Setting APPROPRIATE Alarm Limits in Sterile Manufacturing Processes.

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Introduction

Setting inappropriate Alert and Action alarms on your Environmental Monitoring System (EMS) is a major contributor to loss revenue, longer downtimes and a lot of discarded product. This Coupled with misinterpretation of the regulatory guidelines and an inadequate approach to the use of your EMS Alarming functionality sets you up for failure before you have even got out of the start gates. Partnering with the right EMS supplier can have a major impact on your process, revenue and regulatory approval.

Life Science companies are restricting themselves based on a table of recommended alarm limits which is based on a volume of air sampled (cubic meter (m^3)) which has been adopted from ISO 14644-1 a standard with an emphasis on Cleanroom Certification and not on continuous particle monitoring. (Continuous particle monitoring means continuous during the production lifecycle and not 24/7).

Why would you implement Alert and Action alarms based on a cleanroom certification which is a snap shot of a set volume (m^3) which correlates to a table of maximum permitted particles per m^3. This quickly becomes an apple to oranges scenario when the medium to collect real-time particle counts is a remote particle counter with a sample rate based on 60 second interval or 1 cubic foot per minute sample rate and the time frame is continuous for the duration of the manufacturing process. In short it does not make any practical sense.

The Life Science Industry concentrates on reporting particle counts for 0.5um and 5.0um with 5.0um being more stringent as that's normally considered the size range of bacterial types (viable particles) of particles, (but as we have learned in recent updates to ISO 14644-1 (2015) 5.0um is not really statistically significant in a Grade A environment) Also bacteria actually range from around 0.1um-18um according to published studies. Below EUGMP Annex 1 Table and ISO-14644-1 with Alarm limits based on a m^3 sample volume. You notice the 5um limit is 20 counts per m^3 per EUGMP Annex 1 Table below and was previously 29 (1999) in the ISO 14644-1 table and is now (2015) removed based on statistical limitations when sampling in low concentration areas such as Grade A or ISO Class 5 environments.

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		**In operation**	
Grade	**0.5 µm**	**5.0µm**	**0.5 µm**	**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

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ISO Classification Number(N)	0.1µm	0.2µm	0.3µm	0.5µm	1.0µm	5.0µm
ISO 1	b 10	d 2	d	d	d	e
ISO 2	100	24	10	d 4	d	e
ISO 3	1,000	237	102	35	d 8	e
ISO 4	10,000	2,370	1,020	352	83	e
ISO 5	100,000	23,700	10,200	3,520	832	d,e,f 29
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO 7	c	c	c	352,000	83,200	2,930
ISO 8	c	c	c	3,520,000	832,000	29,300
ISO 9	c	c	c	35,200,000	8,320,000	293,000

5.0µm should be zero according to ISO/DIS 14644-1.2 Table 1 notes;

d) Sampling and statistical limitations for particles in low concentrations make classification inappropriate
e) ... Greater than 1 micron particles make classification at this particle size inappropriate due to potential particle losses in sampling system
f) Specify particle size in association with ISO Class 5, the marcoparticle discriptor M may be adapted.

Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

ISO classification number (*N*)	Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000
NOTE Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level						

So for example following EU GMP the limits set at in a Grade A environment (ISO-5) 0.5um = 3520 particles/m³ and 5.0um = 20 particles/m³ and if using a "rolling average or summation" to track this alarm limit with 5um at 20 particles these are pretty tight limits and the way Micro and Production managers set the Action alarms meant that if they had 1 sample period >20 particles then that was an "Action Alarm" referred to as an excursion– An SOP is typically followed and that mainly meant that they had to segregate the batch running through the filling machine and do a root cause investigation and then go into the cleanroom or in the case of a Clean-air device (Biological Safety Cabinet) maybe a day or two after the event bringing in more people and inadvertently more contamination and when they conducted the root cause analysis 99% of the time they found nothing! In the process managed to add more contamination to the cleanroom environment. Sounds like a futile exercise, waste of resources and money chasing a non-event simply because of inappropriate Alarm settings !

The above introduction helps build up the picture for the solutions outlined below. By the way those root cause analysis may cost upward from $20K to 100K to investigate per event with labor, resource and lab time costs not to mention sometimes a discarded batch which could be a couple of $100K.

So why did the root cause fail to identify a problem? It's simple - Alarm limits were not set up based on the actual process and the baseline of that process and were set up based on a table for certification purposes. It was

assumed that an Action alarm meant that there was a failure of the clean air system, in other words it was not set up to look at adverse trends that may impact product quality in the actual process environment.

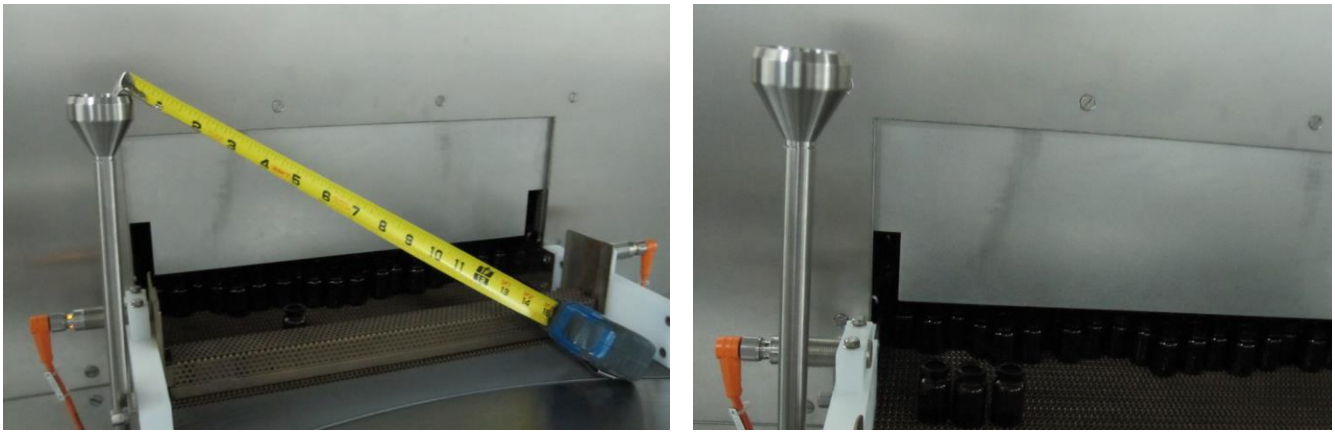
Sample Probe Location & Risk Assessment

The problem is also that the user of the particle counter may not have correctly understood particle counter limitations and functions. Particle counters count all particles regardless of viable or non-viable particles and the sample probe needs to be positioned in a validated position to report meaningful data from the process. The main function of the particle counter is to alarm if the clean air flowing over the process is no longer acting as a clean sterile barrier based on trending data. In the case of a Sterile Injectable or Compounding application, appropriate thought and validation needs to be undertaking to verify the best position of the sample probe and the alert and action limit settings. Most of the knowledgeable consultants or subject matter experts follow a detailed risk assessment into the function, placement and alarming of particle counters.

To correctly identify the sample position in a BSC Cabinet or filling line the actual physical activities in those environments need to be considered as well as the process being monitored.

(1) Probe Placement

The sample probe needs to be positioned above the process zone typically within a foot. (FDA guidelines)



Example of a remote Particle Counter Sample probe placement on filling line as sterile vials exit a sterilization oven. The remote particle counter is under the filling machine and the tubing is kept to a minimum without any bends.

The probe also known as an isokinetic sample probe needs to face towards the incoming clean air from the HEPA filter in that environment.

(2) Process Simulation

A simulation of the process typically can pinpoint the exact location for the probe with the caveat that it does not interfere with the process or get in the operators way. Typically the sample probe is positioned in the middle of the cabinet since most process zones are in that area or along critical locations on a filling line where the product is exposed.

(3) Alarm setting Risk Assessment

Setting appropriate alarm levels is a process that involves understanding of the activities within the sterile zone and the monitoring of that clean zone. The best approach to understand the risks is to validate the

system. This normally occurs during a Performance Qualification (PQ) where once the supplier has handed over the system. After the OQ has been successfully completed the end user will conduct a proper assessment of the system to understand its limitations and to help set appropriate alarm limits. In the case of a filling line or Biological Safety Cabinet the best approach is to setup the process and have a settle plate and air sampler also setup as part of the validation (to monitor the process). Trial runs are conducted under normal operational conditions then separate fail runs are conducted. These fail runs are where the operator purposely generates particles over the process where they can be picked up by the particle counter. The resulting spike in counts are examined as well as the recovery time which in general in a grade A environment with a 0.30-0.45m/s down flow is typically within 1-2 minutes where 0 particles are expected to be recorded. The settle plate and air sampler plates are incubated to back up the expectation. A normal correlation is that very low CFU or even 0 CFU are picked up. The next phase is to repeat this PQ but with the operator not correctly gowned up with wrists exposed or holes in gloves then repeat the test and results typically yield a resultant correlated CFU return with the particle counter spikes. The purpose of this test is to understand that there is a much lower probability of CFU counts when operators adhere to proper sterile gown up procedures and when there is a spike in counts. The overall probability of product contamination is negligible when the compounding or sterile activity is also taken into consideration with respect to vial or connection opening and risk that single CFU enters the opening and that the Cleanroom is performing under the specified conditions. With this PQ validation process end users can establish reasonable and justified alarm limits as they have validated their process and understand the risks and limitations of their facility, tools and processes.

(4) Setting APPROPRIATE Alarm Limits

The bottom line is that a good monitoring system is able to capture transient events as well as repeatable events, interventions and adverse trends. What users should be looking for are trends rather than one off events. The system should immediately notify operators of an action limit event so that they can figure out what is going on at the moment in time as to what caused the particle excursion. In the end it is all about root cause investigations and effective CAPA with meaningful data. If something goes wrong, you capture that event, you notify the right people immediately and importantly you have enough information to help you investigate the root cause. I know this is obvious but it doesn't hurt to restate this because a lot of end users get hung up on setting limits to correspond to the Annex1 and or ISO 14644-1 tables, when in reality they should be set to detect events and adverse trends. See clause 20 below from Annex1, it DOES NOT SAY set "action and alert limits" per the classification table. As one regulator said to me at a PIC/S conference if an end user has a monitoring system I expect them to use it! Meaning it is a process monitoring tool not (just) a compliance tool.

End User validation (PQ) of remote Particle Counter location in a Cleanroom – Grade B Environment.

It is the combination of the alarming features in the LMS software and local SOPs that achieve compliance. What actually happens in the production environment when the alarm beacon goes yellow (warning) or red (alarm) in practice in production environment? Is the alarm beacon in the right place, can the operators hear the sounder, is the sample probe located correctly? Just having a beacon in the QA office may work but if there is no one there during production the system is in effect useless and a complete waste of money. See Annex 1 clause 20 below, the regulators are just as interested in the SOPs that come to life when the alert or action limits are exceeded.

Meaning they are more interested in what you do when an alarm is triggered and they want to see how the reaction is implemented to investigate the issue.

20. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective actions.

Typically in Europe, counts per cubic foot is reported and alarmed on. The main reason for this is the US FDA position that normalizing data is not good practice. So if you report counts per cubic feet then you are expected to have sampled 1 cubic foot of air, this is no problem with 1 cfm remote particle counters as it means we post a result every 60 seconds. The problem is if you report the data in counts per m3 you are expected to have sampled a meter cubic meter of air, which takes 36 minutes,… not so good. Clause 12 and clause 9 below from EU GMP Annex 1 clearly releases us from having to take cubic meter samples when monitoring. (FDA is part of PICs).

There are problems though when using 1 minute samples and reporting counts/ft3, especially around 5 um particle counts when you try to adhere to the Annex 1 Classification table, which is centered around counts per m3. If you set limits for Grade A/m3, 5um =20 for Action and for Alert set to 10 and try to report the data as counts per m3, you will always get an action alarm when there is a single 5um count (1 count at 5um in a minute sample will give you 35.3 counts/m3 when normalized). So reporting particle count data for a sixty second sample interval as count/m3 is not good GMP or easy to alarm on. The alarm limits really need to be set based on the risk assessment and the process baseline during the PQ.

9. For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operation should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of >5.0 um at the point of fill when…..

12. The sample sizes taken for monitoring purposes 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 clean rooms and clean air devices.

Alert limits are typically defined at 2 x SD from the mean historical counts. Strictly speaking the action limits should be at 3 x SD of the historical mean, but in pharma everyone adheres to the classification table in the EU GMP Annex 1 with incorrect limits set. Many companies successfully defend this approach with the regulatory authorities. The alert limits should (*must* unless you have a really good reason not to*)* be periodically reviewed based on historical data, this is back to using the system as a process monitoring tool – something covered by a good quality PQ after the IQ and OQ has been completed. Then once the system has been running in your process then appropriate alarm limits can be set.

The following alarming strategies have been implemented to address the above problem. Please note that these strategies have withstood regulatory scrutiny from the EU regulators and FDA in many applications. As you will see they are different, which one is the right approach? Well we could argue that they both are. Importantly regulatory authorities will expect the end user to support any alarming strategies using sound scientific evidence, in other words historical particle count data and or qualification data and to implement SOP's of their actions once an alarm has been triggered.

1. **Example action limit strategy Grade A in operation**, this strategy allows for occasional events of a single 5um particle and was developed based on the historical particle count trend observed over time. The Strategy shows a good understanding that we are monitoring not classifying. It allows for the odd 5um particle count, it will capture a 5um excursion; the 5um alert limit will notify end user of an adverse trend if one exists. The 0.5um alert limits will capture adverse trends based on setting appropriate alarm levels (after PQ).

    a. Set alert and action limits on a 60 second sample interval. Alarm threshold is zero.
    b. 5um action limit is > 2 Counts /ft3, alert is >1 Count/ft3- this is not in agreement with Annex 1 classification table if you were normalize the data to m3. This does however allow for the occasional 5um particle count per the final sentence in clause 9 of Annex 1.
    c. 0.5um action limit > 100 Counts/ft3, alert is approx... > 40-50 Counts/ft3 or once historical data has been reviewed, the 95th percentile or 2 x SD historical mean counts.
    d. Add SPC for X out of Y events, this can be 2 out of 3 or 5 out of 7 the point is that these SPCs must have some validation around them so you reach a point where X minutes of exceeding alarm limits has a known impact on product quality again something to cover in the PQ.

2. **Another Example action limit strategy Grade A in operation**, this strategy allows for occasional events of a single 5um particle and is really attempting to align with the EU GMP Annex 1 limits.
    a. Set alert and action limits on a 120 second sample interval, alarm threshold is zero
    b. 5um action limit is > 1 particle per sample period, this is > 17.6 particles/m3
    c. 0.5um action limit > 200 particles per sample period, this is > 3520 particles/m3

There are others examples where some users have set a frequency alarm of 10 and set action limits of 100@ 0.5um and 1@5um. There are those who set Grade A action limits of 1 c/ft3 and 100c/ft3 at 0.5 up per minute because they know they never see anything.

Summary

Alarm Limits in sterile manufacturing processes should not be based from a table which has been established for cleanroom certification/classification. The end user should have a well-defined PQ which uses a risk assessment approach and considers the location of the sample probe, length of sample tubing (particle loss issues), sample update rate based on the actual particle counter flow rate, which all assist to establish a baseline from simulated or actual process conditions and has a probability of risks associated based on a scientific approach to set alarm limits that work for the process not against the process.

Investing in the time and expertise to address these issues and development of a well-rounded PQ can literally save thousands of $$ and hundreds of wasted man hours looking for root causes that do not exist in the cleanroom. There are many SME's or Industry consultants out there that can assist the end user in setting up a meaningful PQ as well as leveraging off the Environmental Monitoring Systems suppliers experiences and their level of knowledge in particle monitoring and setting appropriate alarm limits, probe placement and all the regulatory requirements and standards that are expected.

References:

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Biography – Jason Kelly Director of Systems – Lighthouse Worldwide Solutions

20 Years Management positions in Environmental Monitoring Systems Service, Design, Installation, Validation and ongoing support. Has worked on many Projects for top Life-Science companies assisting in procurement, delivery and compliance to ensure regulatory acceptance. Worked across the World on many projects in the UK, Ireland, Europe, Australia and now resides in Oregon USA. He can be contacted by email on jasonk@golighthouse.com or on LinkedIn and always welcomes queries and questions on Monitoring Systems connected to particle counters or environmental sensors.