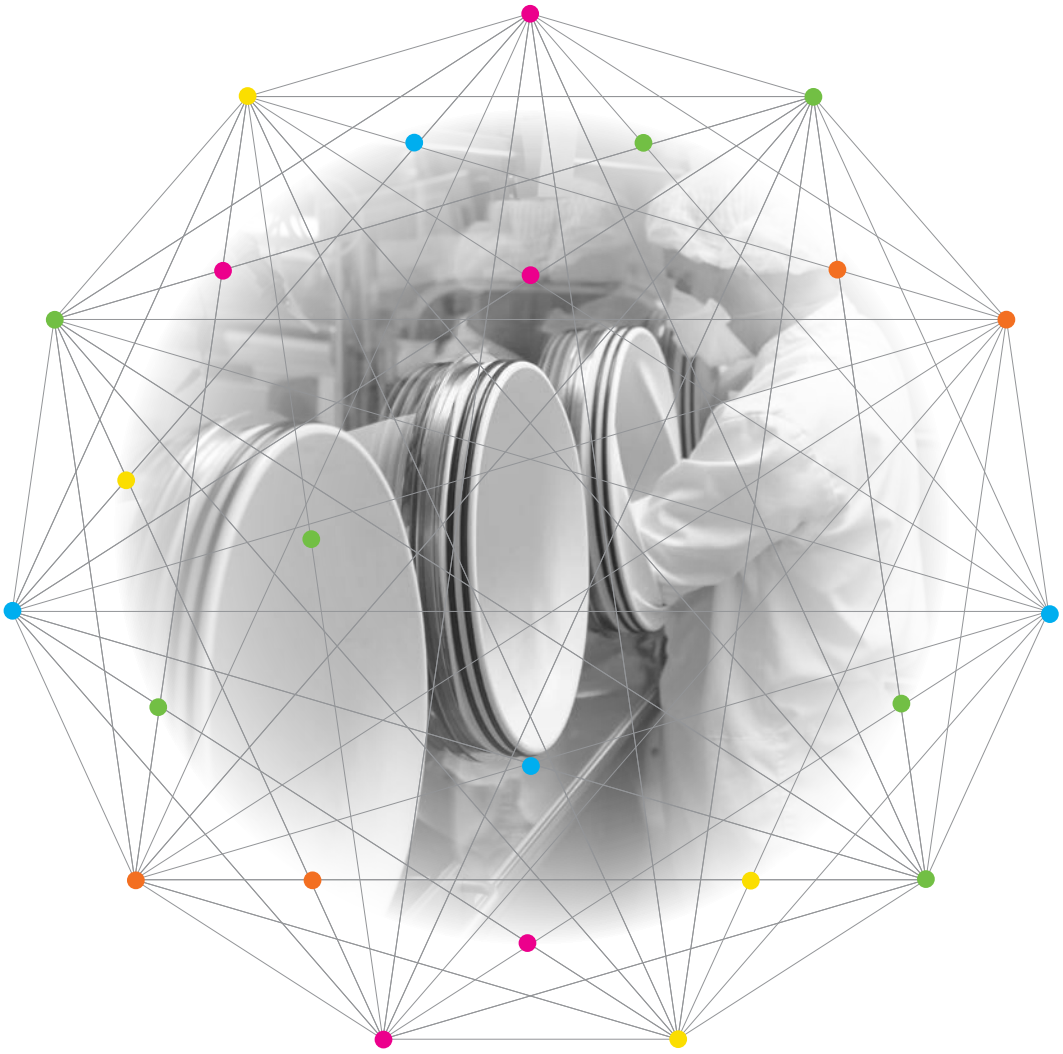
ASEPTIC BIOPHARMACEUTICAL MANUFACTURING: FAQs

THE BIOTRAK® REAL-TIME VIABLE PARTICLE COUNTER



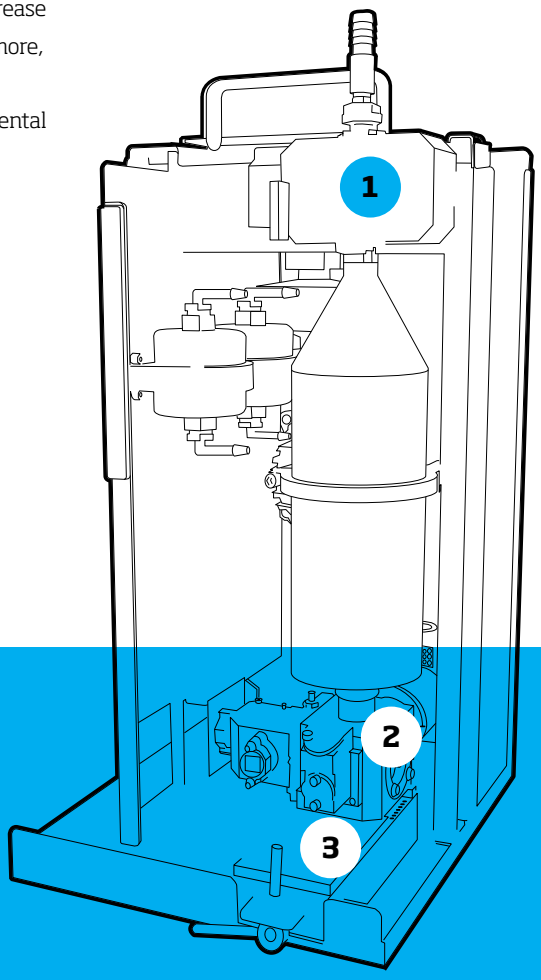
UNDERSTANDING, ACCELERATED

REDUCE RISK
INCREASE EFFICIENCY
IMPROVE PROCESS UNDERSTANDING

The BioTrak® Real-Time Viable Particle Counter enables aseptic biopharmaceutical manufacturing facilities to reduce risk, increase efficiency and improve process understanding. The BioTrak Particle Counter is three instruments in one; offering continuous ISO-compliant optical particle counting, real-time viable particle counting, and microbial sample collection for identification.

For aseptic manufacturing, the BioTrak Particle Counter is best suited for:
+ Fixed-position, automated and continuous monitoring of the aseptic core
+ Routine certification and episodic monitoring of cleanrooms throughout a facility

In either application, the BioTrak Particle Counter offers enormous cost savings over traditional growth-based methods. By eliminating the need for manual agar plate changes in the aseptic core, manufacturers are able to reduce process interventions and line stoppages, cut production downtime, and avoid wasted product, sub-lotting or extra sterility testing. The BioTrak Particle Counter can demonstrate environmental control in real-time to increase readiness, avoid excessive sterilization cycles and minimize air exchange rates. Furthermore, because the instrument provides both total and viable particle counts, as well as sample collection capability, it is the ideal all-in-one solution for simple, cost-effective environmental monitoring throughout a facility.



The BioTrak Particle Counter is three instruments in one

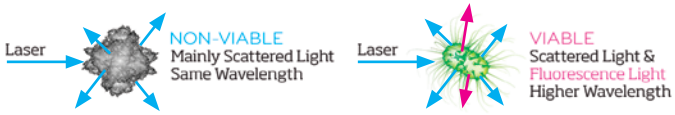
1. ISO-compliant non-viable particle counter
2. Dual-channel LIF viable particle counter
3. 9-hour microbial collection filter

THE BASICS

Q1. How does the BioTrak Particle Counter discriminate microorganisms from non-viable particles?

A: The optical properties of microorganisms are substantially different from non-viable particles.

Non-viable particles simply scatter light. Microorganisms (bacteria, mold, yeast) contain fluorescent molecules which absorb and re-emit light in unique ways. The BioTrak Particle Counter exposes incoming particles to laser light at 405 nm. Particles containing fluorescent components (i.e. microorganisms) re-emit light at higher wavelengths; a process called Laser Induced Fluorescence (LIF). A particle's viable or non-viable status is determined by its fluorescent properties and its size (measured simultaneously by light scattering).



Q2. How does the BioTrak Particle Counter achieve superior viable discrimination?

A: It records more information from each airborne particle.

Laser Induced Fluorescence (LIF) (see question 1) produces a continuum of emitted wavelengths (the emission spectrum). Other LIF-based instruments detect these emissions in a single wavelength region; the BioTrak Particle Counter detects emissions in two distinct wavelength regions (dual-channel LIF). Two fluorescence parameters, combined with particle size, provide more data for superior discrimination.

Q3. Does the BioTrak Particle Counter count non-viable particles as well?

A: Yes, it provides ISO-compliant total particle data.

Before particles enter the viability detector they are first sized and enumerated by a dedicated, 650-nm optical particle counter (OPC). ISO 21501-4 compliant, the BioTrak Particle Counter reports total particle concentrations in 6 size channels according to ISO 14664-1. Combining total particle data with viable counts and identification via the gelatin filter, the BioTrak Particle Counter is the ultimate integrated tool for certifying and monitoring clean rooms.

Q4. Does the BioTrak Particle Counter integrate with environmental monitoring systems?

A: Yes, allowing automated operation and data collection.

The BioTrak Particle Counter seamlessly integrates with TSI's robust and flexible Facility Monitoring System (FMS) software. FMS is compatible with a large variety of monitoring instruments for reliable operation and data management. Data integrity is critical; integrated environmental monitoring systems are a key component of meeting regulatory expectations.

Q5. How do BioTrak Particle Counter viable counts (vcnt) compare to traditional colony forming units (cfu)?

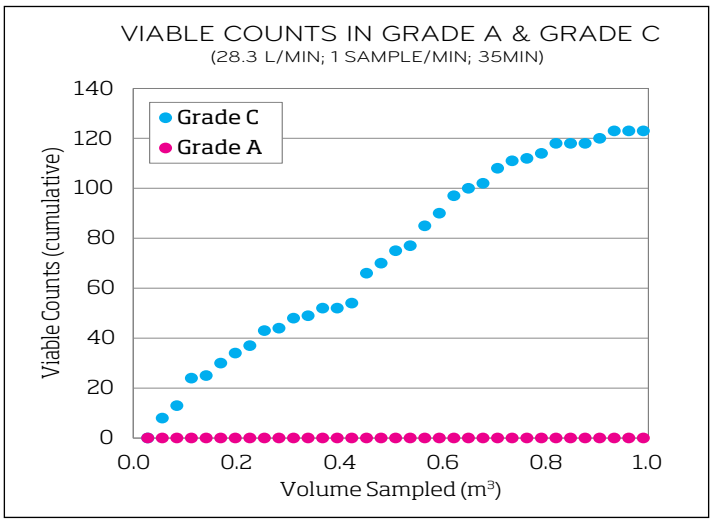
A: The two metrics are proportional, but not always equal.

Growth-based methods and the BioTrak Particle Counter employ fundamentally different approaches to microbial quantitation and therefore report results in different units; cfu and vcnt respectfully. In validation studies, the BioTrak Particle Counter (vcnt/m^3) and slit-to-agar (cfu/m^3) results where highly correlated (r^2 >0.95) over 3-orders of magnitude. When sampling virtually aseptic environments, both methods reported zero (see Q7). In real-world, Grade C/D ISO 8 cleanroom environments, the BioTrak Particle Counter is typically more sensitive than growth-based methods due to detection of VBNCs (see Q8).

Q6. How does the BioTrak Particle Counter respond in Grade A/ISO 5 environments?

A: In rigorously aseptic environments, essentially zero viable particles are detected.

The BioTrak Viable Particle Counter has an ultra-low false-count rate. When it samples HEPA-filtered air, viable counts are essentially zero. In fact, this "zero-test" is part of the operational qualification (OQ). The BioTrak Particle Counter also reports essentially zero viable counts in actual aseptic manufacturing spaces (e.g. isolators, RABS) where traditional methods yield zero cfu.



Q7. In the aseptic core, how does the BioTrak Particle Counter improve quality and efficiency compared to traditional methods?

A: The BioTrak Particle Counter eliminates interventions for changing agar plates.

Traditional microbial monitoring inside the aseptic core requires human interventions for agar plate changes. This activity compromises the integrity of the aseptic environment and defeats the primary purpose of isolators; to exclude human operators. The BioTrak Particle Counter samples air from within the aseptic core but is physically located outside that space, providing continuous real-time microbial data without operator intervention.

Q8. Can the BioTrak Particle Counter detect Viable But NonCultureables (VBNCs) as viable particles?

A: Yes.

TSI's validation studies indicate that the BioTrak Particle Counter detects a substantial proportion (>25%) of certain stressed microbes (a type of VBNC) as viable particles. These stressed organisms were detected at low levels, or not at all, by slit-to-agar instruments. The BioTrak Particle Counter detects VBNCs more sensitively than growth-based methods because detection is not dependent on metabolic status.

"[Microbiological] Sampling methods used in operation should not interfere with zone protection"

European Commission GMP Annex 1, page 5

VS. GROWTH-BASED METHODS:

Q9. How does the BioTrak Particle Counter respond to common interferents?

A: Most materials do not produce viable counts, but site-specific studies are encouraged.

In validation studies, airborne particles from tryptic soy broth (TSB), ethanol, isopropanol, clean room paper or glove-box sleeves were generally not classified as viable (typically 0-0.5% of total particles). Certain gowning materials produced higher viable counts likely due to shedding of VBNCs (see Q7). Application-specific testing should be performed during the BioTrak Viable Particle Counter validation to evaluate interferents specific to your facility and manufacturing process.

Q10. How do users determine alert and action levels for the BioTrak Particle Counter?

A: USP <1116> provides relevant guidance. Location-specific baseline data is recommended.

The BioTrak Viable Particle Counter is a fundamentally different technique from growth-based methods, and does not quantitate microbes in cfu. Therefore, specific alert/action limits in cfu are not useful. USP <1116> suggests initial alert/action levels in Contamination Recovery Rates (CRR), which are readily applicable to BioTrak Particle Counter data. The guidance encourages users to determine location-specific CRR baselines and determine alert/action levels accordingly.

Q11. Can the BioTrak Particle Counter identify microbes?

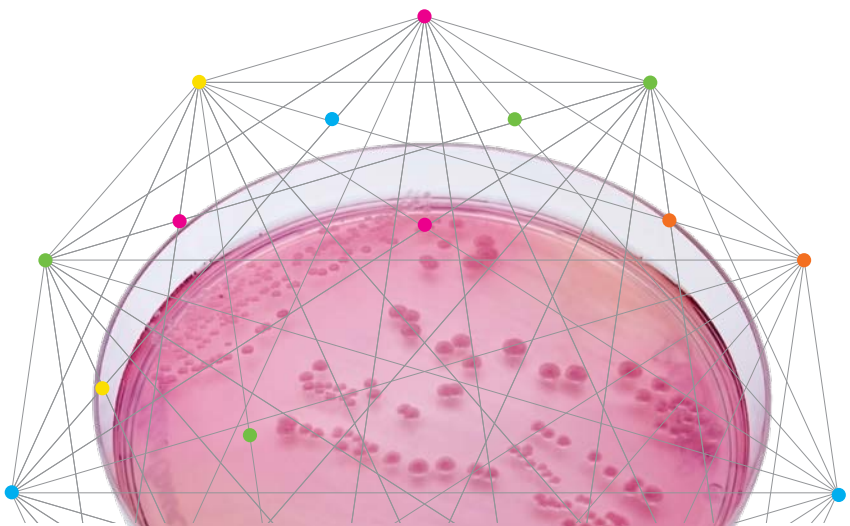
A: BioTrak Particle Counter supports identification, but not in real-time.

The BioTrak Particle Counter discriminates microbes from non-viables in real-time based on size and fluorescent characteristics (see Q1 & Q2). The subtle differences between species are insufficient for unambiguous identification in real-time. Therefore, the BioTrak Particle Counter supports identification by collection and growth via the integrated gelatin filter, validated for 9 hours of continuous collection. Viable and non-viable particle counting operates with or without the gelatin filter.

Q12. Does the BioTrak Particle Counter's gelatin filter quantify microbes?

A: Microbial quantitation is determined in real-time by LIF, not the gelatin filter.

The gelatin filter sample collection device is intended for identification purposes only. It is designed as a qualitative tool to maintain viability of collected organisms for the maximum duration. The gelatin filter collection system is validated for 9 hours of continuous sample collection and does not require intervention into isolators or RABS for access.



REGULATORY COMPLIANCE & VALIDATION

Q13. Do regulatory agencies embrace Alternative or Rapid Microbial Methods (RMMs)?

A: Yes, improving quality through new technology is a priority.

Implementing new techniques to improve quality is welcomed and expected. Many practical guidances and regulations are published to aid and encourage use of RMMs including: USP <1223>, USP <1116>, Ph. Eur. Chapter 5.1.6, and PDA Technical Report 33. Many agencies actively encourage improved quality through new technology with Process Analytical Technologies (PAT) and Quality by Design (QbD) initiatives.

Q14. What are the options for regulatory approval?

A: There are several options for obtaining regulatory approval.

PDA Technical Report 33 contains a succinct and practical guide to approval options and is recommended reading for users considering the BioTrak Real-Time Viable Particle Counter for in-process applications. Options include NDA/ANDA submissions, FDA's Comparability Protocol, EC's post-approval change management protocol, and internal change control programs where appropriate. Communication with regulatory agencies early in the development of the validation plan is encouraged.

"Alternative and Rapid Microbiological Methods have been understood, accepted and encouraged by regulatory authorities..." *PDA Technical Report No. 33 (Revised 2013), page 6*

Drug Master File:
+ Physical Efficiency
+ Accuracy
+ Precision
+ Specificity
+ LOD/LOQ/Range
+ Linearity
+ Ruggedness
+ Robustness

Q15. What validation work has already been done to ensure BioTrak Particle Counter compliance?

A: TSI has a Type V Drug Master File submitted with the FDA.

Inquire with your local TSI partner, or through our website, to review a summary of the validation studies included in the DMF. To directly support users' regulatory submissions, or internal change control documentation, TSI has performed rigorous validation work included in a Drug Master File at FDA. TSI has worked with experts, including former regulators, to ensure the BioTrak Particle Counter is properly qualified to support aseptic pharmaceutical manufacturing.

Q16. How does TSI support customers during BioTrak Particle Counter validation?

A: With dedicated experts and resources, both on-site and off.

TSI has a committed team of professionals ready to assist customers during evaluation and validation. In addition to the qualification studies included in the Drug Master File, TSI offers formal documentation, on-site services and expert consultation from IQ/OQ through PQ. Work with your TSI partner to coordinate validation plans and experiments. Leverage TSI's expert knowledge, and benefit from our experience.

SPECIFICATIONS

BIOTRAK® REAL-TIME VIABLE PARTICLE COUNTER
MODEL 9510-BD

Particle Counting	
Size Range	0.5 to 25 µm
Particle Channel Sizes	0.5, 0.7, 1.0, 3.0, 5.0, 10 µm
Size Resolution	<15% @ 0.5 µm (per ISO 21501-4)
Total Particulate Counting Efficiency	50% at 0.5 µm; 100% for particles >0.75 µm, (per ISO 21501-4 and JIS)
Viable Detection	2 fluorescent channels and 1 sizing channel for discrimination
Sample Collection	Integrated filter holder for 37-mm diameter filters
Concentration Limit	820,000 particles/ft^3 (29,000,000/m^3) @ 10% coincidence loss
Zero Count	<1 count per 5 minutes (per ISO 21501-4 and JIS B9921)
Flow Rate	1.0 CFM (28.3 L/min) ±5% accuracy (meets ISO 21501-4 and JIS B9921)
Calibration	NIST traceable using TSI calibration system
Calibration Frequency	Recommended minimum of once per year
Standards	ISO 21501-4, CE, JIS B9921
Hardware	
Total Particulate Light Source	660 nm laser diode for MIE particle sizing
Viable Particulate Light Source	405 nm laser diode for Laser Induced Fluorescence viability detection
Flow Rate Control	Electronic, automatic closed loop (patented* flow control technology)
Sample Tube Extension	Up to 10 ft (3 m)
Audible Alarm	Built-in; >85 dB at 1 meter (adjustable)
External Alarm Relay	Normally open contact closure rated for 0 to 60 V AC/DC at 1.5A peak, 0.5A continouos. Alarm output rated for 60 V insulation. Relay contact closes under user configurable alarm conditions.
Exhaust	Internal HEPA filter
Vacuum Source	Internal pump
Alarm Output	Dry contacts, closed when alarm is engaged
Display	VGA 5.7-in. (14.5-cm) touch screen display
Printer	Optional built-in thermal printer
Dimension (H x W x D)	19 in. x 10.5 in. x 11.7 in. (48.3 cm x 26.7 cm x 29.7 cm)
Weight	37 lbs (16.8 kg)
Power	110 to 240 VAC universal power supply
Operating Range	41° to 86°F (5° to 30°C),** 20% to 85% RH noncondensing***
Operating Elevation	0 to 10,000 ft (0 to 3,000 m)
Storage Range	32° to 122°F (0° to 50°C), up to 98% RH noncondensing
Housing	Stainless Steel
External Chemical Resistance	Isopropyl alcohol, chlorinated solution, hydrogen peroxide
Environmental Sensor Interface	Supports TSI air velocity, temperature and relative humidity probes

User Interface and Communication	
Sampling Modes	Manual, automatic, beep; cumulative/differential; count or concentration
Sampling Time	1 second to 99 hours
Sampling Frequency	1 to 9,999 cycles or continuous
Data Storage	250 Zones 999 Locations **10,000 sample records including:** Date, time, six total viable particulate size channels, flow status, instrument status; transferable via USB storage device, TrakPro™ Lite Secure software, Modbus® TCP over Ethernet or USB, and optional TSI FMS software.
Status Indicators	Flow, Instrument
Alarm Limits	Programmable for all particle channels (both total and viable)
Languages	English, German, French, Spanish, Japanese, Chinese (simplified), Italian
Software	TrakPro Lite Secure, optional FMS software
Printer Output	Prints in all available languages with optional integrated printer
Unit ID	Configurable IP address
Security	2-level password protection to lock out usage and configuration
Reports	Provides Pass/Fail on ISO 14644-1, EU GMP, and FS209E reports
Communication Mode	Modbus® TCP over Ethernet or USB
Accessories	
Included Accessories	Printed QuickStart guide, operating manual on CD, power supply, isokinetic probe, tubing, zero count filter, USB cable, TrakPro Lite Secure software, viable filter holder, viable collection filters, cleaning swabs, and calibration certificate
Optional Accessories	Electronic filter scanning probe, basic filter scanning probe, TSI velocity probes, Temp/RH probe, isokinetic probes, sample tubing, hard-sided carrying case, printer paper, and FMS Software

*The BioTrak 9510-BD incorporates the following patented technologies: Patent Numbers 6,167,107; 5,701,012; 5,895,922; 6,831,279; 7,261,007.
**Maximum temperature limited by gel collection filter.
***See TSI Application Note CC-104 for operation above 50% RH.

Specifications are subject to change without notice.

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