TECHNICAL PAPER

Remote Particle Counters for Pharmaceutical Applications

Version 01. Rev 01. 08/15/2016

LIGHTHOUSE
WORLDWIDE SOLUTIONS

Remote Particle Counters for Pharmaceutical Applications

Airborne particle counters are an important tool used in the environmental monitoring of pharmaceutical, bio-pharmaceutical and radiopharmaceutical facilities worldwide. The trend of globalization within the pharmaceutical industry has led to increased cooperation and harmonization within the industry. The increased use of particle counters for the continuous monitoring within these facilities is a result of this cooperation and harmonization. Remote airborne particle counters[1] are best suited for carrying out routine particle monitoring of critical locations.

Light scattering airborne single particle counters[2] are the required technology for non-viable particle counting used in the testing, validation and environmental monitoring of cleanrooms and clean spaces. For purposes of this article all particle counting will be in reference to this technology.

Types of Airborne Particle Counters

There are two fundamental types of Airborne Particle Counter (APC); Portable and fixed point remote.

1. A Portable APC is a self-contained particle counter with a user interface or operator panel that controls the instrument. It has a built-in sampling system and is easy to transport. The user interface can be used to establish sample parameters as well as data collection and if required data transmission to an external system. The air sampling system (either a vacuum pump or blower), must also provide an exhaust system that is adequately filtered and all air that exhausts from the instrument must not contaminate the

environment under test. Portable APCs generally are capable of operating on internal batteries or via an AC wall outlet.

Types of portable particle counters are differentiated by airflow sample rates. These are reported in volume per minute in either Cubic Feet / Minute (CFM) or Liters Per Minute (LPM).

Types of Portable APCs:

a. Handheld APC with low sample flow rates of 0.1CFM (2.83LPM) or lower.

b. Low Flow Portable APC with sample flow rates less than 1.0CFM (28.3LPM). Often used for special applications such as aerosol research.

> NOTE: Handhelds and low flow portable APCs may be inadequate for cleanroom certification testing of Grade A and B environments due to the large sample volumes used to test and certify Grade A and B environments. Based upon the requirement of "suitable sample size" in GMP Annex 1. [3]

c. Standard Flow Portable APC with sample flow rate of 1.0CFM (28.3LPM). These are the most common flow rate used in general cleanroom operations.

d. High Flow Portable APC with sample flow rates greater than 1.0CFM (28.3LPM). Examples of common high flow rates are 50LPM, 2.0 CFM, 75LPM and 100LPM. Higher flow rate instruments are quite useful in cleanroom certification testing as the minimum air volume to be sampled per location in a Grade A environment is one cubic meter of air. Where a

standard flow rate particle counter 1.0CFM would require just over 35 minutes to sample one location.

2. A fixed-point remote APC is smaller, less invasive and more robust than a portable APC. This allows for the APC to be attached to process equipment, cleanroom walls, or transport devices. Sample flow rates are either 0.1CFM (2.83LPM) or 1.0CFM (28.3LPM) with the latter being the preferred flow rate[3] in the areas related to this article. They data log or transmit data to external systems such as; Building Management Systems (BMS), Non-Viable Particle Monitoring Systems (NVPMS) or Facility Monitoring Systems (FMS). Remote APCs come in a variety of packages and feature sets. There are two main types of remote APCs; those with built-in pumps and those without built-in pumps.

   a. Remote APCs with built-in pumps

      These APCs have built-in sample handling systems via pumps or blowers as well the required filtration of all air exhausted from the unit. These units are larger, louder and more expensive then units without pumps. However these remote APCs do not require the installation of a larger facility wide vacuum pump and vacuum distribution system. Service costs are higher as internal filters should be replaced at regular intervals and the small internal pumps must be inspected or serviced at calibration.

   b. Remote APCs without pumps

      Requiring an external vacuum source, remote APCs are small, quiet and less expensive than units with built-in pumps. Service costs are also lower as there are no filters or small pumps to maintain. However, the supporting facility wide vacuum pump and vacuum distribution system requires regular service. These systems may be constructed utilizing two

vacuum pumps with the secondary pump providing redundancy when the primary pump is being serviced or has failed.

External vacuum systems must provide adequate flow and vacuum for remote APCs to operate correctly. Proper flow must be monitored or validated as incorrect flow affects APC accuracy. Some remote APCs have built in flow monitoring providing assurance of correct air sample flow.

Cleanroom classification (validation) or process monitoring:

Understanding the difference between cleanroom classification and process monitoring is important when configuring and using particle counters.

Airborne particle counters perform certification testing and the operational process environmental monitoring required within pharmaceutical manufacturing facilities. Classification and process monitoring are distinctly different activities and should be approached as such. GMP Annex 1[3] states "Cleanrooms and clean air devices should be classified in accordance with EN ISO 14644-1. Classification should be clearly differentiated from operational process environmental monitoring."

Cleanroom Classification

Cleanroom classification, often referred to as cleanroom validation is the formal testing of the environment utilizing ISO 14644-1 criteria. The

selections of sample locations, sample volumes as well as other requirements are defined within this ISO Standard.

In addition, GMP Annex 1 has additional certification requirements such as:

1. Monitoring both 0.5 and 5.0 micron particle sizes.
2. Isokinetic sample probes are required when testing unidirectional airflow facilities. *(There is no mention of Isokinetic probes within ISO 14644-1)*
3. Particle sample tube lengths are limited to as short as possible. ([9]Some standards allowed for up to 3 meter sample tubes when testing for particles between 2 and 10 micron)
4. Testing in Operational and At-rest states; with operational testing allowing for normal operations, simulations or media fills.

Sequential Sampling[2] is inappropriate even for larger sample volumes.

Table 1

GMP Annex 1 (2014)	**Maximum permitted number of particles per meter^3 equal to or greater than the tabulated size**			
	At Rest		**In Operation**	
Grade	**0.5µM**	**5.0µM**	**0.5µM**	**5.0µM**
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	Not Defined

Source www.picscheme.org /PE 009-11

The completion of a successful classification activity provides that the air quality of the environment (under test) for non-viable particles is within acceptable parameters. This requires a high level of confidence that

most of the cleanroom or clean zone will comply with the maximum particle concentration limit for the target class of air cleanliness. To perform this testing, sample locations are evenly located in a grid throughout the environment under test. This number of sample locations and sample positions may be best obtained with the use of a portable particle counter or a combination of portables and fixed-point remotes. Additional locations based upon risk assessment may be optionally included however; there is no requirement for the inclusion of these sample points within the certification of the clean space. Non-viable particle testing does not take into account the microbial levels within the environment.

Environmental Monitoring in an Operational Process

Operational process environmental monitoring is not a classification activity rather the ongoing monitoring of high risk operations. It is the continuous particle monitoring of critical locations with alarming and notification systems to alert operating personnel of conditions approaching operational limits or outside of operational limits. Important also is the logging of responses by operating personnel to these alarms and warnings. Such data may become part of the batch release information.

Critical areas requiring monitoring are areas where the sterilized drug product, containers and enclosures are exposed to environmental conditions that must be designed to maintain product sterility. These areas are "critical because an exposed product is vulnerable to contamination and will not subsequently be sterilized in its immediate container"[1]. GMP Annex 1 states that high-risk operations are performed under Grade A conditions, usually referring to uni-directional airflow environments. Areas specifically listed are:

1. Filling Zones
2. Stopper bowls
3. Where there are open ampoules or vials
4. Where there are aseptic connections being made

The sample locations should be based upon a formal risk analysis study included in the justification of these locations. Use of previous classification and monitoring data should be part of the risk assessment. It is important to note that the recommended locations should NOT be based upon ISO 14644-1 grid patterns.

Grade A or critical operations require particle monitoring without gaps for the full duration of the processing including equipment assembly. Exceptions include processes that present a hazard to the instrument or personnel. These include powder-filling operations, radiological or biological hazards. Monitoring prior to the hazard exposure and during simulations is required.

Grade A zones shall be monitored with a frequency and sample size that allows for the detection of all interventions, transient events and any system deterioration. Alarms are triggered if alert limits are exceeded or there is any system deterioration.

Grade B environments require similar monitoring however the frequency of this monitoring may be reduced. The frequency and sample size should be such that the detection of any changes in contamination levels or system deterioration will trigger alarms if alert limits are exceeded or there is a malfunction of any component of the monitoring system.

System deterioration

System deterioration is a reflection on the particle counters themselves as well as any component of the data collection system attached to the particle counters. This system deterioration may include;

1. Failure or loss of communication of any component including operator panels, displays or indicators and annunciators.
2. Particle counter failure or loss of communication.
3. Inadequate sample flow due to vacuum system failure or obstruction.
4. Particle counter laser diode failure or decrease in laser diode output.

5. Particle counter detector failure or malfunction due to excessive noise or contamination.

Timely notification (within 10 minutes) and the specific nature of the deterioration should be reported and recorded so that operating personal may respond accordingly.

Items 4 and 5 are extremely important and often overlooked in the specification and design of these systems. Low laser output, contamination or problems related to the particle detector might not be transmitted to the external system. This potentially is a very troublesome problem as during re-calibration it may be found that the particle counter has been either non-operational or marginally operational for some time. Products produced in the environment the APC has been monitoring subsequently are at increased risk due to undetected or unreported particle counter issues. These issues may arise from cleaning or decontamination of the critical environments these APCs are monitoring.

Particle Counter Fundamental Requirements

Airborne particle counters used for this monitoring must be of suitable design, reliability, durability and calibration.

Suitable design

A particle counter should be designed with the operational environment in perspective. It should not influence the environment it is monitoring. A particle counter that exhausts particles, or produces heat will create additional risks and contaminate the environment. Another consideration is the nature of the cleaning and decontamination associated with these environments. The particle counter should be designed to withstand these processes. Chemical compatibility for the variety of cleaning, sterilization and antifungal agents should be considered. Chemical compatibility should also extend to all fixtures, tubing and cable

materials that would be exposed to the various chemicals used during cleaning and decontamination.

Reliability and Durability

A point of consideration is the particle counters overall construction and durability. Particle counters use laser diodes as the light source in the detection and measurement of particles. Laser diodes have a finite life span that is further reduced by heat and operational current. Some particle counter designs are dependent upon sample air flowing through the particle counter to dissipate heat. When the facility is idle or during decontamination the external vacuum pumps may be turned off. With no airflow through the particle counter to dissipate heat, laser diode life may be reduced. Laser diode failure is the number one factor in remote particle counter repair or replacement. This is an important consideration in the selection of remote particle counters for this application.

Performance and Calibration

Any particle counter remote or portable used in testing, certification or monitoring of a cleanroom environment must be calibrated to perform per ISO 21501-4. This requirement is not limited to original calibration but any re-calibration must be done in accordance to ISO 21501-4. Various manufacturers support, distribution and service organizations have varying degrees of compliance and procedures with this standard. Third party unassociated calibration service organizations should be audited for their approach to calibrating the specific particle counters to be calibrated. Some particle counters are calibrated electronically and access to settings and thresholds may be password protected. This may limit a third party calibration organization from performing a full 21501-4 calibration.

Below is the minimum information that must be included in an

ISO 21501-4 Test report

a) Date of calibration;

b) Calibration particle sizes;

c) Flow rate;

d) Size resolution (with the particle size used);

e) Counting efficiency;

f) False count rate;

g) Voltage limit or channel of an internal pulse height analyzer (PHA).

Additional country specific recommended practices or requirements

Certain countries have specific airborne particle counter usage, performance and calibration requirements or recommended practices. Examples of some of these are:

Japan: JIS B 9921:2010[6]: "Light scattering airborne particle counter for clean spaces"

China: JJF 1190-2008[7]: "Calibration specification for airborne particle counter"

United States of America: IEST-RP-CC014[8]: "Calibration and characterization of optical airborne particle counters"

United States of America: ASTM F50 -12[9] "Standard Practice for Continuous Sizing and Counting of Airborne Particles in Dust-Controlled Areas and Clean Rooms Using Instruments Capable of Detecting Single Sub-Micrometer and Larger Particles"

United Kingdom:" PHSS: Technical Monograph Number 16(2008) [10] "Best Practice for Particle Monitoring in Pharmaceutical Facilities"

Factors to consider in the selection of remote particle counters.

The installation of a particle monitoring system in a regulated environment requires qualification and validation. All validation activities should be planned prior to starting. The validation program should be clearly defined and documented with SOPs to support this activity. Regardless of the qualification and validation approach, the following list of established parameters could be considered.

1. What type of product is being produced?
    a. This allows for the identification of special considerations such as hazards and other environmental conditions that may affect the selection of monitoring equipment.

2. Is the product terminally sterilized or aseptically filled?
    a. Identifies operational conditions that should be considered in designing the system.

3. What Grade are the cleanrooms or clean spaces to be monitored?
    a. This identifies possible locations and considerations for the number of points to be monitored. Operational limits for specific Grade cleanrooms are also to be considered.

4. What country or countries is the product being shipped to?
    a. This identifies any special destination country regulations or recommendations that will need to be addressed in the system design.

5. What type of manufacturing equipment will be used?
    a. This identifies critical locations to be monitored.
    b. This identify locations for the support equipment and utilities.

6. What type of remote APC will be used?
    a. Remote APC with built-in pump.

b. Remote APC without built in pump.

APCs with built in pumps are larger and may require AC voltage connections. Their placement may be more difficult.

7. What locations will be monitored?
    a. This should be based upon a formal risk assessment as well as any previous particle monitoring data, including cleanroom certification data.

Conclusion

Understanding the requirements and specifications of airborne particle counters specifically remote airborne particle counters used in pharmaceutical biopharmaceutical and radiopharmaceutical facilities is an important aspect in providing the required particle monitoring for these facilities. This article has provided the fundamental information that may be used in specifying or implementing remote airborne particle counters.

End of Technical Paper

Footnotes:

[1] US FDA "Guidance for Industry Sterile Drug Products Produced by Aseptic Processing- Current Good Manufacturing Practice" September 2004.

[2] ISO 14644-1:1999 "Clean rooms and associated controlled environments- Part 1: classification of air cleanliness" Note: This standard at the time of writing is being revised. Please refer to IEST.org for additional information regarding the current standard: 1999 and the Draft International Standard DIS: 2010

[3] "Pharmaceutical Inspection Co-Operation Scheme, Guide to Good Manufacturing Practice for Medicinal Products Annex 1 Manufacture of Sterile Medicinal Products PE 009-11, 1 March 2014". GMP Annex 1 refers to EU Annex 1 as well as PIC/S Annex 1. Both annex's are essentially the same document. As PIC/S Membership and Guidelines extend outside of Europe to the United States, South America and Asia it is more inclusive to refer to this Guidance as GMP Annex 1.

[4] Determination of particle size distribution — Single particle light interaction methods —Part 4:Light scattering airborne particle counter for clean spaces.

[5] JIS B 9921:2010: "Light scattering airborne particle counter for clean spaces" Source: Japanese industrial standards committee.

[6] JJF 1190-2008[7]: "Calibration specification for airborne particle counter" Source: China, state administration of quality supervision, inspection and quarantine.

[7] IEST-RP-CC014: "Calibration and characterization optical airborne particle counters" Source: Institute of Environmental Sciences and Technology (IEST)

[8] ASTM F50 -12 "Standard Practice for Continuous Sizing and Counting of Airborne Particles in Dust-Controlled Areas and Clean Rooms Using Instruments Capable of Detecting Single Sub-Micrometer and Larger Particles" Source: ASTM (formerly known as the American Society for Testing and Materials)

[9] PHSS: Technical Monograph Number 16(2008) "Best Practice for Particle Monitoring in Pharmaceutical Facilities". Source: Pharmaceutical and Healthcare Sciences Society

End of Technical Paper

