STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Validation of Air Filtration System	**Effective Date:**
Supersedes: Nil	**Review Date:**
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1.0 OBJECTIVE:

To lay down a Procedure to define the Standard Operating Procedure for "Qualification of Air filtration system".

2.0 SCOPE:

2.1 This SOP is applicable for Qualification of Air filtration system at …….

2.2 This SOP is applicable for Validation of HVAC unit.

2.3 This SOP is also applicable to Validation of HEPA unit installed in the Equipment such as (Laminar air flow units, sterile garments cabinets, Dynamic pass box, but not limited to).

3.0 RESPONSIBILITY :

3.1 Quality Assurance shall be responsible for:

3.1.1 Executive QA shall be responsible for preparation of validation protocol.

3.1.2 Head QA shall be responsible for review of validation protocol & Report

3.1.3 Executive QA shall be responsible for review of calibration certificates of measuring Instruments received from external agency.

3.1.4 Executive QA shall provide the guidance during execution of validation activity.

3.1.5 Preparation of validation report after execution of validation activity.

3.2 Head-EG/designee shall be responsible for:

3.2.1 Arrange the External Agency to performed validation activity

3.2.2 Review of validation protocol and report of Air Filtration systems.

3.2.3 Co-ordination with external agency and user departments to execute the validation activity.

3.2.4 Ensuring the Online data recording required for the report compilation during validation.

3.3 Head/Designee MF, WH, QC shall be responsible for:

3.3.1 Concerned department head shall be responsible for review of validation protocol and report of Air Filtration system.

3.3.2 To provide support in execution of validation activity.

3.4 Head Quality/Designee shall be responsible for approval of validation protocol and report.

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4.0 ACCOUNTABILITY:

Head-Quality shall be accountable for ensuring over all compliance of this Standard Operating Procedure.

5.0 DEFINITIONS:

5.1 **As-built:** Condition where the installation is complete with all services **c**onnected and functioning but with no production equipment, materials, or personnel present.

5.2 **At-rest:** Condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

5.3 **Operational:** Condition where the installation is functioning in the specified manner, with the specified number of personnel present and working (Simulated for working) in the manner agreed upon.

5.4 **Clean zone:** Dedicated space in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the zone, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary.

5.5 **Clean room:** Room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary.

5.6 **Particle :** Solid or liquid object which, for the purposes of classification of air cleanliness, falls within a cumulative distribution that is based upon a threshold (lower limit) size in the range from 0.1 mm to 5 mm.

5.7 **Particle size:** Diameter of a sphere that produces a response, by a given particle-sizing instrument that is equivalent to the response produced by the particle being measured.

NOTE: For discrete-particle-counting, light-scattering instruments, the equivalent optical diameter is used.

5.7.1 **Aerosol generator:** instrument capable of generating particulate matter having appropriate size range (e.g. 0.05 µm to 2 µm) at a constant concentration, which may be produced by thermal, hydraulic, pneumatic, acoustic or electrostatic.

5.7.2 **Test aerosol:** Gaseous suspension of solid and/or liquid particles with known and controlled size distribution and concentration.

5.7.3 **Ultrafine particle:** Particle with an equivalent diameter less than 0.1 mm.

5.7.4 **Macro particle: P**article with an equivalent diameter greater than 5 mm.

6.0 PROCEDURE:

6.1 Validation of the Air filtration system includes following test parameters:

- Air velocity (ACPH) measurement
- HEPA Filter Integrity Test
- Air flow pattern test (Smoke test)
- Non-viable particulate counts measurement
- Recovery test
- Pressure Differential Monitoring
- Temperature and Relative Humidity monitoring
- Viable Particle count (Active & Passive air sampling)

6.2 All the test shall be done as per given Annexure-I and accordingly protocol & report shall be prepared.

6.3 Air velocity (ACPH) measurement:

6.3.1 The objective of this test is to demonstrate that:

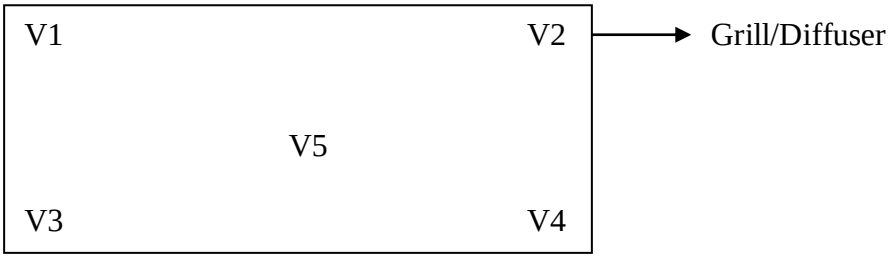
6.3.1.1 The air system is balanced and capable of delivering sufficient air velocities to maintain a minimum cross sectional velocities as per design.

6.3.1.2 To demonstrate that the number of air changes are equal to or more than the designed number of air changes and should not be less than designed number of air changes

6.3.1.3 The air velocity and air changes test shall be performed by qualified and trained person only.

6.3.1.4 Measuring instrument being used shall be calibrated with reference to NPL traceable reference standard.

6.3.1.5 Measure the air velocity by taking five reading at approx 6" distance, (i.e. at four corners and one at centre), with calibrated anemometer below the grill / diffuser by selecting anemometer in feet per minute.



6.3.1.6 Calculate the average velocity of each grill present in room as per below mention formula:

$$\text{Average Velocity} = \frac{V1+V2+V3+V4+V5}{5}$$

6.3.1.7 Calculate the CFM of each grill by as per below mention formula:

CFM = Average velocity X Face area of grill (Length X width)

6.3.1.8 Calculate the room volume in Cubic Feet as per below mention formula.

Volume= Length (in ft) x width (in ft) x Height (in ft)

6.3.1.9 Calculate the Air change per hour of particular cubical by using below formula.

$$\textit{Air changes per hour} = \frac{\textit{Total CFM of the room} \times 60}{\textit{Volume of the room in } ft^3}$$

6.3.1.10 Acceptance criteria:

6.3.1.10.1 Air Changes per hours for a clean rooms as per given below

ISO class	ISO-6	ISO-7	ISO-8
Acceptance criteria for ACPH	NLT 60	NLT 40	NLT 20

6.3.1.10.2 Average velocity should be 90±20% feet/min for equipment like Pass box, sterile cabinet, LAF, dispensing & Sampling booth.

6.4 HEPA Filter Integrity Test:

6.4.1 The objective of HEPA filter integrity test is to ensure that the HEPA filters installed are not damaged during, transit, installation or operation and fixed properly inappropriate place such that there is no leakage in the filter and periphery.

6.4.2 The filter integrity test shall be performed by qualified and trained person only.

6.4.3 Measuring and testing instrument being used shall be calibrated with reference to NPL traceable reference standard.

6.4.4 Filter testing shall be performed after measuring the air velocities of that supply.

6.4.5 Poly Alpha Olefin (PAO) shall be used for the generation of particles/fumes. MSDS of the same shall be provided by the external agency.

6.4.6 Position the aerosol generator such that aerosol is produced into the upstream of the subjected HEPA filter.

6.4.7 Provide Compressed air to the fume generator at pressure of 1.5-2 kg/cm^2.

6.4.8 The fume concentration shall be in between 20 mg/m^3 to 80 mg/m^3. (Calibrate upstream conc. up to 100% scale).

6.4.9 Actual fume concentration shown in aerosol photometer shall be recorded.

6.4.10 Select the downstream scanning mode for the control panel. Scan the subjected HEPA filter by holding the photometer probe approximately 1 inch from the filter face and passing the probe in the slightly overlapping strokes, at rate of NMT 15 cm^2/s, so that entire filter face is sampled.

6.4.11 Similarly scan the entire periphery of the filter along the bond between the filter medium and frame and along all other joints in the installation through which leakage might by pass.

6.4.12 **Acceptance Criteria:** The leakage through HEPA filter should not be more than 0.01%.

6.5 Non-Viable Particle count measurement:

6.5.1 The objective of this test is to demonstrate that the critical work stations within the clean rooms / equipments comply with their designed conditions or the cleanliness class as per the ISO standard 14644-1 & EU–cGMP.

6.5.2 The particle count test shall be performed by qualified and trained person only.

6.5.3 Measuring instrument being used shall be calibrated with reference to NPL traceable reference standard.

6.5.4 Particle count shall be performed at rest condition & in operation condition.

6.5.5 Operation condition shall be simulated during the particle count sampling if no such activity is performing in area.

6.5.6 Ensure that the sampling locations are evenly distributed throughout the area of the clean room.

6.5.7 Selection of sampling location for non viable particle count with justification shall be prepared as Annexure- III and also Schematic diagram of the sampling location shall be prepared as per annexure-IV.

6.5.8 Minimum sampling time for each location shall be 1 minute. The sampling probe shall be positioned at working level and air flow probe shall be directed vertically upward (Take sampling volume as per ISO 14644-1).

6.5.9 Switch "ON" the particle counter and set the particle size channel at 0.5 micron and 5 micron and set sampling time as per sample volume calculation (Take sampling volume as per ISO 14644-1).

6.5.10 Hold the airborne particle counter and then take print of test.

6.5.11 While taking the room particle count, the isokinetic probe shall be positioned at the height of working activity (30" to 40") above the floor.

6.5.12 Minimum 3 samples shall be taken in case of low volume equipments i.e. pass box, sterile cabinets etc.

6.5.13 **Acceptance Criteria:** All the clean rooms should comply as per the designed Class in rest and in operation condition.

S.No.	EU -cGMP	Limit for non viable particle count monitoring for clean room.		
		Particle size	Acceptance criteria (At Rest)	Acceptance criteria (In operation)
1.	Grade- A	≥ 0.5 µ Particle	3520	3520
		≥ 5.0 µ Particle	20	20
2.	Grade- B	≥ 0.5 µ Particle	3520	352000
		≥ 5.0 µ Particle	29	2,900
3.	Grade- C	≥ 0.5 µ Particle	352000	3520000
		≥ 5.0 µ Particle	2,900	29,000
4.	Grade- D	≥ 0.5 µ Particle	3520000	ND
		≥ 5.0 µ Particle	29,000	ND

6.6 Recovery Test

6.6.1 For Non-Viable particle count:

6.6.1.1 The objective of the recovery test is to determine the amount of time that is necessary for clean rooms or clean spaces or equipment and their systems to reach a specified steady state cleanliness level after a brief particle generation event within the clean space.

6.6.1.2 The recovery test shall be performed by qualified and trained person only.

6.6.1.3 Measuring instrument being used shall be calibrated with reference to NPL traceable reference standard.

6.6.1.4 Locate the particle counter in the highest particle count location at rest condition identified in particle count test and take the reading before switch off the equipments / HVC of the room.

6.6.1.5 Immediate Switch off Equipment/ HVC of the room under test and adjacent rooms.

6.6.1.6 Generate the particles 100 times multiply with the normal limit with the help of Aerosol generator.

6.6.1.7 Take particle count reading in HVC/Equipment OFF condition and when limit exceed the 100 times then turn on the HVC/Equipment for ensuring the recovery of Particle count (beyond the limit as per the designed ISO class).

6.6.1.8 Record the time taken for particles to drop from initial to the base line level obtained in unmanned conditions.

6.6.1.9 **Acceptance Criteria:** Recovery time shall be established in order to ascertain the time required to switch on the air handling device prior to start of work or not more than 15 minutes.

7.0 Air flow pattern test (Smoke test):

7.1.1 The objective of this test is to ensure that the air flow pattern in the classified areas is uniform, unidirectional and is evenly distributed; there should not be any turbulence in the air.

7.1.2 Air flow pattern test shall be done as per below mentioned procedure.

7.1.3 The Air flow pattern test shall be performed by trained and qualified person only.

7.1.4 This test shall be carried out by using fog generator used to generate aerosols (mist), utilizing phase transition between gases to liquid by cooling steam boiled DI water.

7.1.5 Place the probe near to supply air terminal and return riser and record the air flow pattern with the help of video camera.

7.1.6 To record the flow of air between two rooms by placing the probe at the door entrance and see the direction of the fog into or out of the room.

7.1.7 Track the fog direction and record the observation with help of video camera and save in the compact disc as a backup.

7.1.8 Acceptance Criteria:

7.1.8.1 Fog should flow through these critical areas in unidirectional pattern. If the fog return or back flow due to turbulence, system cannot be accepted and must be rebalanced or readjusted.

7.1.8.2 There should not be any short-circuiting of airflow; dead pocket and flow of air should be unidirectional from supply to return.

7.1.8.3 Fog should flow from high-pressure zone to low-pressure zone.

7.2 Pressure Differential Monitoring:

7.2.1 The objective of this test is to demonstrate that the HVC system/ equipment are capable of maintaining the desired designed differential pressure to avoid flow reversal to avoid contamination and cross contamination.

7.2.2 This test shall be applicable for area where monitoring of differential pressure is required

7.2.3 The differential pressure monitoring shall be performed by trained person only.

7.2.4 Measuring instruments being used shall be calibrated.

7.2.5 Operate the HVAC system about 24 hrs. prior to performing these tests in order to stabilize the system.

7.2.6 To avoid unexpected changes in pressure and to establish a baseline, all doors in the aseptic facility must be closed and no traffic is to be allowed through the facility during the test.

7.2.7 Record the pressure differentials of all rooms after every 2 hours for 3 Days.

7.2.8 **Acceptance Criteria**: The Pressure differential of all the areas / equipments shall be within limit as applicable.

7.3 Temperature and Relative Humidity Monitoring:

7.3.1 The objective of this test is to demonstrate that the HVAC system is capable of maintaining room conditions i.e. temperature and relative humidity as per the designed room conditions.

7.3.2 This test shall applicable for that room where temperature and RH monitoring is required.

7.3.3 This test shall not applicable for Air filtration system like pass box, sterile cabinets, air shower, LAF, dispensing and sampling booth.

7.3.4 HVAC system should be in running condition at least from last 24 hrs. All lights in the subjected room should be kept on during the testing as well as during the pre-conditioning period.

7.3.5 All doors in the facility must be closed and the test should be carried at rest condition.

7.3.6 Measure and record the temperature and RH for three days with frequency of every Two hour.

7.3.7 **Acceptance Criteria:** Temperature shall be NMT 25°C and Relative Humidity shall be NMT 55% (or as per requirement)

7.4 Viable particle Count (Active & Passive air sampling):

7.4.1 Viable particle count by Settling Plate Method:

7.4.1.1 The objective of this test is to demonstrate that the clean room and the critical work stations within the clean rooms comply with their designed conditions by settling plate method.

7.4.1.2 The microbial count testing shall be performed by trained person only.

7.4.1.3 Measuring instruments being used shall be calibrated.

7.4.1.4 Check the microbial count at rest & in operation condition continues 03 days.

7.4.1.5 Inform the manufacturing pharmacist regarding plate exposure activity before commencing the activity. Enter in the clean area and clean the containers with 70 % IPA then remove the plates from the container, mark number to the sterile pre-incubated Soya bean casein digest agar (SCDA) plates and expose the plates at all locations for 4 hours on the plate exposure stand. **Incubate the exposed plates along with positive and negative controls at 20-25 °C for 72 hours and followed by 30-35°C for 48 hours. After completions of incubation period record the colony forming units (CFU) per plate in the formats.** After completion of incubation period, count the number of colonies on each agar plate and record.

7.4.2 Viable particle count by Air Sampling Method:

7.4.2.1 The objective of this test is to demonstrate that the clean room and the critical work stations within the clean rooms comply with their designed conditions by Air sampling method.

7.4.2.2 The microbial count testing shall be performed by trained person only.

7.4.2.3 Measuring instruments being used shall be calibrated.

7.4.2.4 Check the microbial count at rest & in operation condition continues 03 days.

7.4.2.5 Inform the manufacturing pharmacist regarding plate exposure activity before commencing the activity. Enter in the clean area and clean the containers and air sampler with 70 % IPA then remove the plates from the container, mark number to the sterile pre-incubated Soyabean casein digest agar (SCDA) plates and at the location of air sampling open the top lid of pre incubated SCDA plate immediately remove the aluminum foil of perforated sieve and set it with head of air sampler over the SCDA plate. Vertically put the air sampler at the location and carry out the air sampling of 1000 liter.

7.4.2.6 Incubate the exposed plates along with positive and negative controls at 20-25^{o}C for 72 hours and followed by 30-35^{o}C for 48 hours. After completions of incubation period record the colony forming units (CFU) per plate in the formats. After completion of incubation period, count the number of colonies on each agar plate and record

7.4.2.7 Acceptance Criteria:

Grade	Recommended Limits for microbial contamination	
	Active air Sampling (CFU/m^3)	**Settle Plate (Diameter 90 mm) CFU/4 Hours**
Grade A	<1	<1
Grade B	NMT 10	NMT 5
Grade C	NMT 100	NMT 50
Grade D	NMT 200	NMT 100

7.5 Revalidation Criteria: Re-Qualification of Air filtration system shall be performed under the following conditions**:**

7.5.1 The Air Filtration system is not performing well within the pre-defined acceptance criteria.

7.5.2 If any of the test results are not within the limits defined in the acceptance criteria.

7.5.3 The revalidation Schedule of the test parameters shall be defined as annexure-IV.

7.5.4 If any major modification/change in facility.

7.5.5 If any of the critical components of air filtration system is replaced due to technical problem.

7.5.6 Any revalidation trigger through change control.

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8.0 ABBREVIATION:

SOP	Standard Operating Procedure
QA	Quality Assurance
HVAC	Heating Ventilation air conditioning
HEPA	High Efficiency Particulate Air
%	Percent
Mg	Milligram
CFM	Cubic Feet per minute
ft^3	Cubic feet
CFU	Colony Forming Unit
RH	Relative Humidity
QC	Quality Control
MF	Manufacturing
EG	Engineering

9.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Revalidation Frequency	
Annexure-II	Justification for selection of sampling location for non-viable particle count	
Annexure-III	Schematic Diagram: Sampling Location for Non viable count.	

10.0 DISTRIBUTION DETAILS:

- ☐ Master Copy Quality Assurance Department
- ☐ Controlled Copy No. 01 Quality Assurance Department.
- ☐ Controlled Copy No. 02 Quality Control Department.
- ☐ Controlled Copy No. 03 Production Department.
- ☐ Controlled Copy No. 04 Engineering Department.
- ☐ Controlled Copy No. 05 Warehouse Department (Store).

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11.0 REFERENCE:

- PIC's "Manufacture of sterile medicinal Products" Annexure-1,
- ISO 14644 PART I, II & III.
- EU Guideline Annexure-1,
- In-house

12.0 REVISION HISTORY

Revision No.	Change Control No.	Details of Changes	Reason of Changes	Effective Date	Done By
00	Not Applicable	Not Applicable	New SOP		

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ANNEXURE- I

REVALIDATION FREQUENCY

S.No.	Test	Frequency
1.	HEPA Filter Integrity Test (By using poly alpha olefin)	12 months ± 30 days
2.	Air velocity (ACPH) measurement	6 months ± 30 days
3.	Air flow pattern test (Smoke test)	24 months ± 30 days
4.	Nonviable particulate counts measurement	12 months ± 30 days (FOR ISO CLASS 8) 6 months ± 30 days (FOR ISO CLASS 5, 6,7)
5.	Recovery test	12 months ± 30 days
6.	Pressure Difference*	During Area Qualification / as per routine monitoring.
7.	Temperature and % Related Humidity*	During Area Qualification / as per routine monitoring.
8.	Viable Particle count*	During Area Qualification / as per routine monitoring.

Note '*' are tests to be performed on routine/regular basis as per frequency specified in the respective SOP and at the time of Qualification and Re-Qualification activities.

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ANNEXURE-II

JUSTIFICATION FOR SELECTION OF SAMPLING LOCATION FOR NON-VIABLE PARTICLE COUNT

HVAC No.	Room Name	ISO Class	Area in Square Meter (A)	No. of Location for non-viable Count (√A)	Identified Total Location	Considered No of locations	Location	Location details	Justification

Prepared By	Reviewed By	Approved By
Quality Assurance	Quality Assurance	Quality Assurance

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ANNEXURE-III

SCHEMATIC DIAGRAM: SAMPLING LOCATION FOR NON VIABLE COUNT

Name of the Room/Equipment.: _____

Room/Equipment ID.: _____