INCORPORATION OF PARTICLE AND MICROBIAL DETECTION INTO ENVIRONMENTAL MONITORING SYSTEMS

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Agenda

Why perform Particle and Microbial monitoring

Regulatory agencies

Cleanroom Grades

Classification of a cleanroom

Monitoring of a cleanroom

Typical system components

Reports

Why Monitor

Contamination will affect product quality and possibly effectiveness

Manufacturing Failures: Human error, use of incorrect ingredients, inadequate cleaning procedure and undetected contaminants

Particulate matter (Inert or Nonviable and Viable) can range in size from sub-microns to several hundreds of microns, and shape and density may vary widely.

Clean rooms can be exposed to particulate matter shed by gowns, gloves, skin flakes (personnel), sample preparation equipment, glassware, metal, metal oxides, building materials, ceramics, dust, process air, air filtration systems, and machines.

Humans are the largest source of microbial contamination

Why to Monitor

Typical systems consist of:

Particle Monitors

Microbial Samplers

> Portable

> Fixed location

Temperature

Humidity

Pressure

Other parameters that affect cleanroom operations

Reasons for an Environmental Monitoring System (EMS)

Automation

> Eliminate routine tasks influenced by humans

> Assure conditions are under control

Data Integrity

> 21 CFR Part II

> Backup or redundancy of system

Simplicity

> Notification of out of control conditions

> Done the same way every time

System integration

> Automated Reports

> Access to the data across the company

Monitoring in Air

Air

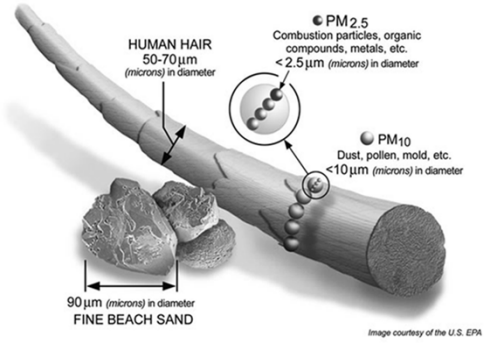
Total Particulates (Inert or Nonviables [plus Viables])

> Particle Counting (0.5 µm in diameter and/or larger)

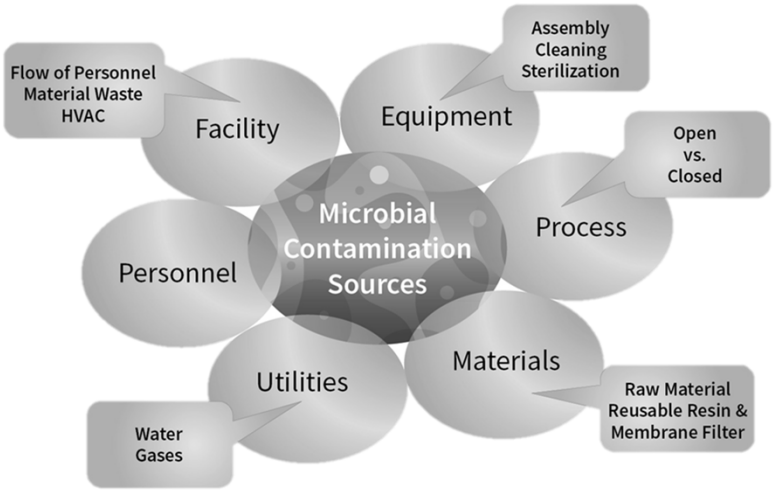
Viables (typically bacterial and fungal spores)

> Settle or Settling Plates (Passive Air Sampling)

> Air Samplers (Active Air Sampling)



Microbial contamination



Processes to monitor

Non-sterile production

API

Tablets

Granules

Syrups

Topical
(lotions, creams,
ointments, etc.)

Critical non-sterile production

Aerosol

Nasal spray

Powder inhalers

Processes to monitor

Sterile production

Injections

Ophthalmic preparations

Irrigations solutions

Hemodialysis solutions

Topicals (for open wounds or critical applications)

Radiopharmaceuticals

Cell factories

Compounding centers

Regulatory Agencies/Organizations

EMA (European Medicines Agency) – EU

FDA (Food & Drug Administration) – USA

WHO (World Health Organization)

PIC/S (Pharmaceutical Inspection Convention and Cooperation Scheme)

International Organization for Standardization (ISO),
Technical Committee 209 (TC 209) [ISO 14644-1]

United States Pharmacopoeia (USP) [USP 36, Chapter <1116>"
Microbiological Control and Monitoring of Aseptic
Processing Environments", 2013]

Relevance of standards

EU GMP
requirements for EU production and export/import

FDA
requirements for USA production and export/import

JP 15
requirements for Japanese production and export/import

WHO
requirements for Global production to WHO

PIC/S
requirements for Global production and export/import

PIC/S

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP.

PIC/S' mission:

"To lead the international development, implementation and maintenance of harmonized Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products."

- **Founded** November 1995
- **Membership:**
  - 48+ Country Authorities
  - 4 Partners (EDQM, EMA, WHO, UNICEF)
  - New members go through a detailed assessment
- **Promote Global Harmonization Of GMPs**
- **Benefits to Industry**
  - Reduced duplication of inspections
  - Cost savings
  - Export facilitation
  - Enhanced market access

GMP Regulatory Documents

Pharmaceutical Manufacturing

FDA GMP: 21 CFR Parts 210/211

EU GMP: EudraLex Volume 4 Guidance for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use

Aseptic Processing

FDA: "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing"

September 2004

EU: Eudralex vol. 4 Good Manufacturing, "Annex 1, Manufacture of Sterile Medicinal Products"

EU GMP Annex 1

The EU GMP Annex 1 outlines three phases that need to be performed:

1. Certification: Each cleanroom and clean air device should first be classified.
2. Monitoring: The cleanroom should then be monitored to verify that conditions are being maintained relative to product quality.
3. Data review: The data accrued from the monitoring must be reviewed in light of the risk to finished product quality.

Room Classification, Clause #4

- Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1
- Classification should be clearly differentiated from operational process environmental monitoring.

Cleanroom Grades

EU Annex 1 establishes 4 grades for cleanrooms

> Grade A: Local zones for high risk operations (filling, closing, etc.)

> Grade B: The background environment of the Grade A zone

> Grade C and D: Clean areas for less critical stages

FDA defines 2 types of clean areas

> Critical areas: areas where the drug product, sterilized containers and sterilized closures are exposed

> Supporting clean areas: where non-sterile components and materials are prepared, held or transferred

FDA Classification table

Particulates ↔ Microbes

Clean Area Classification (0.5 um particles/ft³)	ISO Designation[b]	≥ 0.5 µm particles/m³	Microbiological Active Air Action Levels[c] (cfu/m³)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

EU Classification table

		AT REST [(b)]		IN OPERATION [(b)]	
(ISO)	Grade	Maximum permitted number of particles/m³ equal to or above[(a)]			
		≥0.5µm[(d)]	≥5µm	≥0.5µm[(d)]	≥5µm
4.8 / 4.8	A	3,520	20[(e)]	3,520	20[(e)]
5 / 7	B[(c)]	3,520	29[(e)]	352,000	2,900
7 /8	C[(c)]	352,000	2,900	3,520,000	29,000
8 / U	D[(c)]	3,520,000	29,000	not defined[(f)]	not defined [(f)]

EU and FDA microbial limits

EU (In Operation)

Recommended limits for microbial contamination (a)				
Grade	Air sample cfu/m^3	Settle plates (diameter 90 mm) cfu/4 hours (b)	Contact plates (diameter 55 mm) cfu/plate	Glove print 5 fingers cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

FDA (In Operation)

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
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Monitoring of a cleanroom, GMP Guidance

EU Annex 1:

"Cleanrooms and clean air devices should be routinely monitored in operation."

"Classification should be clearly differentiated from operational process monitoring."

FDA Aseptic Guidelines:

"In aseptic processing, one of the most important controls is the environmental monitoring program."

"Routine particle monitoring is useful in rapidly detecting significant deviations in air cleanliness."

Monitoring of a cleanroom

- Particle and microbial monitoring are required
- Decisions for monitoring frequency and locations are similar
  - Risk-based design applies to both
  - Commonly, particle and microbial points are next to each other
- Batch records must include both sets of data (V and NV), alarms, and data on Temp, humidity, and differential pressure

Monitoring locations

EU Annex 1

"Monitoring locations based on a formal risk analysis study and the results obtained during classification"

FDA Aseptic Guidelines

"Measurements taken at sites where there is the most potential risk to the exposed sterilized product, containers, and closures"

Note: Risk analysis has to be described in a formal written plan. Following a rational plan with attention to all details and good descriptions

Monitoring Frequency

EU Annex 1

Grade A: Continuous monitoring required during setup and operation

Grade B: Recommend same as Grade A; frequency can be reduced

Grade C, D: In accordance with principles of quality risk management

> "Monitoring should be… using methods such as settle plates, volumetric air and surface sampling"

> "Sampling methods should not interfere with zone protection"

FDA Aseptic Guidelines

Critical areas: Continuous monitoring during setup and operation

Supporting clean areas: Frequency of sampling depends on nature of cleanroom activities

> "The additional use of settling plates is optional"

> "Active air sampling is required"

> "Each individual sample result should be evaluated. Averaging of results can mask unacceptable localized conditions."

Microbial sampling options

Passive Monitoring

Settling Plates

Active Monitoring

Slit-to-Agar (STA) Air Sampler (air through a narrow slit, rotational agar plate)

Sieve Impactor (Air through a perforated plate)

> Single stage (contact plate or Petri dishes

> Multi-Stage Cascade (stacked perforated plates)

> Sterlizable Atrium (stainless steel head collection device

> Single-Use Sterile Atrium

Centrifugal Propeller Sampler (Agar coated strip)

Filtration (Polycarbonate, cellulose acetate, gelatin filters

Impingers (use fo liquid medium for particle collection

Real-time Laser Induced Fluorescense Systems

Microbial sampling integrated

Fixed location sensors for microbial sampling

Automated sampling processes

Monitoring summary EU and FDA

	EU	FDA
Monitoring locations	Risk-based	Risk-based
Monitoring frequency in critical areas (Grade A/B)	Continuous (for Grade B, continuous is recommended)	Continuous
Monitoring frequency in support areas (Grade C/D)	'Routine'	'Routine'
Microbial and particle monitoring?	Required	Required
Compressed gas monitoring?	Required Microbial and Particulate	Required Microbial and Particulate

Monitoring

Sample point positioning

Filling lines

Lyophilization

Monitoring locations

ISO standards

Parts of a Monitoring System

Reports

Sample point positioning

Measure to one side, close to critical location

FDA guidance (within 1 ft.)

Just above critical point

Verifies clean air is being supplied to the critical area

Not up by the filters

But not directly above the critical point

Starve of clean air

Create turbulence

Filling Lines

Typically at least 3 monitoring locations

> Entry / accumulator

> Point-of-fill (fill needle)

> Stopper area / stopper bowl

Monitoring for critical areas should be continuous and the zone immediately surrounding the product whenever the product or open container is exposed to the environment.

The monitoring locations should be as close as possible to the exposed product or semi-stoppered vials.

End of filling line and semi-stoppering, and loading of the lyophilizer, the product should be maintained within an ISO Class 5 environment and monitored throughout this distance

Lyophilization

EU Annex 1:

34. Prior to the completion of stoppering, transfer of partially closed containers, as us
done either in a grade A environment with grade B background or in sealed transfer t

116. Partially stoppered freeze drying vials should be maintained under Grade A cond
stopper is fully inserted.

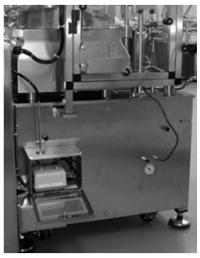
> Monitor the transfer from filler to freeze dryer

> Lyo transfer carts

Mounting locations

Directly to a wall

Directly to a machine



"Flush mount" enclosure

Outside the cleanroom

Bring tubing through wall

ISO Standards

EU Annex 1 says:

"This guidance does not lay out detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. References should be made to other documents such as the EN/ISO Standards."

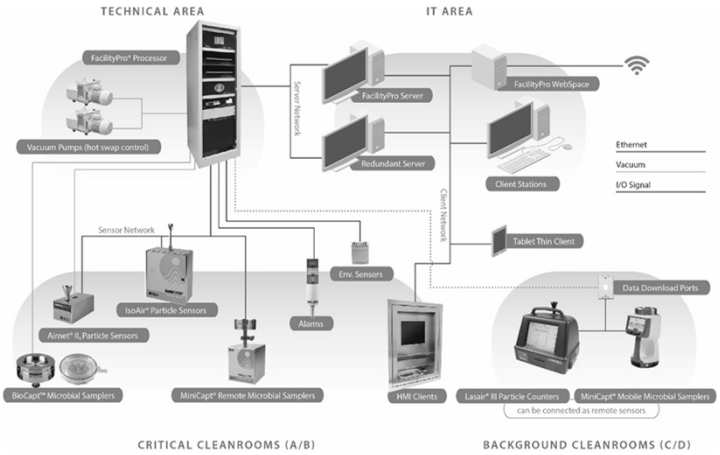
ISO 14644 – Cleanrooms and Controlled Environments
Defines cleanroom classes, certification methods, frequency, etc.

ISO 14698 – Bio contamination in Cleanrooms
Defines biological monitoring programs, choosing a sampling device, etc.

ISO 21501 – Particle Counters
Defines particle counter performance characteristics and calibration

ISO 8573 – Compressed Air
Defines compressed air contaminants, purity classes, test methods

Key parts of a monitoring system



Monitoring Software

Environmental monitoring

Viable and non-viable

Floor layout

Report generator

Alarming

Automation

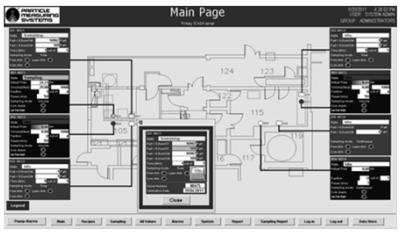
Security

21 CFR Part 11 compliance

Secure database

E-signatures

Audit trail



Types of Reports

Report types

> Audit reports

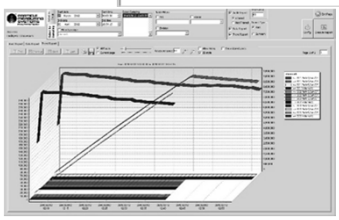
> Data/statistics reports

> Trend reports

Batch identifiers & filters

Functional filters

> All Data, At Rest, Operational



Alarming

Alarm notification required by GMP

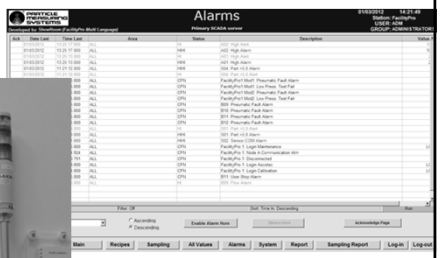
> Alarm beacons

> On-screen

Alarm log

Acknowledgement

Audible alarm silencer



Cleanroom HMI Stations

Operator interface in the cleanroom

> Enter Batch ID information

> Sampling control

> Change operating modes

> View and acknowledge alarms

Flush-mount or arm-mount

Monitoring systems

Design of monitoring systems should be based on a formal risk analysis

Microbial and particle contamination (viable and non-viable) must be monitored in air and gas

Consider typical use for all system components and software when designing and establishing requirements

Summary

- Contamination may come from humans, manufacturing failures, or outside contamination.
- Total particle contamination is a mixture of nonviable and viable particles.
- Monitoring of a cleanroom should be done to meet regulatory requirements for nonviable and viable particles.
- Historically, nonviable particles are monitored continuously. Viable particles are monitored on a less frequent basis.
- In modern aseptic manufacturing, both types should be sampled continuously to obtain an accurate indication of the cleanroom's condition.
- An ideal monitoring program provides the sampling data required and ensures data integrity with the use of an
- automated system to track any changes.
- The system used to track and record data must also meet certain requirements, i.e. personnel ID and change details. These actions meet the requirements of 21 CFR Part 11 and should be incorporated into any automated Environmental Monitoring System.

Thank You for your attention

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