PARTICLE MEASURING SYSTEMS
www.pmeasuring.com
5475 Airport Boulevard, Boulder, Colorado 80301-2339
303.443.7100 1.800.238.1801 Fax: 303.546.7380
Customer Service Center 1.877.475.3317
Instrument Service 1.800.557.6363

Process Analytical Technologies (PAT) and Non-Viable Particle Counting

Pharmaceutical manufacturing environments have traditionally seen particle counting as a burden required to demonstrate compliance to a cleanroom standard. Now, however, Process Analytical Technologies (PAT) changes the focus to be on the final quality of the product. To achieve this, continuous facility monitoring is recommended. This follows the original intent of PAT, which is "to understand and control the manufacturing process: quality cannot be tested into products; it should be built-in or should be by design using a system for designing, analyzing, and controlling manufacturing through process measurements of critical quality and performance attributes of materials and processes with the goal of ensuring final product quality."

Lasair III Portable Particle Counter for PAT

Portable counters are very useful in demonstrating that a cleanroom is generally compliant to regulatory limits and certifying to international standards. Occasional particle counting does not, however, catch all instances of contamination in a cleanroom that can be useful in trending analysis and that is imperative to ensure product quality has not been risked. Given the cleanliness techniques used within a pharmaceutical processing environment, the particle sizes of concern, 0.5 and 5.0 micron, are unlikely to enter a cleanroom via the filtration system. Contamination is therefore either a process or personnel issue, both of which can be very fleeting. For example, if a vial is broken and immediately cleaned up, and the incident lasts for less than one minute, it is very unlikely to be noticed by a portable particle counter technique. However, the event will be witnessed using a continuous monitoring system.

The importance of continuous particle monitoring can be demonstrated through an examination of the two most critical areas within aseptic pharmaceutical manufacture: the area of exposed product (ISO Class 5, GMP Class A) and the immediate supporting areas (ISO Class 7, GMP Class B). We can identify that a significant improvement over control can been witnessed with the implementation of continuous monitoring as opposed to the use of a portable device.

In the examples below portable and continuous monitoring systems are compared in a Class B cleanroom that has an associated Class A zone. In **Example 1** a 50 m^2 room has a laminar zone (Class A) of an additional 25 m^2. A portable particle monitoring system used eight locations in the background and five beneath the laminar zone; each was monitored three times a day for three minutes per location. A risk classification has been applied that will bias the data according to the perceived risk. If the same area was monitored continuously at two locations in the background and three in the critical zone (sample points assigned in accordance with legislative guidelines and based upon risk assessment), a significant improvement over the difference relative to risk is achieved. The Class B has only a 2.5% confidence result when compared to continuous monitoring, although fewer sample locations are used. The Class A has only a 1% confidence rating compared to continuous monitoring. Although the analysis is not exhaustive, we can see that continuous monitoring is a far more reliable method of detecting events.

Room Class	Monitoring Method	Room Area (m^2)	Sample Points [1]	Risk to Final Product Rating [2]	Duration of sample (min)	Samples per day	Total Duration of Sampling (min)	Duration x Risk	% Diff Rel to Risk
Example 1									
B	Portable	50	8	3	3	3	72	216	2.50
B	Continuous	50	2	3	1	1440	2880	8640	
A	Portable	25	5	4	3	3	45	180	1.04
A	Continuous	25	3	4	1	1440	4320	17280	
Example 2:									
B	Portable	25	5	3	3	3	45	135	3.13
B	Continuous	25	1	3	1	1440	1440	4320	
A	Portable	10	4	4	3	3	36	144	1.25
A	Continuous	10	2	4	1	1440	2880	11520	

[1] Portable based on ISO14644-1

[2] Risk based upon factor: A = 4 Highest; B = 3; C = 2; D = 1 Lowest

Example 2 shows a similar situation but with a smaller room area and therefore significantly fewer monitoring locations. In this model, the Class B area is 25 m^2 and the Class A area is 10 m^2. Again, based upon the number of samples measured per day, a significant improvement in data collected can be seen and the confidence rating with the portable system is very low.

The above numbers are functions only of time verses number of samples taken; no account is made for operator activity during the sample periods. It is assumed that an operator maintains normal Standard Operating Procedures (SOPs) during the test period.

This shift to continuous data has translated itself into legislative guidance in the revisions of both the *EC Guide to Good Manufacturing Practice Revision to Annex 1*, September 2003 and the *FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice*, September 2004.

The EC guide states:

> *a continuous measurement system should be used for monitoring the concentration of particles in the grade A zone, and is recommended for the surrounding grade B areas.*

The FDA states:

> *we recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters.*

Both guides direct manufacturers to continuously monitor the critical activities within a clean process environment to prove control of these environments.

In practical terms the gathering and collection of more data can be difficult to manage and therefore the feedback loop into improved quality assurance, the driving aim for PAT, becomes clouded. The design of a continuous monitoring system, therefore, needs special considerations, such as how operators react to out-of-tolerance conditions. Alarm systems and pagers can be used to gain the fastest response to failures; product can then be isolated or quarantined awaiting microbial support, therefore ensuring final product quality. Reporting of data takes on a new direction instead of just reporting the samples that showed pass results, it now looks at trending analysis. For **Example 1** above, the total portable number of samples was 72 measurements; for continuous this becomes 2880. The emphasis becomes: identifying what events occurred, how long the event lasted, and how the operator reacted to such events.

Particle monitoring has evolved from snap-shots of an environment into a tool that allows for continuous feedback and improved environmental controls. This has resulted in changes to SOPs applied to how cleanrooms are used and managed.

Author: Mark Hallworth
Mark Hallworth is the Pharmaceutical Manager for Particle Measuring Systems in Boulder, CO USA. He has managed the installation and validation of over 400 facility-monitoring projects for over 14 years and has managed the company transition to 21CFR part 11 compliant software. He currently lectures for pharmaceutical societies throughout Europe and the US on non-viable particulate monitoring, cGMP compliance (both for FDA and EU approval processes), and facility monitoring systems and the implications of validating those systems to GAMP. He can be contacted at mhallworth@pmeasuring.com.