USING REMOTE PARTICLE MONITORING

in Isolators Microbiological Safety Cabinets, and Laminar Flow Benches

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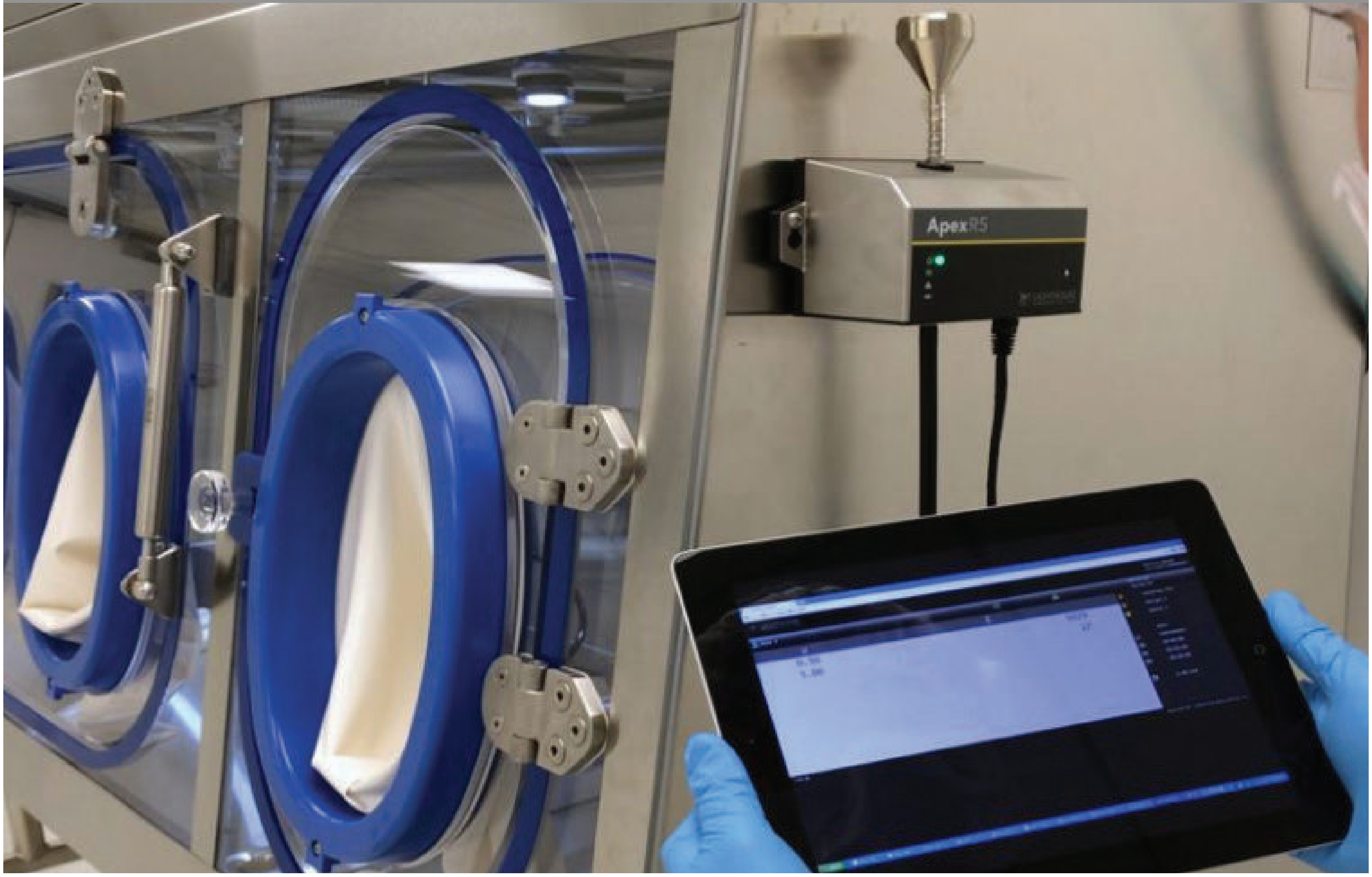
Overview

In controlled manufacturing environments, Isolators, Biological Safety Cabinets (BSCs), and laminar flow benches (LAFs) as well as barrier technologies are often crucial for maintaining clean and safe workspaces. However, each type of separative device offers unique features, applications, and levels of protection. Understanding these differences is essential for choosing the right equipment for specific tasks and ensuring adherence to regulatory standards.

Isolators and safety cabinets are crafted in various designs to meet specific needs. They can be generally categorized into three groups: enclosures that provide clean air to the process (e.g., vertical or horizontal laminar flow benches), those that safeguard the operator (e.g., Class 2 Biological Safety Cabinets), and those that completely separate the product from the operator with a physical barrier (various types of isolators). Each category presents distinct challenges for particle monitoring.

In September 2003, the EU-GMP Annex 1 revision established new standards for non-viable particle counting in pharmaceutical Grade A and B areas. While these updates have been widely covered in relation to cleanrooms, there has been less discussion on their application to Isolators and other separative devices, such as BSCs and LAFs. This guidance seeks to fill that gap and provide a clear pathway to compliance.



Operator monitoring particle counts in background ISO 7 environment next to isolator

Isolators

Isolators are enclosed systems designed to provide a physical barrier between the operator and the product or process. They completely isolate the product from the external environment, ensuring that both the operator and the product are protected.

Key Features:

Complete Isolation: Isolators offer the highest level of separation, protecting the product from contamination and the operator from potential hazardous materials.

Controlled Environment: They maintain a controlled internal environment, often with positive or negative pressure, depending on the application and product.

Versatility: Suitable for a range of applications, including sterile manufacturing, handling hazardous materials, and performing sensitive research.

Applications:

Pharmaceutical Manufacturing: Ensures sterility in the production of drugs.

Hazardous Material Handling: Safely contains cytotoxic or radiopharmaceutical substances.

Research and Development: Provides a controlled environment for conducting sensitive experiments.

Example Installation: In pharmaceutical facilities, remote particle counters are often installed to monitor air quality and to record the environmental data for cGMP compliance with batch releases. Remote particle counters are connected to monitoring system software allowing for operator notifications if any out of tolerance issues arise during the aseptic processing of a sterile product inside the Isolator, BSC or LAF.

Biological Safety Cabinets (BSCs)

Biological safety cabinets, also known BSCs, are designed to protect the operator, the environment, and the product from exposure to biohazardous or infectious agents.

Example of remote particle counter inside a BSC monitoring clean air passing over the critical processing zone

Key Features:

Operator Protection: Uses airflow and filtration to protect the operator from exposure to hazardous agents.

Product Protection: Prevents contamination of the product by providing a clean air environment.

Environment Protection: Ensures that harmful agents do not escape into the surrounding environment.

Types of BSCs:

Class I: Provides operator and environmental protection but no product protection.

Class II: Provides protection for the operator, product, and environment, making it suitable for work involving microorganisms in containment levels 1, 2, and 3.

Class III: Offers the highest level of protection by being entirely enclosed and ventilated, used for high-risk biological work.

Applications:

Microbiological Research: Used in laboratories handling pathogens.

Clinical Testing: Ensures safety in diagnostic laboratories.

Vaccine Production: Maintains sterility and safety during the production process.

Example Installation: In a hospital production facility, particle counters might be connected to a vacuum line with a filter capsule on the exhaust to prevent hazardous material from exiting the isolator, ensuring safety and compliance.

Laminar Flow Bench

Laminar flow benches are designed to provide a clean air environment by projecting a laminar flow of HEPA-filtered air across the work surface, protecting the product from contamination.

Key Features:

Product Protection: Ensures a clean work surface by directing filtered air in a uniform flow.

No Operator Protection: Unlike BSCs, laminar flow benches do not provide protection for the operator.

Types of Flow: Can be either horizontal or vertical, depending on the direction of airflow.

Applications:

Laboratory Work: Suitable for general lab work requiring a clean environment.

R&D Facility: For product protection from external contamination

Electronics Manufacturing: Provides a dust-free environment for assembling sensitive electronic components.

Operator working on liquid product inside LAF cabinet with horizontal HEPA filtration

Example Installation: In electronic manufacturing, a laminar flow bench might be used to ensure that no particulates contaminate sensitive components during assembly.

Why is Particle Monitoring Important?

The updated EU-GMP Annex 1 reflects a growing recognition of the importance of particle monitoring. The guidelines now require continuous monitoring of particles in Grade A zones and recommend it for Grade B areas. For Grade A areas, the monitoring must detect particles >0.5μm and >5.0μm continuously during production. This requirement extends to any isolator or safety cabinet classified as a Grade A area, necessitating compliance with these stringent monitoring standards. In order to meet EU-GMP Annex 1, these areas must be properly monitored. Note that Grade A zones are equivalent to ISO 5 certified environments.

Proper monitoring begins with correct installation and a proper understanding of the key considerations to be made during install. The following information will help you determine which setup is right for your facility and its needs.

Installation Considerations

for Isolators, Biological Safety Cabinets, and Laminar Flow Cabinets

Isolators

Installing remote particle counters into isolators involves several steps to ensure accurate monitoring and compliance with safety standards. Here's a general overview of the process:

Planning and Design:

Assessment: Begin with a thorough assessment of the isolator's design and the specific requirements for particle monitoring.

Location Selection: Determine the optimal locations for sampling points, considering areas where contamination is most likely to occur. Most Isolators come with standard access points.

Safety Considerations: Conduct a risk assessment to address potential hazards and ensure the installation does not compromise the isolator's containment.

Selection of Equipment:

Particle Counter Selection: Choose a particle counter that fits the specific needs of the isolator, such as footprint, flow rate, sensitivity, and compatibility with the isolator's environment.

Sampling Probes: Select appropriate sampling probes, ensuring they can be integrated with the isolator without disrupting operations and gather meaningful data.

Sterilization of Particle Counter: Select a particle counter that has is compatible with VHP and has a proven track record showing the resistance of the sensor components to VHP.

Integration with Isolator:

Port Installation: Install sampling points in the isolator. This may involve making precise openings in the isolator walls to insert the sampling probes. Work with the Isolator supplier on custom port locations which may have been determined by a risk assessment.

Sealing and Containment: Ensure that the points are sealed properly to maintain the isolator's integrity and prevent leaks. Again, work with Isolator vendor on this and add validation of the seals into the IQ/OQ.

ISO/TR 14644-21: Should be consulted to assist in particle losses in transport tubing to ensure tube length, bends are within acceptable limits. You may have to validate the particle losses in the transportation tubing.

Connect to Particle Counter:

Tubing Installation: Connect the sampling probes to the particle counter using appropriate tubing. The tubing should be routed in a way that does not interfere with the isolator's operation. (ISO/TR 14644-21)

Exhaust Handling: If the sample air is potentially hazardous, incorporate a filter system or route the exhaust air to a safe handling unit to prevent contamination.

Calibration and Validation:

System Calibration: Calibrate the particle counter to ensure accurate readings. This involves setting the flow rate and verifying the particle sizing and sensitivity of the counter. (ISO 21501-4 calibration is highly recommended).

Validation: Validate the entire system to confirm it meets regulatory requirements and performs as expected under operating conditions.

Monitoring and Maintenance:

Continuous Monitoring: Set up the particle counter for continuous monitoring during production to detect any deviations in particle levels.

Regular Maintenance: Perform regular maintenance and calibration of the particle counter to ensure ongoing accuracy and reliability. At least an annual calibration should be setup.

Isolator Installation Examples

Direct Ducting: In one facility, the exhaust from the air sampling pump of the particle counter was ducted back into the building's air handling unit, which was filtered before discharging into the open air. This approach ensures that the particle monitoring system does not compromise the containment integrity of the isolator and ensures a safe working environment for operators.

Filter Capsule Integration: For sampling from cytotoxic and radiopharmaceutical isolators, a filter capsule was incorporated into the vacuum line within the production area. This setup prevents hazardous material from exiting the facility and ducts the exhaust back to the air handling system, providing a dual-layer safety measure.

Tips for Installation:

- Use of external sampling with air drawn through secure tubing to avoid breaching the isolator's integrity may be an option but ensure the exhaust air is safely recirculated back into the Isolator filtration system.
- Employ particle counters designed for compatibility with decontamination procedures.
- Opt for compact particle counters when space is severely restricted. Remote particle counters work best but some small footprint portable particle counters may be suitable.

Installation Considerations

for Isolators, Biological Safety Cabinets, and Laminar Flow Cabinets

Biological Safety Cabinet Installations

Hospital Pharmacy:

In a hospital pharmacy compounding area, a remote particle counter is installed with the sampling point located near the center of the BSC's working area above the working area within 12". Tubing runs externally to a wall-mounted particle counter, with the exhaust air filtered through a HEPA filter before being routed back into the BSC's exhaust system.

Pharmaceutical Manufacturing:

In a pharmaceutical production facility, remote particle counters are installed in multiple BSCs with centralized monitoring. The sampling points are placed at strategic points to capture representative samples, and the exhaust air from all counters is ducted to a central filtration unit before being expelled. The strategic sampling points are typically selected based on a risk assessment of process flow, environment, equipment, people and product flow and where the product integrity is most at risk.

Tips for Installation:

- Position sampling probes to minimize airflow disruption, ensuring isokinetic sampling.
- Ensure the area over the critical processing zone is monitored by the particle counter.
- Implement procedures to account for and mitigate the effects of aerosols on particle count data.
- Use particle counters with minimal intrusion to avoid interfering with cabinet operations.

Installation Considerations

for Isolators, Biological Safety Cabinets, and Laminar Flow Cabinets

Laminar Flow Cabinets

Laminar flow benches are designed to provide a sterile working environment by directing HEPA-filtered air across the work surface. Integrating remote particle counters into these benches requires careful planning to ensure accurate monitoring without disrupting the laminar airflow. Here are the steps and considerations for installing remote particle counters in laminar flow benches:

Selecting the Appropriate Particle Counter:

- Choose a particle counter that is compact and suitable for the specific environment of a laminar flow bench.
- Ensure the particle counter has the appropriate flow rate and sensitivity to detect particles of interest (e.g., >0.5µm and >5.0µm).

Positioning the Sampling Probe:

- The sampling probe should be placed in a location that accurately represents the air quality over the critical zone work surface without interfering with the laminar flow.
- Typically, the probe is positioned at a height where it can sample air from the HEPA filter passing over the critical zone, but not too close to the critical zone to avoid contamination from the processes being sampled. The objective of the particle counter is to ensure clean air is passing over the critical processing zone.

Ensuring Isokinetic Sampling:

- Isokinetic sampling ensures that the air entering the sampling probe is at the same velocity as the surrounding airflow, preventing distortion of particle concentration measurements which provide more accurate results.
- Use specially designed isokinetic probes that match the airflow characteristics of the laminar flow bench.

Routing the Sample Tubing:

- The sample tubing should be routed carefully to avoid any disruption to the laminar airflow.
- Secure the tubing along the walls or framework of the bench to keep it out of the work area and maintain a clean, organized workspace.
- Having a flexible sampling point is something to consider where the sample location can be manually moved around the LAF based on process configurations.

Connecting to the Particle Counter:

- Connect the sample tubing to the particle counter, ensuring all connections are airtight to prevent leaks.
- Position the remote particle counter above the critical work area to avoid any potential contamination and to facilitate easy access for maintenance.

Monitoring and Calibration:

- Regularly monitor the particle counter's readings to ensure it is functioning correctly and providing accurate data.
- Perform routine calibration and maintenance according to the manufacturer's guidelines to maintain the reliability of the particle counter.

Laminar Flow Installations:

Horizontal Laminar Flow Benches:
In a horizontal laminar flow bench, the sampling probe can be placed towards the back of the work surface, ensuring it does not obstruct the airflow or workspace but monitors the clean air passing over the critical process zone.

The sample tubing is routed to the side or back of the bench, connected to a particle counter mounted externally.

Vertical Laminar Flow Benches:
For vertical laminar flow benches, the sampling probe can be installed towards the top of the work surface, where the clean air first contacts the critical zone.

Custom Configurations:
In specialized applications, custom brackets and mounting solutions can be used to position the sampling probe and particle counter optimally.

These configurations ensure minimal disruption to the laminar flow and maintain a sterile environment.

Tips for Installation:

- Use low-profile, isokinetic sampling probes specifically designed for laminar flow environments.
- Route sample tubing outside the work area to maintain sterility and prevent airflow disruption.
- Regularly calibrate and maintain particle counters to ensure consistent and reliable performance.

Common Considerations Across All Devices

Calibration and Maintenance:

- Regular calibration is necessary to ensure particle counters provide accurate and reliable data. This is particularly challenging in environments where decontamination processes can affect instrument performance.
- Maintenance schedules must be established to prevent downtime and ensure continuous monitoring, which is crucial for compliance with regulatory standards.
- ISO 14644-1:2015 standard requires particle counters used to certify cleanrooms are calibrated to ISO 21501 standard.

Data Integration:

- Integrating particle count data with environmental monitoring systems requires careful planning to ensure real-time data availability and compliance with regulatory reporting requirements.
- Appropriate Alarms need to be configured that trigger on trends rather than one off events.
- Data interpretation must consider the specific challenges and operational characteristics of each controlled environment to avoid misinterpretation and ensure meaningful insights.

Risk Assessment:

- Conducting thorough risk assessments before installation and operation of particle counters helps identify potential hazards and establish appropriate safety measures and gather meaningful data.
- Contingency plans must be in place to address any breaches in containment or disruptions to sterile conditions, ensuring swift and effective responses to any issues that arise.
- Ensure there is redundancy built into the system to avoid longer than necessary down times.

Conclusion

Remote particle monitoring in isolators, biosafety cabinets, and laminar flow benches is essential for maintaining clean and safe working conditions in controlled environments. Each type of device—whether it is an isolator providing complete isolation, a biosafety cabinet protecting both the operator and the product, or a laminar flow bench ensuring a sterile workspace—presents unique challenges for particle monitoring. Understanding these differences is crucial for selecting the appropriate equipment and ensuring compliance with regulatory standards.

Across all devices, regular calibration, maintenance, and integration of particle count data with environmental monitoring systems are vital to ensuring accurate monitoring and regulatory compliance. By addressing these challenges and implementing effective solutions, we can maintain the integrity and safety of controlled environments, supporting the high standards required in pharmaceutical and research applications.

By understanding and addressing these challenges, particle monitoring in isolators, biosafety cabinets, and laminar flow cabinets can be effectively managed, ensuring the integrity of the controlled environment and compliance with regulatory standards. While particle monitoring in isolators may initially seem daunting, careful design and the right equipment make it achievable.