Contamination Control Strategy (CCS)

INJECTION SECTION

(Liquid Vials)

CONTENT

1.0 INTRODUCTION:

….……., is drug manufacturer have employed control measures in the plant as well as across the dedicate manufacture lines which is a core element of Good Manufacturing Practices.

The ongoing evolution of contamination of contamination control principles that this document addresses is a shift to holistic approach, (considering as a whole thing rather than a collection of part), where the practices are designed to work together to achieve proactive contamination control and are evaluated for their collective effectiveness.

This contamination control strategy includes, for example, how processes and facilities designed (including cleaning and disinfection), how raw material and consumable are selected and managed, and how personnel are trained and developed.

In this document we compile the GMP practices documented across numerous operational procedures and program. The rationales for those practices are often captured in risk assessments, validations and technical documents.

This document record, an umbrella document that brings the relevant information together so it can be understood and evaluated holistically, CCS documents summarize the contamination control practices, along with the underlying rationales, and reference the supportive procedures and reports.

2.0 PURPOSE:

As we are manufacturer of sterile products and covers wide range of sterile product types (Dry injection and liquid injection) manufactured in different pack sizes, single dose and multiple dose, process with manual and automated for manufacturing of sterile product, this document provide general guidance that should be used for manufacturing of all sterile products using principle of QRM (Quality Risk Management) to ensure that microbial, particulate and pyrogenic contamination is prevented in the final product.

The document covers organizational control measure such as design of premises, clean room classification, qualification, monitoring and personnel gowning, and Quality risk management principle together with procedural control through SOP and associated risk taking account of human factors.

3.0 SCOPE:

This **Contamination Control Strategy** is applicable to the Sterile dosage form manufactured at general block like General Dry Powder Injections, General

Liquid Vial Injection, General Liquid Vials Injection and Cephalosporin Dry Powder Injection.

4.0 DEFINITION OF CONTAMINATION AND CONTAMINATION CONTROL STRATEGY:

4.1 Contamination

What is contamination?

- The act of contaminating or polluting, including either intentionally or accidently, unwanted and potentially dangerous substance or factor.
- Simply the state of being contaminated (with something you don't want and don't expect to be present)
- Contamination can be

  Physical – e.g. dust, fiber, human skin cell, particles etc.

  Chemical- e.g. cleaning agent residue, process gases, molecule, Vapor

  Microbiological- e.g. bacteria, virus, yeast, mould

Understanding the enemy: Types of contamination

To fight off contamination effectively, you need to know what are you're up against. Contamination can come from various source it is important to understand these to develop an effective CCS

- **Microbial Contamination:** this involve bacteria, viruses, fungi and other microorganism, these invisible invaders can come from the environment, personnel and raw material and can potentially ruined your product.
- **Particulate Contamination:** this refer to physical particle like dust, fibers or metal shaving that can contaminate the product imagine finding a piece of metal in a Vials of medicine.
- **Chemical Contamination:** extractable and leachable contaminants are a concern of both sterile and non-sterile products. It happens when unwanted chemicals are release into the product, either from manufacturing process or from cross-contamination with other products.

Where can contamination comes from?

- Building and premises
- Equipment
- Personnel
- Utilities

- Raw material and packing material
- Vendor approval / outsourced activity
- Environment
- Process and production
- Sampling procedure
- Cleaning procedure

Consequences of contamination

Risk to patient health:

- ***Adverse drug reaction, health complications leads to life threatening.***
- ***Penicillin Contamination may trigger hypersensitive exaggerated allergic immune response***

Risk to Organization

- ***Organization get GMP Non-compliance***
- ***Recalls and complaints***
- ***Sales loss***
- ***Company regulation***

What is contamination control?

Contamination control in a set of system and techniques that ensure the minimization or reduction of contamination.

"A Quality Risk management process should be used to access and control cross-contamination risks presented by the product manufactured"

OR

"The outcome of quality risk Management process should be the basis for determining the extent of technical and organizational measures require to control risk of cross contamination"

These could include following but not limited to

Technical Measures	Organizational Measures
Dedicated Manufacturing Facility (premises and equipment)	Dedicating the whole manufacturing facility followed by a cleaning process of validated effectiveness
Self-contained production areas having separate processing equipment and separate heating, ventilation and air conditioning (HVAC) system	Keeping specific protective clothing inside areas where products with high risk of cross contamination are processed
Design of manufacturing process, premises and equipment to minimize risk for cross-contamination during processing, maintenance and cleaning	Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the quality risk

	Management approach for products deemed to present higher risk
Use of “closed system” for processing and material / product transfer between equipment	Depending on the contamination risk, verification of cleaning of non-product contact surfaces and monitoring of air within the manufacturing area and / or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer
Use of physical barrier system	Specific measures of waste handling, contaminated rinsing water and soiled gowning
Controlled removal of dust close to source of the contaminant	Recording of spills, accidental events or deviations from procedures
Appropriate use of air locks and pressure cascade to confine potential airborne contaminant within a specified area	Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross contamination risk
Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air	Design of detailed record for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas.
Use of automatic clean in place systems of validated effectiveness	Supervision of working behavior to ensure training effectiveness and compliance with the relevant procedural controls.

Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedure

An initial risk assessment should be critical step in implementing CCS but don’t set and forget! The CCS should be considered a living document and can be continually strengthened. Ongoing risk assessment should be apply whereby the initial risk assessment for the area/ facility / process should be periodically reviewed and updated as necessary.

4.2 Critical Control Strategy (CCS)

This is the first time that an overview strategy is required for the area of contamination control that links the various aspects of contamination control and associated measures, records the interactions and facilitates a corresponding analysis for gaps in the system. This can be used in existing companies to meaningfully record, coordinate and supplement existing measures or, in newly emerging facilities, to coordinate the implementation of the necessary contamination control measures across departments.

What is CCS?

A contamination control strategy (CCS) is a comprehensive approach to prevent and manage contamination in the manufacturing of pharmaceutical products. It involves a planned set of controls for microorganisms, Endotoxins / Pyrogens, and particles, ensuring process performance and product quality.

The strategy is based on current product and process understanding and includes parameters and attributes related to materials, facility and equipment operating conditions, in-process controls, finished product specifications, and the methods and frequency of monitoring and control.

The CCS is a key element of Annex 1 of the EU GMP Guide, which emphasizes a risk-based and holistic approach. It requires documenting all aspects of contamination control, including organizational, technical, and procedural measures, to ensure comprehensive effectiveness.

This strategy helps identify, assess, and mitigate risks associated with contamination, aiming to enhance product quality and patient safety.

Implementing a CCS involves three main pillars:

Prevention: Establishing controls to avoid contamination.

Remediation: Addressing any contamination that occurs.

Verification: Monitoring and verifying the effectiveness of the controls in place.

Defining a well-documented cross-contamination strategy involves several key steps.

When defining a CCS (contamination control strategy), it is recommended to consider not only cross-contamination but also all other types of contaminants.

5.0 CORE PRINCIPLE

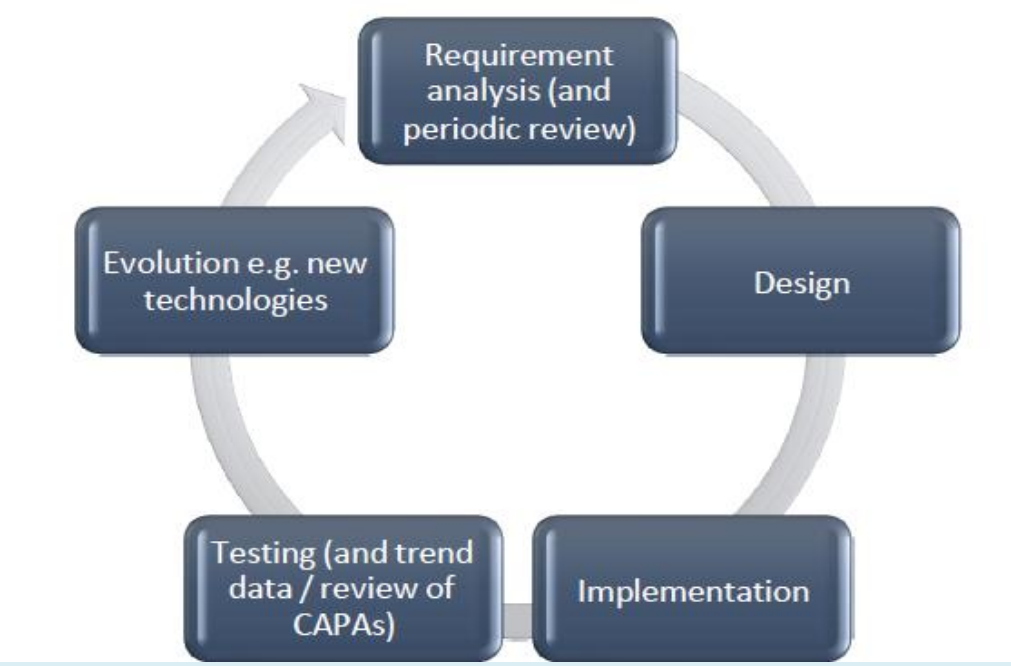
The core principle for contamination control is control. Control is achieved through a series of measures, which will include:

Quality by Design with Quality Risk Management: This encompasses contamination control by design via technical control measures that are applied based on science and knowledge of process and risks.

Organizational Control Measures: The organization of operations, as defined in the Pharmaceutical Quality System, should follow Quality Risk Management principles together with procedural control (through SOP’s) and associated risks taking account of human factors.

- It is important to understand the product and process in enough detail to be able to effectively assess the hazards to product quality from contamination and ensure control measures are in place which proactively mitigate the risk of the product becoming contaminated.
- Once control is established, systems are in place to detect contamination events. This will include environmental monitoring systems and assessment of other forms of contamination. Central to this is trend analysis. a functioning contamination control strategy (CCS) will act as a 'health check' on the control and monitoring functions. In interpreting this, it is important to recognize that to collect data on the status of manufacturing operations is not enough; there is an expectation that responsible departments evaluate these data and look for trends that could be an indication of the beginning of a loss of control and, more importantly, to prevent the control breakdown from happening.
- As part of the periodic review of the control strategy, the review of trend data should inform as to the development of the CCS, making this document a 'living document' that adjusts as required, including describing any risk mitigations. Assessing quality metrics and the reasons behind deviations can signal things that require assessing and putting into a future version of the CCS.

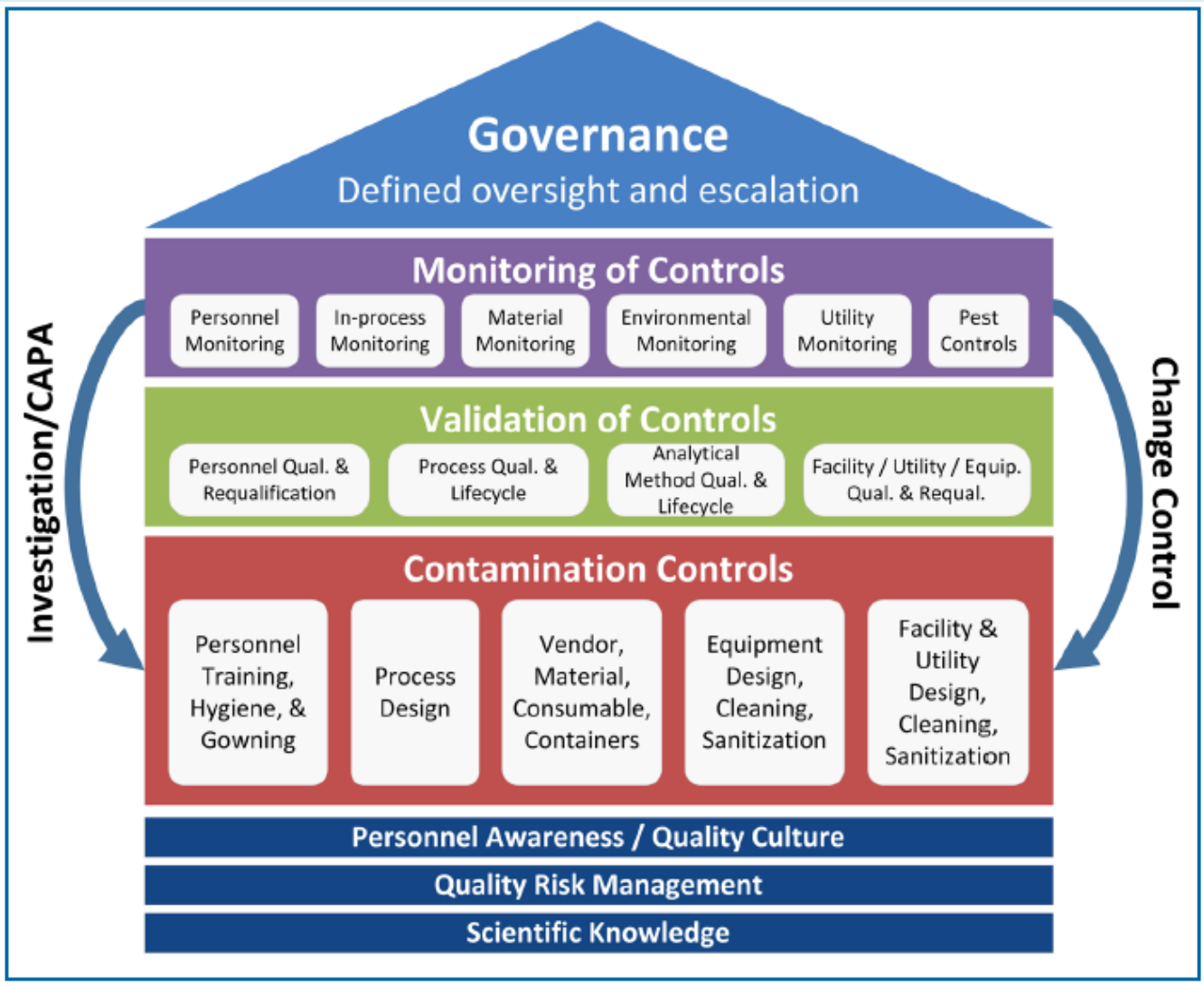
Figure-1 (Contamination Control Life Cycle)



6.0 ELEMENT OF CONTAMINATION CONTROL STRATEGY

The CCS is a combination of interwoven and successively linked elements, which includes many elements of a pharmaceutical quality system and GMP measures. **Figure-2** illustrates this concept.

Figure-2



The *foundational* elements—scientific knowledge, quality risk management, and personnel awareness/ quality culture (dark blue)—inform and influence every other aspect of the CCS. These foundations of CCS align well with the enablers described in ICH *Quality Guideline Q10: Pharmaceutical Quality System*.

The *individual control* elements (red) are designed using the foundational elements, validated to show they can reasonably achieve the appropriate level of control (green), and then monitored to verify they achieve ongoing control (purple). The individual controls in the red row do not comprise an exhaustive list.

The *quality* systems, such as investigation, change control, and corrective and preventive actions (CAPA)—feedback loops—provide the mechanisms to continuously refine and improve controls and respond to unexpected events.

The *governance* (light blue) assesses the output of each CCS element (e.g., monitoring data, validation results, investigations, change controls) to ensure the overall CCS remains holistic and effective. A weakness in any of these elements or a mismatch between elements can lead to an ineffective CCS and therefore, contamination.

Elements to be considered within a documented CCS should include (but are not limited to):

- Design of both the plant and processes.
- Premises and equipment.
- Personnel.
- Utilities.
- Raw material controls – including in-process controls.
- Product containers and closures.
- Vendor approval – such as key component suppliers, sterilization of components and single use systems (SUS), and services.
- For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly.
- Process risk assessment.
- Process validation.
- Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.
- Cleaning and disinfection.
- Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination.
- Prevention – trending, investigation, corrective and preventive actions (CAPA), root cause determination and the need for more comprehensive investigational tools.

7.0 CONTAMINATION CONTROL STRATEGY

The Annex states that *"A contamination control strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational), and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the*

CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and where appropriate, updated and should drive continuous improvement of the manufacturing and control methods."

The CCS should describe the control measures and steps to minimize the risk of contamination from microbial, Endotoxin/pyrogen and particle contamination. It should include a series of interrelated events and measures which even if they assessed, controlled and monitored individually their collective effectiveness should be considered together.

7.1 CCS Implementation Method

For implementation of contamination control strategy follow three step mention below:

Environmental scanning and Strategy formulation: Description of the Facility, premises, equipment design 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:

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.

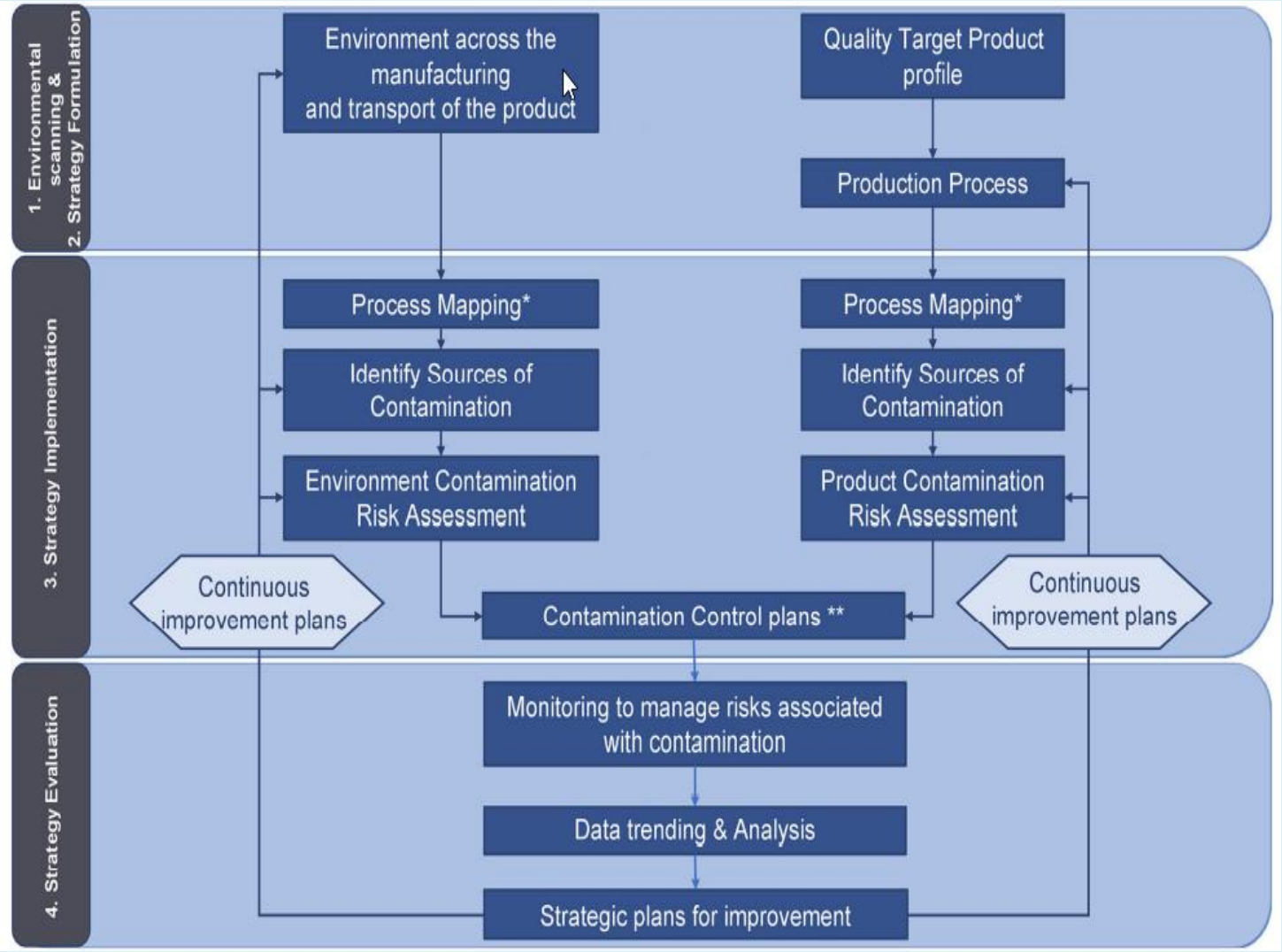


Figure 1: CCS Methodology – ref PDA J Pharm Sci and Tech 2021, 75 445-453

7.2 Design of Plant and processes

7.2.1 Design of Plant

7.2.1.1 Facility Design

Facility design is Key elements of the CCS should be decided during the design phase of a production facility to minimize the risk of contamination based on the specific process design and hazards. Facility designs provide environmental control through air pressure cascades, area classifications, cleanability, physical segregation, and flows based upon Good Engineering Practices (GEPs). These design features establish the structure-based barriers that reduce the airborne movement of contaminants into the manufacturing areas and enable the removal of contaminants that do enter.

Design of plant comprises of below:

- Facility design
- Personnel flow
- Material and Waste controls

- Cleaning and disinfectants
- Utility design, controls and validations
- Water and steam
- Heating, Ventilation and Air conditioning

Sterile product manufacturing facility, including Liquid Vial line is dedicated for sterile products 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.

7.2.1.1.1 Facility Design:

Facility of Vial injection design in such a way that facility of injection block is separated from Oral solid dosage form and quality control laboratory.

Dedicated raw material store for injectable raw material where separate receiving, quarantine, under test and approved area, entry and exit in core area is separate with restrict barrier system.

Internal wall partitions are of GI powder with coated and SS modular panel with smooth finished allowing the surfaces to be washed down for injection block, which further reduces any risk of contamination.

The flooring of manufacturing area, filling and sealing area primary packing, secondary packing, sampling and dispensing area with epoxy coating/flooring, alone with coving on the corners of floor and roof to minimize any accumulation of dust particle.

All doors in the manufacturing area are modular coated steel doors equipped with heavy duty door closure.

All washing area provided with modular coated steel doors and drain pits meeting GMP requirements. powder coated modular type, extruded aluminum single glazed aluminum doors are used in other area where ever required door are provided with inter locking arrangements to prevent sudden ingress of air across the rooms hence minimize any risk of contamination.

All the ducting, electrical lines and utility lines are either taken above the false sealing or concealed under the wall. All electrical control panels and the switches are flushed to the wall.

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 Qualified HVAC system are in place 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: General injection First Floor

General Injection Ground Floor

General Injection Ground Floor

Man & Material Movement layout ref: Basement Floor

Ground Floor

First Floor

- Pressure Zoning: First Floor
    - Ground Floor
    - Basement Floor
- Pest Control is in place in the whole facility to prevent any external contamination from insects, rodents, etc. and document related to pest control, managed by HR.

7.2.1.1.2 Personnel flow:

Access to different area is through change rooms and adequate gowning person enter in there respective area following personnel flow, separate secondary change room available in sampling and dispensing area with secondary gowning.

Clean room grades have Restricted Barrier System and man and material movements (Entry & Exit) are different from separate air-locks system, for personnel and separate entry and exit for materials are available in plant, facility filling and sealing are separate for Vial section

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

- Grade A/B- Filling, sealing and other critical operations eg. Unloading of Sterilized components, filtration process, 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/ De-pyrogenation of Vial

7.2.1.1.3 Material and Waste controls

Material air look used for material and equipment transfer, as per Batch record and essential accessories required for the operation transfer from grade to grade with approved procedure and sanitization procedure, critical accessories (sterile) are transferred through qualified Mobile LAF under class A.

Waste has been discarded in separate are far from manufacturing area, the waste move in closed condition followed material movement once operation completed in manufacturing, filling and packing areas.

Finished goods product moved from packing area to finished goods store through material lift and store in segregated / separated racks with status labelling.

7.2.1.1.4 Cleaning and disinfection

Disinfection of cleanroom done through SOP, where we clean and disinfect surface, ceiling, light fixture, AHU grill, LAF top, Door and door closure, glass and view panel has been disinfecting as per schedule with different disinfectant mention below:

S.No.	Rotation	Name of solution	Usage of disinfectant
1.	Monday and Thursday	2.5 % Endomax	Surface disinfectant
2.	Tuesday and Friday	1.5 % Microlyse	Surface disinfectant
3.	Wednesday, Saturday and Sunday (if working)	3% Savinox	Surface disinfectant
4.	Alternate days	5% Acitar	Spray disinfectant
5.		20% Silivicide	Spray disinfectant

The disinfectant used in area for disinfection has been validated as per protocol and in this protocol and report effectiveness and suitability has been defined, along with validity.

Disinfectant used in the sterile are has been sterile based on validated loads pattern.

7.2.1.1.5 Utility design, controls and validations

Utilities designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.

- We design utility separate for each other, HVAC system, gases (Compressed air generation and distribution system/Nitrogen generation & distribution system) and water system (purified and water for injection generation and distribution system, steam generation plant)
- All the utility system has DQ/IQ /OQ and PQ.

Each utility has control, periodically validated and preventive maintenance program for further reduce any risk of incident and contamination.

7.2.1.1.6 Water and Steam

We have Purified Water and Water for Injection generation and distribution system, having Source of water supply is from 2 bore wells with depth 160 feet. Freshly drawn water from the bore well is collected into underground RCC tank (60KL) by pump with online dosing of 2-3ppm chlorine with the solution of sodium hypochlorite.

The water then passed through multi-grade filter to remove suspended matter if any. Raw water then transferred through softener to reduce the hardness to below 5 ppm. The soft water is then stored in soft water storage tank (capacity 5KL).

The water then treated with Sodium Meta bi-sulphite solution with a online dosing to oxidize excess of chlorine and monitored through ORP meter oxidation up to less than 400 mv. The ORP meter (oxidation reduction Potential) is installed in the feed line to RO to check for chlorine free water. Chlorine free water is supplied along with anti-scaling dosing to RO- 1 & RO- 2 then to mixed bed & UV for making purified water.

The capacity of the RO system is 3000 Ltr./hr. To check the conductivity, the conductivity sensor is installed in the supply and return loop of the distribution system. The conductivity of the purified water is continuously monitored through programmable logic control panel and in the event of variation in the conductivity above the limit. It

automatically drains the water to prevent of going into the storage tanks with help of online dumping valve. Finally, conductivity passed purified water is stored in Purified water storage tank. The capacity of the purified water storage SS316L tank is 3KL.

This water system is installed in general block and distributed through a closed recirculation loop inside the plant for appropriate user points at ambient temperature.

Purified water is used to produce Water for Injection. To get high quality water for injection, Installed 1 Multi Column Distillation plant at general block. The capacity of the multi column distillation plant is 1000 Ltr./hr. This unit is fully automatic and microprocessor based. Water for injection stored in water for injection tank (Capacity 3KL). This water for injection system is installed in general block and distributed through a closed recirculation loop inside the plant for appropriate user points at temperature 80-90°C. TOC of water for injection continuously monitored through monitoring sensor installed in return loop of distribution of WFI in general Block.

Vent filters provided to purified water storage tanks and water for injection storage tanks. Storage tank temperatures are continuously monitored through temperature thermograph. Fresh

Control in water system

- We review the Results for critical parameters and critical quality attributes of water Purified Water, Water for Injection, Pure Steam Generator and trend analysis perform to ensure that system capabilities remain appropriate.
- Pipes, ducts and other utilities is far from cleanrooms, however, transfer line from holding to filling station is available and installed in such a way that no unsealed opening and surfaces found and easy for clean to maintained clean room area and transfer line are easily accessible for cleaning and disinfection of outer surface of the pipes.
- The **water generation system,** routine cleaning and sanitization has been done as per approved procedure SOP Preventive Maintenance for the water system perform on quarterly basis including Reverse osmosis, and regular checking and replacement frequency of membranes

- Purified water and water for injection sampling and testing schedule is in place to check the water quality (Refer format No. for water schedule)
- Daily microbial and bacterial endotoxin test is part of Water for injection testing (refer Specification)
- In water system regular ongoing chemical and microbial monitoring of water specification performed to ensure water must meet the compendia expectation, further alert and action limit defined and performance of water system has been reassessed by using routine monitoring, periodically verification of water system and trend monitoring.
- TOC and conductivity in WFI systems continuously monitored by online sensors installed in return line of distribution loop, and in purified water online conductivity sensor installed in supply and return line of distribution loop.
- Feed water to a pure steam (clean steam) generator is feed through Water for injection. Pure steam generator is designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and Endotoxin levels.
- Water-for-Injection (WFI) storage tanks should be equipped with hydrophobic bacteria retentive vent filters, the filters are sterilized, and the integrity of the filter tested before installation and after removal following use.

7.2.1.1.7 Heating, Ventilation and Air conditioning

All the Area are providing with appropriate air handing units to maintain the required environment conditions with respect to the temperature, relative humidity, particulate matter count and potential risk of air bone particle contamination. Heating ventilation and air conditioning systems have been designed to be energy efficient, operate quietly and be cost effective in conformance with regulatory standards. Manufacturing operations are designed to take place within designed controlled areas. There are controlled through air handling unit. Sufficient numbers of AHU’s and ventilation units are provided to cater various area of the facility.

Air handling system is designed as per the cGMP requirement in each area of the plant. Separate air handling units are provided for the critical production and surrounding areas.

An environment monitoring program is in place to monitor the critical manufacturing areas.

The area for handling sterile products meets Grade-A requirements. The background of the Grade- A area meets the requirement of Grade-B.

Pressure differentials are maintained as per the specified guidelines for the respective dosage forms. Temperature & Relative humidity in the different sections is as mentioned below.

Table-

Section	Temperature	Relative Humidity
INJECTION DEPARTEMENT		
Liquid injection Manufacturing	23 ± 4°C	45 ± 10%
Autoclave and bung processor room	23 ± 4°C	45 ± 10%
Sterile Filling & sealing Liquid Vial section	23 ± 4°C	45 ± 10%
Washing area (Vial)	23 ± 4°C	45 ± 10%
Cool zone liquid injection	23 ± 4°C	45 ± 10%
Filtration Room	23 ± 4°C	45 ± 10%
Injection quarantine area	23 ± 4°C	45 ± 10%
Visual inspection room and packing area	23 ± 4°C	Not applicable
WAREHOUSE		
Raw Material Dispensing area (Injection)	23 ± 4°C	45 ± 10%
Liquid Dispensing area	NMT 25 °C	Not applicable
Raw Material Storage area (Injection)	NMT 25 °C	45 ± 10%
Secondary and tertiary packing Material Storage area	NMT 30 °C	Not applicable
PPM sampling / dispensing area	23 ± 4°C	45 ± 10%
Refrigerator	2°C -8°C	Not applicable
Finished goods storage	NMT 30 °C	Not applicable
PPM Storage Area	NMT 25 °C	45 ± 10%
FG Recall / Return Room	NMT 30 °C	Not applicable
Control Sample	15°C to 25 °C	Not applicable

The ventilation system design is based on re-circulation of air. 85-90% of the air is re-circulated and 10-15% fresh air is taken from outer atmosphere. The air changes Grade-B area is not less than 60 air change/hr and for Grade-C & D area is not less than 40 & 20/Hr respectively. Terminal HEPA filter placed to reduce contamination in the area.

Filtration system for different grade of area:

Table-

Grade of area	Pre filter	Return air filter	Fine filter	Final filter
GRADE-A	……..	……..	3µ (EU-7)	0.3µ (EU-14)
GRADE-B	10µ (EU-4)	10µ (EU-4)	3µ (EU-7)	0.3µ (EU-13)
GRADE-C	10µ (EU-4)	10µ (EU-4)	3µ (EU-7)	0.3µ (EU-13)
GRADE-D	10µ (EU-4)	10µ (EU-4)	3µ (EU-7)	0.3µ (EU-13)
Controlled but non Classified	10µ (EU-4)	10µ (EU-4)	Not applicable	3µ (EU-7)

The HVAC System shall be validated initially, and substitution of existing system or its component with new one, any major modification in the existing system design and operational parameters if the system is found to be malfunctioning, shifting of the system from one location to another location, and periodic requalification shall be performed based on the criticality of dosage form being manufacture the frequency for requalification shall be performed as per Table

The Validation shall include the verification of the following-

- Air Velocity
- Filter Integrity test
- Non-Viable Particle Count
- Air Flow Pattern
- Viable Particle Count
- Differential Pressure
- Temperature & RH
- Recovery Test

The frequency of test perform in HVAC qualification and

*Name of Test	Frequency for test	
	For Injection Facility and Micro Lab	**For OSD Facility & warehouse**
Air Velocity	Every Six Month	Once in a year
Filter Integrity Test	Every Six Month	Once in a year
Non-Viable particle Count	Every Six Month for Grade A & B continuous monitoring as per SOP	Once in a year
	Once in a month for grade C & D	
AIR Flow Pattern	One in a year	Once in Two Year
Recovery Test	Once in a year	Not Recommended for Grade D
Differential Pressure	Continue for three day but routine monitoring continue as per sop	
Temperature & RH	Continue for three day but routine monitoring continue as per sop	

Viable Particle Count	Continue for three day but routine monitoring continue as per sop
*In Case of any major modification, major breakdown, relocation and replacement of HEPA Filter Complete re-Qualification shall be performed, based on risk assessment test to be performed.	

7.2.1.1.8 Gases

Most common gases used in pharmaceutical industries is Nitrogen and compressed air.

1. **Nitrogen gas:** Nitrogen is to be provided to the facility as a utility. The nitrogen is generated by PSA based nitrogen gas generation plant capacity: 15 Nm^3/hr.

   - Nitrogen gas that come in direct contact with the product/primary container surfaces we perform appropriate chemical, particulate and microbial quality periodically.
   - All relevant parameters, like Dew point, oil mist, water content, carbon dioxide, carbon monoxide description, nitrogen oxides, hydrocarbon oxygen content, sulphur dioxide, oxygen content, Non-viable particle count has been performed and acceptance criteria specified, taking into account the use and type of the gas, the design of the gas generation system is of Class-2 and comply with the regulatory requirement.
   - Nitrogen gas is distributed through nitrogen generation plant to aseptic area, the gas is filtered through a sterilizing grade hydrophobic filter having pore size 0.2 Micron.
   - In compounding, filtration and filling where filtered gas used for overlay of aseptically filled products or as product vessel vent filter, then the filter integrity tested and the results recorded in batch certification process.
   - In between holding tank and filling tank transfer pipework or tubing is located is sterilize through CIP/SIP module to reduce any chance of contamination.
   - Nitrogen gas sterility has been performed as per routine schedules plan at critical user (based on operation usage) point of use. To prevent backflow which pose risk of contamination in storage tank Non-returnable valve is placed to prevent any chance of back flow.

2. Compressed air:

Compressed air installed in plant is of class-2, six oil free air compressors with 3.11 cum/min. Each with drier provided to supply process air & Instrument air, The compressed air is stored in air receiver, Filtered by 2 micron filter at the header and dried to (-40°C dew point) by heat supplied from compression type air drier prior to distribution network @ 7.5 bar pressure. The header and distribution legs are kept under pressure.

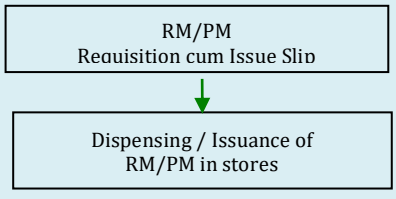
- Where sterile air is required for product contact the air is sterile filtered by 0.2 micron filter local to the user point. Sampling provisions are ensured at appropriate locations.
- All relevant parameters, like Dew point, oil mist, water content, carbon dioxide, carbon monoxide description, nitrogen oxides, sulphur dioxide, Non-viable particle count has been performed and acceptance criteria specified, taking into account the use and type of the gas, the design of the gas generation system is of Class-2 and comply with the regulatory requirement.

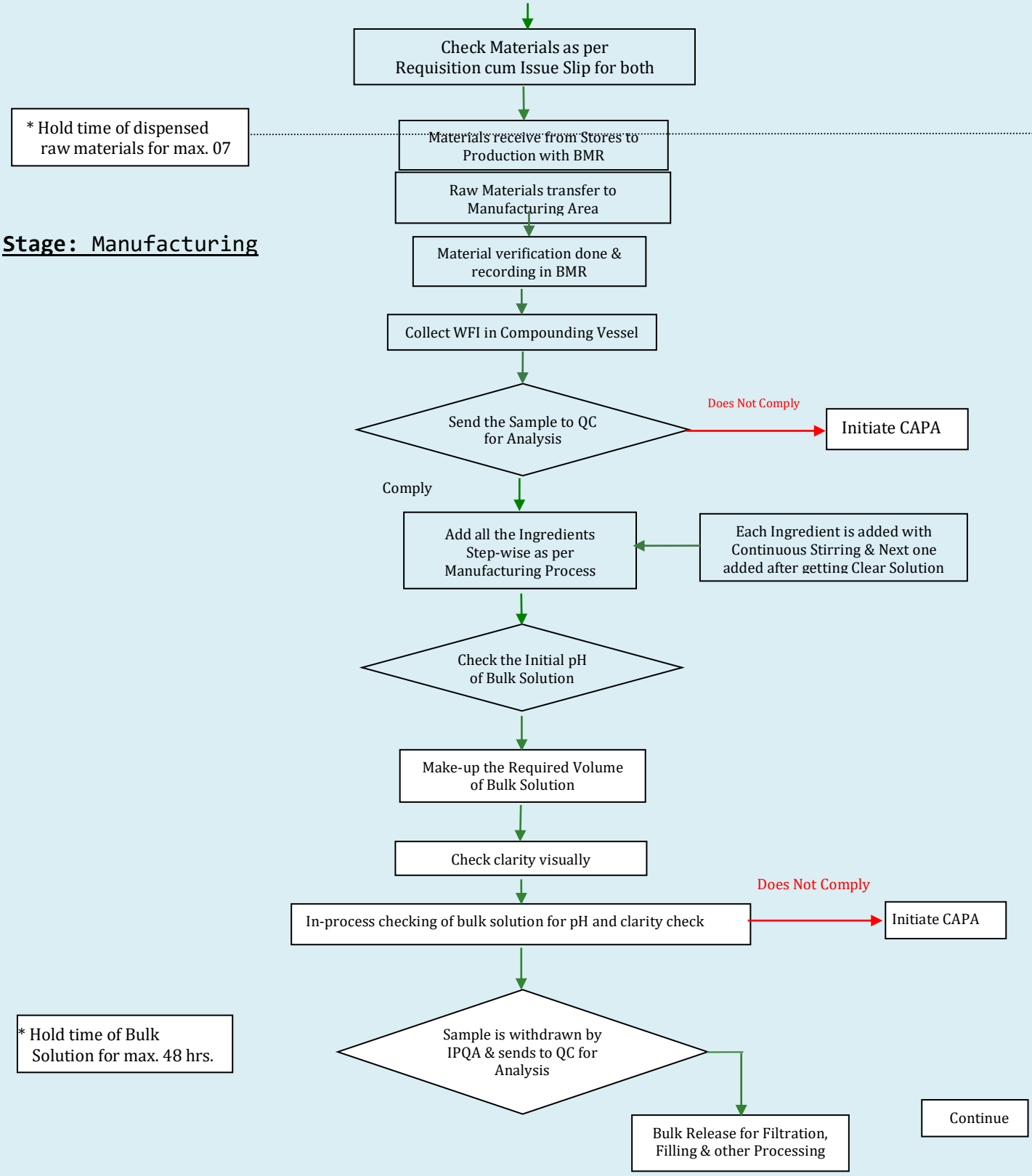
7.2.2 Design of Process

In Liquid Vial line manufacturing processes are carried out in aseptic area and manufactured product either through double filtration method by using sterilized grade filter pore size 0.2 micron (Aseptically filled) or by terminal sterilization (product is filled and sterilized terminally at appropriate temperature)

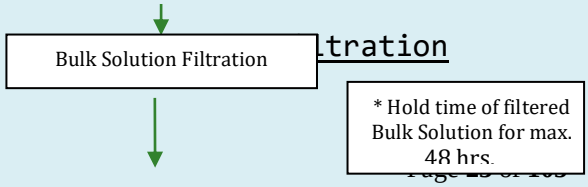
Process workflow of Liquid Vials manufactured in Vial line is as follows:

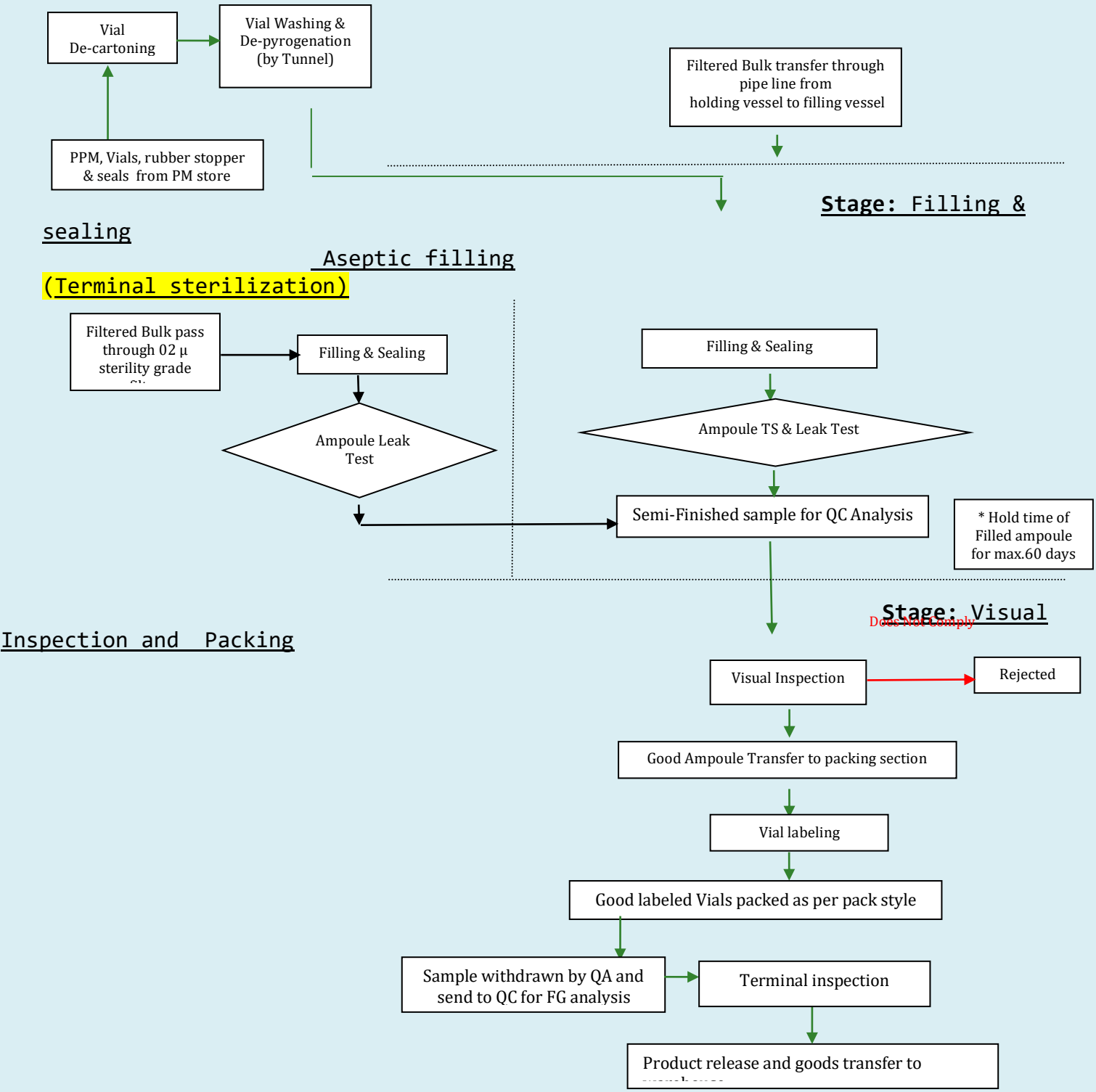
Stage: Dispensing





Stage: Decartoning, washing Sterilization & Depyrogenation





Above flow chart shows both manufacturing process Aseptically filled and terminal sterilization

PRODUCT QUALITY TARGET PROFILE

RAW MATERIALS

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

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

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

FINISHED PRODUCT:
All Approved specification & Standard Test Procedure of finished product prepared as per SOP.

Note: If any impact on microbial, Pyrogen /Endotoxinon Specification & STP revision shall be discussed on Monthly QRM,

7.3 Premises and Equipment's

- Premises of sterile preparation is separate and the manufacture of sterile products carried out in appropriate cleanrooms Grade A/B/C.
- The Processing area / Rooms entry is through change rooms that act as airlocks for personnel and Dynamic pass box installed at appropriate position entry and exit for equipment and materials.
- Cleanliness of Cleanrooms and change rooms maintained appropriately and air passed through HEPA filter having pore size 0.3 micron.
- The various operations like manufacturing, cleaning of accessories, product filtration, holding and filling and sealing carried out separate clean rooms and further separate with control measures like airlocks, personnel and gowning to prevent mix up and contamination.
- Restricted Access Barrier Systems (RABS) installed in the filling line which give benefit to assure cleanroom conditions and minimizing microbial contamination associated with direct human interventions in filling and Sealing.
- In cleanrooms and critical zones (Filtration and filling and sealing), all exposed surfaces are smooth, impervious and unbroken, Stainless steel gliding done on walls of critical area and cleanrooms like filtration, manufacturing, Aseptic area in order to minimize the shedding or accumulation of particles or micro-organisms and minimize

generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.

- Ceilings are designed and sealed to prevent contamination from the space above them.
- There are no Sinks and drains available in the grade A and Grade B area, drains and sinks area prohibited in both areas.
- The transfer of materials, equipment, and components into the grade A or B areas carried out via a unidirectional process. Item has been sterilised and passed into sterile / aseptic areas through double-ended sterilisers (e.g. through a double-door autoclave and de-pyrogenation tunnel) sealed into the wall.
- Cleanrooms supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and flush the area effectively. Adjacent rooms of different grades have an air pressure difference of a minimum of 10 Pascal's.
- Airflow patterns within cleanrooms and zones has been visualised to demonstrate

A. There is no ingress from lower grade to higher grade areas and air does not travel from less clean areas (such as the floor).

- Large view panel has been provided in the Vial filling and sealing line which allow observation of production activities from outside the grade A and B areas.
- Machine has been provided with various sensors (Advanced technology) to minimize the manual intervention during the production.
- In facility equipment are installed are made up of Stainless steel (non-reactive), smooth in surface, easy to clean, free from cracks and scratches and qualification shall be performing in schedule basis which ensure performance of equipment for intended use)
- Equipment management system comprises of equipment qualification and re-qualification validation Master Plan is in place VMP.
- Preventive maintenance (PM) program of each equipment is in place PM SOP.
- Cleaning validation document for equipment of Vial line has been in place Cleaning Validation SOP.

- Appropriate cleanliness levels in the “at rest” and “operational” states maintained as below:

Grade	Maximum Limits for Particulates ≥ 0.5 µm/m^3		Maximum Limits for Particulates ≥ 5 µm/m^3	
	At Rest	**In Operation**	**At Rest**	**In Operation**
A	3520	3520	Not applicable	Not applicable
B	3520	352000	Not applicable	2900
C	352000	3520000	2900	29000
D	3520000	Not defined	2900	Not Defined

- The microbial contamination level of the cleanrooms determined as part of the cleanroom qualification. The number of sampling locations decided based on a documented risk assessment and done through, air visualization studies and knowledge of the process and operations to be performed in the area, the alert and action limit of Active air sampling, and passive sampling (settle and contact plate) defined in approved procedure number SOP.
- The time interval for the qualification and re-qualification has been defined in Validation Master plan.
- Adequate lighting are available in all the areas to perform operations adequately where light sensitive product sodium light available in the area.
- All Water line / transfer line which used in routine operation for supply water and solution, the plumbing system is free from all defects that could contribute contamination to any drug product.
- Closed system like compounding vessel and holding vessel filling tanks area available to reduce any chance of contamination.
- Equipment System Surfaces are smooth and easy to clean, equipment design are such a way the there is no any chance of stagnate of water and material, change part is designed such a way that they are easily sterilized.

7.4 Personnel’s

- People are the major variable within pharmaceutical processing.
- As manufacturer we recruit personnel as per approved procedure SOP and minimum qualification of person are qual fied in subjects related to sciences, like Bachelor / Master of Pharmacy, Bachelor / Master of

sciences (chemistry or biochemistry), person must have experienced in Manufacture and testing of sterile drug preferred, to ensure compliance with GMP applicable to the manufacture and handling of sterile products.

- In process simulation study we validate and determine minimum / maximum numbers of personnel required to carry out operation in cleanrooms initially. The number of persons are documented and considered during activities such as initial qualification and Aseptic Process Simulation, so as not to compromise sterility assurance.
- Personnel who enter in aseptic area including those performing cleaning, maintenance, monitoring and those that access cleanrooms are qualified before entering in the aseptic area and requalification shall be done annually basis and persons who enter in the aseptic area receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products.
- This training provided to the personnel based on ***ON JOB CALENDAR*** include the basic elements of microbiology and personnel hygiene, with a specific focus on cleanroom practices (aseptic behaviour), contamination control, aseptic techniques and the protection of sterile products. For Example: The Personnel should be trained on ***Basic microbiology, Personnel flow and associated requirements, Material and waste flow, Environmental control, Cleaning and disinfection, Process design.***
- The personnel accessing grade A and B areas are trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures has been done through personnel monitoring and done at every exit of the person. which involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask / forehead).
- All aseptic area has electronic door access system to restrict the entry of Unqualified personnel in aseptic area i.e. grade B cleanrooms or grade A in operation.
- Visitor entry exit procedure is effectively implement in plant through SOP and visitor accompanied by a trained personnel, and he /she allow to access the area including manufacturing area.
- As personnel represent the primary source of contamination in any production process, personnel training is a key contributor towards

implementation of an effective contamination control strategy, hence training is very important and the regular training programme as Annual training calendar and On Job Training schedule available in plant.

- Personnel training given to personnel is practical, frequent, and continuous and cover theoretical, practical and cGMP aspects with the curriculum including basic microbiology, personal hygiene, and aseptic technique.
- In Aseptic process simulation all personnel enter in aseptic area are trained before execution of the process simulation.
- Personnel qualification procedure also include the disqualify criteria for the person which also include insufficient gowning techniques, movement in aseptic area during operation, and / or exceeding established microbial count. And person return to accessing cleanrooms based upon appropriate corrective actions being taken and successful completion of qualification.

7.5 Raw Material controls- including in-process controls

Raw material can introduce contamination in the finished products, hence need to be implement control measures to reduce any chance of contamination in the product.

- Specification of Raw material, packing material, in-process and finished goods has been prepared as per approved procedure SOP.
- Each material container has been sampled for identification and testing procedure including excipients
- Bioburden and Bacterial endotoxin test part of specification where applicable.
- Each specification has been prepared through monograph as per respective pharmacopoeia.
- During sampling, material for retention sample has been withdrawn atleast for two analyses till one year from date of expiry.
- Retention sample Finished goods product has been withdrawn for altleast two analysis till one year from expiry.
- Testing has been done in control area, free from any contamination.

- Microbiology laboratory is separate for physical and chemical laboratory, and microbial testing shall be done by separate personnel trained in microbial testing and entry exit procedure.
- For both products terminally sterilized or aseptically filled shall be tested for sterility to check and evaluate any contamination during filling and sealing process.
- OOT/OOS handling procedure already in place, in case of any abnormal results, which is against the pre-defined specification limit.
- In laboratory some other step has been taken to reduce microbiological risk
  - Maintain good housekeeping and usage of clean glass ware and instrument during testing.
  - Separate facility for packing material storage and sampling, and packing material area cleaned and environmental condition is controlled in primary packing area.
  - Pest and rodent control procedure for area has been establish and implemented in storage area to reduce other contaminant as per procedure SOP.
  - Inspection of finished goods product has been performed to identify particulate contaminants after the product and packing material combined.

7.6 Product Containers and Closures

- Container closure systems are an essential means of controlling microbial and foreign-particulate contamination of excipients, APIs, and finished products.
- In the case of sterile products, a failure of container closure systems integrity may impact patient safety due to the potential for microbial ingress and product contamination.
- A Container Closure system is required to “not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.”
- In addition, the Container Closure System should “provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product”

Therefore, the Container Closure system designed to ensure that the material is protected from factors that may impact product quality over its shelf life, including light, evaporation, product loss, exposure to gases, absorption of water, or microbial and particulate contamination.

- Container Closure system for finished are frequently composed of primary and secondary container closures. The primary Container Closure comes in direct contact with the drug and represents the main physical barrier preventing interaction of the product with the exterior environment.
- The Container Closure system may include a delivery device assembled into the primary container closure for product functionality. Secondary packaging may help protect the primary Container Closure system from microbial or foreign particulate contamination due to physical damage during handling and shipping.
- In Vial Container Closure system and the associated container closure integrity (CCI) is critical for the prevention of product contamination throughout the shelf life of a finished drugs.
- In Vial we perform leak test as per SOP to ensure and check the integrity of container closure system, in addition to the leak test we challenge container closure integrity at the time of media fill including microbial ingress method through microorganism Brevundimonas diminuta.
- Stability study also conduct to check the integrity of the Vial throughout shelf life and as per schedule we perform sterility test of the Vial as per SOP.

7.7 Vendor Approval

Vendor plays an important role in pharmaceutical where we procure different materials used during manufacturing like Raw material, Packing material, sterile accessories like tubing, gloves, filters etc, and services provider like laboratory and qualification agencies.
The vendor must be approved before procuring the materials, and approval system for a vendor govern by different approved procedure followed by quality audits and quality agreements.

Title of procedure	SOP No.	SOP related to
Vendor Qualification of Consumable Item	---	Qualification of accessories used in injection section including sterile and Non-sterile items
Vendor Qualification	---	Qualification of Raw Material and packing material
Qualification of External Agencies (External Laboratory / Calibration Agency / Qualification Agency)	---	Qualification of external agencies like laboratory, qualification, calibration, pest control, garment washing agency etc.
Quality Agreement for Out Sources Activity	---	Quality agreement of vendors

Control Measures

- Procedure for Receipt of materials SOP in place and at the time of receipt of material, and warehouse personnel check the details of approved vendor and verify the received materials with purchase order generated through SAP.
- The Vendor management system is in place and govern through different SOP mention in above table which is available for qualification of RM, PM & Consumable items and qualify periodically.
- All Raw Materials/ PPM tested prior to use for chemical and micro/ BET test as per approved specification and further retest policy as definite interval available SOP.
- Quality agreements from vendors in place between the firm and the vendor.
- Qualification of vendor shall be performed, based on criticality based either through document evaluation, sample testing, suitability testing (where applicable) and vendor site audit and compliances.
- As a continuous evaluation part vendors of RM and PM shall be evaluated annually for quality, deliveries, physical condition of the materials received.
- All RM, PM are tested by QC based on approved specification prior to use.
- OOT/OOS handling procedure should be in case of any abnormal results, which is against the pre-defined specification limit.

7.8 Preventive Maintenance

- To improve the cleanroom contamination control strategy, is to schedule regular maintenance on all equipment, we have preventive maintenance schedule which covers equipment related to Manufacturing and filling.
- Regular Preventive maintenance Programme for the equipment and Utility system available and it is the key to preventing failures of the cleanroom environmental control systems (HVAC) and production equipment and ensuring the cleanrooms and equipment are operating in their validated state, preventive maintenance governs through SOP which have separate checklist for each equipment including utility also.
- Regular Preventive maintenance activities executed as per planner at particular frequencies based on the operation of the equipment criticality equipment preventive maintenance frequencies are decided (Monthly, Quarterly, Half Yearly and Yearly), if equipment are not frequently maintained can also pose contamination if not done correctly.
- In case of cleanroom equipment, after completion of preventive maintenance cleaning and disinfection cycle shall be perform and followed by EM before releasing the areas for routine operation.

7.9 Environment Monitoring System

The purpose of the environmental monitoring programme is to provide data that can be used to assess the adequacy of contamination controls in the cleanroom or manufacturing area.

An environmental monitoring program, which provides assurance of compliance with regulatory requirements is established. This program also is designed to detect excursions from environmental limits triggering investigation and assessment of risk to product quality (annex 1, 2022). The environmental program covers both viable and non-viable particles.

- Environmental monitoring targeted at critical points of operator and material transfer and key interactions in the preparation process, filling and sealing including adjacent areas like corridor, change rooms etc.
- The Environmental Monitoring (EM) program for a facility is used to monitor and determine the type and level of microbial and non-viable particulate contamination present in a cleanroom environment.

- We carryout Viable environmental monitoring as per SOP and is performed by exposing microbiological nutrient medium plates in sampling locations that represent the areas of highest contamination risk in the cleanroom.
- In Vial line we carryout continuous Non-viable particle monitoring as per SOP by using Isokinetic probes and online particle counter to assess the number of non-viable particles in the air and are also used for classification purposes as per ISO 14644. The sampling locations for both viable and non-viable monitoring are selected using a documented risk based approach that is reviewed and repeated periodically to account for any changes in the process or the cleanroom.
- In approved procedure appropriate alert levels and action limits set for the results of viable and non-viable particle monitoring. Alert levels established based on results of cleanroom qualification tests and trend data which is periodic review.
- Batch filling in the Vial section shall be continuously monitored for viable and non-viable monitoring, during operation and data shall be attached in respective Batch records and reviewed by production and IPQA and before release of batch.
- Risk assessment for both viable and non-viable monitoring perform to evaluate risk of contamination.

7.10 Prevention- Trending, Investigation, CAPA, Root Cause Analysis Determination

All applicable QMS elements like Deviation, Change Control, Incident, CAPA, OOS, OOT available and these are handle through QMS system.

As part of prevention mechanism, trend analysis, incident/ deviation, detailed investigation & root cause analysis using different tools i.e. 5 WHY, Fish bone etc. and corrective and preventive actions (CAPA) procedures is in place and governed through respective SOPs.

Trending of all QMS elements i.e. incidents, deviations, Market Complaint, Change Control available and prepare as per the frequency given in respective SOP.

7.11 Process validation

Process validation is to "establish documented evidence which provides a high degree of assurance that a specific process will consistently produce

a product meeting its predetermined specifications and quality attributes". Staff taking part in the validation work should be appropriately trained.

Process validation documentation shall include, but not limited to-

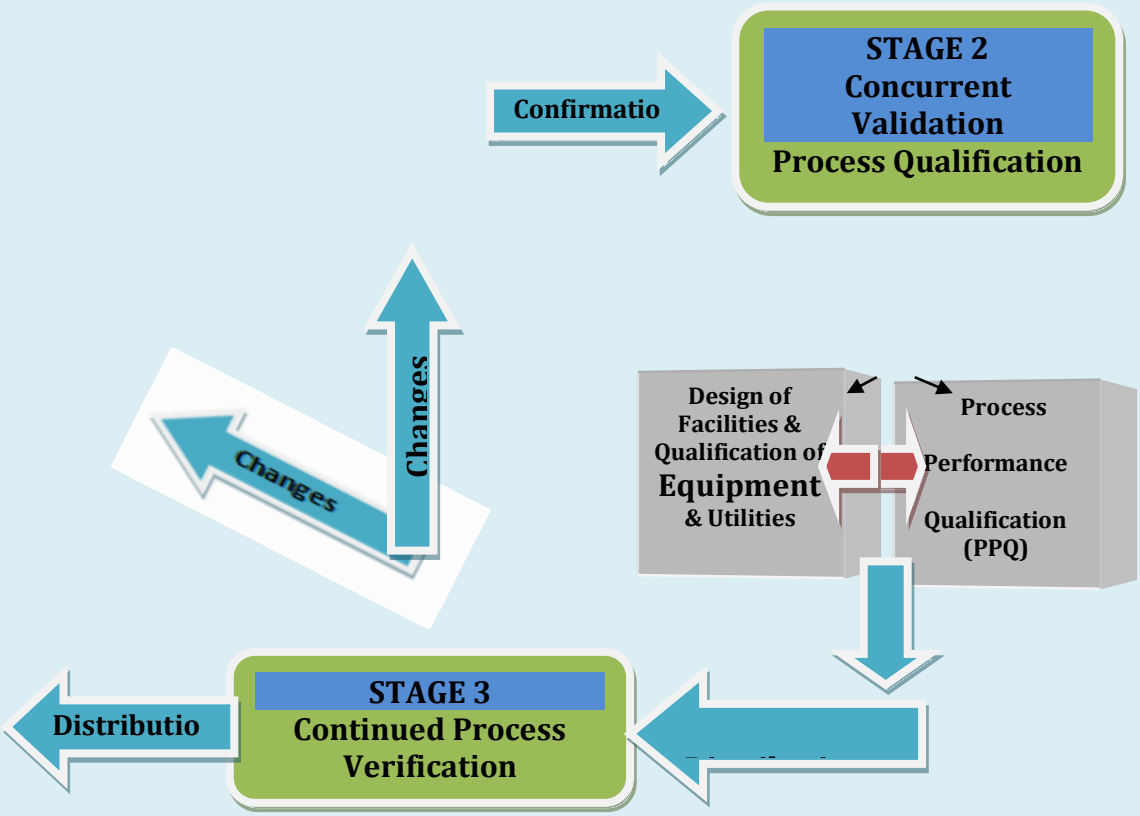
- Purpose of the document
- Scope of the document
- Personnel responsibility
- Short description of the process and flow diagram
- List of the equipment/facilities to be used (including measuring / monitoring / recording
- Equipment) together with its calibration status
- Proposed in-process controls with acceptance criteria
- Sampling plan.
- The product performance characteristics/attributes to be monitored, Together with the test method.
- Finished product specifications and acceptable limits for release
- Methods for recording and evaluating results

The above parameters are for guidance purpose and may change as per requirement. unless significant changes are made in the validated state of the process or product, Re qualification shall not be carried out. However re-qualification is considered where there are negative trend and investigation warranting the same.

The Validation of Product /Process are of different type depending upon the approach used to carry out the activity: Details of each type are given below-

The Validation of Product /Process shall involve following types depending upon the approach used to carry out the validation activity.

OVER VIEW OF PROCESS VALIDATION



TYPE OF VALIDATION

- Prospective validation
- Concurrent validation
- Retrospective validation
- Revalidation
- Continuous process verification

PROSPECTIVE PROCESS VALIDATION

Prospective validation is validation carried out before routine production of products. This approach is followed for all new products to be manufactured at site. Based on the requirement of the process, risks associated and identified key parameters, Experimental protocol shall be generated and the parameters shall be established in the initial /optimization/experimental batches. After establishing the key process and product parameters **three** consecutive batches shall be validated for confirming the predefined parameters written in the validation protocol. These validation batches shall be kept for complete **stability study.**

For prospective process validation, minimum of **three** consecutive batches are evaluated to meet pre-determined acceptance criteria. Batch size of such batches shall be same as intended for commercial scale batches. the

sampling and testing plan is defined based on an evaluation of the process to be validated. if it is intended that validation batches be sold or supplied, The same shall be done after completion of validation exercise, receipt of all data & results, Its review and compliance and final approval by head Quality Assurance. As a prerequisite to process validation, all equipment, Facility and analytical testing methods to be used shall be validated. Staff taking part in the validation work shall be appropriately trained.

CONCURRENT PROCESS VALIDATION

Concurrent validation is validation carried out during routine production of products. This involves monitoring of critical processing steps and end product analysis to generate data to establish that the process is under control.

Following are the instances where it is appropriate to validate a process during routine production- Change in process or product parameters, Change in master formula, New product, any negative trend observed in the process or product parameters, change in manufacturing facility, On the basis of findings of annual product review, change in raw material supplier, Change in equipment, change in process etc. In any case **three** consecutive batches/runs will be studied.

The batches may be kept on **stability study** depending upon the reason for which the validation is carried out. The completed protocols and reports should be reviewed and approved before product is released for sale or supply.

RETROSPECTIVE PROCESS VALIDATION

Retrospective Validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remains unchanged; such experience and the result of in-process and final control tests are then evaluated.

Retrospective process validation shall be carried out on minimum ten Commercial batches. It is normally conducted on a product already being commercial distributed and is based on accumulated production, testing and control data.

More batches shall be needed if all critical parameter cannot be verified with three batches.

Extracting the in process and finished product results and yields from each batch and plotting the results on graphs or in charts.

Reporting deviations, change controls and product complaints of the product.

PROCESS REVALIDATION

The major change in process will require for re-validation of the critical parameters to show that it does not affect product quality. The process will be revalidated in case there is known changes. For example: formula, Critical equipment, Critical process parameters, Batch size, Site and change in vendor for API. The critical parameters identified in the prospective or concurrent validation will be monitored during re-validation. The number of the batches to be studied will depend on the nature of change for which study is planned. In case there is no change in process, Re-validation shall be carried out once in 5 years. Refer SOP.

CONTINUOUS PROCESS VERIFICATION

The CPV is the third stage of Process Validation involving a scientific and risk-based approach, wherein the manufacturing process performance is continuously monitored and evaluated and documented evidence is established to prove that the process operates within the specified parameters and consistently produces material which meets all its CQAs and control strategy requirements. The continuous process verification shall be follow as per SOP.

APPROACH OF CONTINUOUS PROCESS VERIFICATION:

- The Continued Process Verification is the third stage of Process Validation involving a scientific and risk-based approach, wherein the manufacturing process performance is continuously monitored and evaluated and documented evidence is established to prove that the process operates within the specified parameters and consistently produces material which meets all its CQAs and control strategy requirements.
- The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacturing.

- The collection and evaluation of information and data about the performance of the process will allow detection of undesired process variability.
- This stage will help in evaluating the performance of the process, identifying problems and determining whether action should be taken to correct, anticipate, and prevent problems so that the process remains under control.
- The data collected shall include relevant process trends, quality of incoming critical material attributes, in-process material and finished products.
- In this stage, only the variable numerical data should be considered.
- In Continued Process Verification monitoring, the following parameters shall be monitored

  ✓ Critical Material Attributes (CMA) analysis.
  ✓ In-process analysis tests (CQA) (QC test).
  ✓ In-process analysis tests, performed by production during manufacturing of the batch for CQA.
  ✓ Finished Product analysis tests (CQA).
  ✓ Critical Process Parameters during manufacturing of the batch.
  ✓ Yield trend (theoretical yield and accountable yield).
  ✓ Addition tests for monitoring of addition parameters or intensive sampling as per requirement.

VALIDATION SHALL BE CARRIED OUT IN FOLLOWING CASES:

- New products including products transferred from other location.
- Product transferred between plants.
- Change in equipment, which has a direct impact on the manufacturing process.
- Change in production area (areas with equipment's of different make / capacity / working principle) and major changes in the support system as identified by the validation committee members.
- Well set products where process validation is still not carried out.

RE-VALIDATION SHALL BE CARRIED OUT IN FOLLOWING CASES:

- Change in primary packaging material.
- Change in source of API and primary packing materials.
- Any change in formulation shall be evaluated for need of revalidation

- Change of any major equipment in the chain of equipment which may affect the earlier validation study.
- Any major modification to the equipment, which may affect the earlier validation status.
- If batch size is changed ±10% of standard batch size. In case batch size validated on Minimum and Maximum Batch size on the basis of equipment capacity than batch can be taken under operating range of the equipment capacity and process shall be evaluated though continuous process verification.
- Based on any request from customer or regulatory agency.
- On the basis of Continuous Process verification, Revalidation is performed as per following criteria.
  - ✓ Multiple failures during Continue process verification.
  - ✓ Apply new PV approach to legacy products (in case of multiple rejections, Process re- verifications triggered by changes, etc)
  - ✓ Shift in process trends.
  - ✓ OOS/ Deviations related to product/ Process design.
  - ✓ Outcome of management review.
  - ✓ Product consistency issues.

Product manufactured as per validated batch size and further parameter followed during validation shall be monitored continuously for each batch to evaluate process capability.

7.12 Process simulation study (Media fill)

Process simulation study known as Media fill study and study is carried out to check performance of an aseptic manufacturing procedure using a sterile microbiological growth medium in place of the drug solution. Microbiological growth medium is used in place of the drug solution during media fills to test whether the aseptic procedure are adequate to prevent contamination during actual drug production. A media fill is one part of the validation of an aseptic manufacturing process.

Media fill shall be perform

- Initial three consecutive successful run
- As per revalidation Frequency (Every Six month ± 30 days).

- Any major modification to any of the existing Equipment, System or Area.
- Change in Environment, Disinfection Procedures, Equipment Cleaning and Sterilization (Including Containers and Closures).
- Major Maintenance and Qualification of Equipment's, e.g. Autoclave, Depyrogenating Tunnel, Vial Washing Machine, HVAC (Heating, Ventilation and Air Conditioning) System, Water System, etc.
- Change in Maximum or Minimum Batch Size.
- Change in Maximum or Minimum Container Size.

This is protocol based study which check the performance of the aseptic manufacturing the protocol consists of routine and non-routine interventions.

In requalification media fill container size shall be selected based on the minimum container for Std. batch size minimum filled volume, Std. batch size maximum filled volume of Vial & optimum filled volume Successful Single Runs alternatively shall be performed to evaluate the State of Control of the Aseptic Process.

Media fill shall be conducted with Media (Soya bean casein digest media) and media shall be filled in the Vials as per routine manufacturing and filled Vials shall incubate in incubation room with controlled temperature for 14 days. During Incubation Temperature shall be controlled for Ist 7 days suitable for Fungal Growth: 22.5°C ± 2.5°C, Incubation Temperature for Next 7 days suitable for Bacterial Growth: 32.5 ^{0}C ± 2.5 ^{0}C, media fill procedure shall be available in current version of SOP.

Container closure integrity test shall perform in the media fill for the assurance of leakage through chemical and microorganism, this provide assurance that the product not contaminated through environment.

Acceptance criteria for media fill as below:

No. of Units	**Acceptance criteria**
Less than 5000 units	No contaminated unit should be detected
Between 5,000 to 10,000	• One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill • Two (2) contaminated units are considered cause for revalidation, following investigation,
More than 10,000	• One (1) contaminated unit should result in an investigation • Two (2) contaminated units are considered cause for revalidation, following investigation,

7.13 Continuous Improvement

As part of a contamination control strategy it is imperative that a culture of continuous improvement is established. This is based on information from the current PQS and quality risk management processes. It is important that there are systems in place to continually review and identify where improvements are required for ongoing quality of Products and that should be thoroughly review timely as below mentioned programme

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- Deviation, complaints management should be thoroughly reviewed and trending
- Change Management
- Site self-inspection program, quality and sterility assurance field observation, global quality audits
- Supplier management and audit program
- Management review of the quality systems and process/product performance and quality metrics
- Regulatory inspections trends and observations
- Regulatory expectations and Technological evolutions survey
- Continuous process verification and Annual product quality review
- Trend analysis of Environment monitoring, gases, steam and QMS documents
- For quality check and evaluation of the product stability studies expiry plus 01 station shall be continuously monitored at fixed interval of time as per schedule.
- At every six-month media fill shall be perform to check the product simulate with current practice and to evaluate the impact of the personnel, environment and process

7.14 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, FMECA (Failure Mode Effects and Criticality 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, and Engineering and QA expertise.

Method used is as follows:

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 refers for risk mitigation and final statement about Risk under control.

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 FMECA exercises.

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

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 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.

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

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 impacts / 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:

S.No.	RPN Rating	Category	Action plan
1.	101 to ≤ 125	High	Recommendation and Mitigation plan to be taken
2.	51 to 100	Medium	
3.	Upto 50	Low	No action taken risk acceptable

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 next section, 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.

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
1.	Receiving & storage of Raw material in warehouse	Raw materials contaminati on	Raw material may be received from an unapproved vendor. (V/NV/End-Py)	High	- Approved vendor list is available in warehouse, QC and production to check the material received from approved vendor. - Before dispensing person ensure the vendor as per the approved vendor list. - BMR also contain the approved vendor name of API which further ensure during verification of raw material before manufacturing	Low	Procedural	Yes
			Contaminated or damaged container may be received (V/NV/End-Py)	High	- 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 further damage shall container shall be handle through as per approved procedure	Low	Procedural	Yes
				High	- De-dusting Area available at receiving of material along with vacuum cleaner to remove	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					the external contamination of the container. - SOP for operation and cleaning of vacuum cleaner available to guide the person for operate the vacuum cleaning and ensure cleaning of container externally.			
			Controlled Temperature conditions not maintained during storage (V)	High	- Storage condition of Raw Material is available in the Approved vendor list which further guide person for appropriate storage condition of the material - AHU available in the area to maintain environment condition as per the requirement i.e. temperature NMT 25°C. - SOP for temperature monitoring for the area is in place along with the recording template. - Temperature monitoring Performed by Warehouse & Verified by QA	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Storage of material done on racks or pallets to reduce any chance of contamination			
			Material may be received without vendor COA. (V/NV/End-Py)	High	- Consignment received from vendor contains all relevant document like invoice and COA - COA availability checked by QC person before sampling.	Low	Procedural	Yes
			Mix-up of material during storage. (V/NV/End-Py)	High	- Different raw materials stored separately on different pallets or Racks. - Storage area separated from production area Adequate space for storage of materials available. - Quarantine, under test and approved area differentiate through demarcation and status labeling on container done during storage. - As per good warehouse practices movable separate board used to segregate material within the racks	Low	Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Rope way method also part of SOP during storage of the material.			
			Storage at improper conditions. (V/NV/End-Py)	High	- Temperature Mapping of storage area is in place including seasonal variation (summer, rainy and winter) - Temperature monitoring Records are in place - Hot point located in area for routine monitoring of temperature	Low	Procedural Technical Design	Yes
			Staging of material without status Labeling. (V/NV/End-Py)	High	- Material is labeled with Quarantine, Under Test, sampled, Approved & Rejected at different stages based on the material status. - Separate Rejected material storage area under lock & key is available.	Low	Procedural Design	Yes
			Using / Dispensing wrong material (V/NV/End-Py)	High	- Approved BOM enter in SAP system - Before creation of batch, production check the material status as per the BOM - Batch release for manufacturing in SAP shall be checked by QA, with respect	Low	Procedural Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					to the material BOM as per Batch record - Before dispensing material checked with the Batch record and SAP requisition slip.			
			Storage areas cleanliness not maintained (V/NV/End-Py)	High	- Area cleaning procedure is in place using cleaning agent and disinfectant - RLAF operation and cleaning procedure is in place including type of cleaning (Type-A and Type-B cleaning)	Low	Procedural	Yes
2.	Component Sampling	Raw materials contamination	Un-adapted Design for sampling (V/NV/End-Py)	High	- RLAF available in the area for sampling of Raw material - Sampling is done under A/D, for non-sterile material - Sampling area separate from production area	Low	Technical Design	Yes
			Contamination through analysts (V/NV/End-Py)	High	- Protective Clothing is being used during sampling. - Person are trained for sampling of RM	Low	Procedural Organization	Yes
			Un-adapted environment for sampling (V/NV/End-Py)	High	- Sampling is being done under RLAF only. - Temperature monitoring in area	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			Inefficient protection to avoid any contamination (V/NV/End-Py)	High	- HVAC qualification performed & HEPA filter of porosity 0.3 micron provided at terminal of AHU - AHU and RLAF qualification performed as per schedule planner - Filter integrity check at every 06 months	Low	Procedural Technical Design	Yes
			Contamination brought through sampling tools (V/NV/End-Py)	High	- Cleaning Validation include sampling tools. - Cleaning procedure is in place for used Sampling Tool & utensils - Sampling utensils cleaning record in place - storage of Cleaned Sampling Tools - Dedicated Sampling Tools according to API/Excipients	Low	Procedural Technical Design	Yes
			Mix up between materials (V/NV/End-Py)	High	- As per procedure only one batch / material to be sampled at one time - After every sampling cleaning process is in place	Low	Procedural Organizational	Yes
			Wrong status of the material	High	- As per SOP person shall check the status of the consignment	Low	Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			(V/NV/End-Py)		to be sampled and check the availability of status of product - Proper status label affixed after sampling of material till approval of the material. - Status labeling shall be affixed quarantine, under test and approved label affix on the container			
			Dirtyness of RLAF (V/NV/End-Py)	High	- RLAF cleaning procedure is in place - Filter cleaning procedure and record in place - Person are trained to carry out the activity.	Low	Procedural	Yes
			Area and equipment dirtiness (V/NV/End-Py)	High	- Area cleaning and sanitization is being done for area and equipment as per approved procedure. - Trained person available for cleaning activity.	Low	Procedural	Yes
			Contaminated raw material(API) (V/NV/End-Py)	High	- Container physical check is in place at warehouse and QC. - Specification prepared as per official monograph which comprises of all test for the material	Low	Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- QC specification cover microbial testing including Bioburden + Endotoxin - Testing execute as per the specification.			
3.	Raw Material Dispensing	Raw materials contamination	Un-adapted Design for Dispensing (V/NV/End-Py)	High	- RLAF available in the area for dispensing of Raw material - Dispensing is done under A/D, for non-sterile material - Dispensing area separate from production area	Low	Procedural Technical Design	Yes
			Contamination through Operators (V/NV/End-Py)	High	- Protective Clothing is being used during Dispensing. - Person are trained for dispensing of RM	Low	Procedural Organizational	Yes
			Un-adapted environment for dispensing (V/NV/End-Py)	High	- Dispensing is being done under RLAF only. - Temperature monitoring in area	Low	Procedural Technical Design	Yes
			Un-efficient protection to avoid any contamination (V/NV/End-Py)	High	- HVAC qualification performed & HEPA filter of porosity 0.3 micron provided at terminal of AHU - AHU and RLAF qualification performed as per schedule planner	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Filter integrity check at every 06 months			
			Contamination brought through Dispensing tools (V/NV/End-Py)	High	- Cleaning Validation include Dispensing tools. - Cleaning procedure is in place for used dispensing Tool & utensils - Dispensing utensils cleaning record in place - storage of Cleaned Dispensing Tools - Dedicated Dispensing Tools according to API/Excipients	Low	Procedural Technical Design	Yes
			Mix up between materials (V/NV/End-Py)	High	- As per procedure only one batch / material to be sampled at one time - After every sampling cleaning process is in place	Low	Procedural Organisational	Yes
			wrong status of the material (V/NV/End-Py)	High	- As per SOP person shall check the status of the consignment to be sampled and check the availability of status of product - Proper status label affixed after sampling of material till approval of the material. - Status labeling shall be affixed quarantine, under	Low	Procedural Organisational	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					test and approved label affix on the container			
			Dirtyness of RLAF (V/NV/End-Py)	High	- RLAF cleaning procedure is in place - Filter cleaning procedure and record in place - Person are trained to carry out the activity.	Low	Procedural	Yes
			Area and equipment dirtiness (V/NV/End-Py)	High	- Area cleaning and sanitization is being done for area and equipment as per approved procedure. - Trained person available for cleaning activity.	Low	Procedural	Yes
			Particulate contamination through polybags used to store dispensed materials (V/NV/End-Py)	High	- Container physical check is in place at warehouse prior to dispensing - Double polybags used for storage of dispensed API and Excipient after dispensing - Store the polybag in cage trolley with lock and key provision	Low	Procedural	Yes
			35. Contamination from the bags used to store materials after dispensing (V/NV/End-Py)	High	- Food grade polybags used to store dispensed product	Low	Procedural Technical	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
4.	Transfer dispensed material to solution preparation	Raw materials contamination	36. raw material contamination through transfer (V/NV/End-Py)	High	- After dispensing material stored in polybags (double) and transfer material in production area through material lift. - Before transferring of material status labeling checked and verify on each material. - Material transfer through material life available in warehouse - Material transfer in cage trolley with lock and key provision - Material verification is in place before manufacturing	Low	Procedural	Yes
5.	Solution preparation	Contamination of Raw materials or solution during compounding	Compounding tank or manufacturing tank dirtiness (V/NV/End-Py)	High	- Approved RM used in manufacturing ensuring free from any foreign particle or contamination. - Cleaning process for the tank is validated - CIP/SIP module for cleaning of tank is in place for cleaning of tanks or closed vessel	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Validated cycle is used to clean the tank before manufacturing - Wash water analysis is in place to check and ensure adequate cleaning			
			Unadapted Design of compounding area (V/NV/End-Py)	High	- Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron - HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges - Procedure for Cleaning of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor	Low	Design Technical	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Epoxy on the floor available in area, area design in such a way which further reduce any chance of contamination in area.			
			Lack of grade protection due to power cut (V/NV/End-Py)	High	- Written procedure is in place to handle any power failure during operation. - DG with auto start / stop provision installed in plant which provide electricity within 3 minutes in production area - Compounding of solution done in closed vessel hence chance of contamination is negligible	Low	Procedural	Yes
			Contamination through Operators (V/NV/End-Py)	High	- Cleaned garment available in are - Cleaning procedure for garment is in place - Integrity / visual check after cleaning has been checked and if required garment replace with new garment set - Personnel are dedicated for compounding area	Low	Procedural Organizational	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Personnel hygiene checked for each person as per approved procedure and record is in place. - Trained and experience person execute the activity of compounding.			
			Contamination through WFI used (V/NV/End-Py)	High	- Qualified water system available in plant - Specification for analysis is in place - Daily monitoring and testing of WFI - Schedule verification of water system is in place	Low	Technical Design Procedural	Yes
			Contamination through N2 used (V/NV/End-Py)	High	- Qualified nitrogen generation plant is in place - Schedule filter integrity check is in place - Replacement of filter after ____ sterilization cycle is part of procedure. - Filter integrity check and if required replacement of filter shall be done. - Hydrophobic filter with porosity 0.2 micron fixed in the terminal of user point.	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Schedule re-qualification of nitrogen plant as per planner perform covering generation and distribution point			
			Compounding Area dirtiness (V/NV/End-Py)	High	- Procedure for Cleaning and disinfectant of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce	Low	Procedural	Yes
	Filtration and Holding process	Contamination of solution	Contamination through transfer pipes (V/NV/End-Py)	High	- Transfer pipes dedicated for each product - Transfer pipes integrity checks in place - Replacement frequency after __ sterilization cycle shall be done - Handling of new transfer pipes procedure implemented in plant	Low	Procedural Technical Design	Yes
			Contamination through un-	High	- Area design as A/B clean room area	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			adapted design of area (V/NV/End-Py)		- Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron - HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges - Procedure for Cleaning of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce			
			Contamination through area dirtiness	High	- Procedure for Cleaning and disinfectant of area is in place	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			(V/NV/End-Py)		- Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce			
			Contamination through holding tank (V/NV/End-Py)	High	- Cleaning process for the tank is validated - CIP/SIP module for cleaning of tank is in place for cleaning of tanks or closed vessel - Validated cycle is used to clean the tank before manufacturing - Wash water analysis is in place to check and ensure adequate cleaning - Visual checks of the tanks is in place - Hold time after cleaning and sterilization define in the procedure	Low	Procedural Technical Design	Yes
			Contamination through filtration method	High	- Filtration assembly cleaned and sterile as per validated load pattern	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			(V/NV/End-Py)		- Transfer of filtration assembly done through mobile LAF maintaining grade A - LAF having final HEPA filter of porosity of 0.3 Micron - Filtration done through 0.22-micron sterility grade filter - Pre and post integrity of sterility grade filter checked and procedure define for in case if integrity of filter found fail. - Filtration done in grade A under LAF having terminal HEPA filter of 0.3 micron			
			Contamination through operators (V/NV/End-Py)	High	- Personnel qualification of person who enter in aseptic area - Cleaned Sterile garment used in filtration process - Cleaning procedure for sterile garment is in place - Integrity / visual check after cleaning has been checked and if required garment replace with new garment set - Personnel are dedicated for filtration process	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Personnel hygiene checked for each person as per approved procedure and record is in place. - Trained and experience person execute the activity of compounding. - Aseptic behavior training provided to the persons - Entry / exit restrict in the area - After completion of 30 sterilization cycle gowning has been replaced			
			Contaminated environment condition (V/NV/End-Py)	High	- Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron - HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
6.	Vials decartonning	Contamination from Vials	Particulates contamination (broken or damaged (NV)	High	- Visual inspection of each Vial is in place - Rejected Vial reconcile and destroyed - Trained person performs the de-cartonning activity - Rejected Vial Pictorial displayed in the area - Protective clothing used during de-cartonning - Personnel hygiene in place	Low	Procedural	Yes
			Contamination through Operators (V/NV/End-Py)	High	- Protective clothing is being used during de-cartonning. - Personnel trained to carry out the operation	Low	Procedural Organizational	Yes
	Cleaning and sterilization of PPM (Al. seal and flip off)	Contamination of PPM aluminum seal and flip off	Particulates contamination through area dirtiness (V/NV/End-Py)	High	- Procedure for Cleaning and disinfectant of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce	Low	Technical Design Procedural	Yes
			Contamination through utility	High	- Pure Steam has been used for sterilization of PPM	Low	Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			(V/NV/End-Py)		- Validated load pattern has been used to sterilized the PPM		Procedural	
			Contamination through in-proper cleaning and sterilization (V/NV/End-Py)	High	- Load pattern are validated and sterilization shall be done through validated load pattern - Cleaning validation is in place	Low	Technical Design Procedural	Yes
			Contamination through operator (V/NV/End-Py)	High	- Cleaned garment available in area - Cleaning procedure for garment is in place - Integrity / visual check after cleaning has been checked and if required garment replace with new garment set - Personnel are dedicated for bung processor area - Personnel hygiene checked for each person as per approved procedure and record is in place. - Trained and experience person execute the activity of bung processor area.	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
7.	Washing of Vials	Contamination from Vials	Particulates contamination through area dirtiness (V/NV/End-Py)	High	- Procedure for Cleaning and disinfectant of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce	Low	Technical Design Procedural	Yes
			Contamination through un-adapted design of area (V/NV/End-Py)	High	- Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron - HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges - Procedure for Cleaning of area is in place	Low	Procedural Technical Design	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce			
			Contamination through washing machine (V/NV/End-Py)	High	- Qualified machine being used for cleaning of Vial - Automatic stop sensor available in machine to stop the machine when pressure of WFI/PW and compressed air get low - Protective covering available in the machine - Periodic re-qualification	Low	Procedural Technical Design	Yes
			Microbial contamination through utilities WFI/ compressed air (V/NV/End-Py)	High	- Compressed air used in washing operation is filtered through terminal filter of porosity of 0.2 micron - WFI used during washing which was tested before use as per specification - Qualified compressed air system and water system is in place	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Periodic re-qualification of compressed air and water system done as per VMP.			
			Contamination through Operators (V/NV/End-Py)	High	- Cleaned garment available in are - Cleaning procedure for garment is in place - Integrity / visual check after cleaning has been checked and if required garment replace with new garment set - Personnel are dedicated for washing process - Personnel hygiene checked for each person as per approved procedure and record is in place. - Trained and experience person execute the activity of washing.	Low	Procedural Technical Design	Yes
			Contaminated environment condition (V/NV/End-Py)	High	- Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges			
8.	Sterilization & Depyrogenation of Vials	Contamination from Vials	microbial and pyrogen contamination through machine (V/NV/End-Py)	High	- Qualified Machine used for sterilization of Vial - Alarm and autocut facility available in machine to stop machine when temperature under shoot or over shoot as per prescribed limit - Tunnel is fitted with magnihelic gauges to monitored pressure across filters during operation - Machine is synchronized with filling and washing machine - HEPA filter fitted in the tunnel is non-shredded and withstand with higher temperature - HEPA filter integrity check is in place	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			Unadapted environment for Sterilization & Depyrogenation (V/NV/End-Py)	High	- Operation execute in Grade-C clean room - Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron - HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges	Low	Technical Design Procedural	Yes
			Lack of grade protection due to power cut (V/NV/End-Py)	High	- Written procedure is in place to handle any power failure during operation. - DG with auto start / stop provision installed in plant which provide electricity within 3 minutes in production area - Recovery study for the tunnel is validated	Low	Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			Contaminated environment condition (V/NV/End-Py)	High	- Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron - HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges	Low	Technical Design Procedural	Yes
			Contamination through Operators (V/NV/End-Py)	High	- Cleaned garment available in are - Cleaning procedure for garment is in place - Integrity / visual check after cleaning has been checked and if required garment replace with new garment set - Personnel are dedicated for washing process - Personnel hygiene checked for each person as per approved	Low	Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					procedure and record is in place. - Trained and experience person execute the activity of washing.			
			Particulates contamination through area dirtiness (V/NV/End-Py)	High	- Procedure for Cleaning and disinfectant of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce	Low	Procedural Organizational	Yes
10.	Aseptic filling	Empty or filled Vials contaminati on	Unadapted Design for Filling (V/NV/End-Py)	High	- Operation design in grade A/B, filling and sealing done under LAF (Grade-A), area - LAF length is sufficient to cover filling tanks and filling and sealing station - Qualified HVAC system available to control the contamination in the area - HVAC system contains filter having terminal filter of porosity of 0.3 micron	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- HVAC system periodically re-qualified as per the validation planner - Temperature and humidity monitoring and recording is in place - Pressure differential monitoring during operation through calibrated gauges - Procedure for Cleaning of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce any chance of contamination in area.			
			Lack of grade protection due to power cut (V/NV/End-Py)	High	- Filling LAF (Grade A) connected with UPS for uninterrupted power supply - For filling room (Grade B) Clear written down procedure available to handle the	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					situation in case of power failure - Written procedure is in place to handle any power failure during operation. - DG with auto start / stop provision installed in plant which provide electricity within 3 minutes in production area - AHU recovery time establish			
			Contamination from Grade B environnent (V/NV/End-Py)	High	- Restricted Barrier system provided in the area to reduce contamination from Grade-B area - ORABS gloves used for operation of machine which is sterile before batch filling - Replacement frequency of ORABS gloves sterile up to 30 sterilization cycle - Integrity check of the ORABS check procedure is in place.	Low	Technical Design Procedural	Yes
			Contamination through Operators/garment (V/NV/End-Py)	High	- Personnel qualification of person who enter in the aseptic area done before entry of the person in aseptic area	Low	Procedural Organizational	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Aseptic behavior SOP in the place - Personnel sterile gowning cleaning and sterilization procedure is in place - After 30 sterilization cycle gowning has been replace - Protective accessories like googles, gloves shall sterile before use.			
			Contamination through operators/interventions (V/NV/End-Py)	High	- Process simulation study is in place - Frequency and condition for process simulation study defines in the SOP - Routine and non-routine intervention challenge during process simulation study - Person like engineering who enter in the area at the time of breakdown also challenge during process simulation study - Breakdown handling, power failure handling, maximum no. of person challenge during process simulation study. - Planner for process simulation study is in place	Low	Procedural Organizational	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Review of aseptic behavior during process simulation study has been mimic.			
			64. Contamination through materials/equipment entered with Autoclave after sterilization (V/NV/End-Py)	High	- Autoclave validation (double door) has been validated - Load pattern validated during validation including biological challenge test - Load pattern displayed in area - Unloading of the material or accessories done in aseptic area and store under LAF Grade-A - Transfer of material done through mobile LAF, having terminal HEPA filter - No exposure to grade B	Low	Technical Design Procedural	Yes
			Contamination between holding tank and filling (V/NV/End-Py)	High	- Fixed transfer pipe line available in the area - Filling tanks are clean and sterile through CIP/SIP validated cycle including transfer pipe line - Second sterile grade filter of 0.2 micron fixed between holding and filling tank.	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Pre sterilization and post filtration Integrity test of filters available - Wash water analysis of equipment is in place - Cleaning validation including filling accessories available - Hold time establish for filling accessories and equipment is in place			
			Contamination through Nitrogen purged in solution (V/NV/End-Py)	High	- Qualified nitrogen generation plant is in place - Schedule filter integrity check is in place - Replacement of filter after ____ sterilization cycle is part of procedure. - Filter integrity check and if required replacement of filter shall be done. - Hydrophobic filter with porosity 0.2 micron fixed in the terminal of user point. - Schedule re-qualification of nitrogen plant as per planner perform covering generation and distribution point	Low	Technical Design Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
			Contamination through sealing / lack of integrity (V/NV/End-Py)	High	- 100% particle detection by visual inspection - Leak test done by leak test and terminal sterilizer is in place - In-process checking is in place and recorded in BMR for clarity check - CCIT is in place during process simulation study - Sealing quality check is part of in-process control - Visual inspection done by qualified visual inspector	Low	Technical Design Procedural	Yes
			Filling area Dirtiness (V/NV/End-Py)	High	- Procedure for Cleaning and disinfectant of area is in place - Design of area consist of Stainless steel walls, which is non-reactive, non-shredded and easy to clean - Coving done on the corner of walls and floor - Epoxy on the floor available in area, area design in such a way which further reduce - Fogging with routine disinfectant is in place	Low	Technical Procedural	Yes

S.No.	Process steps	Potential failure mode	Potential cause of failure Type of contamination risk (Viable/Non-Viable /Endotoxin-Pyrogen)	Risk	Critical control point risk mitigation	Risk	Type of Measure Organizational Procedural, Technical, Design	Risk under control ? Yes/No& Action ref
					- Disinfectant effectiveness and validation for surface and spray			
11.	Other Critical Control Points	Contamination through external pest	Pest Control in place (V/NV/End-Py)	High	- Pest Control in place including rational for each location	Low	Design Procedural	Yes

8.0 STRATEGY EVALUATION

The Strategy evaluation cover all critical control points identified through the process mapping established. 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 monitoring 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,

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Reception	Approved vendor list is available, checked by warehouse and dispensing people to ensure the material is received from approved vendor	Deviation System	Quality Meeting, daily checks, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Reception	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.	Intimation of damaged material to QA department, physical verification of container is part of checklist	Quality Meeting, self-inspection, Radom checks	Quarterly	Quality Management Review SOP	NA
Reception	De-dusting area provided to remove the external contamination of the container.	Deviation System	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Reception	COA of all Materials is being obtained from the vendor, Verified by QA.	Deviation System, routine checks of vendor COA with consignment	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Reception	Different raw materials stored separately on different pallets.	Warehouse Self-inspection Every 6 Months	Self-inspection	every 6 Months	Self-inspection SOP	NA
Reception	Storage area separated from production area Adequate space for storage of materials available.	Warehouse Self-inspection Every 6 Months	Self-inspection	every 6 Months	Self-inspection SOP	NA
Reception	Temperature monitoring in storage Area	Any issue managed through deviation	Quality Meeting, quarterly basis	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
			trend of deviation is in place			
Reception	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.	Warehouse Self-inspection Every 6 Months	Self-inspection	every 6 Months	Self-inspection SOP	NA
Reception	BOM QA approved in ERP system (SAP) Dispensing check	BOM approved By QA Batch record review Any issue managed through deviation	Evaluation through deviation, quarterly basis trend of deviation is in place Quality Meeting	Once in a year Quarterly	Quality Management Review SOP	NA
Reception	Area cleaning is being done for area and equipment's as per approved procedure.	Warehouse Self-inspection Every 6 Months	Self-inspection	every 6 Months	Self-inspection SOP	NA
Sampling	Qualified RLAF, Grade A provided to control the contamination. Supporting area of RLAF is Grade D	Any Issue managed through deviation	Quality Meeting, equipment qualification planner	Once a year for RLAF and sampling area	Quality Management Review SOP	NA
Sampling	Protective clothing is being used during sampling.	Any Issue managed through deviation	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Sampling	Sampling is being done under RLAF only.	EM air Sampling and passive sampling plan	Quality meeting, trend of deviation in place	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
		Control of Media used: Media COA + GPT/Contamination test performed incoming inspection Any Issue managed through deviation Notification for EM Excursions managed through deviations.	At every consignment before use			
Sampling	HVAC qualification performed & 0.3 micron HEPA filter provided at terminal stage	RLAF Qualification Periodic requalification once a year (A/D) Any issue managed through deviation	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Sampling	Cleaning Validation of sampling tools Cleaning to Sampling Tools Storage of Cleaned sampling Tools Dedicated Sampling Tools Not Available as per API / Excipients	Dedicated Sampling Tools Required For API & Excipients, Description of Storage of Tools Washing of the tools recorded in specific form review in place Any issue managed through deviation Self-inspection Every 6 Months Deviation	Evaluation through deviation and self-inspection Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Sampling	Sampling Room / areas are separated from Production area	Self-inspection Every 6 Months	Self-inspection	every 6 Months	Self-inspection SOP	NA
Sampling	At a time only one material/batch is being sampled.	At the time of sampling and record of sampling Self-inspection Every 6 Months Deviation	After each sampling Self-Inspection Quality Meeting	Any issue managed through deviation Every 6 Months Quarterly	Quality Management Review SOP Self-inspection SOP	NA
Sampling	Proper status label affixed after sampling of material till approval of the material.	SOP for sampling Self-inspection Every 6 Months self-inspection check list for action to update Deviation	After each sampling Quality Meeting Self-inspection	Any issue managed through deviation Quarterly Every 6 Month	Quality Management Review SOP Self-inspection SOP	NA
Sampling	Clear written instructions for RLAF filter cleaning & replacement.	SOP for cleaning of filters of RLAF Filter Cleaning Record Self-inspection Every 6 Months Deviation	Quality Meeting Any issue managed through deviation	Quarterly Every 6 Month	Quality Management Review SOP Self-inspection SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Sampling	Clear written down procedure available to handle the situation in case of power failure.	SOP in place and any excursion handle through deviation	During each and every sampling Quality Meeting	Deviation Quarterly	Quality Management Review SOP	NA
Sampling	Area cleaning and sanitization is being done for area and equipment as per approved procedure.	Area Cleaning & Sanitization RLAF Equipment Cleaning Deviation Notification for EM Excursions managed through deviations	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Sampling	QC Testing of materials for Bioburden + Endotoxin	Endotoxin & Bio burden Analysis performed for API Any issue managed through OOS/OOT Management CoA check / vendor management	OOS/OOT through Quality Meeting	Quarterly	Quality Management Review SOP OOS SOP	NA
Dispensing	Qualified RLAF provided to control the contamination. Supporting area of RLAF is Grade D.	Deviation system	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Dispensing	Protective clothing is being used during Dispensing	SOP for Entry Exit in Dispensing Area Any Issue managed through deviation	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Dispensing	Dispensing is being done under RLAF only.	EM air Sampling and passive sampling plan Control of Media used: Media C o A + GPT/Contamination test performed incoming inspection Any Issue managed through deviation Deviation Notification for EM Excursions managed through deviations	Quality meeting, trend of deviation in place At every consignment before use	Quarterly	Quality Management Review SOP	NA
Dispensing	HVAC qualification performed & 0.3 Micron HEPA filter provided at terminal stage	RLAF Qualification Periodic requalification once a year (A/D) Any issue managed through deviation	Quality Meeting, quarterly basis trend of deviation is in place	Quarterly	Quality Management Review SOP	NA
Dispensing	Cleaning Validation of Dispensing tools Cleaning procedure for Used Dispensing Tools Dedicated Dispensing Tools for API/Excipients	Cleaning Validation Report Ref. Washing of the tools recorded in specific form Document Review in place Any issue managed through deviation Self-inspection Every 6 Months	Evaluation through deviation and self-inspection Quality Meeting	Quarterly	Quality Management Review SOP	NA
Dispensing	Dispensing area separate from production area	Area Layout	Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Dispensing	At a time only one material/batch is being dispensed.	SOP for Dispensing Self-inspection Every 6 Months Deviation	Self-inspection	every 6 Months	Self-inspection SOP	NA
Dispensing	Only approved materials are brought to dispensing area	SOP for dispensing BMR QA reviewed Self-inspection Every 6 Months Deviation	After each dispensing Quality Meeting	Any issue managed through deviation Quarterly	Quality Management Review SOP	NA
Dispensing	Clear written instructions for RLAF filter cleaning & replacement.	SOP for cleaning of filters of RLAF Self-inspection Every 6 Months Deviation	Any issue managed through deviation Quality Meeting	Deviation Quarterly	Quality Management Review SOP	NA
Dispensing	Clear written down procedure available to handle the situation in case of power failure.	SOP for Handling of Power failure in place and handle through Deviation	During each and every Dispensing Quality Meeting	Deviation Quarterly	Quality Management Review SOP	NA
Dispensing	Area cleaning and sanitization is being done for area and equipment as per approved procedure	Area Cleaning & Sanitization RLAF Equipment Cleaning Deviation Notification for EM Excursions managed through deviations	Quality Meeting	Monthly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Dispensing	Double polybags used for storage of dispensed API and excipients after dispensing / Pharmaceutical Grade of Polybags	SOP for dispensing is in place Self-inspection Every 6 Months Deviation	SOP already in place which include check of Pharma grade poly bags used to store dispensed materials Any Issue managed by deviation and assessed through Quality Meeting Quality Meeting	Quarterly every 6 Months Quarterly	Quality Management Review SOP	NA
Transfer dispensed material to solution preparation	36.1 After dispensing material stored in polybags (double) & Dispensed material Transfer to RM Day store area through Dynamic Pass box. 36.2 Cross verification of all materials by QA persons in RM day Store area & Production Day Store	Cross verification of all materials by QA persons in RM day Store area & Production Day Store Document Review in place Deviation	Any Issue managed by deviation and assessed through Quality Meeting	Quarterly	Quality Management Review SOP	NA
Compounding	Tanks: IQ/OQ for both tanks and validated CIP in place SIP validated on Compounding & Holding tank CIP/SIP in place reviewed through BMR by production and QA	**Compounding and Holding tanks:** CIP and SIP periodic qualification on both tanks CIP and SIP check in BMR by Production and IPQA	Quality Meeting	CIP/SIP once a year Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
		Any Issue managed by deviation and assessed through Quality Meeting				
Compounding	Qualified HVAC system provided to control the contamination.	EM air Sampling and passive sampling plan Control of Media used: Media C o A + GPT/Contamination test performed incoming inspection Any Issue managed through deviation Notification for EM Excursions managed through deviations	At every consignment before use Quality Meeting	Quarterly	Quality Management Review SOP	NA
Compounding	HVAC qualification performed & H14 HEPA filter provided at terminal stage	HVAC Qualification Periodic requalification once a year Any issue managed through deviation	Quality Meeting	once a year for Compounding area Quarterly	Quality Management Review SOP	NA
Compounding	Clear written down procedure available to handle the situation in case of power failure.	SOP for power failure is in place	During each and every Compounding Tank Quality Meeting	Deviation Quarterly	Quality Management Review SOP	NA
Compounding	Protective clothing is being used during compounding.	Procedure for entry & Exit in Solution Preparation Area	Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
	Fresh Garments change every entry in solution preparation area.	Any Issue managed through deviation				
Compounding	Qualified System for WFI production	Sampling plan in place Including daily generation and loop return Sample taken from the tank for each compounding Any issue managed through deviation or OOS/OOT Self-inspection, every 6 Months	Quarterly review of OOS/OOT through Quality Meeting	Quarterly	Quality Management Review SOP	NA
Compounding	Qualified system for N2 production Filter Integrity Frequency Quarterly Bases Sterilization Cycles of filter 80 cycles	Nitrogen System Qualified Filter Integrity record Filters management Self-inspection Every 6 Months Deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Compounding	Cleaning and disinfection	Area Cleaning & Sanitization Disinfectant Validation	Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
		Notification for EM Excursion managed through deviation				
Compounding	Double layer 1µm +0.2µm filtration between compounding and holding tank Filter integrity test done before and after filtration Product Filter Integrity recorded in BMR	Integrity Testing Performed before & After filtration Record in Place BMR review by QA Any issues with filter integrity tests managed through deviations	Deviation/quality meeting	Quarterly	Quality Management Review SOP	NA
Vials decartonning	Visual inspection after decartonning and before to feed washing machine	Vials Decartonning & Visual inspection Record In Place Operation recorded in BMR	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Vials decartonning	Protective clothing is being used during de cartonning	Gowning in De cartonning area / de cartonning Procedure Any Issue managed through deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Washing of Vials	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 Procedure before operation	initial validation and Periodic validation of the cycle once a year SOP for operation of Vials washing Machine Recorded In BMR & Verified by QA	Deviation/Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
	Operation/In-process of washine machine recorded in BMR	In-process Recorded In BMR &Checked by Production & QA Any issues managed through Deviation				
Washing of Vials	WFI system qualified and 0.2µm filtration in place Integrity testing once a month Replacement once a Six month	WFI System qualified Filter Integrity & Filter Management Self-inspection Every 6 Months Deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Washing of Vials	Compressed air system qualified and 0.2µm filtration in place Integrity testing once a month Replacement once a Six month	Compressed Air System Qualified Filter Integrity & Filter Management Self-inspection Every 6 Month Deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Sterilization& Depyrogenation of Vials	Tunnel qualified and Depyrogenation cycle validated Alarms in place to stop the process in case of issue (eg low Temperature)	initial validation and Periodic validation once a Year SOP for operation of Depyrogenation Tunnel Any issue managed through deviation	Deviation/Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Sterilization& Depyrogenation of Vials	Qualified HVAC system provided to control the contamination, grade C (Area including washing machine and tunnel)	HVAC Qualification Periodic requalification once a year Any issue managed through deviation EM air Sampling and passive sampling plan Control of Media used: Media C o A + GPT/Contamination test performed incoming inspection Notification for EM Excursion managed through deviation	At every consignment before use Quality Meeting	NA Quarterly	Quality Management Review SOP	NA
Sterilization& Depyrogenation of Vials	Clear written down procedure available to handle the situation in case of power failure.	SOP to be prepared for Handling of Power failure Deviation	During each and every Tunnel Sterilization Quality Meeting	Quarterly	Quality Management Review SOP	NA
Sterilization& Depyrogenation of Vials	HVAC qualification performed & H14 HEPA filter provided at terminal stage	LAF Qualification& Tunnel Periodic Qualification once a Year(grade A) Area Qualification Any Issue managed through deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
Sterilization& Depyrogenation of Vials	Cleaning and disinfection/Supporting area	Area Cleaning & sanitization Disinfectant Validation EM Passive & Active Air sampling Plan Notification for EM Excursion managed through deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Sterilization& Depyrogenation of Vials	Protective clothing is being used during washing and depyrogenation.	Area Gowning Any Issue managed through deviation	Quality meeting	Quarterly	Quality Management Review SOP	NA
Aseptic filling	Qualified HVAC system provided to control the contamination, grade A/B with extended LAF Required	Extended LAF required for A/B Grade LAF EM air Sampling and passive sampling plan Continuous NVPC in filling room for grade A , Surrounding Area Grade –B NVPC with Off line counter at Initial & End of filling Notification for abnormal count EMP Control of Media used: Media C o A + GPT/Contamination test	Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
		performed incoming inspection Deviation / Notification for EM / NVPC Excursion managed through deviation				
Aseptic filling	HVAC qualification performed & H14 HEPA filter provided at terminal stage	HVAC initial Qualification Periodic requalification every 6 months grade A/B Qualification issue managed through deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Aseptic filling	Grade A (Filling LAF) connected with UPS for uninterrupted power supply For filling Room Grade –B Handling the situation in case of Power Failure	SOP for Handling of Power Failure Deviation	Any Issues managed through deviations/Quality Meetings	Quarterly	Quality Management Review SOP	NA
Aseptic filling	Open RABS in place Integrity test on gloves at the end of the batch Periodic change of RABS Gloves RABS gloves vendor approval Aseptic Connection Minimized	Any Issue managed through deviation	Deviation/Quality Meeting	Quarterly	Quality Management Review SOP	NA
Aseptic filling	Protective clothing is being used during the filling.	Entry & Exit Procedure in Aseptic Area	Deviation/Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
	Sterile gowning / secondary gloves / Sterile Googles	Personnel Qualification Sterile Garment Management /Garment Check after washing & sterilization Personnel Monitoring Goggles cleaning & Sanitization Deviation				
Aseptic filling	Media fill Validation QA oversight, interventions check/observation Qualification of personnel Entering in Aseptic Area viable and non-viable monitoring performed before machine assembly till end of filling activity. Aseptic Connection Minimization	Media fill Validation every 6 month (process) QA Oversight Each personnel (Aseptic area)observed every 3 months Personnel Qualification of Each personnel Enter in Aseptic area Interventions monitoring through EM and NVPC continuous monitoring since set up of the line Personnel Monitoring	Any Issues managed through deviations / Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
		Any issues managed through deviation/ notification Deviation/EM Notification				
Asepticfilling	Autoclave validation Unloading in grade A/B under LAF and transfer to the filling line with mobile LAF within grade A No exposure to grade B	Initial validation & Periodic revalidation once a year Min and Max load Unloading LAF Qualified QA Oversight to check periodically aseptic operations and grade A continuity Deviation	Any Issue managed through deviation Quality Meeting	Quarterly Quarterly	Quality Management Review SOP	NA
Aseptic filling	One cartridge 0.2µm filters between holding Tank and filling Pre sterilization and post filtration Integrity test of filters available	Qualified Filter Integrity test Machine & Procedure for Filter integrity test Integrity test on both filters Results recorded in BMR BMR QA reviewed Deviation	Any issue managed through deviation Quality Meeting	Quarterly Quarterly	Quality Management Review SOP	NA
Aseptic filling	0.2µm filters for pre and post N2 purging provided, integrity test performed	Integrity test on both filters after filling Results recorded in BMR	Any issue managed through deviation Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
	Pre sterilization and post filtration Integrity test of filters available	BMR QA reviewed Deviation				
Aseptic filling	100% particle detection by visual inspector 100% leak test detection by terminal Autoclave to be implement	Qualified visual inspector available to detect rejection in filled Vial Recorded in BPR Leak test of Vials done through terminal sterilizer and record in BMR any excursion handle through deviation	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Aseptic filling	Cleaning and disinfection program Fogging on a weekly frequency	Cleaning & sanitization Disinfectant Validation EM program Notification for EM / NVPC Excursion managed through deviation Deviation Fogging frequency	Quality Meeting	Quarterly	Quality Management Review SOP	NA
Other Critical Control Points	Pest Control in place including rational for each location	Pest control frequency & Rational For Location Inplace Self-Inspection every 6 months	Quality Meeting	Quarterly	Quality Management Review SOP	NA

Process Step	Critical Control point Description	Monitoring in place If none, describe action	Evaluation in place If none, describe action in red	Evaluation Frequency or expected Frequency	Documentation ref.	Action
		Deviation				

9.0 STRATEGY EVALUATION ACTION PLAN

As per above evaluation we already have sufficient controls to minimize / detection of contaminants in Vial line (sterile liquid preparation), as the Contamination control strategy covers all critical control points, process step description and related implementation and monitoring through pharmaceutical quality system.
During review of each element we emphasis on the generation of contamination, risk and controls available to detect and mitigate contamination in the Vial preparation without breaching its safety, efficacy and quality.
During evaluation we found that risk as per current control is Low.
Hence continuous improvement strategy to be implement which describe in next section.

10.0 STRATEGY FOR CONTINUOUS IMPROVEMENT

10.1 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 Quality Review Meeting, and discuss on daily basis / monthly basis 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				
PQS					
Self-Inspection			X		
APQR				X	
Vendor Quality Management				X	
CAPA		X			
Specification / STP If any effect on Microbial,pyrogen/Endotoxin		X			
PERIODIC QUALIFICATION					
Progress of Validation Master plan				X	
HVAC Qualification grade C/D			X	X	
HVAC Qualification grade A/B			X	X	
Autoclave loads			X	X	
CIP/SIP/WFI				X	

	Monthly	Quarterly	6 Months	Yearly	2 years
Washing cycle & Tunnel Cycle				X	

All systems and data generated reviewed during the Quality meeting/ self-inspection on half-yearly basis 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.

11.0 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 data's and systems according the control dashboard defined in **above said section.**

- 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 found adequate to control contamination in the Vial section.

The CCS periodic review shall be based on routine data generated and significant changes such as introduction of new molecule and or new equipment, as a minimum CCS will be reassessed in two years.

However, on a quarterly 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.

12.0 APPROVAL:

Contamination Control Strategy (CCS_ has been Prepared, Reviewed, & Approved by the following and has been accepted as a policy document by the management.

PREPARED BY

FUNCTIONAL AREAS	NAME	SIGN AND DATE
OFFICER/EXECUTIVE QA		

REVIEWED BY

FUNCTIONAL AREAS	NAME	SIGN AND DATE
ASSISTANT MANAGER/ MANAGER QA		
HEAD ENGINEERING		
HEAD PRODUCTION (Injection)		
HEAD QUALITY CONTROL		

APPROVED BY

FUNCTIONAL AREAS	NAME	SIGN AND DATE
HEAD QUALITY ASSURANCE		

13.0 REVISION HISTORY

Revision No.	Effective Date	Review Date	Revision summary
00			New study prepared