

## Improving Facility Monitoring Systems for Regulatory Compliance Requirements

A facility monitoring system (FMS) is a process monitoring tool that collects data from sensors such as optical particle counters, differential pressure sensors, and temperature probes in real-time. Acronyms are independent monitoring system (IMS) or environmental monitoring system (EMS). Software presents that data as information; real-time alarms notify facility operators of alert limits to enable an immediate response to an unwanted event or excursion. Reports and trend graphs can be produced.

This information can then be used to help improve process understanding and enhance process knowledge. The quality of the data input into the facility monitoring system will directly impact the quality of the process information and knowledge gained from the system.

In the pharmaceutical industry, aseptic processing is monitored—in accordance with regulatory requirements—to prove the environment surrounding a process does not negatively impact product quality and, ultimately, patient safety. Environmental parameters monitored include temperature, relative humidity, differential pressure, and airborne particles.

Compliance to regulatory guidelines such as the European Union's *Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1* (2008), and the U.S. Food and Drug Administration's (FDA's) *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice Guidance on Aseptic Processing* (2004), which require continuous monitoring of airborne particle cleanliness, has been a driver for pharmaceutical companies to install facility monitoring systems.

### Quality-Based Monitoring

The first facility monitoring systems to include optical airborne particle counters were installed in semiconductor and hard drive manufacturing facilities in the early 1980s. There were no regulatory requirements to monitor particulate cleanliness of the air. A key driver was—and continues to be—Six Sigma. The aim of Six Sigma is to reduce variation, waste, and cycle times, while increasing the level of quality. This data-driven approach for analyzing root causes of business processes and problems can lead to improved yields, cost savings, and increased profits.

It is quality-based decision making.

Pharmaceutical industry regulators are now encouraging quality rather than compliance-based thinking and are keen to encourage industry to use the latest and best practices. Achieving the “desired state” is a term that is used to describe the initiative: “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight”.<sup>1</sup>

Complementary guidelines provide a framework to encourage innovation and quality-based thinking in the pharmaceutical industry. For example, ICH Q8 (R2) *Pharmaceutical Development* (2006) encourages a greater understanding of pharmaceutical and manufacturing sciences.

Knowledge is gained from the application of scientific approaches and *ICH Q9 Quality Risk Management* (2005) for product development and manufacturing process.

The FDA's *Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (2004) provides a regulatory framework to facilitate innovation. The guidance recommends: "Sensor based measurements provide a useful process signature that may be related to underlying process steps and could relate to product or process quality". The microbiological quality of the air surrounding the manufacturing environment is one potential in-process measurement; optical particle counters connected to facility monitoring systems have been a surrogate measurement for this up until now.

Covering the entire product lifecycle and strengthening the link between pharmaceutical development and manufacturing activities, *ICH Q10 Pharmaceutical Quality System (PQS)* (2009) encourages an environment where quality is everyone's responsibility. This includes quality-based decision making; compliance-based decision making is simply not sufficient.

Optical particle counters have historically been the only way of monitoring the cleanliness of the air in real-time in pharmaceutical applications. These instruments are installed based on the principles of quality risk management (QRM) in locations where there is the greatest risk of airborne particle contamination to the process. These instruments could not determine particle viability; they can only count and size particles in real-time.

Recent innovations in optical particle counting technology have made it possible to determine airborne particle viability in real-time. For example, TSI Inc.'s BioTrak Real-Time Viable Particle Counter counts airborne particles in compliance with ISO 21501-4: *Determination of particle size distribution – Single particle light interaction methods – Part 4: Light scattering airborne particle counter for clean spaces*. Then, each particle is analyzed for viability using a laser induced fluorescence sensor. Finally, the particles are captured on a filter to enable laboratory speciation. When integrated directly into a facility monitoring system, it enables the continuous monitoring of airborne viable and non-viable particles.

### **Detecting the Root Cause Source**

The following example demonstrates the impact of this new technology on the outcome of root cause investigations when compared with outcomes using traditional optical counting data.

This example is based on real data taken by the BioTrak Particle Counter in a supporting Grade C (ISO 7) area. A viable particle excursion did occur, which was supported by positive active air sampling data received several days after the event took place.

The BioTrak Viable Particle Counter "nonviable" total particle count (TCNT = viable + non-viable) trending data is shown in Figure 1. This information is commonly provided by a facility monitoring system and is reviewed to help support root cause investigations of airborne microbiological excursions. The question is: Which of these peaks corresponds to the viable particle event?

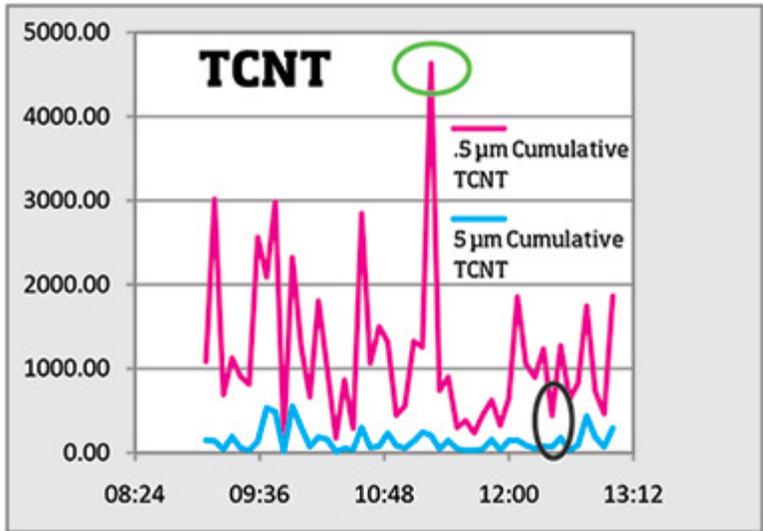
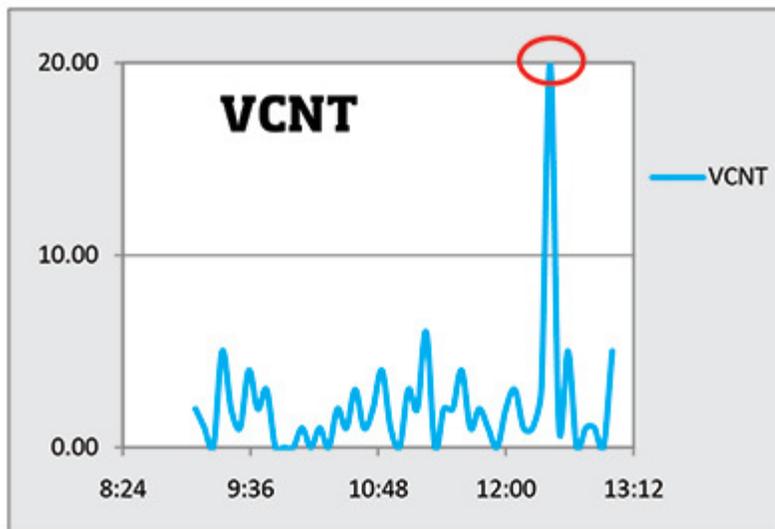


Figure 1. TCNT - Total particle counts at  $\geq 0.5 \mu\text{m}$  and  $\geq 5 \mu\text{m}$ . Figures: TSI Inc.

The non-viable continuous particle data is analyzed and an excursion is identified. There were other candidates where the particle counts appeared to be high, but the event circled in green is significant. In this example, one conclusion was that the event that caused the viable particle excursion occurred around 11 a.m. There may not be enough granularity in the environmental airborne microbiological data to come to any other conclusion. Production logs may even indicate that an operator activity was performed at the time associated with the particle spike, which could then be logically associated with the viable particle excursion.

Figure 2 shows the real-time viable particle count (VCNT = viable particles only) trend data taken over the same time by the same instrument. The red circle marks a clear candidate for a single viable particle event around 12:30 p.m. A closer look at the TCNT data in Figure 1 around 12:30 p.m. does not reveal a particle excursion (black circle), and that time would give the end user no cause for concern. Real-time viable trending provides more insight to detect root cause.



## Conclusion

A facility monitoring system plays an important role in supporting the ICH Q8, Q9, and Q10 guidelines in the pharmaceutical industry. Data collected by the system provides useful real-time and historical trending information about the environment surrounding critical processes. Over time, this information builds process knowledge.

Recent innovations in real-time airborne viable particle counting technology, when integrated into a facility monitoring system, enables real-time end user response to microbial excursions. Real-time detection of excursions in process critical areas supports risk reduction. Correlating excursions with cleanroom activities at specific moments in time will lead to improved root cause investigations, which in turn will lead to more effective corrective and preventative actions. Opportunities exist to implement real-time quality control strategies, potentially including the immediate segregation of product that is at risk.

Better real-time data presents more meaningful information, contributing to a better knowledge and understanding of the process, an increase in product quality, and a safer product. Improved yields, cost savings, and increased profits will be the result.

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