Real Time Airborne Viable Particle Detection

Technology Overview and Applicability To Pharmaceutical Quality Systems
Overview

Introduction

Technology Overview
  Laser Induced Fluorescence
  Critical Operational Parameters

Application Scenarios
  Application roadmap
  Real-time evaluation of aseptic techniques
  Root cause investigations
  Quality risk management
Introduction: The Desired State

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight”

An opportunity for a less restrictive regulatory paradigm and drives innovation and continual improvement in manufacturing processes.
Pursuit of Faster Results: Traditional Microbial Monitoring

- Process Environment
- Sampling
- Incubation
- Results
- 2 - 14 Days
- Review Levels
  - Above Limit
  - Below Limit
- Reaction

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Pursuit of Faster Results: Lab-Based RMM

2-14 Days

Majority of RMM’s Reduce Incubation Time

8-48 hours
Pursuit of Faster Results: Real-Time Viable Particle Detection

+ BioTrak™ Detector
  • New category of RMM
  • Optical spectroscopy
  • Laser Induced Fluorescence (LIF)
+ Real-time results
Environmental Monitoring in Real-Time

- Real-time viable particle data
- Respond in real-time
- Segregate Product
- Root Cause Investigations
- QRM ICH Q9
- CAPA
- PAT
- QbD ICH Q8

- Knowledge
- Information
- FMS
- Training
- Qualification
- Risk Analysis
- Understanding, Accelerated
Three Stages of TSI’s BioTrak™ Real-Time Particle Counter

- ISO 21501-4 compliant particle counter 28.3 lpm
- Viability detector - Laser Induced Fluorescence
- 37mm Collection Filter for speciation of analyzed particles
Airborne Particle Counter

- Proven TSI AeroTrak 9510 Airborne Particle Counter Engine
- ISO 21501-4 Compliant Specification and Calibration
- Full Airborne Particle Counter Functionality
Particle Concentrator

28.3 lpm flow is too fast viability detection

The flow is slowed down for the viability detector using a concentrator

Inlet Flow

Major Flow

Minor Flow

Clean air and small particles

Most particles of interest

Particle Counter

28.3 L/min Inlet flow

Particle Concentrator

HEPA filter

27.3 L/min concentrator exhaust

1.0 L/min concentrated aerosol + 4.0 L/min clean "sheath" flow

Collection filter

5.0 L/min viability filter exhaust

Viability Detector

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What impact does the concentrator have on the particle transport efficiency?

Air Samplers also have particle transport efficiency concerns.
Laser Induced Fluorescence

Laser Induced Fluorescence (LIF)

Viable cell metabolites tryptophan, NADH, and flavin’s (riboflavin) fluoresce when excited by ultra-violet light

“Advanced Trigger Development” Jeyes et al, Lincoln Laboratory Journal Volume 17, Number 1, 2007
Laser Induced Fluorescence

- Want to differentiate the microorganisms from the nonviable particles with fluorescence properties
- Difficult task even with **full** excitation and emission spectrum information
- Not possible to implement full spectroscopy in affordable portable instruments
- TSI Collaborative development since 1990’s
- TSI has fundamental single particle LIF patents*

*TSI Patents 5,701,012; 5,895,922; 6,831,279
Laser Induced Fluorescence

\[ f(x) = a_0 + \sum_{n=1}^{\infty} \left( a_n \cos \frac{n\pi x}{L} + b_n \sin \frac{n\pi x}{L} \right) \]
Viability Detector

- Patented* Laser Induced Fluorescence (LIF) Viability Detection
- TSI collaborative technology development over the past 20 years

*Patents 5,701,012; 5,895,922 and 6,831,279
Discrimination - Impact of Additional Optical Parameters

Single Fluorescence Channel

Two Fluorescence Channels
Discrimination - Another way to visualize

- Algorithms are used to calculate a discrimination parameter
- Particles with a discrimination value higher than a threshold are classified as viable
- Particles with optical signatures near the intersection have potential to be misclassified (False Positive or False Negative)
Discrimination

- Better Discrimination
- Number of analysis parameters
- Algorithms
- Orthogonal measurements
Sensitivity

Discrimination Parameter
LIF Dual Sensitivity

+ Ability to adjust instrument response to application space

TABLE 1 - Air Classifications

<table>
<thead>
<tr>
<th>Clean Area Classification (0.5 μm particles/ft²)</th>
<th>ISO Designation</th>
<th>≥ 0.5 μm particles/m³</th>
<th>Microbiological Active Air Action Levels (cfu/m³)</th>
<th>Microbiological Settling Plates Action Levels (diam 90mm: cfu/4 hours)</th>
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</tbody>
</table>

“Clean” Environments
- Low number of viable particles
- Low number of total particles
- Lower number of particles with fluorescent characteristics
- Unacceptable to miss viable particles
- HIGH SENSITIVITY

“Dirty” Environments
- Higher number of viable particles
- Higher number of total particles
- Don’t want excessive false positives
- Higher limit of viable particles acceptable to miss some
- LOW SENSITIVITY
Collection Filter

37mm Collection Filter: Provides sample for speciation of optically analyzed particles
Real-Time Viable Particle Counting - Important Considerations

+ Need to understand the product’s capabilities and limitations
  • Effectiveness of LIF Measurement
    - Discrimination capability
    - False Positives versus False Negatives
  • Functionality
    - Ease of use
    - Total particulate sizing capability
    - Viable particle detection capability
    - Data availability
  • Particle capture capability
  • Regulatory Challenges
Characterization of Real-Time Viable Particle Counter

+ Needs to be characterized with existing methods
+ Comparability studies: efficiency of the instrument under test and the reference sampler must be considered
+ Desire correlation to existing methods

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Regulatory Guidance-Challenges

Active Air Sampling

ISO 14698-1

Real-Time Aerosol Viable Detection

Rapid Method

Compendial Method

Comparison: Equivalent or Better

USP 1223, EP 5.1.6, PDA TR33
Applicability

+ LIF results will be different than current active sampler based results
+ What is the value?
  • Real-time data
  • Continuous data
  • Characterization of processes
  • Training feedback
+ Evolution to real-time release
Application Road Map
“The Innovation Highway”

Vendor Validation
Operator Training
Comparability Studies
Root cause Investigations
Monitoring Locations + Zone Qualification

Immediate benefit
Long term benefit

Real-time release

Validated in Process Measurement

Confidence in the measurement
Environmental Monitoring in Real-Time

- Real-time viable particle data
- Respond in real-time
- Segregate Product
- Root Cause Investigations

QRM ICH Q9
CAPA
PAT
QbD ICH Q8

Information

Knowledge

Training
Qualification
Risk Analysis

FMS
New Information: Grade C Example

Grade C Monitoring Location
In Operation

- Clean Corridor
- Transfer Hatch
- Equipment Transfer
- Change Out
- Change In
- Change Out
- Change In
- Change Out
- Filling Line
- Filling Room

Grade C = Light Green
Root Cause Investigations

Particle Counts compliant to ISO 21501-4
Root Cause Investigations

Particle viability detector

VCNT

12:30PM

Particle Count er

Viability Detector

Collection filter

HEPA filter

Particle Concentrator

#/M^3

0.00

10.00

20.00

8:24 9:36 10:48 12:00 13:12

Viable Counts
Root Cause investigations

2 different conclusions.....

TCNT

VCNT

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Root Cause Investigations

Root cause Investigations

TCNT

#/M^3

08:24 09:36 10:48 12:00 13:12

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Root Cause Investigations
Collection Filter

- Particle Counter
- Particle Concentrator
- HEPA filter
- Viability Detector
- Collection filter

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ICH Q8(R2) – Improved Process Knowledge

Root Cause Investigations

The BioTrak detector high temporal resolution means you know when a microbial excursion occurred

Leads to

Improved root cause investigations
ICH Q8(R2) – Improved Process Knowledge

Identifying Microbiological Contamination Sources

Investigation Tool

Quickly determine the source of airborne microbiological contamination

“Geiger Counter” mode – User configurable Beep for Viable counts
ICH Q8(R2) – Improved Process Knowledge

Root Cause Investigations

Understanding the source of airborne microbiological contamination will help determine the cause.

Leads to

Improved root cause investigations
ICH Q8(R2) – Improved Process Knowledge

Root Cause Investigations

Improved root cause investigations

Leads to

More effective CAPA
ICH Q9 – Quality Risk Management

Qualification Tool:
Early risk based release of (manufacturing) areas
-Supported by existing methods: results days later

- OPC Monitoring location
- Environmental Monitoring location

- BioTrak Real-time OPC and Airborne Viables

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ICH Q9 – Quality Risk Management

Risk Analysis:
Data to support monitoring position rationale for Settle Plates, Active Air Sampling and Particle Monitoring: Monitoring location fine tuning

Clean room and clean air device monitoring
8. Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

OPC Monitoring location

Environmental Monitoring location

BioTrak Real-time OPC and Airborne Viables
ICH Q9: Quality Risk Management

Training- Immediate notification of poor practice

Gowning
ICH Q9: Quality Risk Management

Training- Immediate notification of poor practice
Aseptic technique
ICH Q9: Quality Risk Management

Training- Immediate notification of poor practice
Poor cleanroom practice
Innovation Highway

Vendor Validation

Operator Training

Comparability Studies

Monitoring Locations + Zone Qualification

Root cause Investigations

Short to medium term benefit

Long term benefit

Real-Time Release

Goal

Validated in Process Measurement

Confidence in the measurement

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Thank You

Contact Information:
Tim Russell
tim.russell@tsi.com

Darrick Niccum
darrick.niccum@tsi.com