TECHNICAL PAPER

Risk Based Particle Monitoring In Pharmaceutical Manufacturing

Version 01. Rev 01. 08/15/2016

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Risk Based Particle Monitoring in Pharmaceutical Manufacturing

Introduction

Airborne particle counters are an important tool used in the environmental monitoring of pharmaceutical, bio-pharmaceutical and healthcare facilities worldwide. In addition to determining air quality as part of the facility qualification, particle counters are required tools used in confirming air cleanliness in critical areas where high-risk operations are carried out. Non-viable particle counters and their associated systems are part of a larger environmental monitoring program that includes;

- Non-viable particle monitoring of air
- Viable particle monitoring of air, surfaces and personnel
- Pressure differential monitoring
- Temperature and relative humidity monitoring

Computer Based Systems

Particle counters may be attached to a computer based monitoring and alarm system that handles data collection, report generation and alarm notification. These systems are referred to generally as a "Facility Monitoring System" FMS or more specifically as a "Non-Viable Particle Monitoring System" NVPMS. There may be other names for these systems and they may be part of a larger Laboratory Information Management System (LIMS). For purposes of discussion in this article NVPMS is used to describe a computer based non-viable particle monitoring system. These systems can monitor other environmental parameters such as temperature, relative humidity and pressure differential. Monitoring and data collection provides proof that critical environments are in control

prior to and during manufacturing operations. Any equipment, system or facility used in manufacturing pharmaceuticals should be validated[1] and be maintained in a validated state. The NVPMS system is more than several particle counters connected to a computer with a database. The NVPMS is a project that requires planning, qualification and validation. A risk-based approach should be used to determine the scope and extent of the validation.

The NVPMS project as with any part of an environmental monitoring program should systematically assess risks by the review of manufacturing processes and activities in relationship to equipment, facilities and personnel. The primary risk the NVPMS addresses is the quality of air in the manufacturing process environment.

Though there are various approaches with varying complexity for assessing risk, some type of scoring system should be used. Independent of the approach used the following items should be considered.

Considerations for the non-viable particle monitoring system:

1. Identify high-risk operations for particle monitoring.
2. Determine the optimal sample locations for monitoring.
3. Establish a monitoring frequency with alert and action levels.
4. Establish a system to verify the particle monitoring system is working effectively.
5. Establish and maintain the validated state of the non-viable particle monitoring system.

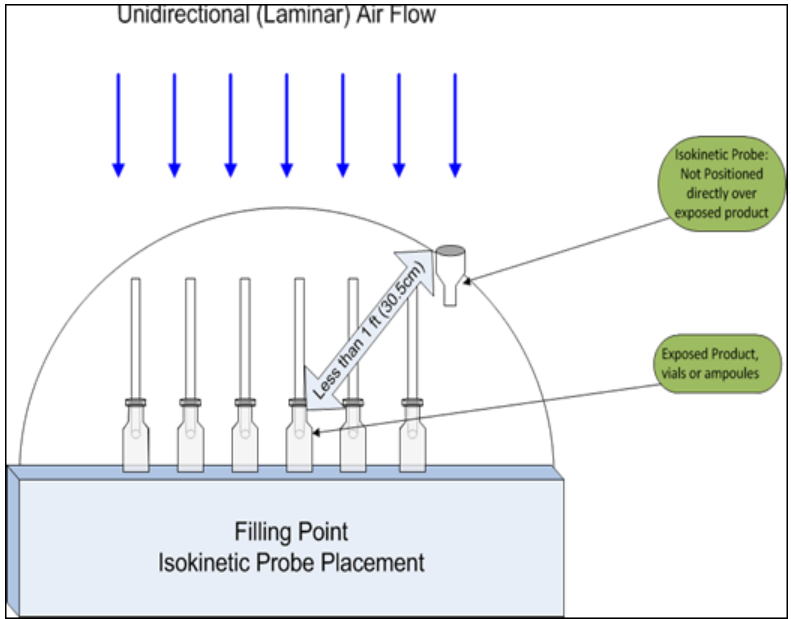
1. Identify high-risk operations for particle monitoring

GMP Annex[2] 1 states that cleanrooms and clean air devices are to be monitored in operation, with the monitoring locations based on a formal risk analysis study and the results obtained during the classification of cleanrooms and/or clean air devices.

Critical areas are where an exposed product is vulnerable to contamination and will not be subsequently sterilized in its immediate container.

Typically high risk areas in manufacturing are:[2]

- The filling zone (were containers are filled).
- Stopper bowls (were stoppers are loaded and kept prior to filling within the Grade A zone).
- Stopper insertion (the point stoppers are inserted into filled containers).
- Loading areas for freeze drying (where partially closed containers are loaded into freeze dryers (Lyophilizers).
- Isolator transfer devices.
- Transfer areas between Grade A and Grade B areas.
- Panels or access points (where operators are most likely to perform interventions or load components such as stoppers).
- Wherever there are open ampoules, viles and containers (turntables or the exit of a sterilization tunnel).
- Where there are aseptic connections.



It is in these locations within 1 foot (30.5 CM) of the operation where particle counting (when suitable) should occur prior to and during operations.

The NVPMS monitors air quality and address the risks associated with critical locations by providing an early warning system to detect and prevent contamination.

Figure 1: Isokinetic Sample Probe Placement Example

Per the FDA guidance[3], remote airborne particle counters are best suited for carrying out routine particle monitoring of critical locations. This is because remote particle counters are typically attached to the equipment. They are installed in such a way as to not interfere with manufacturing operations or disturb the airflow. The selection of the precise monitoring location as well as the attachment of the particle counter to the location is important.

Suitability of NVPMS components

The suitability of the remote particle counter, isokinetic sample probe and the associated vacuum system for the manufacturing operations must be considered not only upon cost but durability and continued operations.

The remote particle counter needs to be compatible with the environment being monitored. Points to consider for avoiding additional risks are:

a. The ability to withstand the operational environment: High heat and excessive humidity may be present during the operations carried out and may impact particle counter performance and service life. Particle counter failure or marginal operation during production creates additional risk.

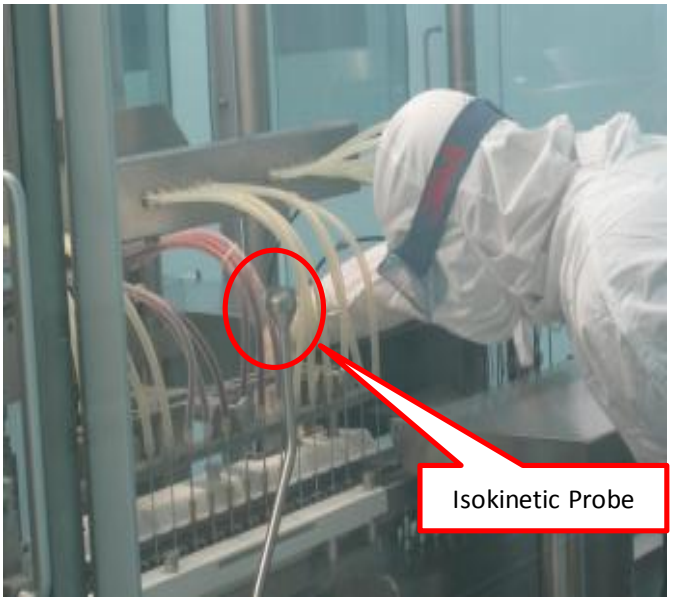
b. Chemical compatibility: The frequency and nature of cleaning and decontamination should be considered when selecting a remote particle counter, probes and fixtures. As the isokinetic particle sample probe will be located within 1 foot (30.5 CM) of filling and closing operations, it should be assumed the particle counter as well as the associated sample

probe, tubing and vacuum system will be exposed to the product being filled. Chemical compatibility as well as occupational safety and health of maintenance staff when servicing all these components should be considered. As product residue may be present during service and calibration activities.

Cleaning solutions may be applied directly to the surface of the particle counter or directly above it. These solutions may drip or accumulate on the upper surface of the particle counter. The particle counter should be constructed or installed in such a manner as to prevent the ingress of these solutions. Where there is a risk of this occurring the particle counter should be of a sealed design or it should be installed inside an enclosure to protect the instrument from cleaning and decontamination materials and activities.

Vapor decontamination cycles may also be frequently used. As some operations may require decontamination of the particle counter and it's associated sample probe. Vapor decontamination compatibility may also be an important consideration. Where most particle counter designs are for the infrequent and accidental exposure to vapor decontamination, frequent and intended exposure is in itself another associated risk that may need to be addressed. Failure modes in remote particle counters associated with vapor decontamination may include loss of calibration that could go undetected until recalibration. Particle counters intended for frequent and deliberate vapor decontamination should have significant test data to support the concentrations and methods used.

2. Determine the optimal sample probe locations for monitoring.



Specifically from the risks previously identified in the risk assessment.

Once a general location has been selected the placement of the isokinetic probe and particle counter are extremely important.

The isokinetic probe should be placed in a position that will best allow the particle counter to detect contamination.

Figure 3: Isokinetic Probe Placement
Probe positioned to detect elevated particle counts resulting from operators accessing critical areas during interventions or equipment set-up.

Probe placement example:

An example of this would be an operator access panel identified as being a location where an operator would perform an operation or intervention. The isokinetic probe is placed so that when the operation or intervention occurs the particle counter detects increased particles generated by the operation or intervention.

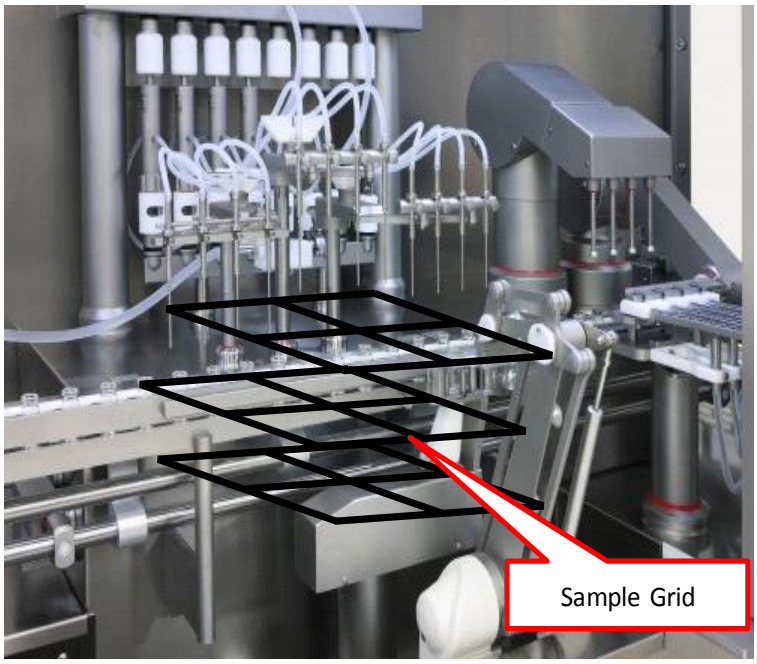


Figure 4: Sample grid at various hieghts

Testing with a portable particle counter during a simulation for this purpose is recommended. This is performed by using particle sampling grid patterns to test at locations considered and at various heights during actual or simulated interventions. The isokinetic probe and particle counter must be attached to the equipment and equipment design should also be considered.

The isokinetic probe and any fixtures used to attach the probe should not interfere with uni-directional airflow, equipment or personal. Airflow visualization is a useful tool for this. Each location must be documented as to why this position is monitored with supporting information as to the placement of the isokinetic probe.

3. Establish a monitoring frequency with alert and action levels.

How often particle counts are taken and reported as well as action and alert limits must be determined. Particle sample volumes and reporting frequencies are often a source of confusion. As particle data is reported in particles per unit volume, GMP Annex 1 and ISO 14644-1 indicate particle limits in particles/M^3 and remote particle counter flow rates have sample flow rates of 1 CFM (28.5 LPM). This leads to the confusion as a 1 CFM Instrument will take greater than 35 minutes to sample 1 M^3. However 35 minutes between particle data counts is too long for operating personnel to respond. Therefore, particle data should be recorded every minute and no interruptions in particle counting for

critical locations (Grade A). A rolling total may also be used that updates every minute showing the accumulated particles/M^3 based upon the last 35 samples. Normalization of particle count data in this application is not advised.

Though GMP Annex 1 does state that for Grade B operations sample frequencies may be reduced it is commonly accepted to use the same monitoring frequency as that of Grade A. Supplemental monitoring with sequential sampling systems for non-critical locations may also be deployed with consideration to the limitations of these such sampling.

Alert and action limits can only be determined by observations of actual operations, simulations or media fills. These limits may be different from the GMP Annex 1 or ISO Class limits. For 0.5µm particles a 95% confidence limit is considered.

The data for 5.0µm particles can be problematic as the limits (per GMP Annex 1) are low. However occasional detection of low levels of 5.0µm particles is acceptable. In Grade A regular or frequent occurrences of low levels of 5.0µm particles should be investigated. A common way to address this is to set alert limits for 5.0µm particles and action limits at 3 events in any 10 minutes for Grade A operations.

4. Establish a system to verify the particle monitoring system is working effectively.

It is required to have some type of indicator that the NVPMS is active, recording data and reporting conditions related to the environments monitored. There should be some way to notify personel of malfunctions or that alert and action limits have been reached.

This notification system should be visible to operators inside the manufacturing environment and any observers. It also should be such that it draws attention to problems in such a manner, as they cannot be ignored. This indicator may be an operator panel, light beacon with

audible alarm or some other visual and audible indicator. This indicator should also provide notification of particle counter problems such as low sample flow or loss of instrument calibration. This indicator is extremely important as it provides a single point status if the NVPMS is working and the environment is suitable for operations to be carried out. A common application is a three-color light beacon with the following status being displayed:

- Green: Indicating the NVPMS and all supporting components are operational and environmental conditions monitored are within operational specifications. (Environmental conditions may include particle counts, temperature, relative humidity and differential pressure).

- Yellow: Indicating environmental conditions have reached alert limits.

- Red: Indicating the NVPMS or supporting components require attention or that environmental conditions have reached Action Limits. Red indicators often are attached to an audible indicator that may be acknowledged or temporarily silenced by operator interaction.

5. Establish and maintain the validated state of the particle monitoring system.

Validation is ongoing and does not stop with the successful installation of the particle monitoring system. Equipment must have maintenance schedules and calibration must occur at predetermined times. As components or equipment may fail and need to be replaced, spare parts should be available. Spare parts and repair/replacement SOPs should be on hand so that operations continue uninterrupted. System re-validation should occur at specific intervals to determine the NVPMS is operating correctly and remains in the validated state. Calibration to current industry practices[5] is mandatory. Per ISO 14644-1 calibration and re-calibration is to be done in compliance with ISO 21501-4. Organizations

performing this calibration[6] should have the proper equipment, procedures and documentation to support all aspects of this calibration[4].

Footnotes:

[1] **Annex 15** to the EU Guide to Good Manufacturing Practice

[2] **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 accurate to refer to this Guidance as **GMP Annex 1**.

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

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

[5] **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**

[6] **ISO 21501-4** "Determination of particle size distribution — Single particle light interaction methods —Part 4:Light scattering airborne particle counter for clean spaces"