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SETTING APPROPRIATE ALARMS

for Particle Monitoring Systems following CGMP

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Overview

Setting appropriate alert and action alarms for particle monitoring systems is essential for maintaining compliance in cleanroom environments. These alarms play a crucial role in adhering to regulatory standards, such as EU GMP Annex 1 and ISO 14644-1. Alert limits signal deviations from normal conditions, prompting increased monitoring, while action limits indicate significant issues that require immediate corrective measures.

Continuous monitoring offers significant advantages, including real-time detection of deviations and comprehensive data for assessing cleanroom performance. This approach allows facilities to proactively manage contamination risks and maintain product quality throughout the manufacturing process.

When establishing alarm settings, it's important to base them on thorough risk assessments and historical data trends specific to the cleanroom environment. Implementing continuous non-viable particle counting further enhances monitoring by allowing for early detection of potential issues, such as equipment malfunctions or breaches in contamination control.

By prioritizing a robust alarm rationale and continuous monitoring system, cleanroom operators can ensure high environmental standards, uphold product integrity, and demonstrate compliance with critical regulatory requirements. This proactive strategy not only protects product quality but also supports ongoing process improvement.

Section Header

Alarm Testing Overview

Alarms are typically configured based on per-minute particle data, with thresholds set for different particle sizes. The purpose is to warn operators of potential contamination while maintaining operational flexibility.

Example thresholds include:

- **0.5-Micron Particles:**
  - Action alarm at 100 particles per cubic foot (p/ft^3) or more.
  - Warning alarm at 75-99 p/ft^3.
- **5-Micron Particles:**
  - Warning alarm with 1 particle detected.
  - Action alarm with 2 or more particles detected.

These thresholds aim to detect contamination early without introducing oversensitivity, which could disrupt operations with false alarms.

3. Objectives and Constraints

The goal in a Grade A cleanroom is to keep particle counts as low as possible, particularly for 5-micron particles, where historical thresholds have been set to zero. However, practical monitoring systems now allow slightly more flexibility, aiming for zero particles while still permitting minimal particle counts that trigger yellow alert warnings before reaching critical levels. When monitoring the concept is to look for trending rather than one off events.

4. Test Procedure for Alarm Setting Validation

To ensure alarm thresholds function correctly, the following test procedure is used:

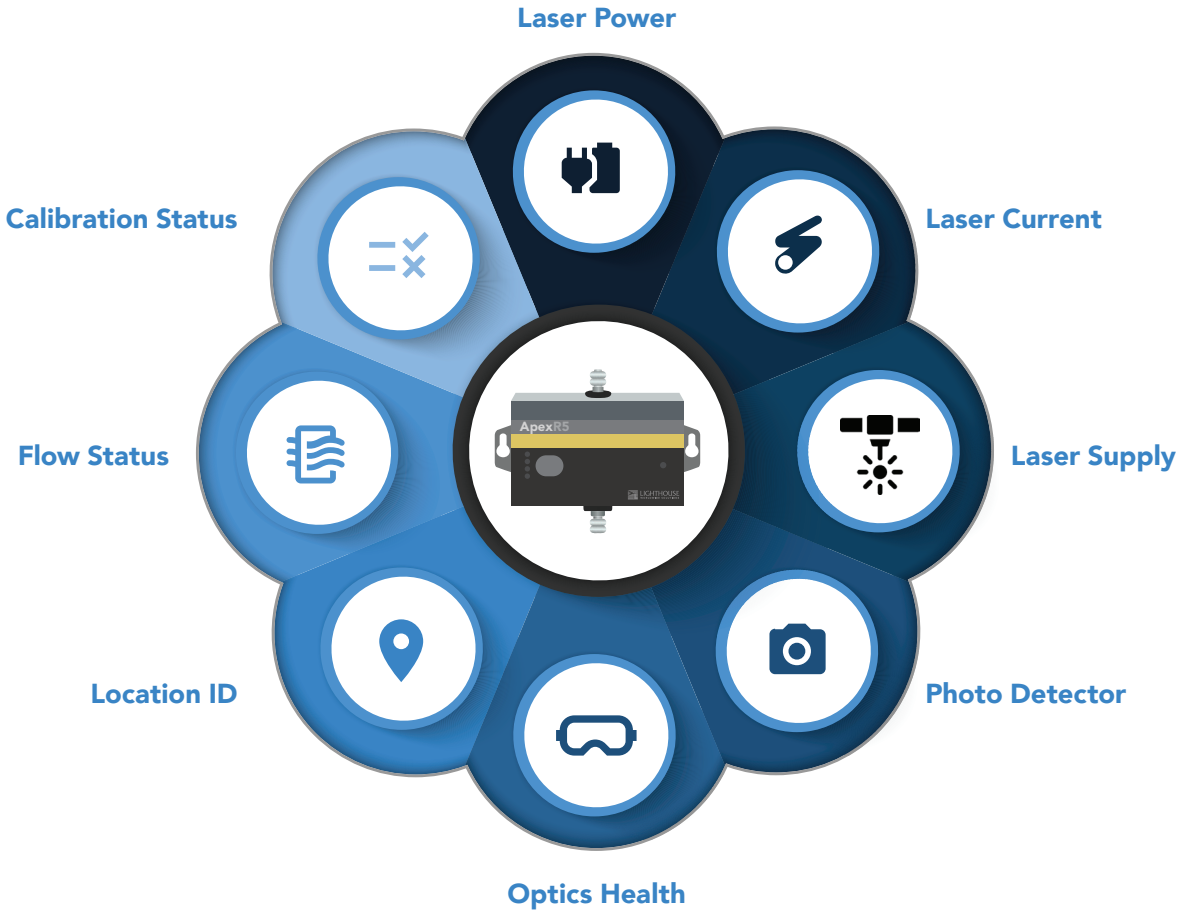
1. **System Setup:**
   - Ensure that the particle counter flow rate and update rate are set appropriately for the cleanroom environment.
   - The counter should be able to record data every minute for real-time monitoring.
2. **Alarm Threshold Configuration:**
   - Set the alarm thresholds for 0.5-micron and 5-micronparticles based on predetermined limits:
   - 0.5-micron particles: Yellow alarm for 75–99 p/ft³, red alarm for 100+ p/ft³.
   - 5-micron particles: Yellow alarm for 1 particle, red alarm for 2+ particles.
3. **Testing Procedure:**
   - Introduce controlled contamination into the environment by injecting quantities of 0.5-micron and 5-micron particles.
   - Measure the response of the particle counter and ensure that the yellow alarm is triggered when particle counts reach the lower threshold, and the red alarm is triggered at the higher threshold.
   - Record any false positives or missed alarms during testing.
4. **Volume-Based Monitoring:**
   - At the end of the production run, review the total particle volume sampled vs. the total counts.
   - Compare the results to ensure the environment still meets Grade A classification.
5. **Adjustment and Calibration:**
   - Adjust the alarm settings if necessary to avoid oversensitivity, especially for the 5-micron particles, which are particularly critical in a Grade A environment.
   - Re-test until the alarm system accurately reflects real-world particle levels without excessive false alarms.

Procedure Step	Specified Result	Actual Result	Verified by:
Background Count	Room should met ISO Class 5 / Grade-A conditions after a 5-min purge, with < 100 particle/ft³ (0.5µm) and < 1 particle/ft³ (5.0µm). Record 3 successive counts		
Zero Count Filter	After 5 minutes, particle counter should report 0 particles/ ft3 for both 0.5µm and 5.0µm channels		
High Particle Count Test	Introduce high particle count by tapping the sample inlet. Both channels should register increased counts		

5. Conclusion

Setting appropriate alert and action alarms is essential for ensuring product safety and regulatory compliance in cleanrooms. This procedure helps verify the functionality of the alarms, ensuring they are sensitive enough to detect contamination while avoiding unnecessary disruption due to false alarms. The balance between operational efficiency and safety is maintained through regular testing, calibration, and analysis of real-time monitoring data.

Every Data Record **Should** Include a Health Check of all Sensor Components



PQ Test:

Validation of Alarm Limits using Statistical Process Control (SPC)

1. Objective

- This test validates the alarm limits for a particle monitoring system by correlating particle counts with practical thresholds, ensuring they remain effective without being overly sensitive. A focus on 5.0µm particles and the use of Statistical Process Control (SPC) are key elements in this test.

2. Procedure Steps

- **Setup Alarm Thresholds:**
  - Using the 5.0µm threshold, start with an action alarm set to 1 particle per cubic foot based on the calculation of 20 particles/m^3.
  - This will yield an initial action alarm limit of 1 particle per cubic foot for 5.0µm particles. However, due to real-world variables such as vibration, electronic noise, and dark noise, this threshold is very tight and prone to false alarms so SPCs are used to ensure that the monitoring system is seeking out trends rather than one off events.

- **SPC Approach:**
  - Introduce **Statistical Process Control (SPC)** by setting up X out of Y alarms instead of a one-off alarm trigger. This allows trending of data, reducing false positives.
  - **Example:** Trigger alarms only if **2 out of 3 readings** exceed the limit for **5.0µm particles**. Adjust these thresholds after considering real-time operations, downstream air sampling, and intervention impacts.
- **Risk-Based Assessment:**
  - Perform a risk assessment to define appropriate thresholds based on operational conditions.
  - Consider setting the alarm for **2 out of 3 readings** or adjusting further to **5 out of 7 readings**, or where the systems comfort zone is based on viable data from air sampling and gowning conditions and even operator interventions during simulation media runs. (Validate at what level of particle concentration would the product be contaminated with a viable particle).
- **Intervention Testing:**
  - Introduce operator interventions during production to measure the effect on particle counts and the operators gown up aseptic conditions. (Is the operator a cause for contamination? Are they gowned up aseptically and are they maintaining aseptic gowning?)
  - Monitor downstream sampling for particle spikes and confirm recovery to baseline conditions within the next sample window. Failure to recover could indicate equipment failure, such as a **HEPA filter issue or operator contamination.**
- **Root Cause Analysis:**
  - If particle levels do not return to baseline, perform a root cause analysis to identify potential system failures or contamination sources. The system's ability to recover is key to determining if an alarm event reflects a serious contamination issue.

3. Objective

Procedure Step	Expected Result
Alarm Threshold Test	Thresholds set at 1 particle/ft3 for 5.0µm particles, applying SPC logic.
Risk-Based Threshold Validation	Validate risk-based thresholds using X out of Y events, ensuring practicality.
Operating Intervention Impact on Particle Counts	Observe particle spikes, ensuring baseline recovery within the next few samples.
Post-Intervention Monitoring	Particle counts should return to baseline after interventions or action alarms.

4. Conclusion

This PQ test ensures that alarm limits are appropriately set to detect actual contamination risks while reducing false alarms. The use of SPC and risk-based assessments offers a practical approach to alarm management, balancing sensitivity with operational feasibility. The validation of these alarms and SPCs can add confidence in the systems performance and ability to avoid nuisance alarms.

Appendix A

Statistical Process Control (SPC) Note:

If your application is prone to nuisance alarms, then SPCs may be more suitable for your alarming notifications.

To apply X out of Y events in Statistical Process Control (SPC) analysis, follow these steps:

1. **Define X and Y:** Determine the number of consecutive events (Y) you want to monitor, and how many (X) out of these events would be considered a threshold for action. For example, if 2 out of 3 events exceed limits, an alarm is triggered.
2. **Monitor Data Trends:** Track data in real time and apply SPC to detect trends or recurring out-of-specification (OOS) events.
3. **Set Action Triggers:** When X out of Y consecutive events exceed your pre-set threshold (such as particle counts), initiate corrective action.

This approach allows you to balance sensitivity with practicality, focusing on sustained trends rather than reacting to single anomalies.

Q. How does Statistical Process Control help in trend monitoring?

Statistical Process Control (SPC) helps in trend monitoring by providing a data-driven approach to

track variations in a process over time. SPC uses control charts to distinguish between **common cause variations** (natural fluctuations within the process) and **special cause variations** (abnormal fluctuations requiring intervention). By applying SPC, trends can be monitored to detect when a process shifts beyond acceptable limits, enabling timely corrective actions. It also helps in identifying consistent patterns that may indicate potential future issues, preventing defects and optimizing process control.

Q. What are advantages of applying SPC to Particle Monitoring Systems?

Applying **Statistical Process Control (SPC)** to Particle Monitoring Systems offers several advantages:

1. **Trend Detection:** SPC identifies trends and patterns in particle counts, allowing operators to address issues before they become critical.
2. **Early Warning:** It helps differentiate between normal variations and true process deviations, leading to earlier warnings of contamination.
3. **Process Stability:** By monitoring particle data over time, SPC maintains process stability and quality control.
4. **Reduced False Alarms:** SPC reduces false positives by focusing on trends rather than single, isolated anomalies.

These advantages improve overall cleanroom performance and product quality.

In the 2022 revision of **EU GMP Annex 1, Section 9** discusses the importance of continuous environmental monitoring in sterile manufacturing environments. Specifically, it emphasizes that alert and action limits should be scientifically justified, based on the performance of the cleanroom or controlled area during routine operations. The limits set for alarms must ensure the detection of any contamination risk to the product without being overly sensitive to minor disturbances that could cause **nuisance alarms**.

For alarms in **particle monitoring systems**, the document encourages using a **risk-based approach**. It recommends considering factors like **process type, production flow, and critical control points**. Alarm thresholds should be adjusted for **real-time monitoring** and should reflect the cleanroom's ability to maintain required conditions under normal operations and during interventions.

The document also underscores that alarm systems should not solely rely on one-off events but instead focus on **trends** and **repeat occurrences** that could indicate potential contamination. Therefore, **Statistical Process Control (SPC)**, like the **X out of Y approach**, is particularly useful for setting alarms to minimize unnecessary shutdowns while ensuring a quick response to significant deviations.

EU GMP Annex 1: 2022, Section 9 also focuses on **environmental and process monitoring** for sterile manufacturing, providing specific guidance on the **setting of alert and action limits** for both **viable and non-viable particles**. Key references to alarms and monitoring include:

1. **Alert and Action Limits:**
Appropriate alert and action levels should be set for particle and microbiological monitoring. These limits must be scientifically justified and based on the cleanroom qualification results, and they should be periodically reviewed using trend data. This ensures that any deviations are detected early before contamination risks escalate.

2. **Trend-Based Monitoring:**
The section emphasizes the importance of **trend analysis** in determining adverse trends in the cleanroom environment. Rather than reacting to isolated events, the system should detect repeat occurrences that indicate a possible deterioration in environmental control. This approach is crucial for preventing **nuisance alarms** by focusing on **meaningful data trends** rather than sporadic

fluctuations.

3. **Statistical Process Control (SPC):**
The concept of using **SPC** to monitor particle counts in real-time is referenced, where alarms are set based on continuous monitoring trends. For instance, monitoring thresholds such as **X out of Y** events are suggested for real-time monitoring to minimize unnecessary shutdowns due to one-off events like **vibration or electronic noise**.

These guidelines encourage a risk-based approach to monitoring, suggesting that systems should be calibrated and alarm thresholds set according to the criticality of the process and the environment. More stringent action limits may be applied based on ongoing data trends and contamination control strategies. It is also important to periodically review alarms, and the effectiveness of the alarm system based on six monthly or annual data from batch results both for viable and non viable data.

Appendix B

Nuisance Alarm Note

In the context of particle monitoring systems, a nuisance alarm refers to an alarm that is triggered due to false positives or non-critical events, rather than actual contamination issues. These alarms can result from factors such as electronic noise, vibrations, or other environmental conditions that momentarily affect the particle counter without indicating a real contamination threat. Nuisance alarms lead to unnecessary interventions, disrupt normal operations, and reduce the efficiency of the monitoring system. SPC helps minimize these by focusing on trend-based alarms rather than single events.

In **aseptic manufacturing processes**, particles generated by operators or equipment may not necessarily be biological or viable in nature. These particles can include dust, clothing fibers, or other inert materials that do not pose a microbial contamination threat. Despite this, such particles can still trigger nuisance alarms, especially if particle counters are too sensitive. While these non-viable particles don't carry microorganisms, their detection in critical areas can prompt unnecessary interventions. Proper calibration and the use of **Statistical Process Control (SPC)** can help distinguish between harmless particles and actual contamination risks.

Other Nuisance alarms in particle monitoring systems are typically caused by several factors, including:

1. **Electronic Noise:** Interference from electrical equipment can cause false particle counts.
2. **Vibration:** Mechanical vibrations from equipment or building structures can influence particle counters, leading to false readings.
3. **Dark Noise:** Environmental factors such as solar radiation or background light can cause particle counters to register false particles.
4. **Air Turbulence:** Sudden airflows or disturbances can temporarily increase particle counts, triggering alarms.
5. **Calibration Issues:** Incorrect or infrequent calibration of particle counters can also contribute to nuisance alarms.
6. **Particle losses** in sample tubing are an issue and require validation according to ISO/TR 14644-21. Any vibration along the sample tubing can trigger a false positive alarm. It is important that the sampling system is set up following the guidelines of ISO/TR 14644-21.

By identifying and mitigating these factors, you can reduce unnecessary alarms and improve system reliability.

Appendix C

Regulatory requirements for Setting Monitoring Systems Alarms

EU GMP Annex1:2023
In EU GMP Annex1, cGMP states that the sample volume should not be that used in Cleanroom Certification following ISO 14644-1 and the update rate is based on the sample period time of the particle counter which is typically every minute.

If you apply ISO 14644-1 particle count/volume count thresholds to real time monitoring and setting your thresholds in line with current tables for Certification/Classification based on EU or ISO 14644-1 standards, then you are at risk of setting your alarming system up with an unworkable alarm sensitivity. (Nuisance Alarms)

9.21 The size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.

FDA Sterile Drug Products Produced by Aseptic Processing (2004)
The FDA guidance on sterile drug products highlights that alarm systems in cleanrooms should rapidly detect atypical changes in environmental conditions, such as pressure, particle counts, or microbiological contamination. For trending, it recommends continuous monitoring of critical areas (e.g., Class 100 or ISO 5) with systems like remote particle counters to track air quality. Trends in environmental monitoring should be used to ensure consistent adherence to air cleanliness and microbiological standards, with alarms set for deviations from established limits to allow quick corrective actions.

IEST-RP-CC001 and IEST-RP-CC003 standards
Focus on cleanroom design and testing, also provide detailed information on monitoring systems:

Alarm Systems: IEST recommends the use of automated particle monitoring systems with real-time alarms to detect deviations from control limits in critical zones like ISO 5 or Grade A environments. These systems should be configured to trigger alarms when particle counts exceed specified thresholds for each classification level, ensuring quick responses to contamination risks.

Summary of the Particle Counting Methods

1. **Particles per ft³ (Cubic Foot):**
- **What it does:** The particle counter measures particles in one cubic foot (28.3 liters) of air each minute.
- **Pros:** It provides direct, real-time data for each cubic foot, allowing for fast identification of particle exceedances in cleanrooms.
- **Cons:** It doesn't reflect ISO or GMP standards, which use a cubic meter (m³) for measurement, meaning the results are not fully aligned with regulatory requirements.

2. **Normalized Particles per m³ (Cubic Meter):**
- **What it does:** The software converts each ft³ reading into a calculated value for one m³ by multiplying the particle count by 35.3.
- **Pros:** You get a cubic meter value that can trigger an alarm if the value exceeds thresholds.

- **Cons:** Since the measurement is not from a real m^3 of air, even a small particle count can get multiplied and exceed alarm limits, creating false alarms. For example, if only one particle is measured in a cubic foot, it becomes 35.3 particles when converted to m^3, which may trigger an alarm even if the particle count didn't truly exceed limits.

3. **Rolling Sum Particles per m^3:**

- **What it does:** The particle counts from each cubic foot are added up over 36 minutes to create a total value for one m^3 (1000 liters) of air.
- **Pros:** This method provides a more accurate representation of air cleanliness over a period of time rather than a single instant.
- **Cons:** If a high particle count is detected, it remains in the data for 36 minutes, potentially causing longer alarm periods. Additionally, if an alarm is triggered, the system may not trigger a new alarm during that 36-minute window even if further issues arise.

Alarm Implementation and Understanding Alarm Actions

Setting Alarms for ft^3 Counts:

- **How it works:** Alarms are set based on the number of particles counted per cubic foot of air. If a threshold is exceeded, an alarm is triggered.
- **Action:** Operators can immediately assess and act when an alarm is triggered. However, because small counts in cubic feet are multiplied when normalized to m^3, alarms may be triggered more easily.

Setting Alarms for Normalized m^3 Counts:

- **How it works:** When the particle count is multiplied by 35.3 to normalize to a cubic meter, the system checks this value against set alarm limits.
- **Action:** Alarms may clear the next minute if the particle count drops below the limit after multiplication, but false alarms due to small initial counts are possible.

Setting Alarms for Rolling Sum Method:

- **How it works:** The system continuously adds particle counts over 36 minutes to calculate a total value for one cubic meter. Alarms are triggered when this rolling sum exceeds a set limit.
- **Action:** Once an alarm is triggered, it remains active for the full 36-minute window, even if the particle count drops. You need to wait until the older values (from 36 minutes ago) are cleared from the rolling sum.

Key Formulas

Normalized Particles per m^3:

- Multiply the particle count for 1 ft^3 by 35.3 to convert to 1 m^3.

Rolling Sum Particles per m^3:

- This method uses a "First-In, First-Out" (FIFO) system. Over 36 minutes, the software adds each minute's particle count (measured in ft^3) to the running total and removes the oldest count.
- Formula example:
  - 1st minute m^3 value = 1st ft^3 value
  - 2nd minute m^3 value = 1st ft^3 value + 2nd ft^3 value
  - 36th minute m^3 value = 35th minute m^3 value + 36th minute ft^3 value, etc.

Partial Rolling Sum Option:

During the first 36 minutes, the system sums the particle counts even before the full m^3 is reached. You can set the system to allow alarms during this time by using the "Allow Partial" setting.

Practical Application

For Biosafety Cabinets: Use the Normalized per m^3 method for real-time monitoring, as it provides faster alarms and can be cleared immediately when particle counts drop.

For Cleanrooms: The Rolling Sum method is better for longer-term monitoring as it provides a more stable measurement but is slower to clear alarms.

By understanding these methods, you can set the proper alarm thresholds and choose the appropriate method based on your cleanroom's needs. Ensure that alarm limits are carefully chosen to avoid false alarms while maintaining compliance with ISO and GMP standards.

Conclusion

In conclusion, the establishment of appropriate alert and action alarms for particle monitoring systems in cleanrooms is vital for maintaining compliance with regulatory standards such as EU GMP Annex 1 and ISO 14644-1. These alarms serve as critical tools for ensuring product safety and quality by providing real-time monitoring of particle counts, thereby enabling timely responses to potential contamination risks. The outlined procedures emphasize the importance of configuring alarm thresholds based on empirical data while balancing sensitivity to avoid nuisance alarms that can disrupt operations.

The integration of Statistical Process Control (SPC) into the alarm management process further enhances the reliability of these systems. By focusing on trends rather than isolated events, SPC allows operators to differentiate between normal fluctuations and significant deviations, ultimately leading to improved operational efficiency. Regular testing, calibration, and validation of alarm settings are essential to ensure that monitoring systems function effectively without generating excessive false alarms.

As cleanroom environments continue to evolve, adherence to these best practices will be crucial in fostering a culture of quality and safety in sterile manufacturing processes. Continuous assessment and adjustment of alarm thresholds based on real-time data will not only help in maintaining compliance but also contribute to the overall integrity of the production environment.