ENVIRONMENTAL MONITORING NEWS
LIFE SCIENCES

PARTICLE MEASURING SYSTEMS®

August 2010 - Issue 2, Volume 1

IN THIS ISSUE

Regulatory Updates
- EC GMP Annex 1
- WHO Guidance

Application Note
- Large Particle Transportation

- **Product Spotlight**
- Lasair® III 5100 Particle Counter
- Lasair III 350L Particle Counter
- Lasair III 310C Particle Counter

NEXT ISSUE PREVIEW

- **Liquid Particle Counter Applications**

UPCOMING EVENTS

- **ISPE Great Lakes Fall Meeting**
  Indianapollis - Sept 14-15
- **ISPE Boston** - October 6
- **PDA Microbiology Conference**
  Washington, D.C. - October 25-26
- **ISPE Annual Meeting**
  Orlando - November 7-9

CONTACT US

www.pmeasuring.com
info@pmeasuring.com
1.800.238.1801

REGULATORY GUIDANCE FOR PARTICLE LOSS IN TRANSPORT TUBING

The 2009 revision to the Annex 1 of the EC GMP for sterile products requires that:

- Cleanrooms be classified in accordance with ISO 14644-1.
- The methodology for selecting the location of sample points and minimum sample volume at each location should be taken into account.

It also lists the following certification requirements:

- Particle counters should only use short lengths of sample tubing due to the drop out of large particles in the transport tubing. *Read more.*

WHO ENVIRONMENTAL MONITORING OF CLEANROOMS IN VACCINE MANUFACTURING FACILITIES

The current Draft version of the World Health Organization has harmonized with the EC GMP in many regards; it also offers assistance in the interpretation of what constitutes acceptable tubing lengths, recommending that long lengths of tubing greater than about 2 meters should not be used due to the potential loss of larger particles on tubing surfaces.

It is therefore important to understand these losses. The application note on page 3 aims to address why 2 meters is deemed to be an acceptable distance.

APPLICATION NOTE - LARGE PARTICLE TRANSPORTATION

Transportation of particles through tubing between the sample inlet and the optics of a particle counter has often been at the forefront of discussion regarding the truth of readings. With the release of the 2009 EC GMP Annex 1 the issue of particle loss of large particles has been elevated such that a better understanding and measurement of those losses is warranted. When the validation implications of losses due to various forces are reviewed, the absolute certainty of a result is always in question. So what are these forces? What are the losses? What are acceptable results? The goal of this paper is to address several of these issues and provide a better understanding of the problem. *Read more.*

PRODUCT SPOTLIGHT

The **Lasair® III** Particle Counter is available in three different flow rate configurations to meet a variety of cleanroom applications; from portable cleanroom classification to routine cleanroom monitoring.

All Lasair III Particle Counter products include long life battery power, large touch screen, recipes for multiple functions, and printer or paper-free operation. Contact Particle Measuring Systems for more information.

Lasair III 5100 Particle Counter
- 100 liters per minute
- Sampling $1m^3$ in 10 minutes
- 0.5 to 25 μm channel sizes
- Cleanroom classification
  - ISO14644
  - EC GMP Annex 1
- Compressed gas monitoring with accessories
- ISO 21501-4 compliant

Lasair III 350L Particle Counter
- 50 liters per minute
- Sampling $1m^3$ in 20 minutes
- 0.3 to 25 μm channel sizes
- Cleanroom classification
  - ISO14644
  - EC GMP Annex 1
- Compressed gas monitoring with accessories
- ISO 21501-4 compliant

Lasair III 310C Particle Counter
- 1 cubic foot per minute (28.3 LPM)
- Sampling $1m^3$ in 35.3 minutes
- 0.3 to 25 μm channel sizes
- Cleanroom classification
  - ISO14644
  - EC GMP Annex 1
- Compressed gas monitoring with accessories
- ISO 21501-4 compliant

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REGULATORY GUIDANCE FOR PARTICLE LOSS IN TRANSPORT TUBING

The 2009 revision to the Annex 1 of the EC GMP for sterile products requires that:

- Cleanrooms be classified in accordance with ISO 14644-1.
- The methodology for selecting the location of sample points and minimum sample volume at each location should be taken into account.

It also lists the following certification requirements:

- Particle counters should only use short lengths of sample tubing due to the drop out of large particles in the transport tubing.
- Long lengths of tubing should not be used.

This revision does not clearly define what constitutes “long” or “short” tubing.

One reason behind the requirement for short lengths of tubing is that this is a single measurement made once per 6 or 12 months, depending on the class of room. For this reason, the measurement should be the most accurate possible, taking into account flow direction and isoaxial sampling.

Routine operational process monitoring is performed as a continuous or frequent activity and as such, the risks associated with loss in tubing are managed through:

- The volume of data gathered and
- Clause 20: the appropriate setting of alarm limits.

These limits should account for losses in tubing as determined either from manufacturer data or as a result of direct testing. There is no defined requirement on the length of tubing, “long” or “short,” only that tubing lengths be validated.

UPCOMING EVENTS

ISPE Great Lakes Chapter Fall Meeting
14 - 15 September 2010
Indianapolis, Indiana USA

Boston Product Show 2010
October 6th Gillette Stadium Clubhouse, Foxboro, MA.

PDA’s 5th Annual Global Conference on Pharmaceutical Microbiology
Advances in Microbial Control and Product Quality

October 25-28
Capital Hilton
Washington, D.C.

ISPE Annual Meeting 2010
7-10 November
Swan and Dolphin Resort
Orlando, Florida, USA

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PARTICLE MEASURING SYSTEMS
www.pmeasuring.com
5475 Airport Boulevard, Boulder, Colorado 80301-2339
303.443.7100 1.800.238.1801 Fax: 303.546.7380
Customer Service Center 1.877.475.3317
Instrument Service 1.800.557.6363

Particle Transportation

Transportation of particles through tubing between the sample inlet and the optics of a particle counter has often been at the forefront of discussion regarding the truth of readings. With the release of the 2009 EC GMP Annex1 the issue of particle loss of large particles has been elevated such that a better understanding and measurement of those losses is warranted. When the validation implications of losses due to various forces are reviewed, the absolute certainty of a result is always in question. So what are these forces? What are the losses? What are acceptable results? The goal of this paper is to address several of these issues and provide a better understanding of the problem.

External Influences

Forces Acting on Particles

Cleanroom certification and monitoring activities can be seen as those tests performed to quantify the dynamics of the body of air within a confined space. This space may be either the air in the general cleanroom or the air in a transport duct or a laminar flow zone. The following describes particle behavior mechanisms and will assist in the understanding of sampling difficulties and how to improve the efficiency of sampling.

- The *Stokes number* is the ratio of a particle's radius to the dimension of an obstacle in fluid flow. This is an important factor in determining when a particle in motion will be collected by an obstacle or will pass around it. An obstacle could be a filter fiber or the sample inlet.
- The *drag coefficient* is the ratio of the force of gravity to the inertial force on a particle in fluid. It indicates how a particle will resist any force that could cause a change in the particle velocity. Smaller particles have smaller drag coefficients due to their lesser masses.
- The *relaxation time* is the time for a particle initially in equilibrium with a moving fluid to match a change in fluid velocity. Large particles have a long relaxation time. Therefore, when an air stream moves through tubing that contains small-radius bends or elbows, the large particles will deposit on a tube wall because they cannot adapt easily to sudden velocity changes because of tube curvature, and thus the particles will continue in their original direction until they impact on the tube wall. A related term to relaxation time is *stopping distance,* which is defined as the distance for a particle initially moving within a gas stream to come to a stop when the gas flow is halted, as by an obstacle.
- The *deposition velocity or settling velocity* is the ratio of particle flux (distance per unit time for sedimentation to occur) relative to the ambient particle concentration.

Table 1. Settling velocities of particles

Particle Size (μm)	Settling Velocity (cms^{-1})
0.00037	
0.01	6.95×10^{-6}
0.1	8.65×10^{-5}
1.0	3.50×10^{-3}
10	3.06×10^{-1}
100	2.62×10^{1}

There are also additional forces in effect on particles. These additional forces on the particles and the particles' subsequent response to such forces control the particles' migration through the air:

- **Viscous forces:** The fluid dynamic force from a moving fluid stream or the viscous nature of an air stream will 'pull' particles along that flow path. If this flow is laminar, then other forces act upon the larger particles encouraging settling and deposition, while smaller particles remain buoyant on a laminar flow. In turbulent flow streams the larger particles are re-entrained back into the airflow and smaller particles are more prone to additional forces acting upon them.
- **Brownian motion:** As the particles migrate through a body of air, random impacts from individual molecules will cause them to veer from course.

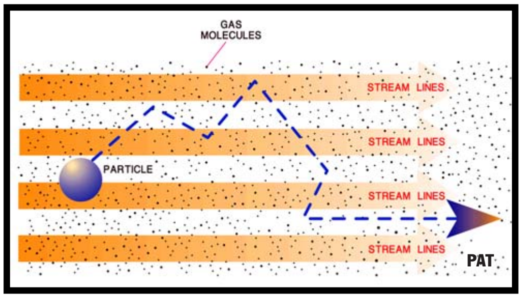

Figure 1. Migration of a particle along a mean free path, due to Brownian motion.

- **Gravitational force:** The gravitational force on a particle varies with particle mass and the difference between particle and air density; the larger the particle the greater the interaction.
- **Electrostatic forces:** The electrostatic force on a particle varies with the particle's electrical charge (surface area controlled) and the strength of the electrical field in which the particle is located. Electrostatic charge can develop as a particle slips through the air stream. It is important therefore to minimize these interactions in order to ensure all particles reach the final destination.
- **Diffusion forces:** This force on a particle varies inversely with the particle's radius. Therefore smaller particles are more prone to interactions due to diffusion.
- **Thermophoretic forces:** These forces (effective mainly for small particles) vary with the particle's surface area and temperature gradient.

A particle's response to these forces is controlled by the particle's size, mass, shape, and electrical charge. For essentially all of these forces the major parameter is particle size, because the magnitude of the several forces varies with particle size squared or cubed.

Isokinetic Sampling

There are several ways in which one can design a system to minimize these forces and their impact on sampling errors. In laminar flow environments, or in ducts leading to a filter, the air is considered to be moving unidirectionally. The sampling of this air flow must neither over-sample nor under-sample the distribution of particles within that flow. This requirement is satisfied when isokinetic sampling is performed. Isokinetic sampling means that the air velocity in the supply air is the same as the air velocity in the particle counter's sample-tubing inlet.

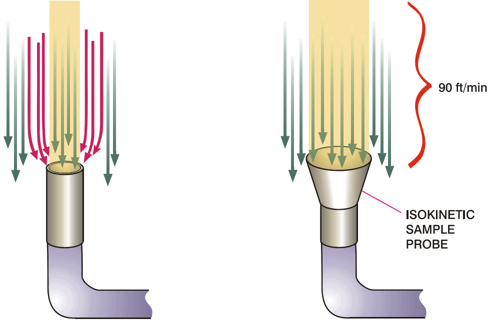

Figure 2. Isokinetic sampling

If the velocities differ, then either a positive- or negative-sample-collection error occurs. An isokinetic sample error increases with particle size, but is not of great concern for particles smaller than 1–2 µm. Federal Standard FS209E[1] shows that isokinetic sampling errors greater than 5% are not expected for particles smaller than a few micrometers when using a sample probe with inlet diameter of 2 mm or larger, even when sampling and sampled air velocities differ by an order of magnitude. However, when macro particles ≥ 5 µm are to be measured, then isokinetic sampling is required. Particle Measuring Systems has a calculator that accurately assesses the dimensions of the isokinetic probe and the associated errors when a non-standard sample probe is being used.

Particle Loss in Transport Tubing

When a sample is taken for either certification or routine monitoring operations, it is not uncommon for the isokinetic sample probe (ISP) to be in a remote location from the particle counter optics, requiring that the sample be drawn through tubing to the particle counter. When the sample is to be transported any significant distance in the tube from the point of sampling to the point of measurement, some particle losses will occur in the transport tubing. Such losses are dependent on tubing type, flow velocity, particle diameter, and distance. When directional changes occur, large particles are lost by a combination of gravitational settling to the bottom of the duct or tubing and inertial deposition on the walls of the tubing. Small particles are lost to the duct or tubing walls by Brownian motion and diffusion effects.

Figure 3 shows the percentage penetration of different-sized particles sampled through a manifold system over distances up to 125 feet. Particles < 1.0 µm in diameter show no significant losses, and the differences are essentially experimental error. Larger particles show a significant level of loss even over very short distances.

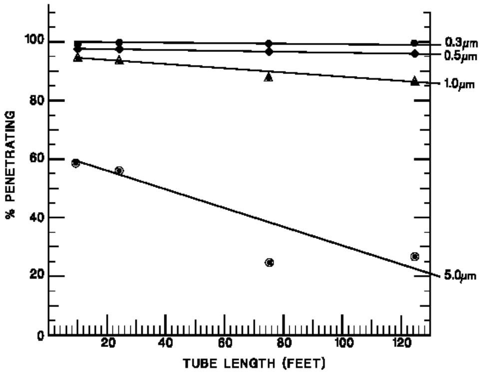

Figure 3. Particle loss in manifold sample tubing (1/2" tubing at 100 l/min flow rate)

When portable particle counters are used (such as the Lasair® III Aerosol Particle Counter), the flow rate in the tubing is significantly reduced, resulting in a reduction of the maximum permissible distance between the sample inlet and the optics of the particle counter. Figure 4 shows a similar pattern to that for manifold sampling but over much shorter distances.

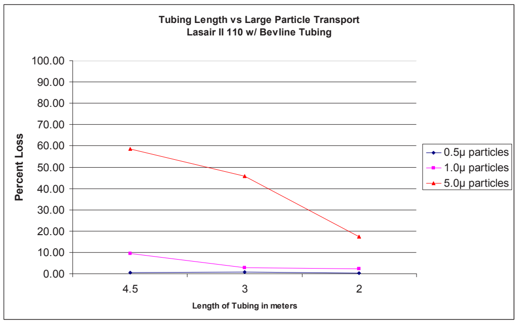

Figure 4. Particle loss in a portable particle counter (3/8" tubing at 28.3 l/min flow rate)

Electrostatic forces also account for a proportion of the losses in a sample. To reduce the effect of these additional forces, the various types of tubing material listed in Table 2 were tested to establish a suitable standard. The order of material preference in the listing is based on a combination of particle loss rate, electrical conductivity, and potential for oxide or sulfide formation when the tubing is exposed to urban air.

Table 2. Particle transport line material preference

No.1 – Stainless Steel
No.2 – Bev-a-line
No.3 – Polyester (as polyurethane)
No.4 – Polyester lined vinyl
No.5 – Copper
No.6 – High density polyethylene
No.7 – Glass
No.8 –Teflon

The diameter of the tubing should be selected to ensure the Reynolds number is between 5,000 and 25,000 as required in FS209E[1]. The Reynolds number range is one for which no significant turbulent deposition occurs for particles smaller than 5–10 μm and residence time in the tubing should be no more than 10–20 seconds in order to ensure the transmission of particles larger than 0.1 μm before any significant losses occur.

Practical Considerations and Guidance

Defining acceptable losses for particle transport is difficult, as any loss can be deemed to be unacceptable. However the practical implications of installing sensors on production equipment can be considered, along with the uncertainties and tolerances for particle counters.

The ideal installation of particle sensors would eliminate tubing to avoid losses altogether. But this is not often a practical choice given that sampling locations are often inside production equipment with limited space where a sensor cannot be installed. When the installation of transport tubing is required, questions arise as to what length of tubing is acceptable and how best to install it.

For particle sensors with a flow rate of 28.3 LPM (1 CFM), a maximum length of 2 meters of transport tubing should be used wherever possible. This guidance is based on establishing a balance between the desire to minimize particle losses and the ability to easily install sensors in proximity of the sampling point.

The study shown in **Figure 4** indicates that 5 micron particle loss at 3 meters of tubing is almost 50%, whereas losses are less than 20% at 2 meters, a significant reduction. Limiting the tube length to 1 meter would certainly yield even fewer losses, but the installation of a 1 meter tube can be difficult or impossible in many applications. This is often driven by the design of the production equipment or the need to avoid interfering with operator movement.

When installing transport tubing, there are basic guidelines that should be followed wherever possible:

- Use isokinetic sampling probes in unidirectional flow zones
- Minimize tubing bends and avoid sharp bends
- Ground conductive tubing to avoid static buildup
- Install the sensor below the sample inlet and avoid 'uphill' sections of tubing (use gravity to help transport)

Knowing that some levels of particle losses are inevitable with transport tubing, many users of monitoring systems may wonder whether to adjust or correct their data. First consider that even without transport tubing there are inherent uncertainties and tolerances for particle counters, as with other optical or electronic instruments. **Table 3** shows a comparison of two standards associated with aerosol particle counting.

Table 3: Tolerances for particle counting standards

	JIS B9921:1997	ISO 21501-4:2007
Particle Size Accuracy		3%
Particle CV		5%
Sizing Accuracy	5%	10%
Counting Efficiency	20%	20%
Sample Volume	10%	10%
Resolution		10%
Coincidence Level	5%	10%
Flow Rate Accuracy	5%	5%
Time Accuracy	1%	1%
Volume Accuracy		5%

Biasing of data is dependent on probe orientation, distance apart, air flow patterns, number of particles being sampled, duration of test, baseline variables between counters, optical variances, etc., making the definition of an absolute error difficult.

The data when sampling with transport tubing could be determined as incorrect relative to a result gained using no tubing. There are two methods for the correction of this data.

- If the data is to be determined as an absolute measurement and no tolerance for sample tubing is allowed, but sample tubing must be used to gain a result, the only way of determining the correct data is to multiply the actual data by a correction factor. The correction factor application is not simple however, as particles not of a single size – they are a range of sizes between two sample thresholds. As such, this is a logarithmic relationship (ISO 14644-1) and the data must be integrated between those two extremes for each size.
- A more suitable method for correcting data for monitoring applications is to adjust the alarm limit to reflect the losses in tubing. A 10% or 20% reduction in the alarm limits is simple to effect and does therefore represent a better reflection of the impact of particle losses.

References

1. Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones, Federal Standard No. 209E. Washington, DC: General Services Administration, 1992

Author: Mark Hallworth