BEYOND MEDIA FILLS BUILDING A CONTAMINATION CONTROL STRATEGY THAT WITHSTANDS REGULATORY SCRUTINY

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1.0 Objective

This document is prepared for development of the Beyond Media Fills Building a Contamination Control Strategy That Withstands Regulatory Scrutiny. **CCS** that requires thorough technical and process knowledge across the facility relevant. CCS is prepared to assess the effectiveness of all controls (**design, Procedure, technical and organizational)** and monitoring measures implemented to manage the risks to product Quality and safety. Potential sources of contamination are attributable to chemical, microbial and cellular debris (e.g. pyrogen, endotoxins) as well as particulate (e.g. glass and other visible). Contamination is unintentionally transferred from one substance or object to medicines having harmful effects that might affect the purity, quality and efficacy of the drug Product. Mitigation strategy is in place with the help of facility design and procedural controls.

2.0 Purpose:

The aim of all contamination control system is to identify, minimize or completely overcome the potential risk of contamination, which are attributable to chemical, microbial and cellular debris (e.g. pyrogen, endotoxins) as well as particulate (e.g. glass and other visible particulates).

Ensure a sufficient level of cleanliness in controlled environments and this is accomplished by maintaining, reducing, or eradicating viable and non-viable contamination either for Aseptic purposes and to maintain the desired quality of drug products.

3.0 Scope

This document is prepared as a guidance document for the element to be considered for Beyond Media Fills Building a Contamination Control Strategy That Withstands Regulatory Scrutiny of the Aseptic Manufacturing .

4.0 Definitions:

Contamination Control Strategy (CCS): A planned set of controls for microorganisms, pyrogens, endotoxins and particulates derived from implemented system and process that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipients, drug product materials and components. Facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

Contamination: The definition of contamination is something that contaminates (causes an impurity) or is something that has been made impure or spoiled. The process of making a material or surface unclean or unsuited for its intended purpose, usually by the addition or attachment of undesirable foreign substances . The three types of contamination are biological, physical, and chemical.

Media fill Activity: To ensure the sterility of products purporting to be sterile, sterilization, aseptic filling and closing operations must be adequately validated. To demonstrate the process of bringing together all these sterilized elements to produce a sterile drug product an aseptic processing operation is validated using a sterile microbiological growth medium (SCDM) in substitution of the product. This process simulation is also known as a media fill, and includes exposing the sterile SCDM to the product contact surfaces of equipment, Container closure integrity testing (both microbiologically and chemically) e.g. Dye ingress test, critical environmental parameters and process manipulations to closely simulate same exposure that material itself will undergo. The sealed containers filled with the sterile a growth medium are then incubated to detect microbial contamination. Results are then interpreted to assess the potential for a unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, and over sealing). Aseptic processing relies heavily on personnel intervention practices, equipment features, facility design/ control and procedures that in combination serve to exclude micro-organisms from sterile components and products. Thus, the aseptic process simulation is only a demonstration of the capability with respect to the sterility assurance of the process to produce sterile products aseptically at the time of its execution using the defined process, materials, facility, equipment and personnel.

But media fill is not sufficient to ensure the drug sterility assurance level is manufacturing as per regulatory requirement.

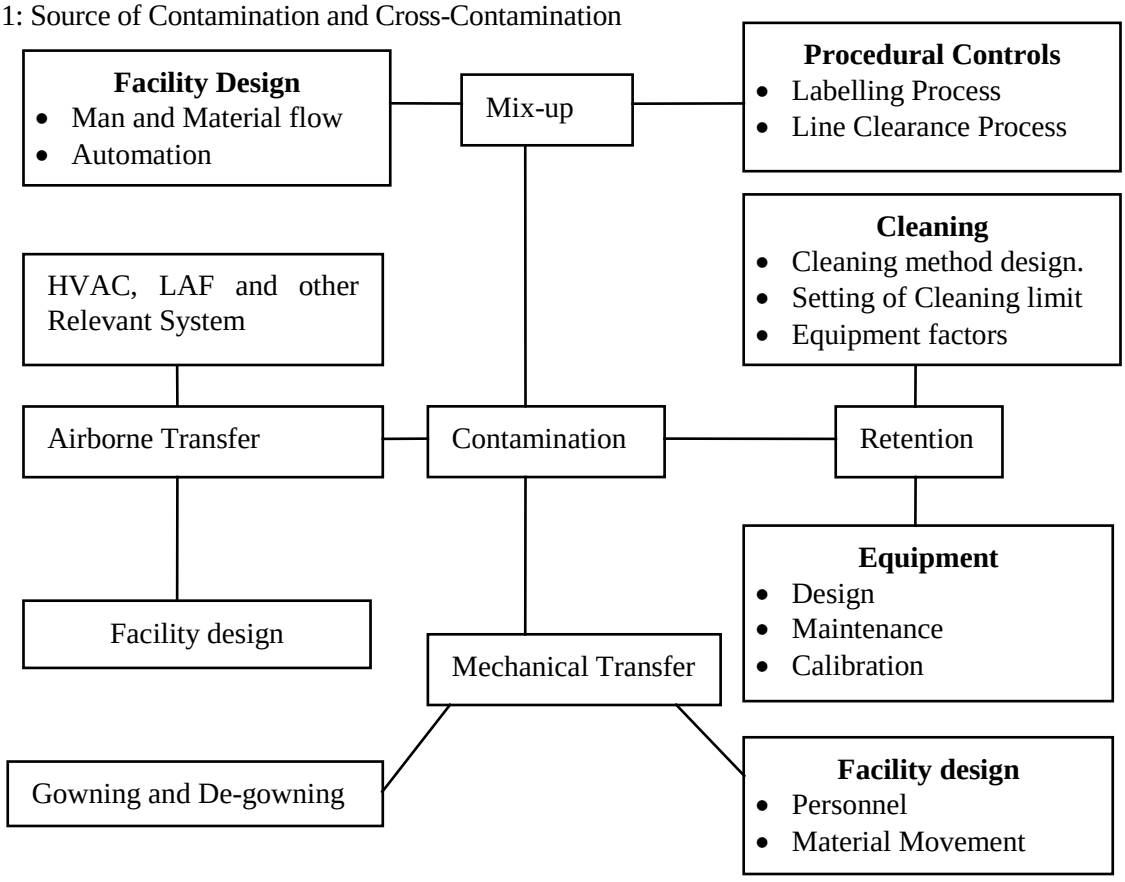
So, what regulators want to see is a connected contamination control strategy. That starts with facility design, utility systems like HVAC and water, equipment design and maintenance, and trained personnel. Then you add material controls, cleaning and disinfection, environmental monitoring, and ongoing process verification. Media fills sit inside that system as evidence, not the foundation. Scrutiny means being ready to show that all the dots connect logically, each risk assessed, each control justified, and deviations trended into CAPA and continual improvement. In your conference presentation, the key message is that a successful media fill demonstrates process capability. But a robust contamination control strategy proves ongoing sterility assurance. That’s what gives regulators confidence. Detail is below.

5.0 SOURCES OF CONTAMINATION AND CONTROL MEASURES:-

Sr. No.	Sources of contamination	Potential Occurrence of contamination	Mitigation & Control measures
1.	Facility	Facility Design, flow of man, material, waste, building maintenance, HVAC and Area qualification	➢ Facility is designed for the manufacturing, processing, packing, holding, cleaning and maintenance of a drug product. ➢ HVAC and Area qualification procedure is in place with respect to area design, air changes, air velocity Unidirectional Air flow, Differential Pressure, %RH, Temperature and integrity and NVPC monitoring. ➢ Environmental monitoring procedure (Viable, Non-viable, temperature & RH) is in place. ➢ Environment monitoring system is in place. ➢ Housekeeping management procedure for facility is in place. ➢ Man and material movement layout is in place. ➢ Building maintenance programme is in place. ➢ Hazardous material/Waste management is in place.
2.	Utilities	HVAC ,Water, Steam & Gases	➢ HVAC is in place with respect to area design, air changes, air velocity Unidirectional Air flow, Differential Pressure. ➢ Qualified Water System [Purified water (PW) & Water for Injection (WFI)] is in place. ➢ Qualified pure Steam Generation (PSG) system is in place. Periodic qualification for pure steam is performed as per respective protocol (Routine monitoring procedure is in place for pure steam). ➢ Qualified compressed air system is in place. Periodic qualification is performed as per respective protocol. ➢ Qualified Nitrogen gas generation system is in place, testing of nitrogen gas is done in the QC. (Routine monitoring procedure is also in place). ➢ Monthly & Annual trending procedure of PW, WFI and Pure steam system is in place.

3	Equipment	Reactive, rough surface, scratches/cracks, qualification	➢ Equipment management system is in place (qualification/ periodic qualification, monitoring. all equipment's are non-reactive, smooth surface, easy to clean, free from scratches/cracks and qualified for intended use.) ➢ Preventive maintenance (PM) and Calibration program is in place.
4	Materials	Raw materials, Packaging material (PPM, SPM), Single use materials.	➢ Vendor management system is in place (utilization of approved vendor of raw material (API & Excipients) & packaging material, and other miscellaneous items. ➢ Material movement flow is in place. ➢ Procedure for handling of raw material (RM), packaging material (PM) and storage procedure for the same is in place. ➢ Dispensing procedure of RM and PM is in place. ➢ Critical product contact materials utilization for use of material is in place (i.e. Filter, silicon tubing, & gloves).
5	Personnel	Personnel hygiene, Shedding Cells, skin, oils, hair, clothing & Personnel qualification	➢ Entry-exit control Procedure is in place. ➢ Personnel gowning qualification program is in place ➢ Man movement flow is in place. ➢ Training program is in place. ➢ Personnel hygiene procedure is in place.
6	Process	Cleaning & sanitization, Sterilization & Depyrogenation, Process Validation, Equipment qualification etc.	➢ Cleaning and sanitization program is in place. (Validation, Selection, Contact time, Concentration). ➢ Sterilization program is in place [Qualification/ periodic qualification of Dry (Depyrogenation tunnel)/Moist (Autoclave)]. ➢ Cleaning/ process validation program is in place. ➢ Qualification / periodic qualification program for equipment is in place. ➢ Procedure for preparation of PQR is in place.

Figure 1: Source of Contamination and Cross-Contamination

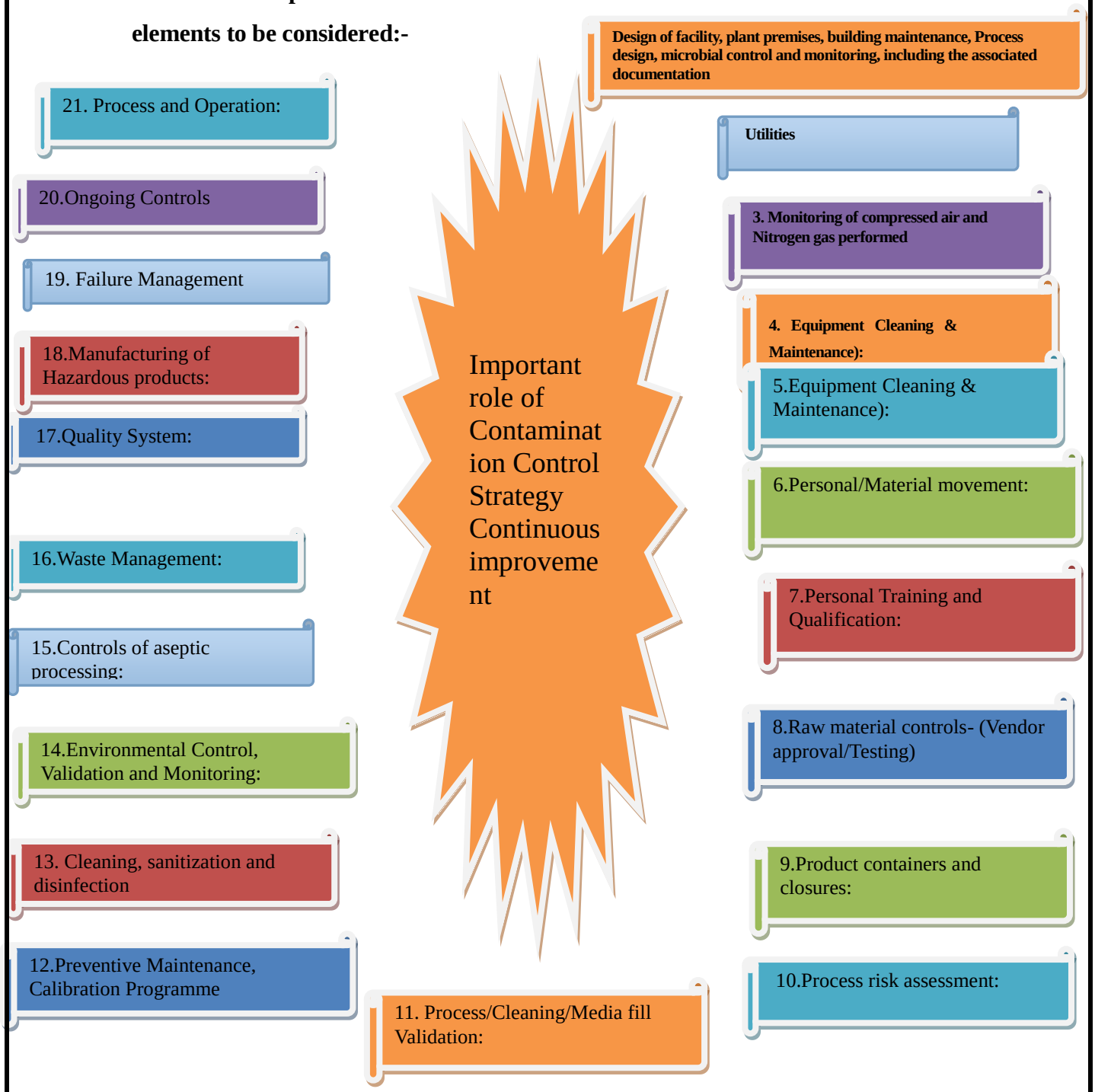


There are mainly four factors which are the cause of contamination:

1. **Airborne transfer:** Airborne transfer can be possible due to improper/wrong/unsuitable design facility of HVAC, LAF, utilities, equipment and other relevant system.
2. **Mechanical Transfer:** Mechanical transfer can be possible due to unavailability of system/procedure (Personnel and material movement not in place)
3. **Retention:** Retention can be possible due to wrong equipment design/cleaning & maintenance of equipment.
4. **Mix-up:** Mix up can be possible due to unavailability of procedure/automation/ man material flow system which can lead to potential microbial contamination.

6.0 Contamination Control Strategy Continuous improvement

- **Further considering this four element, assessment and evaluation of following stages has been carried out with respect to Contamination Control Strategy (CCS) Continuous improvement based on information derived from the below and the elements to be considered:-**



A. Design of facility, plant premises, building maintenance, Process design, microbial control and monitoring, including the associated documentation:

- Vial Injection & Ophthalmic Block (First Floor) is a dedicated facility for the manufacturing of parenteral & ophthalmic drug products i.e. aseptically filled vials & 03 Piece ophthalmic vial. The filling and sealing line is equipped with Grade A, Mobile LAF to maintain the clean room conditions.
- Facility Design and detail of premises is provided in current version of Site Master File.
- The facility concept was initially prepared as per facility URS considering cGMP and good engineering practice requirements and constructed as per URS.
- As a Control strategy facility design such as interior surface (walls, floors and ceilings) in facility are smooth and free from cracks, and permit easy cleaning, painting and disinfection.
- Separate AHU systems provided for aseptic areas and supporting areas (i.e. Manufacturing, Autoclave, Vial Washing &Tunnel, Clean Corridor) (Critical and support areas) to avoid cross contamination.
- Qualified facility having proper grading system as per regulatory requirement, no open area and positive pressure to avoid ingress of air from external environment.
- Qualified air handling systems are available to provide desired environmental condition in processing/ manufacturing areas.
- Performance of AHU (Air handling unit) system is verified periodically by performing various tests i.e. physical verification of area, air velocity, ACPH (Air changes per hours) calculation, air flow visualization, HEPA (High efficiency particulate air) filter integrity, temperature, relative humidity, differential pressure, viable particle count, non-viable particle counts and recovery study.
- During operation of AHU, ON/OFF sequence is maintained to assure maintenance of pressure gradient as per facility design classification.
- The HVAC system used to filter the supplied air to prevent airborne contamination from the atmosphere.
- Supply of filtered air, maintenance of positive pressure to adjacent rooms of different grades as per regulatory requirement and effective monitoring and warning systems (Temperature and RH monitoring system) is in place.
- The preferable approach has an area dedicated Air Handling Unit (AHU) where the same AHU supplied to areas where different products are not manufactured to prevent cross-contamination.

- The filters of AHU system monitored using Differential Pressure (DP) indication to ensure that filters are not torn or clogged.
- HEPA filters are periodically monitored for the leakage as per respective protocol.
- Adequate recirculation is done so that the ratio of filtered fresh air and recirculated air is maintained.
- Processing areas differential pressure maintained such a way that the area classification zones to prevent cross-contamination.
- The area is designed for adequate room differential pressure in the manufacturing facility, manufacturing rooms, clean equipment rooms, unclean equipment rooms, etc.

- Pre filters, fresh air filters and fine filters and exhaust filter cleaned at a defined frequency as per **SOP** Unidirectional airflow systems used to manage the contamination, particularly in Grade-A areas with a low airborne particle limit. This is achieved by passing air through HEPA filters and directing it downward in a constant parallel stream towards filters located on walls near the cleanroom floor or through raised perforated floor panels, which are then recirculated. The activities which are done in different grades are as below:

Grade A	- Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing grade filter. - Replenishment of sterile bulk product, containers and closures. - Removal/Unloading and cooling of unprotected/sterilized items from sterilizers. - Staging and movement of sterile primary packaging components in the aseptic filling line while not wrapped. - Aseptic filling, sealing of containers such as vial closure, transfer of open or partially stoppered vials. - Loading of Rubber Bung and Seal in Vial Filling and Sealing Machine - Loading of Bottles, Nozzle and Cap in 03 Piece in Vial Filling and sealing Machine
Grade B	- Background Cleanroom for grade A (When it is not an isolator) - Movement or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.

Grade C	- Cleanroom used for carrying out less critical stages in the manufacture of aseptically filled products. - Preparation of solutions, products to be filtered and sampling of products also includes.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after cleaning under LAF.

- The airflow visualized using a smoke study (Air Flow Visualization study) to ensure that the LAF is working as intended.
- Sampling/Dispensing of material (API) is done under isolator and dispensing of excipients is done under RLAF to prevent the potential cross-contamination.
- Environmental monitoring program is in place to monitor and ensure that the area is maintained as per defined and qualified gradation.
- Manufacturing area used in manufacturing, processing or holding of a drug product in suitable vessels/container, constructed and located to facilitate cleaning, maintenance, and proper operations within cleanrooms, protection available by airlocks, self-closing doors and combination of the both.
- Floors, walls, and ceilings having smooth surfaces that is easily cleanable.
- Adequate lighting provided in all the areas to perform operations adequately.
- Water supplied under continuous positive pressure in a plumbing system without dead leg, to prevent microbial contamination to any drug product.
- Drains are adequate in size and designed in such a way to prevent back-flow. Drain sanitization procedure is in place.
- Adequate washing facilities provided including soap/liquid soap in washrooms, air driers and hand disinfection in change rooms, air driers and clean toilet facilities.
- The building is free of infestation by rodents, insects and other vermin by installing the roda boxes and insectocutors outside the building of factory premises.
- Pest control for preventing the entry of insects, lizards into the premises by way of building design and facilities
- Dedicated area is provided for each and every process and equipment placement to prevent mix-ups between different components, drug product containers, closures and drug products to prevent

contamination.

- The flow of components, drug product containers, closures and drug products through the building is designed to prevent contamination.
- The building used for the manufacture, processing, Packing or holding of a drug products maintained in a clean condition following the Procedure for Building Maintenance
- Written procedures are in place for suitable rodenticides, insecticides, fungicides agents, and cleaning and sanitizing agents to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products.
- Validated cleaning and sanitization agents used routinely.

B. Utilities (HVAC, Water, Pure Steam & Gases):

➢ **Heating Ventilation and Air Conditioning System (HVAC):**

- Separate AHU systems provided for aseptic areas and supporting areas (i.e. Manufacturing, Autoclave, Vial Washing & Tunnel, Clean Corridor, 03 Piece Ophthalmic Filling and Sealing) (Critical and support areas) to avoid cross contamination.
- Qualified facility having proper grading system as per regulatory requirement, no open area and positive pressure to avoid ingress of air from external environment.
- Qualified air handling systems are available to provide desired environmental condition in processing/ manufacturing areas.
- Performance of AHU (Air handling unit) system is verified periodically by performing various tests i.e. physical verification of area, air velocity, ACPH (Air changes per hours) calculation, air flow visualization, HEPA (High efficiency particulate air) filter integrity, temperature, relative humidity, differential pressure, viable particle count, non-viable particle counts and recovery study.
- During operation of AHU, ON/OFF sequence is maintained to assured maintenance of pressure gradient as per facility design.
- The HVAC system used to filter the supplied air to prevent airborne contamination from the atmosphere.
- Air supplied to the classified area having adequately designed Heating Ventilation, and Air Conditioning (HVAC) system where air supplied through series of filters such as primary (Pre) filter (10µ filter), secondary (Fine) filter (5µ filter), and final air filtration through High-Efficiency

Particulate Air (HEPA) filters with 0.3 µ.

- Supply of filtered air, maintenance of positive pressure to adjacent rooms of different grades as per regulatory requirement and effective monitoring and warning systems (Temperature and RH monitoring system) is in place.
- The preferable approach has an area dedicated Air Handling Unit (AHU) where the same AHU supplied to areas where different products are not manufactured to prevent cross-contamination.
- The filters of AHU system monitored using Differential Pressure (DP) indication to ensure that filters are not torn or clogged.
- HEPA filters are periodically monitored for the leakage as per respective protocol.
- Adequate recirculation is done so that the ratio of filtered fresh air and recirculated air is maintained.
- Processing areas differential pressure maintained such a way that the area classification zones to prevent cross-contamination.
- The area is designed for adequate room differential pressure in the manufacturing facility, manufacturing rooms, clean equipment rooms, unclean equipment rooms, etc.
- Pre filters, fresh air filters and fine filters and exhaust filter cleaned at a defined frequency as per **SOP.**
- Unidirectional airflow systems used to manage the contamination, particularly in Grade-A areas with a low airborne particle limit. This is achieved by passing air through HEPA filters and directing it downward in a constant parallel stream towards filters located on walls near the cleanroom floor or through raised perforated floor panels, which are then recirculated.

➢ **Water:**

- The water system (generation and distribution system) is designed as per the requirements of ASME (American society for mechanical engineering) and ISPE (International society for pharmaceutical engineering) i.e. Slope, velocity, Loop pressure, MOC, roughness valve design, temperature etc. to prevent any contamination carryover i.e. Particulates, Microbial contamination/proliferation, Biofilm formation within the system and pyrogens.
- Water systems designed and qualified based on operating principle for generation of PW is by Reverse Osmosis-EDI System-UV Treatment-PW Storage & WFI is by multicolumn distillation process to maintain the appropriate levels of physical, chemical, and microbial control with taking seasonal variation into account

- Water is circulated at a defined pressure to maintain the water flow in the system to minimize the risk of microbial adhesion and subsequent biofilm formation.
- Online TOC & conductivity monitoring is in place with dumping provision if, WFI fails in TOC & conductivity .
- WFI generation, storage and distribution system including operational controls, monitoring, SIP program and sanitization program is in place .
- Sampling and testing of raw water, process water, reverse osmosis water, purified water, water for injection and pure steam condensate is in place and effective**.**
- Monthly & Annual water trend summary preparation procedure for PW and WFI is in place.

➢ **Pure Steam:**

- Pure steam generation, distribution system including operational controls, monitoring program is in place .
- Pure steam quality test checks for i.e. non-condensable gases, dryness value (dryness fraction) and superheat as per frequency defined in the respective protocol.
- Procedure for preparation of pure steam trend summary is in place.

➢ **Gases:**

- The compressed air system is designed as per the requirements of ASME (American society for mechanical engineering) and ISPE (international society for pharmaceutical engineering) also in the classified area used after filtered through 0.2-micron filter.
- Nitrogen gas is used during manufacturing of drug product, filtered through 0.2-micron filter.
- The material of construction of compressed air line/nitrogen gas line is non-corrosive to prevent any potential contamination.
- Nitrogen gas generation system /Cylinders storage facility available and all user point (product contact) having 0.2-micron filter and tested for integrity at defined frequency **.**
- Nitrogen gas/compressed air tested during periodic qualification for gaseous contamination, viable and non- viable contamination.

C. **Gases** :- Monitoring of compressed air and Nitrogen gas performed oxygen gas .

D. Equipment (Cleaning & Maintenance):

- Qualified equipments used for the intended purpose.
- Material of construction (MOC) of equipment product contact part is non-adsorptive, non-reactive, non- porous, corrosion-resistant and smooth surface which provide easy cleanabilty.
- Product contact surfaces are made of stainless steel SS316 and SS316L, food-grade plastic and rubber, non- leachable glass, etc.
- The product contact surface of the equipment is mirror-finished so that equipment is easy to clean.
- Equipment designed as all the parts of the equipment are easily accessible and visible to ensure adequate cleaning and cleanliness of the equipment.
- Whenever piping is involved in the equipment design, which is the product contact part, that joints are adequately welded. Inert gas and orbital welding used, followed by boroscopy of the piping to maintain smoothness of the surface.
- The dead leg is less than 3D and drain ability of piping ensured during qualification.
- The material of construction of all vessels and piping is SS316L and is electro polished internally.
- Equipments are inspected to check the presence of scratches, dents, and cracks that may impact the Cleanability of equipment.
- Procedure for periodic equipment maintenance are in place to ensure consumable replacement such as gaskets, valves, view glass, lids, tri-clover joints, etc., based on its condition.
- Depending on the nature of the process requirement, product dedicated equipments are used to minimizing the risk.
- Sterilization methods include moist heat (autoclave) and dry heat (depyrogenation tunnel), Qualification and periodic qualification programmed is in place.
- Steam Sterilization processes validated using physical measurements and where appropriate by using biological indicators (BI) and for depyrogenation devices endotoxin spiking is used.
- For sterilization, loading patterns are qualified followed by periodic qualification.

- Equipment specific, cleaning SOP is available for all product contact equipments i.e. manufacturing vessel, and storage vessel, cleaning activity is performed.
- Procedure is in place to perform the cleaning validation for worst case product.
- Identified hard-to-clean parts of equipment during cleaning method development and specified the same in the cleaning procedure.
- Cleanliness verification done visually by personnel using visualization aid for cleaning adequacy i.e. torch, mirror to verify equipment cleanliness.
- Procedure is in place to perform line clearance before utilizing equipment for batch processing.
- When using a manual cleaning process, cleaning method developed to reduce person-to-person variability by optimizing the variables contributing to the cleaning process.
- Dirty equipments hold time study and cleaning efficiency evaluated to ensure the effectiveness of cleaning process.
- Filters are product dedicated to prevent residues of previous product.
- The method used to measure the residue of the previous product after cleaning is capable to accurately and precisely determine the acceptable residual level. The method used to determine the residue after cleaning is validated as per guidance on analytical method validation.
- The operators are trained on the relevant cleaning procedures.
- The setting of the cleaning limit based on the scientific sound rationale to prevent the cross-contamination of the subsequent product by the previous product.
- MACO and HBEL approach is considered to calculate the cleaning limits.
- Criteria for worst-case product selection are Solubility, Clean ability, PDE (Permitted daily exposure), dose and potency.

E. Personal/Material movement:

- Separate entry-exit is available for Man and materials.
- Established procedure for entry and exit for factory personnel /visitor is available.
- Air curtains are available at the entrance to facility of Injection & Ophthalmic (First Floor) Block to remove extraneous dust available at the entrance of Block.

- Separate change rooms are available to remove street wear and wear washed, sanitized and cleaned factory linen each time .
- Only authorized personnel allowed to enter into the manufacturing/Aseptic areas. Unauthorized personnel allowed only when accompanied by an authorized person and access control to prevent unauthorized access is in place
- Gowning and de-gowning procedure is in place and displayed in area.
- Materials (i.e. Vial, Rubber stopper, 03 Piece Vial, Nozzle, Dropper & filling accessories) which come in contact with product are transferred either through validated depyrogenation & sterilization tunnel cycle or through respective validated autoclave cycle
- Material transferred to Grade B through Dynamic Pass box followed by cleaning and sanitization .
- Material transferred to Grade-A through Microenvironment/Mobile LAF.
- Materials entering in the aseptic areas through sterilization using autoclaves, depyrogenation tunnels.
- All materials used in the operations are procured from approved vendors.
- If any non-routine items are required within the cleanrooms transferred after cleaning followed by sanitization from disinfectant.
- Adequate space is available for product storage in FG day store. Raw materials, primary packing material, secondary packing materials are stored in dispensed material store.
- The facility designed for unidirectional personnel and material flow. Material includes raw materials, in- process materials, packing materials, finished goods, and scrap.
- Procedure for handling and transfer of dispensed material from dispensing area to manufacturing area is in place.
- Batch wise dispensed materials transferred to dispensed material store (as applicable) prior to transfer to processing area.
- The different areas provided for clean equipment storage and unclean equipment storage.
- Lock and key arrangement provided for printed packing materials.
- The visual inspection system implemented for product inspection, packed goods inspection is done to verify the overprinting matter

- Designated storage areas provided for: Rejected materials/Dispensed material/Quarantine areas for finished product.
- There is no cross-flow of exposed material or personnel between rooms where different products are manufactured within facility also facility is dedicated for Liquid Injection products.
- The washroom is outside of the manufacturing area's main entry. Gowning and de-gowning procedures followed while accessing the washrooms.
- Personnel involved in the operations of sterile products are qualified, trained and experienced in the manufacturing and testing to ensure compliance with GMP.
- Provision of interlocking of doors of change rooms provided.
- Requirements and procedure for gowning qualification and periodic monitoring programme is in place followed by media fill participation.
- Material movement from one place to another place, it is in closed condition.
- Material container and transfer trolley adequately cleaned as per defined frequency so that it will not carry the residue of product to other areas.
- In case of entry to the aseptic area, the person provides self-declaration of personal hygiene, followed by sterile gowning in change rooms and followed by personnel monitoring during exit from aseptic area

F. Personal Training and Qualification:

- Pre joining health check-up and annual medical check-up procedure is in place and followed as per respective SOP.
- Training provided to all employees to understand the personnel health, hygiene, and records are available.
- GMP training provided on joining and every year as per training scheduled
- Gowning covers head/ hair, beard/ mustache, face, upper body, legs/ pants, feet/ shoes, and hands.
- The gowning is designed and intended to cover all necessary parts of the body to prevent hair, skin cells and other particles on oneself from shedding into the cleanroom environment and/or contaminating the product.

- Gowning qualification performed for all individual entering into aseptic area. Used gown are disposed daily and utilized only after washing as per procedure .
- Entry to clean rooms done only through the personnel entry with proper gowning.
- Gowning done within the designated area in the change room.
- The sequence of gowning properly followed for connect gowning.
- Depending on operations, Personnel Protective Equipment (PPE) is part of the gowning procedure.
- All employees shall remove their personal belongings like ornaments, wrist watch, wallet, rings, belts and cosmetics, which is part of the approved procedure.
- Gowning maintained in the cleanroom throughout the duration up to which person stays inside the area.
- Personnel hygiene is one of the critical components. It includes but is not limited to Shower, Shave, Brush teeth, hair, etc.
- Steps for de-gowning are part of the procedure.
- After de-gowning while leaving the cleanroom, gowns are kept in a designated place to prevent contamination in the change room.
- The garments used for gowning for cleanroom area/aseptic area are non-shredding, same is certified by the vendor in vendor certificate.
- Direct contact between the operator and starting materials, primary packing materials and semi-finished or ready-to-pack products avoided.
- Fresh gowns are used daily before entering into production area of Injection & Ophthalmic Block (First Floor), whereas for the aseptic area, sterile gowns are used.
- While collecting the gowns at the end of the day, segregated to prevent cross- contamination and send for the washing.
- Procedure for gown collection, segregation, washing and management of clean gown are in place to ensure that the same process is followed every time.
- Following are the personnel requirement to qualify and train the personnel before involvement in the assigned activity:

Type of Training	Reference Document
	Title
Induction training	Training of employees
cGMP, GDP training	Good Documentation Practices
Personnel Qualification	Gowning Qualification of Analyst
Medical Check-up	Standard Operating Procedure for medical checkup of employees
General hygiene	Personal Hygiene
Training on Entry and exit to production area	Entry and exit procedure for MEN ,WOMEN and visitors in production injection first floor
Training on Entry and exit to aseptic area	Entry and exit procedure for aseptic area in production injection.
Training on aseptic behavior	Personal behavior & aseptic manipulations of personnel working in the aseptic area
Training on microbial monitoring of parenteral manufacturing area	Monitoring of environment parameters in production injection for first floor

G. Raw material controls- (Vendor approval/Testing):

- Procedure for Receipt of materials is in place and at the time of receipt of material, warehouse personnel check the details of approved vendor and verify the received materials with purchase order slip.
- Inspection of the containers / packs with respect to cleanliness, damage and intactness etc.
- Raw materials are stored in defined area in required storage condition as per approved procedure. Temperature mapping study is performed for all quarantine /storage areas to confirm the uniform temperature distribution.
- Sampling of raw materials API performed in isolator and sampling of raw material excipients performed in RLAF as per approved procedure.
- All Raw Materials tested prior to use for chemical and micro/ BET test and Re-tested as definite interval as per respective procedure.
- All materials tested as per approved SOP/Specification/ MOA/STP.

Raw Material (Starting Material) Controls Description	Reference Document Title
Material Receiving/ Verification	Receipt of raw/packing materials
Sampling	Sampling of Raw Material
	Sampling of Packing Material
Analyst and Reviewer Qualification	Procedure for Analyst and Reviewer Qualification
Practices	Good Laboratory Practices.
Testing of Material	Procedure for Analysis and Release of Samples Received in Quality Control Department and Review of Analytical Documents

- All raw materials tested as per approved MOA/STP against specification.
- OOT/OOS handling procedure in place, in case of any abnormal results, which is against the pre-defined specification limit.
- Vendor qualification performed as per **SOP**

H. Product containers and closures:

- Procedure for Receipt of materials is in place and at the time of receipt of material, warehouse personnel check the details of approved vendor and verify the received materials with purchase order slip.
- Inspection of the containers/packs with respect to cleanliness, damage and intactness etc.
- Primary packing materials are stored in defined area in required storage condition as per approved procedure. Temperature mapping study is performed for all quarantine /storage areas to confirm the uniform temperature distribution.
- Primary packing materials are procured from approved vendor and further sampling is performed as per approved procedure.
- All Primary packing material tested prior to use for chemical and micro/ BET test and Re-tested as definite interval as per respective procedure.
- All materials tested as per approved SOP/Specification/ MOA/STP.

Raw Material (Starting Material) Controls Description	Reference Document Title

Material Receiving/ Verification	Receipt of raw/packing materials
Sampling	Sampling of Raw Material, Sampling of Packing Material
Analyst and Reviewer Qualification	Procedure for Analyst and Reviewer Qualification
Practices	Good Laboratories Practices
Testing of Material	Procedure for Analysis and Release of Samples Received in Quality Control Department and Review of Analytical Documents

- All manufactured drug product tested as per approved MOA/STP against in-process and Finished product specification.
- OOT/OOS handling procedure in place, in case of any abnormal results, which is against the pre-defined specification limit.
- After bulk manufacturing, bulk solution filtration takes place from bulk manufacturing vessel/tank to pressure vessel/tank through sterilized 0.2-micron filter.
- Bioburden sampling performed before filtration (In-routine).
- Container closure (CCIT) procedure is in place for the sampling and testing of container and closure **.**
- To control the performance of container closure in routine leak test procedure is in place.
- All the elastomers/gaskets/O-rings are made up of food grade materials (Silicon/Teflon) and all other product contact parts are of SS316L.
- Filling needle made up of SS3I6L and sterilized needles are used during product filling/process.
- Ready to sterilize rubber stoppers are used in double layer bag and during dispensing, intact bag dispensed.
- Vendor qualification performed as per **SOP No.**

I. Process risk assessment:

- Risk assessment procedure is in place**: " Quality Risk management** and following are the Risk assessments performed for the facility:-

Description	Reference Document

	Title
The Concept of QRM is implemented throughout the organization (SOP)	Quality Risk Management

J. Process/Cleaning/Media fill Validation:

- The manufacturing process is subjected to Process validation to evaluate the reproducibility and of product for all critical process parameters/ critical quality attributes in line with approved registration details, product specific risk assessment performed and activity governed through common procedure /SOP.
- Cleaning validation philosophy/approach based on worst case product identified through Risk priority number considering HBE, solubility, cleanability, purity and therapeutic dose of product category governed through **SOP No.**
- MACO value /limit calculated based on stringent amongst PDE. Therapeutic dose and 10 PPM criteria.
- For all product contact equipments i.e. manufacturing vessel, pressure vessel and filling machine cleaning activity is performed with validated cycle parameters and routine cleaning is performed by trained operators.
- Prior to use all the items and accessories of filling parts are cleaned and autoclaved as per the **SOP No.**
- Media fill validation (Aseptic process simulation study) is governed through **SOP No.** and as per respective protocol.
- The number of units of media fill has been determined based on the minimum quantity of units to be filled and considering the sampling and process loss (sufficient to simulate all activities/interventions) for each vial size respectively.
- The acceptance criteria of successful media fill are considered as per respective media fill protocol considering the target for zero growth in media till containers.

Description	Reference Document
	Title
The concept of PV is described in SOP	• Process Validation Hold Time Study Of Products
The concept of continuous process	Product quality review

verification is described in SOP	
Aseptic process simulation is performed according to SOP	Aseptic Process Simulation
Line specific aseptic process simulation reports (media fill reports)	Re-validation schedule for equipment/ process and selection of container size
The Concept of CV is described in SOP	Cleaning Validation

K. Preventive Maintenance, Calibration Programme:

Preventive maintenance and calibration program procedure is in place and governed through respective SOPs.

L. Cleaning, sanitization and disinfection:

- Area specific (general/clean/aseptic) cleaning procedure SOP is in place.

Description	Reference Document	
	Title	No.
Cleaning & Sanitization of Area	Cleaning and sanitization of grade 'C' and grade B areas in production injection	
Cleaning and sanitization of controlled area	Cleaning and sanitization of grade 'D' and grade 'CNC' area in production injection	
Cleaning & Sanitization of Area	Housekeeping and Cleaning of Plant Premises	

- Approved disinfectants used to perform the routine cleaning and sanitization.
- Disinfectant preparation with details of disinfectants to be used, schedule, sequence of cleaning and all other required details are in place and performed as per **SOP No.**
- All disinfectants and hand sanitizing agent to be used in Aseptic area (Grade A & B) are filtered through 0.22 micron sterilizing grade filter and stored in sterilized containers prior to use and distribution as defined in **SOP No.** Disinfectants used in grade C and D not required to be sterile, due to non-critical operational activities which does not lead directly to potential contamination risk, Hence, unfiltered (Non-sterile) disinfectant used in support area grade C (Clean Area) and grade D (General Area) for cleaning and fogging.

- Equipment specific cleaning SOP is available for all product contact equipment's i.e. manufacturing vessel, pressure vessel, filling machine and packing machine etc.

M. Environmental Control, Validation and Monitoring:

- Monitoring of temperature, % RH and differential air pressure procedure is in place as part of environment monitoring procedure .
- Alarms are trended as part of control mechanism.
- SOP is in place with locations, frequency, limits etc. for online, offline monitoring of NVPC
- Off-line NVPC available for monitoring.
- Procedure is in place to handle any excursion in count observed at any location during monitoring.
- Viable (Settle plate exposure, active air,) monitoring in the filling during assembling of machine parts and filling operation.
- Personnel monitoring programme is in place .
- Viable monitoring procedure is in place as part of environment monitoring procedure and frequency of monitoring for different cleanliness class area **.**
- Summary of viable monitoring are trended in the form of tabulated data and graphical presentation prepared at the end of every month and end of the year data of viable monitoring is summarized in annual summary report.
- Handling of excursion procedure during routine monitoring is in place.
- SOP is in place for routine WFI monitoring (Sampling, testing) at defined frequency on rotation basis and all user points shall be tested within once in a week.
- Conductivity and TOC monitoring is in place with dumping provision if WFI fails.
- WFI generation, storage and distribution system including operational controls, monitoring program and sanitization program is available at the place.
- Summary and Trending Procedure for WFI is in place.
- Pure steam routine sampling and testing SOP is in place.

- Pure steam quality test check frequency is as per protocol no
- Pure steam routine monitoring, all user points tested at on rotation basis as per frequency and generation point monitored daily.
- Nitrogen gas tested for gaseous contamination, viable and non-viable contamination.
- Nitrogen gas user point (product contact) having 0.22-micron filter and tested integrity at defined frequency as per respective **SOP**
- SOP is in place for Nitrogen gas routine monitoring at defined frequency Compressed air all user point (product contact) having 0.22-micron filter and tested integrity at defined frequency as per respective procedure.
- Compressed air tested for gaseous contamination, viable and non-viable contamination.

N. Compressed air operational SOP is in place for routine monitoring at defined frequency

O. Manufacturing of Hazardous products:

- Product category evaluated during product introduction to the manufacturing site.
- Material safety details verified during product introduction to the manufacturing site.
- Cleaning performed followed by disinfectant using three bucket trolley to achieve the desire cleaning on dirty surface as disinfectant not work on dirty surface.
- Area and floor cleaning up to the adequate level that it does not generate dry residue of the previous product once the area is dry after cleaning.
- Only trained personnel perform housekeeping activity in the area.
- Procedure for the handling of spillage is in place.

P. Failure Management:

- Trained engineering staffs are involved in the good engineering practices (GEP).
- Procedure for handling of equipment breakdown is in place
- Preventive maintenance program is in place**.**
- Deviation, OOS & investigation procedures are in place to handle the

Q. Ongoing Controls (Identification of Control System/ Process and Operation/ Controls of aseptic processing):

Identification of Control System

- Availability of the method validation assessed during introduction of the product procedure is in place for executing the method validation to ensure reliability, accuracy, preciseness, and robustness of the analytical method.
- Procedure for preparation of specification and method of analysis is available and only approved specifications used for the analysis.
- Testing of intermediate product, including at applicable hold times, to assess bioburden levels intermediate product up to and including the final formulated bulk prior to sterile filtration.
- In addition, in-coming raw materials assessed against the raw material specifications for bioburden using the Microbial Limits Test (MLT) and chemical composition is in place.
- Environmental monitoring (EM) programs is in place to monitor and control the environment and the data is trended, reviewed, and acted upon to ensure the manufacturing operation is under continuous control.
- Suitable locations identified in environmental microbial monitoring plan within the manufacturing operations which provide meaningful data to provide assurance that appropriate environmental conditions were maintained.
- The monitoring locations defined based on, to be close to the action so a review is required of the operations within the manufacturing areas to identify high traffic areas, hot spots, potential dead zones, critical contact surfaces, high traffic areas and surfaces within the cleanroom.
- Environmental monitoring plan has been determined it considerations include:-

  1 Sampling locations (Qualification and Routine).

  2 Frequency of monitoring

  3 Monitoring method (Effective and does not introduce contamination)

  4 Incubation conditions

  5 Historical data and significant changes

  6 Air visualization studies

  7 Trend analysis, Alert and Action levels

- Routine monitoring of cleanrooms, clean air equipment and personnel needs to be performed in operation throughout all critical stages, including equipment set-up.

- An area assessment is performed for critical locations in both at rest and in operational state.
- All samples tested as per written plans supported by rationales to justify sample selection.
- Cleanrooms are classified in terms of the measurement of non-viable particle monitoring, as per ISO-14644.
- Where limits exceeded, investigations conducted using Out of Specification procedures
- For aseptic processing, personnel monitoring is required following critical interventions and on exit from the Grade B area (gloves, gowns, and sleeves).
- One of the key requirements is to really understand the data and to take appropriate actions in the event of increased numbers of alert/ action level breaches or consecutive breaches or changes in the microbial flora within the facility.
- Microbiological testing of finished products performed for the products are manufactured in the facility.

R. Process and Operation:

- All the elastomers /gaskets/ O-rings are made up of food grade materials (Silicon/Teflon).
- All product contact parts are of SS316L.
- Sterile autoclavable paper is used in the aseptic area for the documentation.
- Rubber stoppers used for the process are pre-cleaned / siliconized, which are ready to sterilize.
- Flip off seal are procured from approved vendor.
- The flip off seals are non-product contact and ready to sterilize.
- 03 Piece Vials, Nozzle/Droppers and Caps are procured from the approved vendor that is ready to use.
- Silicon tubing's used are of platinum cured silicon material and established procedure for cleaning/ wrapping of silicon tubing is in place.
- Operation procedure for non-viable particle counter and microbial air sampler is in place for aseptic area and cleans area monitoring.
- Process validation program is implemented for products manufactured in premises.

S. Controls of aseptic processing:

- In aseptic processing facility the filling and sealing line LAF is equipped with UPS to maintain the clean room conditions.
- Barrier technology is used to reduce the critical interventions and maintenance of grade A conditions during the transfer of materials/components. Furthermore, all product and component contact equipments sterilized prior to use. List of authorized allowable interventions is in place, that may occur during production, and all are simulated during aseptic process simulations (media fill) .
- This assessment performed considering of 'worst case' processing parameters that might lead to a microbial contamination event occurring and include vial size, vial neck diameter, line run speed, stoppages and the number and complexity (including time) of personnel interventions.
- Vial Filling Machine and Ophthalmic filling machine is designed to ensure the product sterility is maintained during Aseptic filling and sealing of the Drug Product by preventing microbial and particle contamination. This is achieved by control measures including minimization of operator interventions in Grade-A area. Aseptic processing is ensured by performing all the activities aseptically during the whole processing of drug product.
- Monitoring and control of microbiological contamination of the product periodic verification of the effectiveness of the controls is in place for aseptic processing include a process simulation test (media fill) using a sterile nutrient media .
- Considering further control measure, the duration of each aspect of aseptic preparation and processing defined and validated maximum time, i.e. Hold time of Sterilized equipment and filling time.
- Sterility samples collected from initial, middle and end stage of filling, representative entire filling operations.
- Total sterility test sample quantity to be distributed equality to each stage (Representative of whole batch).
- In case of major intervention during filling (significant intervention which may impact on sterility and part of media fill simulation) after rectification of the problem additional sample shall be collected, marked and sends to QC for sterility assurance respectively.
- Sampling of aseptically filled finished product performed as per respective .
- Analyst qualified for sterility test as per respective SOP and qualified analyst performed the routine sterility test after completion of sterility test qualification.
- Stability study program is in place and stability study of finished products performed as per **SOP No.**

T. Waste Management:

- Separate area and procedure is available for transfer of scrap generated during processing.
- Scrap is always transferred in the closed condition for example, while taking out the scrap bag from the processing room, it is enclosed in the second bag to prevent residue carryover to the scrap movement.
- There is no nearby industry, which produces excessive soot, dust, and smoke, chemical or biological emissions. Hence surrounding area of facility is adequate for pharmaceutical operation.

U. Quality System:

- All applicable QMS elements are in place & in use refer below table:

Sr. No.	Description	Reference Document Title
1	Handling of change in qualified system	Change Control Management
2	Deviations	Deviation management
3	Investigation of incidents and deviations (Root causes analyses) is in place	Failure Investigation and Root Cause Analysis
4	Corrective and Preventive actions (CAPAs) are handled through	Handling of Corrective and Preventive Action
5	Handling of defects received from market	Handling of market complaint
6	Handling of product recall	Product Recall
7	In-house improvement mechanism	Internal Audit Quality Risk Management
8	The Concept of QRM is implemented throughout the organization (SOP)	Quality Risk Management
9	Review and evaluation of QMS data	Quality Management Review
10	Quality Agreements and Vendor Managements	Qualification of Contract Analytical Laboratory Vendor management

- Trending and matrix approach are implemented to evaluate the quality system at defined frequency.
- 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 are in place and governed through respective SOPs.
- Procedure in place to handle the change in any validated and established system/procedure.

- Summarize processes and procedures for continuous improvement are in place to conclude the document subject to periodic review and updates.
- Preparation of reports for evaluation of incidents, deviations, and related CAPAs periodically.
- Risk assessment procedure is in place and follows for the Risk assessments evaluation.

7.0 Summary :

Based on review assessment with respect to contamination control strategy (CCS) against control and mitigation measures using SOPs, design of facility, premises, utility, equipment, personnel, material, cleaning, process, operations, media fill validation, cleaning and disinfection, waste management, failure management and prevention mechanisms effectively and with some associated risk to manufacturing of drug products. Contamination Control Strategy (CCS) is implemented across the facility in order to review of all key elements as part of assessment, it is concluded that the Injection & Ophthalmic (First Floor) is compliant with respect to current Good Manufacturing Practices (cGMP) and is capable to produce sterile drug products. Facility design, Processes, Equipment functionality, Manufacturing activity, Qualification principles, cross-contamination and Methodologies, Pharmaceutical Quality System (PQS), Quality Management System including Testing and Release, Training and qualification system nullified the Potential sources of contamination are attributable to chemical, microbial and cellular debris (e.g., pyrogen, endotoxins) as well as particulate matters (e.g., glass and other visible particulate matters).

8.0 Conclusion:

A media fill shows that a specific aseptic process can run successfully during a test. But that alone doesn't guarantee ongoing sterility assurance. A robust contamination control strategy (CCS) brings together facility design, utilities, cleaning & disinfection, personnel flow, EM monitoring, training, validation, and risk management into one living system. Under regulatory scrutiny, the question isn't just "did the media fill pass but "does the whole system prevent, detect, and respond to contamination risks reliably So, the conclusion is that a successful media fill demonstrates process capability, but an effective CCS demonstrates sustained contamination control. In short, keep the CCS as a risk-based, continuously improved program where media fill is one important verification tool.

9.0 References:

- ✓ EU GMP Annex: 1 2022.
- ✓ FDA Aseptic Processing Guide (2004)
- ✓ PIC/s Guide to Good Practices for the Preparation of medicinal Products.
- ✓ Quality Risk Management (QRM) ICH Q9.
- ✓ Contamination Control Strategy Development in Pharmaceutical Manufacturing (PDA Technical Report No. 90)