise trays stack on pallets wraped with shrink wrap with proper status label to avoid product mix-up.		Qualification of terminal sterilization for heat treatment	Technical Design Procedural	No Action 37
12.	Other Critical Control Points	Contamination through external pest	80. No or Improper Pest Control in place (V/NV/End-Py)		80.Pest Control in place including rational for each location		SOP– Rational for location in place Operation managed by HR and subcontracted to PCS	Design Procedural	Yes
		Compressed air	81. Compressed air system not properly maintained		81.Preventive maintenance in place and operations recorded		SOP:	Procedural	YES

6 STRATEGY EVALUATION

The Strategy evaluationcover all critical control points identified through the process mapping established in section 5. This section allows to identify systems in place or to be in place to monitor each of the critical control points and assess data generated from monitoring to be performed.

The outcome from the Strategy evaluation allow to make a clear link with the Pharmaceutical Quality System on site and continuous improvement process through CAPA decided based on Monitorings and Assessment performed.

This Strategy evaluation part is divided in 9 parts, as follows:

1 Reference of the Critical Control point identified through process mapping,
2 Process step description,
3 Critical Control point Description,
4 Corresponding Monitoring in place through Pharmaceutical Quality System (Deviation, Self-Inspection, OOS) and/or specific sampling plan and IPC – if no monitoring in place, action to be described,
5 Corresponding referenced documentation for Monitoring,
6 Monitoring Evaluation in place through Quality Meeting or any other specific meetings, if no assessment in place, action to be described,
7 Frequency in place or expected for Monitoring assessment/evaluation,
8 Monitoring Assessment/evaluation documentation referenced,
9 Actions numbering for both Monitoring and Monitoring assessment - when some actions are already covered through the project action plan or previous actions, details are given (refer to X).

Legend used:

Monitoring & Monitoring Assessment/evaluation in place,

Action(s) decided

7 REMEDIATION ACTION PLANS

Both Process mapping and Strategy evaluation did allow to identify some mitigating measures when the corresponding risk was considered as not acceptable and / or when some lack of critical control points monitoring and assessment were identified.

These measures/actions are summarized and tracked through the tables below:

1.1 PROCESS MAPPING ACTION PLAN

For each of the actions to be implemented, impact on MFT and PPQ is mentioned, considering it as pre requisites to go ahead with MFT & PPQ or PPQ alone.

7.2 STRATEGY EVALUATION ACTION PLAN

For each of the actions to be implemented, impact on MFT and PPQ is mentioned, considering it as pre requisites to go ahead with MFT & PPQ or PPQ alone.

8 STRATEGY FOR CONTINUOUS IMPROVEMENT

8.1 CONTROL DASHBOARD

The Strategy evaluation implemented will allow to assess CCS efficiency and effectiveness based on historical performance and trends analysis.

This assessment, made during Monthly Quality Meeting, including quality systems and frequency used to perform it can be summarized in the table below:

	Monthly	Quarterly	6 Months	Yearly	2 years
EVENTS					
Deviations	X				
EM Notifications	X				
Intimations (T° excursion, absence of CoA, Damaged materials, …)	X				
OOS/OOT	X				
TRENDS					
WFI / N2 / Compressed Air / Pure steam	X				
Personnel Monitoring	X				
EM Monitoring	X				
NVPC Monitoring	X				
Biocleaning Monitoring	X				
VI Trends: defect in solution		X			
Alerts/Alarms on critical equipment (Production/Utilities/QC)		X			
PQS					
Self-Inspection			X		
APQR				X	
Vendor Quality Management				X	
CAPA	X				
Specification / STP If any effect on Microbial,pyrogen/Endotoxin	X				
	Monthly	Quarterly	6 Months	Yearly	2 years
PERIODIC QUALIFICATION					

Progress of Validation Master plan		X			
HVAC Qualification grade C/D				X	
HVAC Qualification grade A/B			X		
Autoclave loads			X		
CIP/SIP/WFI decontamination				X	
Washing cycle & Tunnel Cycle				X	
Garment Washing				X	
Passbox decontamination cycle				X	
Temperature mapping					X
UPS Check				X	

All systems and data generated reviewed during the Monthly Quality meeting will allow to get a global and continuous view on the contamination risk trends on the site.

Any adverse trends will lead to take some decision on mitigation actions to be followed through CAPA and/or Change Controls.

8.2 CCS REVIEW

The Structure of this first version of Contamination Control Strategy did allow to document all measures and controls in place or to be done in a holistic document.

It also allows to get a holistic view of the contamination control measures and how well it prevents contamination.

On a routine basis, Senior Management will perform the periodic review of datas and systems according the control dashboard defined in section 8.1 to:

- State if the measures in place are working in preventing contamination,
- Define if the residual risk of contamination is still acceptable based on defined regulatory and process limits and parameters,
- Define if the CCS should be reviewed and improvements implemented, recalculating RPN.

Knowing that Process mapping and Strategy evaluation in this first CCS version have led to identify a total of 82 remediation actions, the first step will be to follow progress of these actions.

As soon as all actions considered as a prerequisite for MFT will be closed, RPN linked with will be recalculated, new decision on risk taken and version 2 of this CCS raised. This will give green light to manufacture and fill APS tests.

With the same approach, a version 3 will also be raised as soon as actions considered as prerequisite for PPQ will be closed. This will give green light for PPQ manufacturing.

Then, a frequency for periodic CCS review will be defined, based on routine data generated and significant changes such as introduction of new product and/or new equipment. As a minimum, CCS will be re assessed once a year.

However, on a monthly basis, Senior Management involved in Quality Monthly review will have to state if the site is in compliance with the rules defined in the CCS and if new actions identified must lead to update the CCS current version

9LIST OF ATTACHMENT

S. No.	Name of Format	Format no.	No. of Pages
1	Appendix for Layouts		
2	RPN		

10REVISION HISTORY

Revision No.	Effective Date	Review Date	Revision summary