PARTICLE MEASURING SYSTEMS
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Review of the PIC/S GMP Annex 1 Interpretation Document, PI 032-2

There are two sections within the PIC/S document, GMP ANNEX 1 REVISION 2008, INTERPRETATION OF MOST IMPORTANT CHANGES FOR THE MANUFACTURE OF STERILE MEDICINAL PRODUCTS (PI 032-2), issued January 2010, which require further clarification from an industry perspective. Section 6 and Section 11 both speak to particle counter performance and tubing length. It is only those two sections that are discussed in this review.

Section 6:

New EC-GMP text: Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥ 5 µm in remote sampling systems with long lengths of tubing.

PIC/S Interpretation: This section implies that old central particle counters with long tube lengths will no longer be acceptable for clean room classification, as they absorb too many particles (especially 5 µm particles). Therefore, modern portable particle counters with short tubes or (even preferable when possible) those without tubes should be used for classification purposes. The certificate of calibration of the particle counter should mention the tube length and nature of material (inox or polymer). When calibration of the particle counter is performed outside by an external laboratory, the particle counting system should be qualified on site with a comparative measurement with an isokinetic probe. For impact on monitoring, see also Section 11.

Section 11:

New EC_GMP text: Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and radii of any bends in the tubing must be considered in the context of particle losses in the tubing.

PIC/S Interpretation: This section addresses concerns especially for the sedimentation of 5 µm particles in remote systems (as a rough example, s-shaped bent tubing of 1.5 m length can already absorb about 30% of the 5 µm particles.). The company must qualify their particle sampler and sampling system for both particle sizes, 0.5 µm and 5 µm.

Particle Loss in Transport Tubing

Particle losses have been discussed at length in a number of Particle Measuring Systems technical papers (*Acceptable Loss of Particles in Transport Tubing*, May 2010). The following summarizes the mechanisms of how particles behave and will assist us in understanding of sampling difficulties and also assist in improving the efficiency of sampling.

- The *Stokes number* is the ratio of a particle's radius to the dimension of an obstacle, an important factor in determining when a particle in motion will be impacted by an obstacle (fiber or tube wall).
- The *drag coefficient* is the reflection of the particle's ability to change direction relative to size. Smaller particles have smaller drag coefficients and hence change direction more dynamically.
- 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 owing to tube curvature, but will continue in their original direction until they impact on the tube wall.
- The *Deposition velocity* or sedimentation velocity is the ratio of particle flux, the distance per unit time for sedimentation to occur, relative to the ambient particle concentration.
- *Reynolds Number* describes the turbulent flow within tubing; ensuring turbulent flow improves particle transport as the factors above are overcome through moving particles off the tube walls post collision.

It can still be determined though that particle attrition does occur, especially with the larger 5 µm particles. Practical experimentation demonstrates that tubing lengths over 2 m should not be used whenever the quantification of 5 µm particles is required.

As the length of tubing is restricted to only 2 m and the particle burden in sample tubing is so low, many of the effects that impact particle transport in tubing are limited, such as orientation of sample tubing (lying flat, vertical etc.) and number of bends (providing they maintain at least a tube diameter*4 radius).

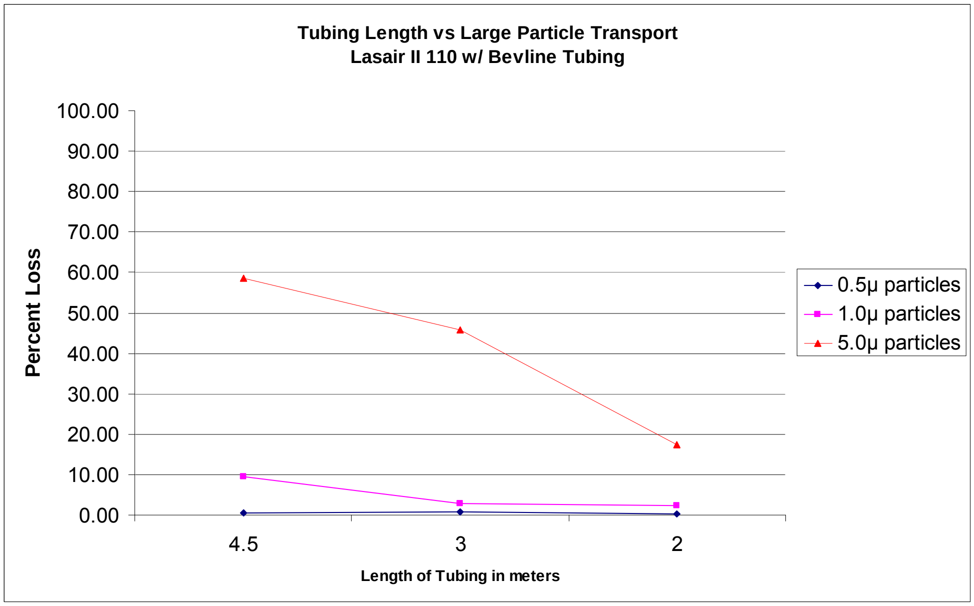

Figure 1 Particle loss in a portable particle counter (3/8” tubing at 28.3 liter/minute flow rate)

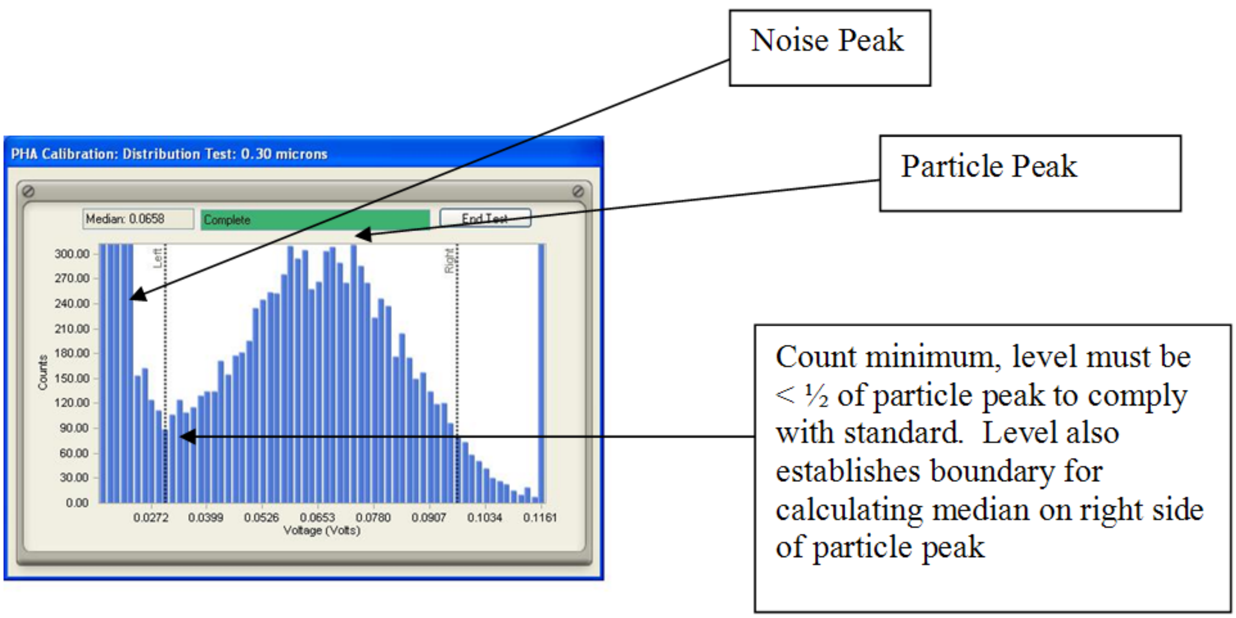

Figure 2 Particle counts for ISO 21501-4 testing

Particle Counter Calibration

EU GMP and therefore PIC/S suggests pharmaceutical manufacturers follow ISO 14644-1 for determining particle counts and classifying cleanrooms (based upon airborne particle data) and ISO 14644-2 for instrumentation guidelines that demonstrate continued compliance. They require that particle counters are calibrated in accordance with industry standards, the new ISO 21501 provides calibration methods to assure data accuracy for optical particle counters (OPC’s) and meet the requirements for ISO 14644-1.

The ISO 21501-4 Scope asserts: “Instruments that conform to this part of ISO 21501 are used for the classification of air cleanliness in cleanrooms and associated controlled environments in accordance with ISO 14644-1”. Consequently, cleanroom users should look to ISO 21501 as a method to meet cGMP, EU GMP, and other requirements.

Overview of the ISO 21501-4 Test Method

- Calibration Particle: PSL particles traceable to an international standard with uncertainty ≤ 2.5%
- Sizing calibrated with a Pulse Height Analyzer (PHA) @ median value for each size channel
- Pulse height distribution of PSL particle signals with noise must increase by 50% from the minimum to the peak

The ISO 21501-4 defines a particle size range from 0.1 – 10.0 µm. The particle counter is defined as an instrument used for classification of air cleanliness in cleanrooms and controlled environments in accordance with ISO 14644-1. Specific parameters defined within ISO 21501-4 include:

- Size calibration:
  - When calibrating a light-scattering airborne particle counter (LSAPC) with calibration particles of a known size, the median voltage (or internal PHA channel) corresponds to the particle size. The median voltage (or internal PHA channel) should be determined by using a particle counter with variable voltage limit (or internal PHA channel) settings. The median voltage is the voltage (or internal PHA channel) that equally divides the total number of pulses counted.
- Verification of size setting
- Counting efficiency:
  - 50% (± 20%) for particles close to the minimum detectable size
  - 100% (± 10%) for particles 1.5 – 2 times larger than the minimum detectable size
- Size resolution:
  - ≤ 15% for calibration particles specified by the manufacturer
- False count rate:
  - When sampling clean air, the false count rate is a measure of particle concentration (counts per cubic meter) reported from the minimum size ranges.
- Maximum particle number concentration
- Sampling flow rate
- Sampling time
- Response rate
- Calibration interval

It must be noted that the critical component of particle counting is that no known concentration is delivered, only that the particle counter must accurately determine the size of a particle and that the instrument measures a known volume of air and that all particles (100% ± 10%) are measured.

Therefore if particle loss occurs in sample tubing during the calibration of a particle counter and as such too few particles are measured to determine an accurate sizing calibration, the calibrating technician will increase delivery of the nebulized particles to the units under test, overcoming any losses and increasing counts to such a level as a sample sufficiently large enough for calibration to occur. This is an independent function of the length of tubing used. For this reason it is not necessary that the particle counter be calibrated using the same tubing length as that used in operation.

Responses to PIC/S Interpretation

Section 6

- It is a known and documented component of particle transport in tubing that losses do occur in tubing, and particle loss manifests itself more pronouncedly in the larger sizes, 5 µm and above.
- The purpose of cleanroom classification is to demonstrate as scientifically as possible the status of the cleanroom or clean air device at a given point in time and as such the most accurate readings must be taken. This requires that either no tubing or as short a tubing as required for an individual test point be used.
- There is no correlation between the particle counter calibration and tubing length; the two are independent components of measurement. It is therefore not required to know the tube length during calibration and ideally during calibration no tubing should be used.

Section 11

- Particle losses in transport tubing are known and manufacturers such as Particle Measuring Systems are able to supply data showing particle losses with specific tubing lengths.
- A maximum length of 2 m is recommended for all point-of-use particle counters. Given this short distance, tubing bends (providing they meet specifications, no less than tube diameter *4), electrostatic forces etc. have a lower impact on transported particles and can essentially be removed from practical considerations.
- Evaluating particle losses on site requires the generation of particles within a controlled zone and testing is prone to multiple errors. To test effectively, either a simulation of the installed sample points for the shortest and longest points being designed in a test laboratory, or the particle counter manufacturer's own data should be used for validation. Particle Measuring Systems can supply data for losses for all portable instruments.
- Manufacturer's data can be used to determine what reduction in action and alert levels for monitoring is optimal. It is important to reduce action limits rather than increase particle values due to the nature of the distribution (log relationship as a function of diameter) of particle populations within cleanrooms.

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