

TSI® BIOTRAK® REAL-TIME VIABLE PARTICLE COUNTER FACILITY MONITORING SYSTEMS

APPLICATION NOTE CC-105 (A4)

Introduction

This application note will demonstrate how real-time viable particle count data will lead to improved root cause investigations when a BioTrak® Real-Time Viable Particle Counter is integrated into a FMS system. Improved root cause investigations and the resulting increased process knowledge is in line with current regulatory initiatives and expectations.

In the Pharmaceutical industry, Good Manufacturing Guidance (GMP) such as US FDA Aseptic Processing Guidance 2004 and EU GMP Annex 1:2008 clearly requires continuous nonviable particle monitoring of aseptic manufacturing processes. To achieve continuous monitoring, systems comprised of many multiple particle counters such as the TSI AeroTrak® Remote Particle Counter 7510-01F, are positioned at critical locations throughout the manufacturing process. All particle counters are connected to facility monitoring software like TSI's FMS which continuously collects data and presents it as useful information to the end user. Particle monitoring locations are determined based on the principles of Quality Risk Management (ICH Q9, QRM).

Continuous nonviable particle counting is an important measurement in critical areas and is the only method to determine airborne particulate cleanliness in GMP classified areas in real-time. The US FDA Aseptic Processing Guidance 2004 states:

“Particles are significant because they can enter a product as an extraneous contaminant, and can also contaminate it biologically by acting as a vehicle for microorganisms.”

To this extent, nonviable particle monitoring is a surrogate measurement for the presence of airborne particulates that transport microorganisms. Process particle cleanliness changes and any particle excursions that exceed configured alert or action limits will be detected by the facility monitoring system. Key personnel are immediately informed through the monitoring system's alarming notification hardware and predefined end-user responses are initiated. The particle excursion information provided by the monitoring system is then used alongside other critical process parameters, such as the microbiological quality of the air, to help determine the root cause of the excursion.



The challenge for Quality Assurance professionals is that historically, the microbiological quality of the air cannot be determined in real time. In Grade A, ISO5 zone where aseptic processing is performed, oftentimes an active air sampling head will be located in close proximity to the nonviable particle monitoring sample probe. Today end users have to wait four or more days to find out if a particle excursion detected by a nonviable particle counter potentially contained particles that were transporting viable microorganisms into the critical work area. Even then, the information provided may prove to be inconclusive if active air sampling was performed intermittently during the critical process. During this waiting and analysis period, valuable product - sometimes with a very short shelf life - is awaiting release.

Should the media plate counts from the lab exceed action or alert limits, correlating this with nonviable particle count data to understand when the contamination event occurred is challenging.

The good news is that the BioTrak Real-Time Viable Particle Counter is three instruments in one package. It detects viable and nonviable particles in real time. The instrument will even collect all optically analyzed particles to enable speciation analysis. It can demonstrate compliance to current regulatory guidelines, **and** is able to inform end users how many counted particles are viable.

The BioTrak Viable Particle Counter can be used as a standalone portable instrument, or as a fixed monitor, integrated directly into TSI's FMS software.

The TSI FMS software is developed and maintained under current GAMP guidelines and enables compliance to 21 CFR Part 11. It is intended for use in Pharmaceutical and Life Science applications where there is a regulatory requirement for end users to demonstrate control of manufacturing environments. Figure 1 shows a typical FMS system.

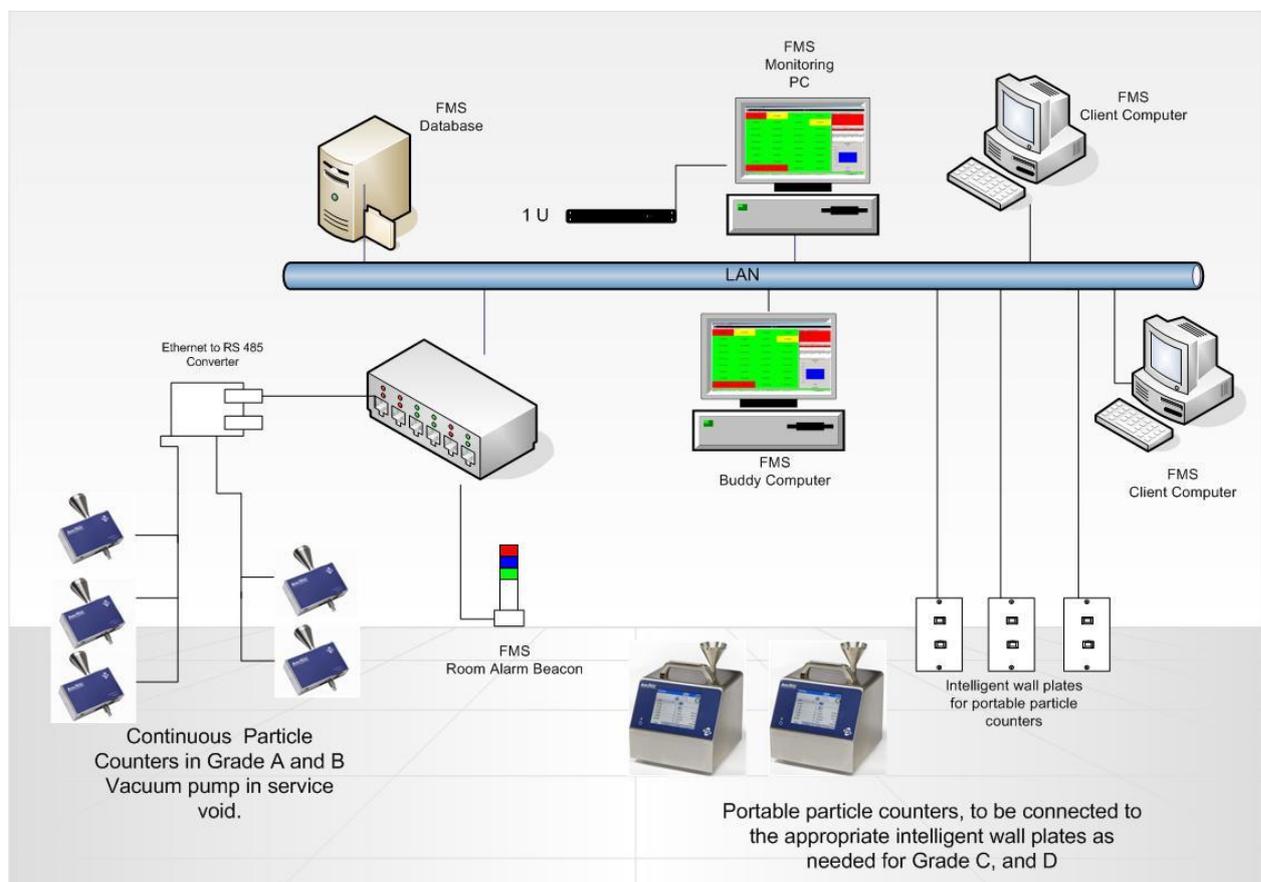


Figure 1 Typical FMS System Utilizing Traditional Particle Counters

Particle Monitoring with the BioTrak Viable Particle Counter

Sample Flow Rate

FDA Aseptic Processing Guidance 2004 states:

“Sample sizes should be sufficient to optimize detection of environmental contaminants at levels that might be expected in a given clean area”.

In Grade A and ISO 5 environments, the number of airborne nonviable and viable particles is expected to be extremely low, if not zero. Put simply, to detect airborne viable particles in very clean areas, relatively large sample sizes or volumes of air must be taken. To ensure a suitable sample size is collected, the BioTrak Viable Particle Counter has been designed with a sample flow rate of 1 CFM (28.3 LPM.)

This means:

1. The BioTrak flow rate is comparable to current active air samplers used to demonstrate compliance to existing regulatory guidelines for airborne environmental quality
2. The BioTrak flow rate is the same as many current nonviable particle counters used to demonstrate compliance to existing regulatory guidelines for airborne particle cleanliness

Microbial Particle Excursions

During critical processing environmental air sampling is not always continuous, and is performed at pre-defined intervals throughout the critical process. The sampling intervals are not consistently applied across industry and vary widely.

The BioTrak Viable Particle Counter monitors the airborne environment continuously. Every minute a result for total particle (nonviable) counts and viable particle counts will be posted to the validated FMS system. When pre-configured alert and action limits are exceeded, end users will be immediately notified, enabling an immediate viable particle excursion response.

Real-time response means product potentially at risk to airborne microbiological contamination can be immediately segregated. End users will now know the exact moment in time when an airborne viable particle excursion took place. A real-time understanding of the in-process microbiological quality of the air is aligned with the principles of ICH Q8 Quality Risk Management (QRM), ICH Q9 Quality by Design (QbD) and Process Analytical Technology (PAT).

Root Cause Investigations

When particle deviations occur in Pharmaceutical cleanrooms, root cause investigations are initiated. The extent of any investigation should be consistent with the severity of the excursion. As the FDA Aseptic Processing Guidance 2004 states:

“Routine particle monitoring is useful in rapidly detecting significant deviations in air cleanliness from qualified processing norms (e.g., clean area classification). A result outside the established classification level at a given location should be investigated as to its cause. The extent of investigation should be consistent with the severity of the excursion and include an evaluation of trending data. Appropriate corrective action should be implemented, as necessary, to prevent future deviations.”

Example:

Below is an example that illustrates how a viable particle event is captured by the BioTrak Real-Time Viable Particle Counter and the potential outcomes of a root cause investigation.

This example is based on real data taken in supporting a Grade C (ISO 7) area. In this case, there were no viable or nonviable particle count action or alert limits in place; although an airborne microbiological particle excursion did occur.

All viable VCNT and nonviable TCNT particle count data, as well as the particles collected for analysis were all gathered by one instrument - a single BioTrak Viable Particle Counter.

First, observe the BioTrak Viable Particle Counter “nonviable” total particle count (TCNT) trending data shown in Figure 2. This is typical information end users are presented with today from non-viable particle counters, possibly in combination with an FMS system. The question is - which of these peaks corresponds to the viable particle event? There are a few candidates.

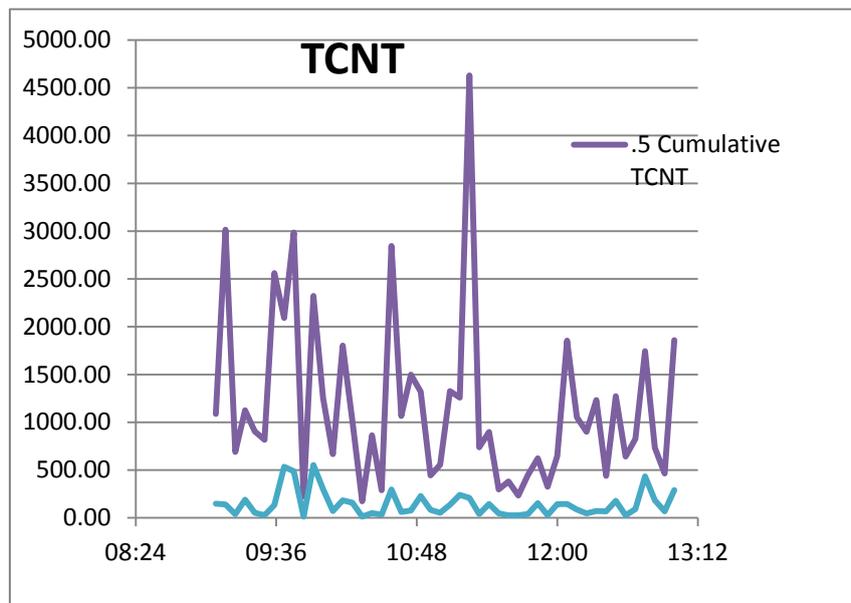


Figure 2. TCNT - Total Particle Counts at $\geq 0.5 \mu\text{m}$ and $\geq 5 \mu\text{m}$

Currently end users may have to wait many days for the results of any active air sampling or settle plate incubation data. In this example, positive results came back from the lab ~5 days later.

The nonviable continuous particle data is analyzed and an excursion is identified. There were other candidates where the $0.5 \mu\text{m}$ total particle counts appeared to be high, but the event circled in green is significant. A potential conclusion drawn from the information available is that the event that caused the airborne microbiological particle excursion occurred at approximately 11:00AM. There may not be enough granularity in the environmental active air sampling 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 circled in green, which could be logically associated with this microbiological particle excursion.

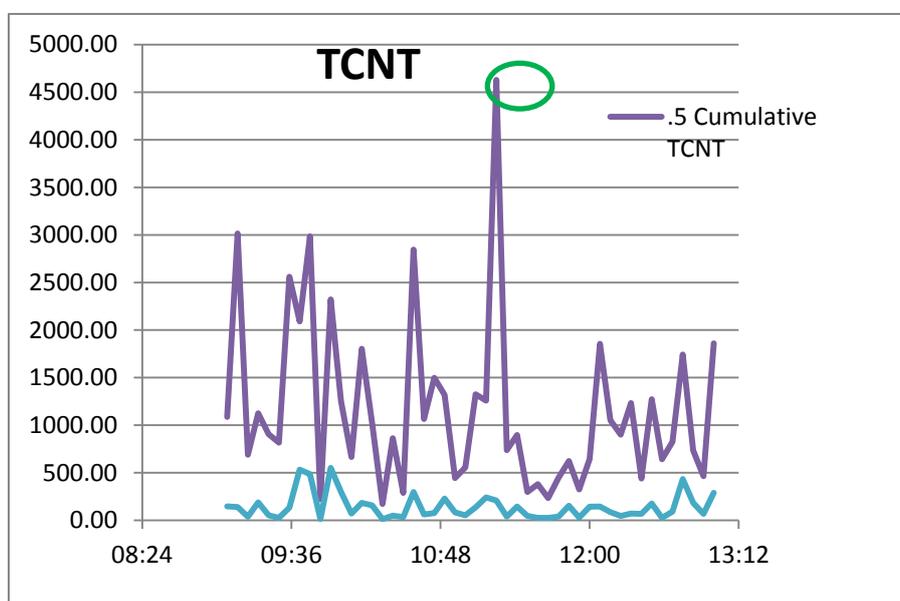


Figure 3. Total Particle Count Excursion at about 11:00

Is this really the correct conclusion? Let's take a deeper look.

Remember, the sampled particles are optically analyzed twice by the BioTrak particle counter. The BioTrak Particle Counter real-time viable particle count VCNT trend is shown in figure 4 below for the same time period. The red circle denotes a clearly defined viable particle event. This occurs at approximately 12:30, over an **hour** later than nonviable TCNT event circled in green in figure 3.

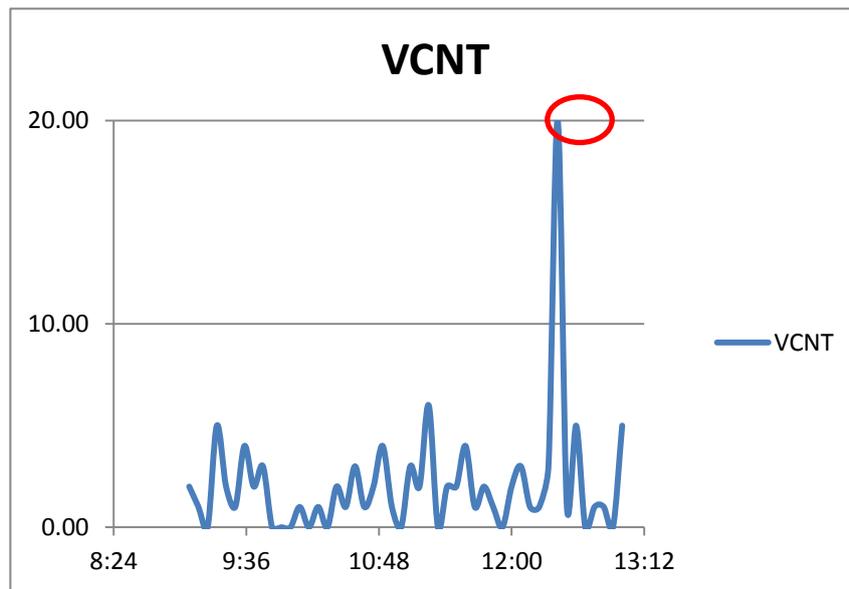


Figure 4. Viable Particle Excursion appears to be at 12:30

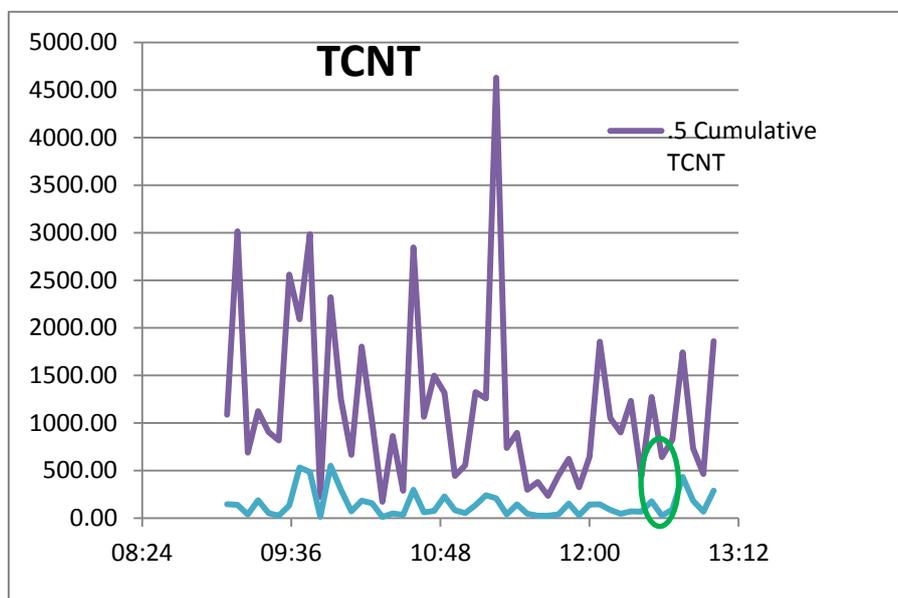


Figure 5. Viable Excursion at 12:30 – Nonviable Counts do not Indicate a Particle Excursion

Let's return to the nonviable TCNT count trend again, see figure 5, and note the green circle. This is the corresponding nonviable TCNT particle data at 12:30PM, when the viable VCNT particle event occurred. There is no indication whatsoever that any airborne particle excursion is taking place that requires investigation. Clearly in this case an event occurred that caused a viable particle VCNT excursion which did not cause a nonviable TCNT particle excursion. In this example, an investigation into root cause could take two very different paths and reach quite different conclusions.

Using the BioTrak Viable Particle Counter as part of a facility monitoring system to initiate alarms based on viable particle count alert or action limits, enables correlating viable particle deviations with operator activities at that moment in time and will help support improved root cause investigations.

This is not to say nonviable particle count data is unimportant or misleading; it is an indicator of process deterioration and poor operator practices and should be responded to appropriately. However, by including viable particle count data, root cause investigations have the potential to be

concluded with greater speed and accuracy, greatly improving the chances of a meaningful conclusion.

Integrating the BioTrak Viable Particle Counter

Grade A B, ISO 5-7

A drawback of real-time airborne viable particle detectors on the market today is that you still need to monitor nonviable particles and perform active air sampling to meet GMP guidelines. This can mean, particularly in ISO 5 or Grade A areas, alongside a viable particle detector sample probe, end users will still need to install:

1. An active air sampler: when the viable particle counter detects a viable particle excursion, the air in the same area is being collected to enable laboratory analysis to identify the contamination source to support any root cause investigations.
2. An isokinetic sample probe for traditional nonviable particles to continue to meet current regulatory guidelines on continuous monitoring for air cleanliness in aseptic manufacturing facilities.

Pharmaceutical cleanrooms are busy places. Finding space inside isolators, RABs and open filling lines is not easy, particularly as sample probes need to be close to critical locations within the process. Additionally, end users will be justifying yet another external interface into their isolator, RABS or open filling line.

The BioTrak Viable Particle Counter solves this problem by providing all three of these measurements in one package. It is a 1 CFM ISO 21501-4 compliant particle counter, it detects viable particle counts in real-time and it collects the sampled air on a gelatin collection filter. You can even reuse the existing and already installed nonviable particle counter isokinetic sample probes and sample tubing, as size requirements for the BioTrak Particle Counter are identical to that of existing nonviable particle counters in use today.

Figure 6 shows how the BioTrak Particle Counter can save space adjacent to critical monitoring locations in existing aseptic manufacturing processes, and utilize existing and already installed isokinetic particle sample probes.

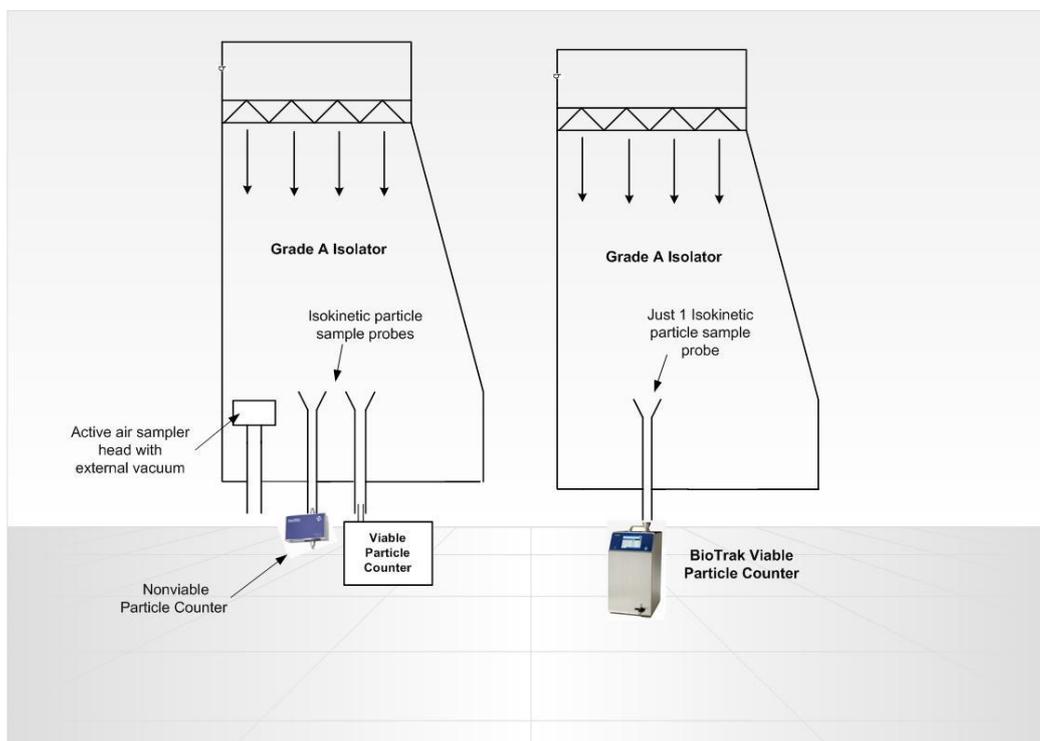


Figure 6. Three Measurements with a Single Sample Probe

Grade C and D ISO 7 and 8

The BioTrak Viable Particle Counter is also an effective tool for the periodic monitoring of Grade C and D locations.

Latest industry thinking highlights the importance of monitoring supporting areas. Risk Profiling and Proactive Response (RPPR) to bio-contamination in GMP classified areas, focusing on preventing contamination and not just monitoring for compliance is the latest concept. Trending environmental monitoring data holistically across all supporting areas can detect an increasing risk of a contamination event in Grade A zones. There is real value to be gained by using real-time airborne viable particle detection as part of holistic monitoring strategy for risk escalation.

TSI's FMS utilizes wall-plate technology to enable end users to periodically monitor viable particles at many locations throughout the manufacturing facility using the BioTrak Particle Counter.

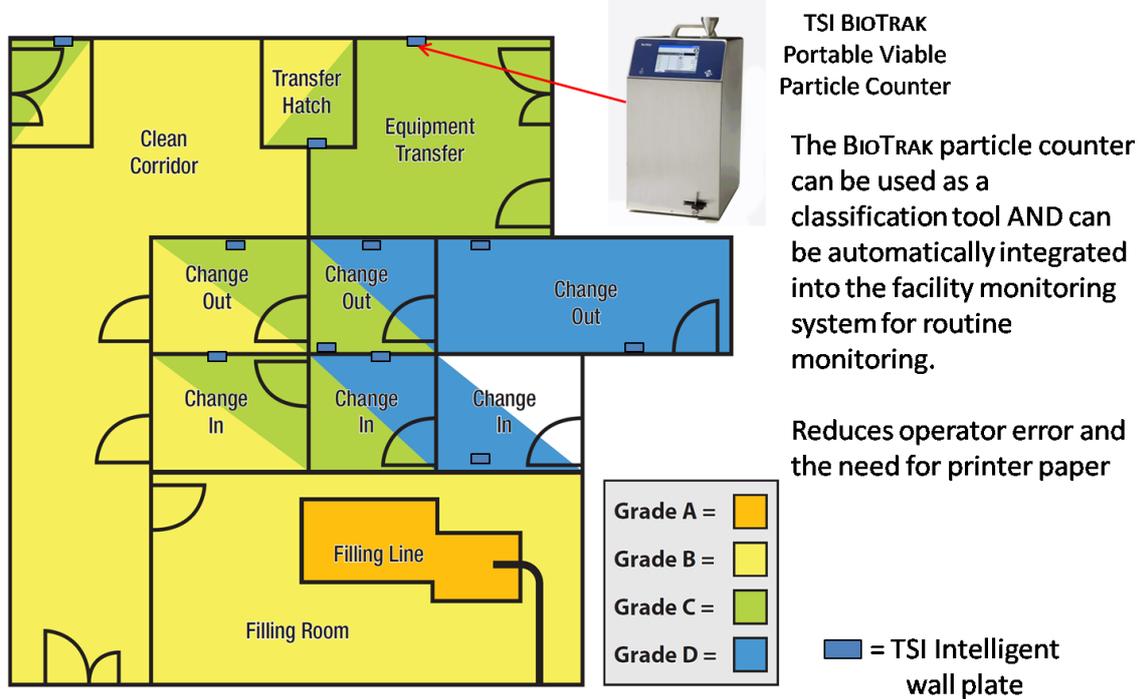


Figure 7. Example of a Cleanroom with Wall-Plate Access for use with BioTrak Particle Counter in Grade C and D Environments

The end user simply positions the BioTrak Viable Particle Counter at the location requiring monitoring, selects the corresponding location on the user interface and connects the particle counter to the wall-plate. The FMS software automatically does the rest. It starts the BioTrak Particle Counter and logs viable and nonviable particle counts. There are no printouts and no data transfer. This data can be used to initiate alarms or be presented as trending reports. All particles analyzed by the instrument are collected on a gelatin filter to enable laboratory analysis.

Conclusion

Real-time viable particle counting in conjunction with the FMS software will deliver important information about your processes and add a new dimension to root cause investigations. This real-time airborne viable particle information builds process knowledge, facilitating Process Analytical Technology PAT and ICH Q8 QbD opportunities for continuous process improvement.

The BioTrak Real-Time Viable Particle Counter has been specifically designed to meet the ISO 21501-4 standard for nonviable particle monitoring, it has a flow rate of 1 CFM and collects the sampled particles for laboratory analysis using a gelatin filter. It is both a portable instrument and can interface with TSI's FMS software.

The instrument connects to existing isokinetic sample probes in critical Grade A ISO 5 environments such as isolators or RABS. Even the sample tubing's internal and external diameters are the same. This means it is easy to replace existing nonviable continuous particle counters used to monitor critical processes. The quantity of analytical equipment and interfaces in critical process areas are kept to a minimum. There is the added advantage of reducing the number of interventions resulting from the need to change active air sampler plates or load growth media into the critical work area.

Please contact TSI if you require further information regarding the BioTrak Particle Counter and TSI FMS Monitoring Software for life science applications.

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