

The Particle Count Newsletter Airborne Particle Counting for Pharmaceutical Facilities

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The Particle Count

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Airborne Particle Counting for Pharmaceutical Facilities: EU GMP Annex 1

EU GMP Annex 1 Update

Lighthouse Worldwide Solutions

On February 14th, 2008, The European Commission updated Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 1: Manufacture of Sterile Medicinal Products.

This update comes into operation on March 1st, 2009. (With the provisions on capping of freeze-dried vials implemented by March 1st, 2010)

Cleanroom and Clean Air Device Classification:

The formal cleanroom testing for classification should be done per the EN ISO 14644-1 standard.

Another key point stated in this update is that classification should be clearly differentiated from the operational process of environmental monitoring.

The maximum permitted airborne particle concentration is given in table 1.

For cleanroom certification testing of Grade A zones, a

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100 Liter / Minute Particle Counter Samples 1 Meter³ of Air in Just 10 Minutes!



**SOLAIR 3350Rx
SOLAIR 5350Rx
100 LPM Portable
Particle Counters**

The SOLAIR 3350Rx and 5350Rx are 100 LPM portable particle counters with 0.3 micron and 0.5 micron respectively minimum detection limits. These state-of-the-art, battery-operated, portable particle counters are designed for the updated European Union GMP Annex 1 changes requiring the sampling of a full cubic meter of air per location for Grade A areas. These units offer state of the art communication and data transfer capabilities with: Open architecture connectivity with OPC server, USB flash drive data transfer, built-in Ethernet, RS-485 and USB connectivity.

Liquid Particle Sampler/Counter for Injectables: USP 788, EP, JP Recipes and Reports built-in



**LS-20 Liquid
Particle Counter**

The LS-20 Liquid Particle Sampler/Counter for Injectables utilizes an internal light obscuration optical particle counter, precise syringe sampler and stirring mechanism. With software developed under GAMP guidelines and designed to enable 21 CFR Part 11 Compliance, the LS-20 is the premier system for injectables.

minimum sample volume of 1m³ should be taken per sample location.

It should be noted that this follows the sampling guidelines of EN ISO 14644-1. For Grade A, the airborne particle classification is *ISO 4.8 and is dictated by the limit for particles ≥5.0µm, which is 20 particles per cubic meter.

*(EN ISO 14644-1 allows intermediate classifications with the minimum increment of 0.1)

For Grade B (at rest) the airborne particle classification is ISO 5 for both particle sizes and in operation, the airborne particle classification is ISO 7 for both particle sizes.

For Grade C at rest, the airborne particle classification is ISO 7 and in operation the airborne particle classification is ISO 8.

For Grade D (at rest) the airborne particle classification is ISO 8 and it is not defined for in operation.

For the classification of a cleanroom or clean air device, EN/ISO 14644-1 defines:

- The minimum number of sample locations
- The sample size (volume) based on the class limit of the largest particle size under consideration
- The means of evaluating the data

Minimum Number of Sample Locations

The minimum number of sample locations for cleanroom certification testing per EN ISO 14644-1 is a simple calculation

$$NL = \sqrt{A}$$

Where NL is the minimum number of sample locations (rounded up to the nearest whole number), and A is the area of the cleanroom or clean zone in square meters. (the square root of the area in square meters)

Minimum Sample Size (Volume)

The minimum sample volume for cleanroom certification testing per EN ISO 14644-1 is determined by largest considered particle size for that particular environment. The Grade A environment at 5.0µm is classified as an ISO 4.8 cleanroom or clean air device. This is where the 1 cubic meter of air / location comes from.

EN ISO 14644-1 states that, for each sample location, sample a sufficient volume of air that a minimum of 20

Table 1. Updated limits in particle counts per Grade.

	At Rest		In Operation	
	0.5µM	5.0 µM	0.5 µM	5.0 µM
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	Not Defined	

particles would be detected if the particle concentration for the largest considered particle size were at the class limit for the designated ISO Class. The Sample volume or Vs per location is determined by the equation below:

$$V_s = \frac{20}{C_{n,m}} \times 1\,000$$

Where :

- Vs is the minimum single sampling volume per location, expressed in liters
- Cn,m is the class limit (number of particles per cubic meter) for the largest considered particle size, specified for the relevant class.
- 20 is the defined number of particles that could be counted if the particle concentration were at the class limit.

(See EN ISO 14644-1 Section B.4.2 for details)

Per ISO 14644-1 the minimum sample volumes for each of the Grade areas in liters is listed in Table 2, based upon the largest considered particle size.

Table 2 Grade	At Rest	In Operation
	Minimum Sample Volume	Minimum Sample Volume
A	1000	1000
B	690	*7
C	*7	*2
D	*2	Not defined

*the volume sampled at each location shall be at **least 2 liters, with a minimum sample time of 1 minute.**

The minimum sample volume presents an unusual situation where the minimum number of sample locations is 1. Per EN ISO 14644-1 where only one sampling location is required, take a minimum of three single sample volumes at that location. For a small Grade A environment where only one sample location is needed, a minimum of 3 cubic meters of air must be tested (see EN ISO 14644-1 Annex B 3.4.3 for details).

For the classification testing, portable particle counters with a short length of sample tubing should be used. This requirement exists because of the loss of large sized particles ($\geq 5.0\mu\text{m}$) in the sample tubing. Though not clearly stated in Annex 1, Lighthouse Worldwide Solutions recommends keeping the length of this tube (when possible) to less than 3 meters.

Isokinetic sample probes must be used in unidirectional airflow systems. Lighthouse Worldwide Solutions recommends using an isokinetic probe in non-unidirectional airflow systems as well.

The in-operation classification may not always be possible during normal operations. This classification may be demonstrated in simulated operations, during media fills or normal operations.

Demonstrating Continued Compliance

In order to demonstrate continued compliance, EN ISO 14644-2 provides information on this testing. The frequency of such testing is in the Table 3.

Table 3: ISO 14644-2 Cleanroom Frequency of Testing

Classification	Maximum Time Interval	Test Method
\leq 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

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

Cleanroom and Clean Air Device Monitoring:

Particle monitoring during the operational process is different from the particle monitoring for classification of the environment.

All Grade environments should be routinely monitored while they are in operation. The locations selected for this particle monitoring should be chosen based upon a formal risk analysis and the results taken during the cleanroom classification testing of the cleanroom or clean air device.

Grade A Particle Monitoring

In Grade A zones, particle monitoring should be done during the entire operation of a critical process, including equipment assembly and setup stages. Justifiable exceptions are where the contaminants in the process would damage the particle counter or present a hazard. Examples of such a hazard are

when working with live organisms or radiological hazards.

Grade A zone should be monitored continuously in such a manner that any interventions in the process, transient events, or air system deterioration is detected, recorded and, if necessary, appropriate alarms or warnings are triggered.

Though not specifically stated in Annex 1, dedicated fixed point remote particle counters with 1 minute sample times have been demonstrated to adequately monitor Grade A Environments. These devices provide adequate sampling frequency to detect all occurrences.

Some operations may generate particles or droplets from the product, thus making the demonstration of low levels of particles $\geq 5.0\mu\text{m}$ not possible. Annex 1 states this is acceptable, especially at the point of fill, when filling is in process. It is still necessary to monitor these locations, both at rest and during setup.

Grade B Particle Monitoring

Particle monitoring of the Grade B zone should be similar to Grade A; however, the sample frequency may be decreased. The importance of the Grade B monitoring is determined by the degree of segregation between the Grade A and B zones.

The Grade B zone should be monitored so that changes in the particle levels or any system deterioration would be detected, and alarm and warnings triggered and recorded if limits are exceeded.

Particle Monitoring

For the particle monitoring system, fixed point remote particle counters, or sequential sampling systems (manifold), attached to a particle counter or a combination may be used.

Regardless of the system used, it must be appropriate for the particle size considered. When using any system, the loss of $\geq 5.0\mu\text{m}$ particles in the sample tubing is a concern. The length of the tubing used, the number of bends and the radius of these bends must be considered.

The system should take into account any risk from the materials used in the operation. An example of the risk is with live organisms or radioactive materials.

The sample volume for monitoring using an automated system is not necessarily the same sample volume used for the formal classification of the cleanroom or clean air device.

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Whereas the classification of a Grade A environment requires a minimum sample (per location) of 1 cubic meter of air. For environmental monitoring during operations as part of an EM system a smaller sample volume may be used.

Particle Monitoring $\geq 5.0\mu\text{m}$ particles

Particles that are $\geq 5.0\mu\text{m}$ are important as they can provide early indication of failure in the environmental system. Occasional $\geq 5.0\mu\text{m}$ particle counts may be false counts because of electronic noise, stray light or the sudden release of particles from the sample tubing. But Annex 1, states that consecutive or regular counting of low levels of $\geq 5.0\mu\text{m}$ particles is an indication of a possible contamination event and should be investigated.

These counts might indicate a failure of the HVAC system, filling equipment failure or poor practices during routine operation or equipment set up.

Clean up Period

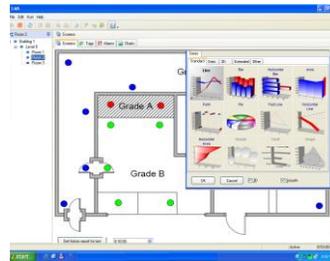
For all Grades, the clean-up time between the "operational state" and the "at-rest" state should be 15-20 minutes in an unmanned state after the completion of operations. This period is referred to as a guidance value.

Particle Monitoring of Grade C and D Areas.

These areas should be monitored for particles in operation and, for Grade C, also at rest. The frequency of such monitoring is determined by quality risk management. The alert/action limits are dependent on the types of operations carried out.

*by Morgan Polen
Vice President, Application Technology*

LMS Pharma Edition Software



Facility Monitoring System for Pharmaceuticals:

LMS Pharma Edition is a GAMP 5 developed system for monitoring pharmaceutical facilities. Designed to enable 21 CFR Part 11

compliance. The system integrates data from: Airborne Particle Counts, Temperature, Relative Humidity and Differential Pressure Sensors. Offering alarming, e-mailing and automatic report generation. LMS Pharma Edition supports network based clients and is the most fault-tolerant particle monitoring system on the market with built-in fail-over design.

About Lighthouse Worldwide Solutions

Lighthouse offers particle counting and contamination monitoring solutions for pharmaceutical facilities. These offerings range from a complete line of portable particle counting systems, remote particle counters, facility monitoring systems, active viable microbiological sampling systems, temperature sensors, relative humidity sensors, differential pressure sensors, air velocity sensors as well as software systems and validation and installation services for these systems.

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