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PARTICLE COUNT CLEANROOM CERTIFICATION VS ROUTINE PARTICLE MONITORING AND CURRENT GMP REQUIREMENTS

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Overview

Routine monitoring is a distinct procedure in which sample locations and warning configurations are determined by process knowledge, sound science, and a rigorous risk analysis technique. Certification and routine monitoring are purposefully separated under GMP guidelines. The distinction between certification and monitoring is clearly defined in Annex 1.

Setting appropriate alarm limits is the best approach for routine monitoring; one size does not fit all, especially when considering the physical size of cleanrooms used for various processes. The number and movement of people within the facility, product movement, and the design and dynamic airflow from the entry into the cleanroom to exiting the cleanroom or clean air decontamination.

This tech paper compares routine monitoring versus cleanroom certification and can help determine which is right for you. Getting the design and operational variables right the first time will avoid downtime, potential product shortages, and wasting resources chasing non-events in the cleanroom.

Particle Count Cleanroom Certification v Routine Particle Monitoring and Current GMP Requirements

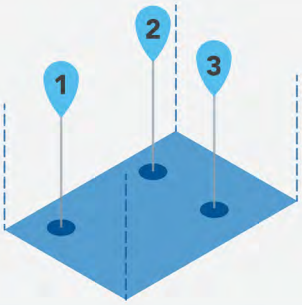
Cleanroom Certification is a process of validation. This validation process certifies that the cleanroom operating conditions meet the intended design parameters. Room Particle Counts are tested using a Portable Particle Counter sampling at a defined volume at evenly spaced test locations around the cleanroom based on current Cleanroom Standards. The most accepted and widely used Cleanroom standard is ISO 14644-1 (2015) Cleanrooms and associated controlled environments -- Part 1: Classification of air cleanliness by particle concentration.

ISO 14644-1 defines the minimum number of samples, the sample volume to be taken at each sample point based on the Cleanroom Classification, and particle size of interest between 0.1 and 5.0 microns. In Life Science manufacturing facilities where aseptic processing is undertaken in ISO 5 Cleanrooms monitoring and reporting 0.5µm, and 5.0 µm data is expected; however, in the new ISO-14644-1 (2015) update, reporting of 5µm is no longer required based on low concentrations in ISO 5 environments and potential particle losses in the Particle Counter system. But the Industry still continues to report 5µm as prior to the 2015 update, this has been the norm, and other GMP standards still call for monitoring 5.0um particles. The following table outlines the maximum permitted particle counts to determine the Cleanroom classification.

Maximum Concentration Limits (Particles m^3 of air)

ISO Classification Number (n)	0.1µm	0.2µm	0.3µm	0.5µm	1.0µm	5.0µm
ISO 1	10	d	d	d	d	e
ISO 2	100	24	10	d	d	e
ISO 3	1,000	237	102	35	d	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
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

For the number of sample points within the cleanroom the new ISO 14644-1 (2015) update has done away with the older method of calculation based on the square root of the area of the cleanroom and instead has introduced a table based on the cleanroom size. The minimum number of sample points can then be determined from this table below.



Area of Cleanroom (m2) Less or Equal to	Minimum Number of Sample Locations to be Tested NL
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
64	12
68	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
500	26
1000	27
>1000	Equation A.1

ISO 14644-1:2015 Number of Sample locations table

In Cleanroom Classification a portable particle counter is setup to take a one cubic meter sample volume and the location ID is also inserted into the program so the data associated with that location is identified and recorded. Reporting capabilities within the particle counter firmware can determine at the end of the sampling within the cleanroom if the particle concentrations are within acceptable concentrations.

Cleanroom Certification is therefore a formula and when applied a determined result is provided based on the accepted limits of allowable particles in a cubic meter sample which are referenced back to the table above in fig 1. With improvements in particle counter instrumentation technology the fastest time to sample a cubic meter is now 10 minutes per location. One portable unit is used for each sample location and the operator manually takes the particle counter to each location after the desired sample volume is reached.

Operator setting up Particle Counter for Cleanroom Certification

Routine Monitoring is a process undertaken when the manufacturing processes commence. This is entirely different from Cleanroom Certification (the formulae), for example in a traditional fill finish aseptic process in an ISO 5 environment along a filling machine, multiple remote particle counters are used. The location of the particle counter sample points are based on cGMP guidelines and should be determined by a risk analysis process. This risk analysis should be based on good science and a full understanding of the sterile manufacturing process. In simple terms when using a filling machine as an example, "at risk" locations would be determined as areas along the filling machine where the product potentially could be at risk, such as when an open vial or partially stoppered vial is moving along the process line.

A true qualification of these locations using a portable particle counter along the filling line would determine where the particle concentrations are highest. This is based on the HEPA air system delivery, the physical design of the filling machine, the airflow over the critical zones and the control of turbulence of air around the critical zones especially where vial and ampoules are open (before been capped).The FDA's Guidance on Aseptic processing (2004) expects that the sample point is within one foot of the "critical zone". Determining the critical zone is greatly assisted by following a risk analysis process. Annex 20, ICH Q9 provide guidance on risk analysis processes.

Most locations along he filling line are typically, at the entry of vials from the sterilization oven, at the accumulator, near the filling head and stopper/capping location and also at transport locations to a freeze drier and within the transport itself up to the freeze drier. A typical filling line could have 6-7 sample locations and then in conjunction ISO 7 locations are monitored (Background locations inside the room where the filling line is located).

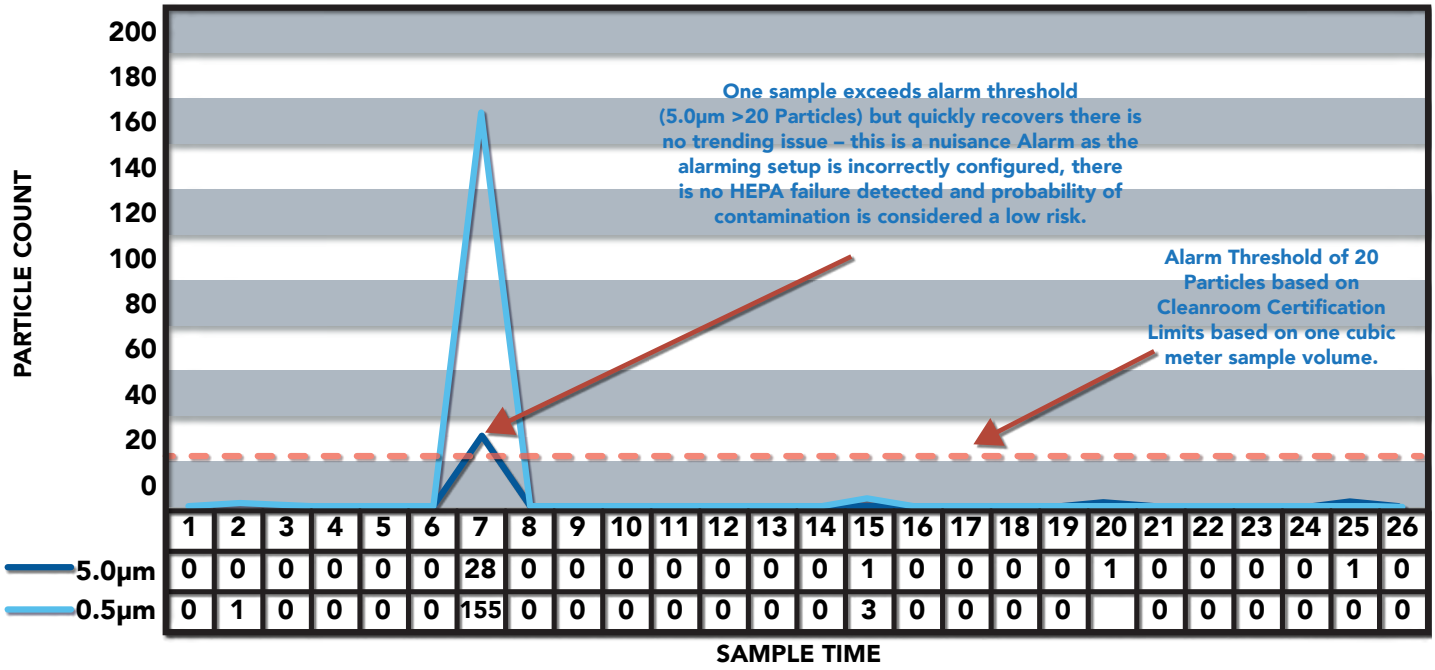
Remote particle sensor continuously monitoring 0.5µm and 5.0µm particle concentrations

The remote particle counters are connected to real-time monitoring software which monitors each location in real time and notifies operators and management if any location particle concentrations shift outside of normal expected operating limits.

What are normal operating limits? In practice these limits have unfortunately been interpreted to match the Certification table however in reality when cGMP is applied correctly the limits need to be considered based on the normal operating conditions, the sampling device parameters and through validation based on trending over time. Unfortunately this validation process is missing and what has been observed in the Industry is a summation type of alarming based on a rolling average of a one cubic meter sample or even worse an extrapolation of a one cubic foot to one cubic meter sample. With this type of approach nuisance alarms are being designed into the system.

The inevitable will happen where a sample will exceed alarm thresholds based on the Certification table
and the monitoring system lights up and uncertainty ensues so much so that a CAPA is created based on one sample out of X going above an unrealistic set-point based on a different principal (Certification).

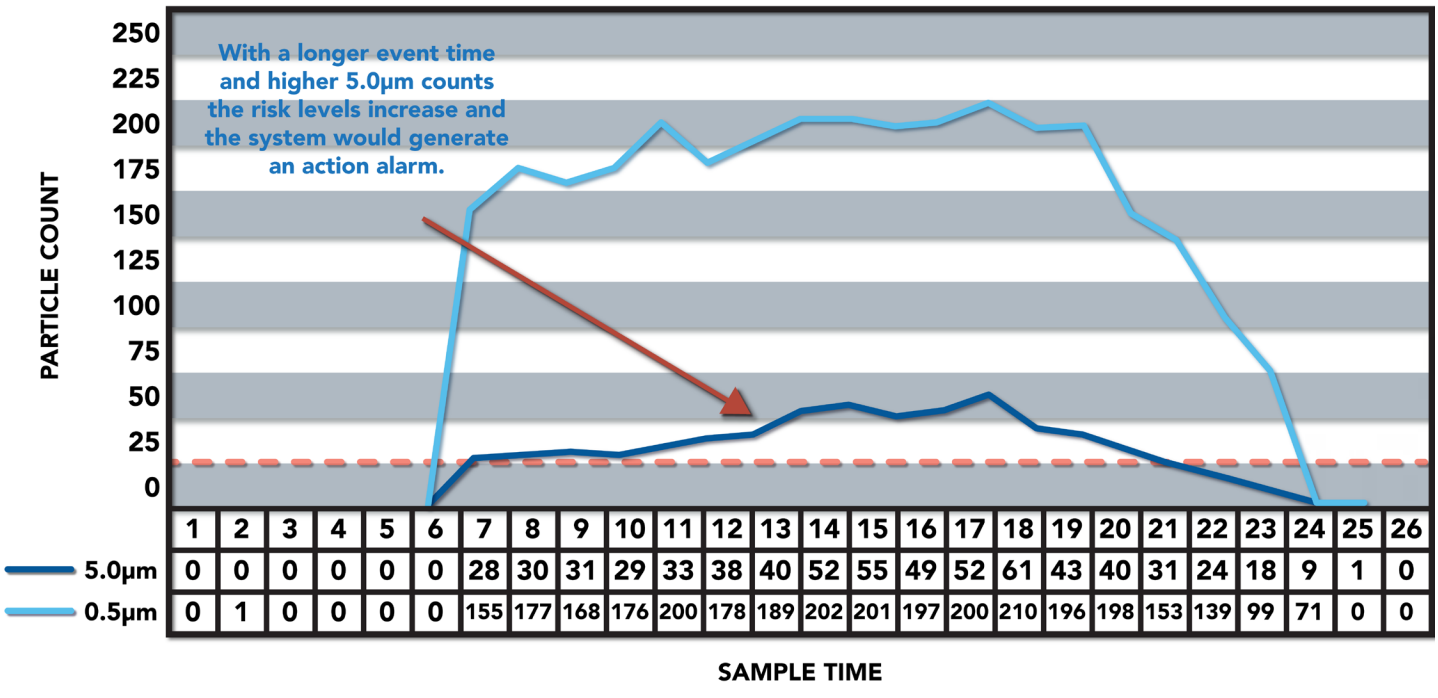
Fill Finish Room Grade A Sample Data



The above table indicates that the monitoring system alarm configuration is too sensitive. We all know in cleanrooms that transient events occur. These events may be operator driven due to process interventions. If the operator is aseptically gowned up correctly the risk of viable contamination is pretty low, furthermore the risk of viable particles getting into an open vial especially if the diameter is small are even lower. A carefully conducted PQ can increase confidence of this scenario where interventions are purposely constructed and the downstream microbial analysis is measured via active and settle plate monitoring. Therefore the system owner can comfortably set alarm thresholds based on validation of the interventions and the results back from the micro lab. (Good Science). Furthermore introducing Statistical Process Control (X out of Y events) into the alarm configuration can increase the robustness of the alarming system so trends are picked up and tracked and alerts are issued prior to the event becoming an actionable alarm.

Looking at the table below where there is a trending event occurring we can certainly see that the risk of probable product contamination is much higher as the time and levels of particulate counts are much higher and the system has taking longer to recover. SPC's X out of Y events in the alarming configuration in this system would notify the system owner of the issue in the early stages and as the event progressed informative decisions can be made in real time and the product that has gone through the system during that time frame could be segregated and tested as well as awaiting microbial results from localized settle plates and active air sampling devices to verify it is safe and low risk. This is using a monitoring system as a process tool and not an expensive door alarm. Such a well-designed system will prevent nuisance alarming and the consequences that come with that

Fill Finish Room Grade A Sample Data



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
5.0µm	0	0	0	0	0	0	28	30	31	29	33	38	40	52	55	49	52	61	43	40	31	24	18	9	1	0
0.5µm	0	1	0	0	0	0	155	177	168	176	200	178	189	202	201	197	200	210	196	198	153	139	99	71	0	0

Summary

In conclusion Cleanroom Certification is a formulae driven process to determine if a sample volume of multiple locations at a specific time has a low expectation of particle counts to determine if the Cleanroom is operating under the design conditions. The result of this process validates that the Cleanroom meets a certain cleanliness level. This validation is ongoing and the re-occurrence of testing is based on the Classification of the cleanroom and outlined in ISO 14644-2.
Routine Monitoring is a separate process where the sample locations and alarming configurations are based on process knowledge, good science and a formal risk analysis approach. In GMP guidance there is a deliberate separation of Certification and Routine Monitoring. Annex 1 clearly defines the distinction between Certification and Monitoring.

Setting appropriate alarm limits is the best approach for routine monitoring, one size does not fit all especially when taking into consideration the physical size of cleanrooms used for different processes as well as controlled environments along with the number of and movement of people within the facility and the movement of product as well as the design and dynamic flow of air from entry into the cleanroom, all the way through to exiting the cleanroom or clean air device. With so many false alarms being triggered which introduce CAPA and the cycle of looking for a needle in a haystack this is not the best approach to take as it is counter-productive with so little return and it increases the risk of cleanroom contamination as personnel are pulled into the cleanroom seeking the golden needle!

Therefore by investing in a robust monitoring system and in subject matter experts getting the design and the operational factors correct first time will significantly reduce down time, potential product shortages and will save wasted resources chasing non-events in the cleanroom. Remember GMP are guidelines and GMP clearly calls for setting “appropriate alarm limits” you can save yourself much pain and loss by having a monitoring system working for you and not against you.

However in reality the locations are planned before the filling line is in place as running services such as vacuum, power and communications to the particle counter locations needs to be completed at the facility build stage, therefore using a Subject Matter Expert or leveraging the knowledge of the vendor during the planning stages is worth the time and investment.