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NON-VIABLE PARTICLE MONITORING TO MEET cGMP REQUIREMENTS

Introduction

Several changes have occurred within the last year that have brought an elevated review of practices with regard to non-viable particulate monitoring, specifically the new Food & Drug Administration's (FDA) Guideline on Aseptic Manufacture, September 2004 and the revision of the EU GMP Annex 1, September 2003. In both of these documents, the focus on proving control over the manufacturing environment has been increased.

This introductory paper aims to identify the common factors in both the FDA and EU guidelines and how pharmaceutical manufacturers can review current practices within these changes. A full review of how to meet both regulations as a common target is being defined and will be issued in the near future.

Legislative Limits

There are three current standards for cleanrooms applicable to pharmaceutical manufacturing: ISO14644-1, for room certification, and the above FDA and EU guidelines on monitoring. The table below identifies where the three standards overlap. The table has been simplified due to the FDA's recent adoption of a metric (and ISO) room classification.

ISO14644-1		ROOM FUNCTION	FDA GUIDE	EU ANNEX 1	
Class	Limit		Operational	Operational	At Rest
5	3,520	Sterile Critical (A)	3,520	3,500	3,500
7	352,000	Sterile Background (B)	352,000	350,000	3,500
8	3,520,000	Support / Preparation (C)	3,520,000	3,500,000	350,000
N/A		Support (D)	N/A	N/A	3,500,000

NOTE: All Data is for 0.5 µm/ m^3. Although the EU imposes limits for 5.0 microns, they are not presented above.

It can be seen that the harmonization on metric limits makes the requirement overlap more apparent where the critical areas need to be maintained around 3500/m^3 at 0.5 microns.

The use of 0.5 micron data is useful to prove control over a cleanroom; statistically it is important to have a dynamic number. If we were to try to control the cleanroom using the 5.0 µm data, we are faced with very few and sporadic events which are difficult for SPC purposes. Based upon the 0.5 µm information, we are best able to define operational limits to 'normal' activities. The greatest issue with cleanroom control and statistics, however, is the source of contamination. People, when present, can significantly increase counts, and when absent, low counts will skew the statistics. However, it is this data that is used to define the maintenance of a room's contamination control with respect to particles, from all sources.

Control of the 5.0 µm data to meet compliance with the EU regulations can prove to be a logistical hurdle; the regulations state that a m^3 of sample be taken for Class A, B and preferred for C rooms. However, this is for portable, routine testing and where an automated

monitoring system is installed a different approach needs to be adopted; this is discussed further in a following paper.

Requirements for Sampling

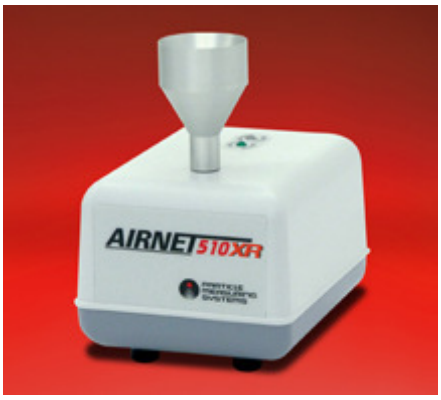
The guidelines and the ISO standards both identify that the measurements must be done using a laser based light scattering optical particle counter. For more information relating to the general operation of these devices, see the Basic Guide to Particle Counting, available from Particle Measuring Systems. The basic principle is that, as particles from any source are passed through the optical chamber of a particle counter, they are sized and counted in real-time, giving immediate information relating to contaminant levels.

The first point of proving room cleanliness is the performance of certification following the ISO14644-1 standards (legacy use of the old FS209E is soon to be dropped). The standard specifically identifies where samples are taken, what volume should be used to take such samples, and how the data is treated to prove compliance to the standard – a very specific set of instructions. Once the room has been tested, it can be used for its prescribed purpose and room monitoring can now begin to prove maintenance of room standard.

Both standards identify the difference in approach required to monitor the environment for critical areas and to support clean areas.

Critical Areas

There is agreement from both standards on how these areas should be monitored. The EU Annex 1 says, “A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone, and is recommended in the surrounding grade B areas”. The FDA says, “Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters”.



Airnet Particle Sensor

To satisfy the FDA and the EU, it is important to review the implementation of an automated measurement system. This gives more frequent data and therefore a greater ability to prove control in the most critical areas. It is also less invasive than a portable particle counter, which can be difficult to use to sample the environment without disruption to personnel, process, or both. Use of the Airnet® 510 and IsoAir® products integrated into the manufacturing environment and filling lines fulfill this requirement.

Treatment of data from the continuous sampling needs to be reviewed. Where once a single page of data existed, now several pages per sensor will be normal. The primary requirement is that one can prove control over the environment; the log of events showing compliance during batch production is therefore key information. This is supported using tabular, graphical, and statistical analysis as required.

Support Clean Areas

Lasair III Particle Counter

This is still the domain of the portable particle counter. Routine testing can be performed at regular intervals; these intervals are based upon risk assessment and essentially follow the PDA guidelines on best practices. For compliance to EU regulations, a m^3 of sample needs to be taken in class B and is preferred in class C areas. This increase over old values is because this is a 'snap-shot' of conditions at a single reference point in time, and therefore to improve confidence in the data a volume expectation is used. There is currently no volume requirement for the FDA routine sampling and so the ISO14644 guide would be the best reference. For most cleanrooms, this would be at least one minute at each location. The Lasair® III particle counter has the ability to not only take routine samples at specified locations to meet the monitoring requirements, but it also comes with embedded statistical routines for performance of room certification, making it the ideal portable device for the manufacturing areas.

For further information and details of changes to particle counting and GMP, please contact Particle Measuring Systems.

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