Cleanroom Validation: An Indian Perspective

Cleanroom in a pharma manufacturing facility

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Introduction

A Cleanroom is designed to meet URS (User Requirement Specifications). In the early days, Cleanroom validation in India consisted of

a) Velocity test
b) Cold DOP test
c) Particle count
d) Pressure differential test

No set standards were followed, and casual references were made to *US FED STD 209 A, B, C & E*. Over the years, with India becoming the pharmacist to the world, the scenario has changed and testing agencies follow stringent norms like *ISO 14644-1999, EUGMP-2008, Schedule M* (Government of India) and *IEST-RP-CC006*. The old warhorse *FED STD 209* E was withdrawn on 29th November 2001.

The recommended tests for the validation of Cleanrooms are given in *Table 1*.

Cleanrooms can be validated for three installation and operational phases:

i. As-built
ii. At-rest
iii. Operational

We will now go into the details of the tests.

Airflow Velocity, Volume, and Uniformity Tests

These test procedures are performed to determine average airflow velocity and uniformity of velocity within Cleanroom, clean zone, or unidirectional flow work zone, as well as to determine air supply volume flow rate and volume uniformity.Typically, either airflow velocity or airflow volume testing will be performed, and results will be requested in only one format: average velocity, average volume, or

About the Author

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Table 1: Recommended test by Cleanroom type

Test	Unidirectional Airflow	Non-unidirectional Airflow
Airflow volume and uniformity Airflow velocity and uniformity	1, 2, 3 1, 2, 3	1, 2, 3 OPT
Filter leak	1, 2	1, 2
Particle count	1, 2, 3	1, 2, 3
Pressurization	1, 2, 3	1, 2, 3
Parallelism	1, 2	NA
Integrity	1, 2	1,2
Recovery	NA	1, 2

Notes:
The order in which these tests are performed is optional, but some sequences are optimal.
NA : Not applicable to this situation
1: Test is suited to as-built phase
2: Test is suited to at-rest phase
3: Test is suited to operational phase
OPT: Test is optional, depending on process requirements

total volume. Total volume may, in turn, be used to determine the air exchange rate (room air volume changes per hour) for the Cleanroom.

HEPA and ULPA Filter Installation Leak Test

These tests are performed to confirm that the HEPA or ULPA filter system is properly installed by verifying the absence of bypass leakage in the installation, and that the filters are free of defects and small leaks. The tests are particularly important for Cleanrooms and clean zones classified at Class 5 (Class 100) or cleaner (according to *ISO-14644-1*).

The tests are performed by introducing an aerosol challenge upstream of the filters and scanning the immediate downstream duct. These procedures detect small holes and other damage in the filter medium and frame seal, bypass leaks in the filter frame and gasket seal, and leaks in the filter bank framework.

Two different leak detection techniques are presented along with recommendations for two different aerosol challenge methods and two different detections instruments. The particle counter method is an alternative to the photometer method, but the two methods are not necessarily equivalent.

Figure 1: Aerosol photometer

Figure 2: Airborne particle counter

Air-generated Aerosol Challenge and Aerosol Photometer Filter Scan Test

This method may be limited to Cleanrooms with small air-handling systems where the specified aerosol challenge concentrations are achievable.

This test procedure has long been the accepted industry method for determining defects in filters or filter systems. The test provides both qualitative and quantitative results in identifying leaks. The test can easily be reproduced. The generation of a consistent concentration of liquid aerosol to challenge most systems is not difficult. A concentration of approximately 10 µg/l of air is an adequate challenge. (This concentration is equivalent to approximately 3x10 droplets/m^3 or 109 droplets/cft of air when the challenge is generated by a Laskin nozzle.)

Airborne Particle Count

This test is performed to verify that the completed as-built, at-rest, or operating facility can meet the *ISO-14644-1* air cleanliness class specified by the user.

Figure 3: Manometer to test room pressure differential

Room Pressurization Test

The purpose of this test is to verify the capability of the Cleanroom system to maintain the specified pressure differential between the Cleanroom and its surroundings. This test should be performed after the facility has met the acceptance criteria for airflow velocity or volume, airflow uniformity, parallelism, and other applicable tests.

Airflow Parallelism Test

The purpose of this test is to verify the parallelism of airflow throughout the work zone and whether the cleanroom is capable of limiting the dispersion of internally generated contamination.

This test may be applied at the discretion of the user when deemed necessary, and is applicable only for unidirectional airflow. This test should be performed after completion of the airflow velocity and uniformity tests.

Enclosure Integrity Test

This test is performed to determine if there is intrusion of unfiltered air into the clean work area from outside the Cleanroom where the ambient background concentration of the particle size to be measured exceeds 100 particles per cubic foot.

Recovery Test

The recovery test is performed to determine whether the Cleanroom or clean zone is capable of returning to the specified cleanliness class within a finite time, after being exposed briefly to a source of airborne particulate challenge in the form

of a smoke or optional aerosol. This test is not recommended for unidirectional flow rooms.

Cleanroom Classification

The Cleanroom grade classifications are given in *Table 2, 3* and *4*.

Table 2: Cleanroom classification as per ISO 14644-1

ISO Classification Number (N)	Maximum concentration limits (partideslm" of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)					
	0.1µm	0.2µm	0.3µm	0.5µm	1.0µm	5.0µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1000	237	102	35	8	
ISO Class 4	10000	2370	1020	352	83	
ISO Class 5	100000	23700	10200	3520	832	29
ISO Class 6	1000000	237000	102000	35200	8320	293
ISO Class 7	352000	83200	2930			
ISO Class 8	3520000	832000	29300			
ISO Class 9	35200000	8320000	293000			

Note: Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in detennining the classification level

Table 3: Cleanroom classification as per Schedule M (Government of India)

Maximum permitted number of particles per m³ equal to or greater than the tabulated size				
Grade	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3520	20	3520	29
B	3520	29	35200	293
C	35200	2930	352000	29300
D	352000	29300	Not defined	Not defined

Table 4: Cleanroom classification as per EUGMP- 2008

Maximum permitted number of particles per m equal to or grealer than the tabulated size				
Grade	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Not defined	Not defined

There is a lot of discussion regarding the air sampling volumes and we will attempt to clarify the issue.

A) As per ISO 14644 -1

The minimum sample volumes for each of the Grade areas in litres are listed in *Table 5*, based upon the largest considered particle size.

Table 5: Minimum sampling point locations

Grade	At rest	In operation
	Minimum sample volume (in liters)	Minimum sample volume (in liters)
A	1000	1000
B	690	*7
C	*7	*2
D	*2	Not defined

$NL = \sqrt{A}$

Where

NL is the minimum number of sampling locations (rounded off to a whole number).

A is the area of the Cleanroom or clean zone in square metres.

Note: In the case of unidirectional horizontal airflow, area A may be considered as the cross section of the moving air perpendicular to the direction of the airflow.

B) As per EUGMP

The EUGMP Revision 2008 mandates a minimum sample air volume of 1 cubic meter for class A and B and recommends the same for class C.

EUGMP Annex 1 outlines three phases that need to be performed:

i. Certification: Each Cleanroom and clean air device should first be classified.
ii. Monitoring: The Cleanroom should then be monitored to verify that conditions are being maintained relative to product quality.
iii. Data Review: Ensure that the data accrued from the monitoring is reviewed in the light of risk to finished product quality.

Demonstrating Continued Compliance

In order to ensure continued compliance, *EN ISO-14644-2* provides information on this testing. The frequency of such testing is given in *Table 6*.

Grade A and B Cleanrooms or clean air devices must be re-tested every 6 months. Grade C and D Cleanrooms must be re-certified at a minimum of every year.

Table 6: Frequency of testing for continued compliance

Classification	Maximum time interval	Test method
<ISO Class 5	6 Months	Annex B in *ISO 14644-1:1999*
>ISO Class 5	12 Months	Annex B in *ISO 14644-1:1999*

Note: Particle count tests will normally be performed in the operational state, but may also be performed in the at-rest state in accordance with the designated ISO classification.

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Continuous Particle Monitoring

There are two types of continuous monitoring systems:

a) Real Time Particle Monitoring

Real time particle monitoring involves the use of a single particle counter or particle sensor at a specific location. This sensor is dedicated to monitoring particles only at the specific location. Every event would be detected and counted. There are no gaps in the particle counting data. Particles are measured in particles per cubic foot or particles per cubic meter.

This system is best used at critical locations where events can happen at any time, to monitor critical or very sensitive operations.

Several types of particle counters are available.

Stand Alone Counter is a dedicated counter with display and vacuum pump built in.

Remote Particle Counter has no display; vacuum for sampling is achieved via process vacuum, or a separate pump dedicated to particle counting.

b) Sequential Particle Monitoring

This involves the use of a single particle counter to monitor multiple points. This is accomplished by adding a sequential manifold sampler that connects the particle counter to several different sample tubes. Each tube is sampled in sequence. Once a tube is sampled, the manifold switches to the next tube to be sampled. During this change, the particle counter stops counting until the change is complete, and then delays to allow any air from the previous sample to be purged.

Classification vs. Monitoring

Classification

When a Cleanroom is certified to a specific class, the room performs to standards that meet or exceed the performance of that class under a specific occupancy status. Certification is the general means of checking the room for various parameters, to guarantee that it is built to a specific set of requirements. The room is also periodically re-tested to those same parameters to ensure that nothing has changed.

Monitoring

Monitoring is done to ensure that

- The cleanroom parameters have not altered in any way; everything in the construction and supporting equipment is 100% operational and is at the same performance level as when the room was certified.
- The process in the room is in control at all times.
- The cleanroom staff follows accepted procedures at all times.

References

1. *ISO 14644-1999*
2. *EUGMP-2008*
3. *SCHEDULE M (Government of India)*
4. *IEST-RP-CC006*