	PHARMAGUIDEHUB		
DOCUMENT NO.	AREA QUALIFICATION PROTOCOL	EFFECTIVE DATE	
XXXXXXX		REVISION No.	00

AREA QUALIFICATION PROTOCOL

PHARMAGUIDEHUB

Location

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1.0 APPROVAL OF PROTOCOL:

Prepared By:

FUNCTIONAL AREA	NAME	SIGNATURE	DATE
QUALITY ASSURANCE			

Reviewed By:

FUNCTIONAL AREA	NAME	SIGNATURE	DATE
HEAD - PRODUCTION			
HEAD - QUALITY CONTROL			
HEAD - ENGINEERING			

Approved By:

FUNCTIONAL AREA	NAME	SIGNATURE	DATE
PLANT HEAD			
HEAD – QUALITY			

2.0 OBJECTIVE:

The objective of this protocol is,

- To evaluate and qualify the Controlled area for the manufacturing of product classified according to requirement of the environment.
- To provide a high degree of assurance that the controlled area are working/maintained as per the design specification.
- To ensure the cleanliness level of area as per intended purpose of operation in that area.

3.0 SCOPE:

This protocol is applicable to monitor the area of oral facility prevails at {Company Name}, {Location}.

4.0 RESPONSIBILITIES:

4.1 Quality Assurance:

4.1.1 To prepare qualification protocol

4.1.2 To review qualification protocol for its technical adequacy

4.1.3 To issue the copy of protocol for execution

4.1.4 To monitor the qualification activities

4.1.5 To ensure the qualification activities are carried out as stated in the protocol

4.1.6 To compile and review the data of qualification

4.1.7 To certify and approve the qualification of area

4.1.8 To approve the qualification protocol and report

4.2 Engineering:

4.2.1 To assist QA in the preparation of protocol to define the parameters

4.2.2 To calibrate the instruments, pressure gauges and measuring devices

4.2.3 To execute the qualification protocol

4.2.4 To provide utilities during area qualification

4.2.5 To review the qualification protocol and report

4.3 Production:

4.3.1 To review the qualification protocol

4.3.2 To execute the qualification protocol

4.3.3 To clean and sanitize the area

4.3.4 To monitor the temperature, relative humidity and differential pressure

4.3.5 To monitor the non-viable particle count.

4.3.6 To provide the monitoring data for compilation.

4.4 Quality Control:

4.4.1 To assist QA in the preparation of protocol to define the parameters

4.4.2 To review the qualification protocol

4.4.3 To Microbiological monitoring as per sampling plan

4.4.4 To record the monitoring data

4.4.5 To provide the monitoring data for compilation

4.5 Plant Head and Head - Quality:

4.5.1 To approve the qualification protocol & report

4.6 Qualification Team:

The following personnel from various functional areas shall be identified for the execution of qualification protocol.

DEPARTMENT	NAME	DESIGNATION	SIGNATURE/ DATE
Quality Assurance			
Production			
Engineering			
Quality Control			

5.0 PRE-REQUISITES FOR AREA QUALIFICATION:

5.1 Calibration review of Instruments:

Calibration status of magnehelic gauges/digital pressure indicator, Temperature and relative humidity monitoring devices, Non-viable Particle counter and other instruments used for testing/monitoring shall be verified prior to startup of activity and recorded in below Table.

Table No: 5.1 Calibration Status of Instruments

Name of Instruments	ID. No./sr. no.	Calibration status	
		Done Date	Due Date

Remarks:

……

……

……

Checked By/Date: **Verified By/Date:**

6.0 METHODOLOGY FOR QUALIFICATION:

HVAC Validation Plan includes following test parameters

6.1 Non-viable particulate count test(Annexure-1)

6.2 Air Velocity measurement & ACPH(Annexure-2)

6.3 HEPA filter leak testing (Annexure-3)

6.4 Monitoring of Differential pressure (Annexure-4)

6.5 Particle Recovery study(Annexure-5)

6.6 Cleaning and Sanitization of Area(Annexure-6)

6.7 Air Flow Pattern (Annexure-7)

6.1 Air Velocity Measurement

Objective: To determine that required air velocity is delivered by HEPA filters to controlled the space as per the design specification for normal mode of operation.

Acceptance criteria:

Test Parameter	Acceptance criteria
For Air velocity	For Process Air Unit Velocity NLT 90 FPM
For CFM	HEPA filters Size 24”X24” CFM should be NLT 305
	HEPA filters Size 12”X12” CFM should be NLT 65

Frequency: Every Six month

Procedure:

6.1.1 Switch on the respective Air Handling unit of clean room

6.1.2 Ensure that AHU is operated at least 10 to 15 minute.

6.1.3 Take the relevant details like, filter no, room no etc.

6.1.4 Switch on the Calibrated anemometer; check the zero reading on display.

6.1.5 Hold the velocity measurement probe at 150 to 300 mm below the filter face of HEPA in clean room.

6.1.6 Measure the velocity at different points of filter face i.e. four at corner and at center.

6.1.7 Calculate the average velocity in report. Attach report

6.1.8 Calculate the volume delivered per minute as follow;

Volume of Air delivered per cubic foot per minute= Avg. air velocity in foot/min X area of the terminal in ft^2

6.1.9 Measure the airflow volume directly from each terminal HEPA filter by using electronic Barometer (Air Flow Hood) at downstream of filter and reading lodged in CFM.

6.2 Verification of Air changes:

Objective: To determine that AHU system is delivered the required quantity of air changes for the controlled area as per the design specification for normal mode of operation.

Acceptance criteria

Test Parameter	Acceptance criteria
Air changes per hour (ACPH)	As per design sheet (Refer annexure)

Frequency: Every Six month

Procedure:

6.2.1 Measure the air volume delivered per hour at all supply terminals within the room.

6.2.2 Measure the airflow for all rooms serviced by AHU.

6.2.3 Sum up air volumes delivered in hour to each room service by AHU.

6.2.4 Calculate the room volume as follow;

Volume = Length (in ft.) X width (in ft.) X Height (in ft.)

6.2.5 Sum up the volume of all room serviced by AHU in ft3

6.2.6 Calculate the number of air changes as follows;

No of Air changes per hour= Total CFM X 60 /Total volume (in ft^3)

6.2.7 Record the number of air changes.

6.3 HEPA filter leak testing

Objective: To confirm that the HEPA filter system is properly installed and that leaks have not developed during use. The test verifies the absence of leakage, relevant to the cleanliness performance of the installation. The test is a leak test of the complete filter installation comprising the filter media, frame, gasket and grid system.

Acceptance criteria

Test Parameter	Acceptance criteria
HEPA filter Integrity Test	Downstream leakage of equal or greater than 0.01% of upstream concentration is unacceptable

Frequency: Once in a Six month

Procedure:

6.3.1 Verification of HEPA filter integrity test performed in accordance with the air generated aerosol and aerosol photometer down steam filter scan test method.

6.3.2 The aerosol generator with the lask in nozzles the means droplet size of aerosol shall be typically between 0.5 µ to 0.7 µ.

6.3.3 Generation of PAO

- Check the PAO of Emery-3004 level in Aerosol generator.
- Connect compressed air /Nitrogen gas to aerosol generator and adjust the pressure through pressure regulator.
- Direct the outlet of the aerosol generator to fresh air intake duct of AHU through the aerosol port.
- Start the aerosol generator by start the compressed air/Nitrogen gas to produce the upstream concentration required for leak test detection till the photometer reading crosses the 20% then set this as reading as photometric concentration of 100%. Using internal calibration button.

6.3.4 Calibration of photometer

- Put the photometer selector switch on upstream concentration.
- Connect the tube of photometer to upstream port of HEPA filter.
- Wait until the photometer display 20-80% reading for upstream concentration then set this reading as 100 % concentration using internal calibration button.
- Remove the tube of photometer and close the upstream port of HEPA filter and ensure for zero leakage.
- Put the photometer selector switch on downstream mode.
- Wait until photometer display 0 (Zero).

6.3.5 Testing Procedure:

- Ensure before starting the activity AHU is in operation for 10-15 min.
- Ensure that the Air velocity, Air balancing and air flow adjustments are done before proceeding to the filter integrity testing of HEPA filters.

- Check that a Sampling point is provided and accessible immediately upstream of the filter to be tested.
- Start the compressed air/Nitrogen gas to aerosol generator to generate the aerosol at minimum 20 PSI and monitor the pressure.
- Introduce the aerosol of Emery-3004 into the supplied HEPA filter, Ensure that uniform challenge concentration at each of the HEPA filter being exposed at the same time.
- Put the photometer selector switch on upstream mode.
- Measure the upstream aerosol concentration immediately using the linear photometer scale.
- For linear read out photometer, stabilize the upstream concentration using laskin nozzle, adjust to read 20 to 80 microgram/m3 of air in upstream concentration.
- Adjust the photometer displays zero.
- After getting the upstream concentrations put selector switch to clear position and close upstream port.
- Put photometer selector switch on downstream position.
- Wait until photometer display zero.
- Hold the photometer scale about 3 cm from the filter face, on the filter gasket joining area scan entire surface area of filter, filter gasket joining area perimeter in jointly overlapping stroke at a transfer rate (sr) of approximately 15/Wp cm/s.
- Where ‘Wp’ = Probe dimension perpendicular to the scan direction, expressed in cm.
- The probe transverse scan rate when using a 3 cm X 3 cm square probe should not exceed 5 cm/s. With a rectangular probe, the maximum area scan rate should not exceed 15 cm2/s
- Report all the leaks which exceed the 0.01 % of the upstream challenge aerosol concentration.l

- Check the upstream concentration of individual HEPA filter prior to scanning the filter face for leakage. The upstream concentration from filter to filter should not vary from more than 15%.
- If there is leak in HEPA filter replace it, if there is leak in gasket frame are re tight it for with food grade silicone sealant (RTV sealant).
- Record the observations and results in report

6.4 Air Flow pattern test

Objective: To determine that Air flow pattern of terminal HEPA filters and laminar air flow. The controlled area as per the design specification for normal mode of operation.

Acceptance criteria

Test Parameter	Acceptance criteria
Air flow pattern of HEPA filter	Turbulent
Air flow Pattern (Area)	As per Differential pressure (Positive pressure to negative Pressure side)

Frequency: Once in Two Year

Procedure:

6.4.1 Ensure that AHU in operation.

6.4.2 Ensure in to the area of which AHU air flow pattern is to be checked as per standard operating procedure for entry and exit.

6.4.3 Use the Glycol for generation of smoke.

6.4.4 Switch on the fogger machine to generate the smoke.

6.4.5 Hold the smoke generating stick below the supply HEPA filter and ensure the flow pattern of smoke in the area.

6.4.6 Observe the smoke pattern to ensure that the smoke generated is diffuses uniformity at supply grill through the return air dust.

6.4.7 Observe the smoke pattern to ensure the pressure differential of each area at opening and closing of doors.

6.4.8 The air flow pattern should be within specification.

6.4.9 Record the air flow pattern by video shooting or take photos and attached with protocol.

6.5 Monitoring of Differential Pressure

Objective: To determine that AHU system is capable to maintain the pressure gradient across room as per the design specification of room.

Acceptance criteria

Test Parameter	Acceptance criteria
Differential Pressure of rooms	As per design

Test Procedure:

6.5.1 Ensure that AHU system is in operation condition and system is stabilized.

6.5.2 Restrict the movement of persons to avoid the unexpected changes in differential pressure due to opening and closing of door.

6.5.3 Use the calibrated magnehelic gauge; measure the pressure differential after the final air balance and pressure is achieved.

6.5.4 Measure the differential pressure in full operation after allowing sufficient time for stabilization of AHU system.

6.5.5 Adjust to magnehelic gauge to give a reading of Zero in accordance with the manufacturer instruction.

6.5.6 Connect one end of tube in area of higher pressure side of magnehelic gauge and place other end of tube in area of higher pressure side.

6.5.7 Connect one end of second tube to lower pressure input side of the magnehelic gauge and place the other end of the tube in area of lower pressure.

6.5.8 Record the pressure difference across the room at every 02 hour time interval frequency for three consecutive days.

6.5.9 Record the result in report

6.6 Non-viable particle count :

Objective: To establish that area meets with the respective standard of class with respective nonviable particle count.

Acceptance criteria

Classification of clean room with maximum permitted number of particles per m^3				
Grade	Particle count - At rest(©)		Particle count - At Operation(Δ)	
	≥ 0.5 µm	≥ 5 µm	≥ 0.5 µm	≥ 5 µm
D	3520000	29000	Not Defined	Not Defined

Test Procedure:

6.7.1 Ensure that HVAC system is in operation and all the systems that can affect the class of area are working.

6.7.2 Calculate the no. of sampling location as per ISO 14644-1. Refer below table

Area of cleanroom (m^2) Less than or equal to	Minimum number of location to be tested (NL)
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
68	12
64	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
500	26
1000	27
>1000	Equation A

Equation A ----- $N = 27 \left[\frac{Area}{1000} \right]$

[Reference is made in **Annexure-2** for particle count sample location]

6.7.3 The sampling point should be evenly distributed throughout the area of clean room at the working height. layout diagram of particle count monitoring location.

6.7.4 Sampling will be conducted for three consecutive days in at rest condition.

6.7.5 In at rest condition equipment will be in place but persons will be absent.

6.7.6 Carry out the sampling not more than one foot away from the work site, with in the airflow, upstream of the airflow.

6.7.7 Particle count test for all critical/controlled AHU's should be carried out.

6.7.8 Establishment of sampling volume at signal location.

- Grade C and Grade D volume should be not less than 1 cubic feet.

- At each location, sample a sufficient volume of air that a minimum of 20 particle would be detected if the particle concentration for the largest considered particle size where at the class limit for the designated ISO class
- The signal sample volume 'Vs' per location is determined by using equation

$$Vs = \frac{20}{Cnm} \times 1000$$

Where Cnm is maximum number of permitted airborne particle concentration of that area as per designated ISO class/Grade.

6.7.9 Particle counting at each location:

- Switch on the AHU and let the system stabilize for 10 to 15 minute.
- Hold the particle count probe at working height at different location of controlled area.
- Run the particle count as per the standard operating procedure for portable particular counter.
- Switch out the particle counter.
- Perform the particle count monitoring activity as per SOP, collect the printouts of particle count data and attach with report.
- Record the observation and results in report
- Particle count test for all the controlled/critical room under AHU to be carried out once in a six month or immediately after any major change in AHU system.

6.7 Particle recovery study:

Objective: To determine the recovery period of HEPA filters installed in critical areas.

Acceptance criteria

Test Parameter	Acceptance criteria
Recovery period	NMT 15 minute

Frequency: Once in two year

Test Procedure:

6.8.1 Ensure that differential pressure within limit.

6.8.2 Set up the particle counter to initiate the measurement.

6.8.3 Place DPC probe at the testing point. The probe shall not be place directly under the air outlet.

6.8.4 Perform the particle counting in clean area before distribution the area for recovery study at rest condition to evaluate the status of area as per design.

6.8.5 The sample volume should be 1 CFM.

6.8.6 Artificial contaminate the area using aerosol. The particle size used in this method shall be less than 1 µ.

6.8.7 Raise the initial particle concentration to 100 times the initial cleanliness level.

6.8.8 Commence the measurement at 1 minute interval note the time when particle concentration reaches 100 times target concentration threshold (t_{100n})

6.8.9 Note the time when the particle concentration reaches at the target cleanliness level (t_n).

The 100:1 recovery time is presented by ($t_{0.01}$) = (t_n-t_{100n})

6.8.10 Carry out the same procedure for other measuring points of clean room and calculate the recovery time for clean room.

6.8.11 Record the results in report

6.8 Cleaning and Sanitization of Area

Objective:

To ensure the cleanliness of area after the installation or major renovation of AHU system.

Procedure:

- After complete renovation of AHU system or after installation of new AHU system in the area, run the AHU in normal mode condition.
- Clean and sanitize the area with qualified disinfectant which is under renovation as per SOP "Cleaning and sanitization of production area after any major renovation"
- Record the cleaning and sanitization record.

7.0 List of Annexure and Attachments:

Annexure No.	Title of Document
1	Non-Viable Particle Count
2	Air velocity and ACPH calculation report.
3	HEPA Filter leak testing
4	Monitoring of Differential Pressure
5	Particle Recovery Study
6	Cleaning and Sanitization of area
7	Air Flow Pattern

8.0 DEVIATION RECORD:

Report and any deviation from the acceptance criteria or from protocol instruction in the table.

Record the total number of deviations reported during the qualification activity of this protocol.

Record the deviation number and title in the bellow given table. Include all deviations report.

Indicate the status of each variance as 'Closed' only when the deviation is resolved.

Deviation Number	Deviation Title	Status

Remarks:……
……
……

Checked By/Date: **Verified By/Date:**

9.0 SUMMARY AND CONCLUSION:

Our Knowledge Sharing Platform:

To get regular updates on pharmaceutical industry you can join us at our following knowledge sharing platforms:

- Web address: www.pharmaguidehub.com
- Telegram Link: https://t.me/pharmaguidehub
- LinkedIn: www.linkedin.com/in/pharmaguidehub
- Facebook Page Link: https://www.facebook.com/profile.php?id=61557224322551
- Twitter Link: https://x.com/pharmaguidehub
- WhatsApp Group Link: https://chat.whatsapp.com/HY09XT4iEL07oCE4Am3JUW