Environmental Monitoring

PDA Aseptic Processing Class

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Mr. David Crance is Life Sciences Sales Manager for Particle Measuring Systems and has been in the Life Sciences business for over 30 years. He has lectured for pharmaceutical societies and organizations throughout the USA and Asia on environmental monitoring systems and their cGMP regulations. He has been an Instructor at the Parenteral Drug Association (PDA) headquarters in Bethesda, Maryland for over twelve years.

Mr. Crance has been involved in the design and implementation of almost 500 environmental monitoring systems. In his role as Life Science Sales Manager, Mr. Crance works with leading engineering firms and manufacturers in the designing of monitoring systems in new construction and renovation.

Agenda

- Contamination in Manufacturing Facilities
- What to Monitor
- Environmental Monitoring
  - Regulatory Agencies
  - GMP Requirements
  - Total Particulate Monitoring
  - Monitoring Systems

Why monitor?

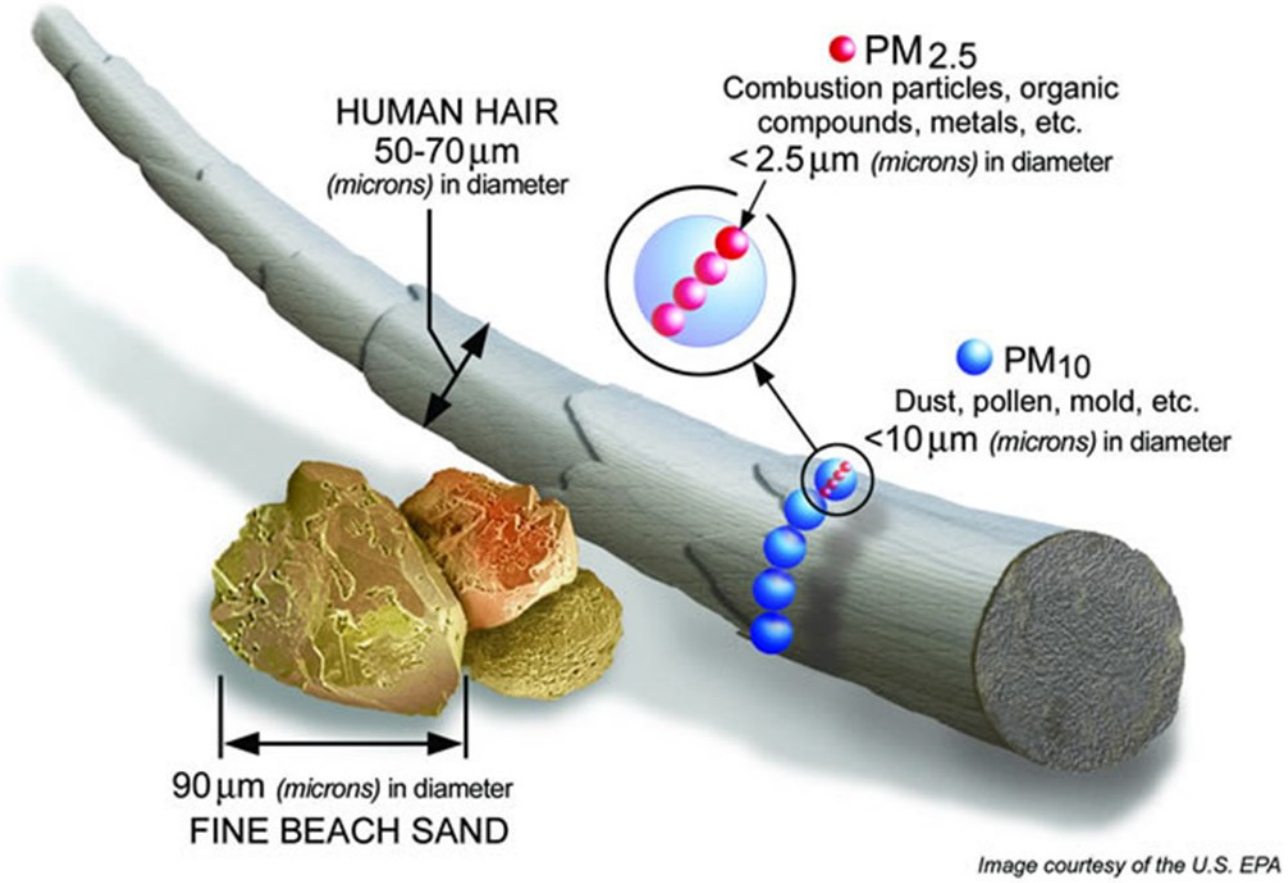


Image courtesy of the U.S. EPA

What to Monitor in Pharmaceutical Manufacturing Environments

Air

1. Total Particulates (Inert or Nonviables plus Viables)
2. Viables
    a. Settle Plates
    b. Active Air Sampling

Surfaces (Viables)

1. Facilities, Instruments and equipment
2. Personnel (Gloves, garment, etc)
    a. Contact Plates
    b. Swabs

Environmental Monitoring

GMP Requirements

Regulatory Agencies & Documents

Cleanroom Grades

Classification of a Cleanroom

Monitoring of a Cleanroom

Regulatory Agencies and Important Organizations

EMA (European Medicines Agency) – EU

FDA (Food & Drug Administration) – USA

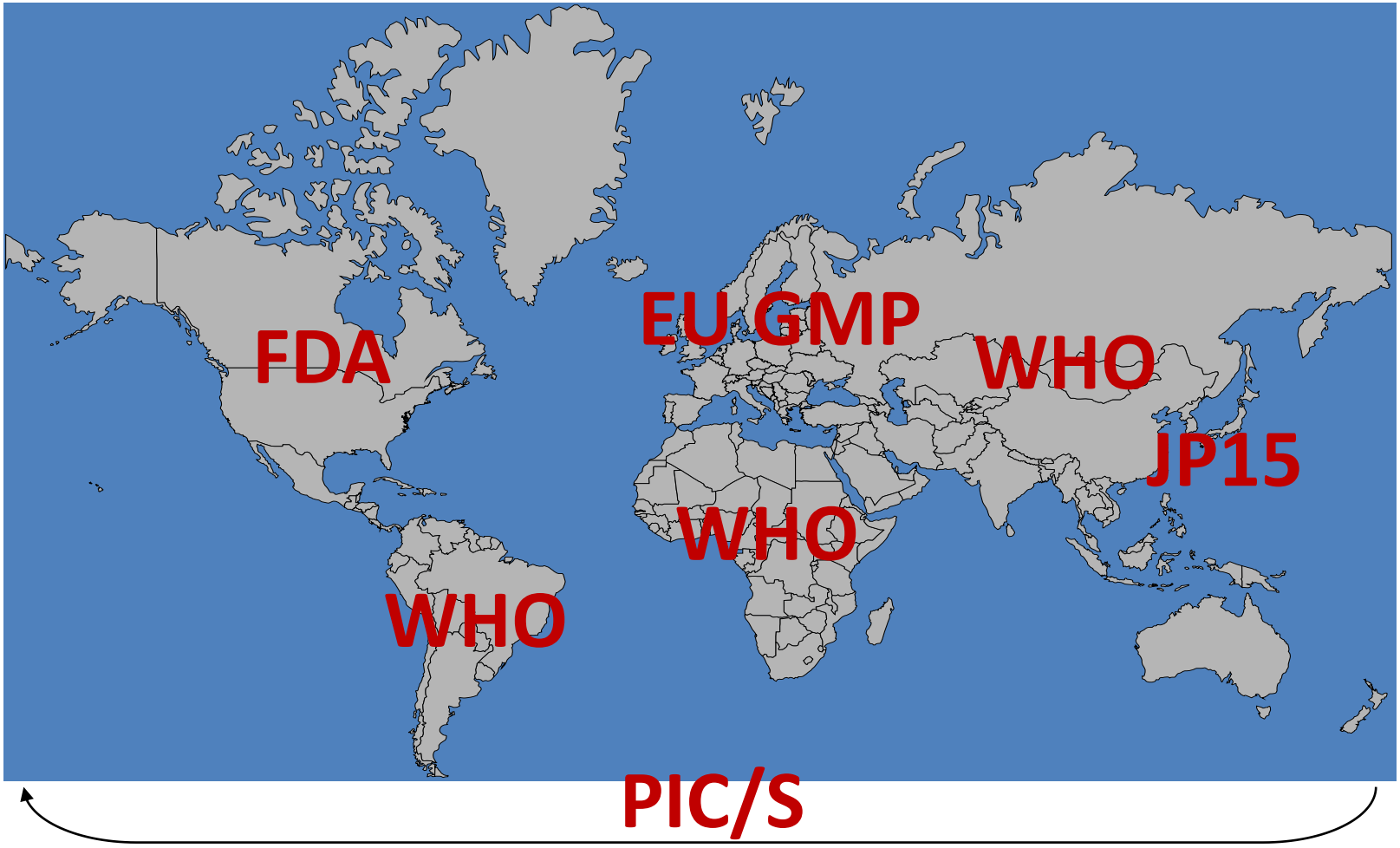
WHO (World Health Organization)

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]

Worldwide GMP



Enforcement of GMP Country Requirements

- Local import requirements
  - Countries only permit the sale of drugs manufactured to their accepted, current Good Manufacturing Practices (cGMP)
  - Location of the manufacturing facility does not matter

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 together provide an active and constructive co-operation in the field of GMP.

PIC/S

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

US and EU 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”
    - Sep 2004
  - EU: Eudralex vol. 4 Good Manufacturing, “Annex 1, Manufacture of Sterile Medicinal Products”
    - Mar 2009

Classification and Monitoring

EU and FDA both require that a cleanroom is classified and then monitored

- **Classification**: Proving that a cleanroom meets the required ISO class (ISO 14644-1:2015)

- **Monitoring**: Continued, ongoing verification that a cleanroom has not shifted from “normal” conditions (ISO 14644-2:2015)

EU GMP Annex 1

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

1. **Classification or Certification**: Each cleanroom and clean air device should first be classified.

2. **Monitoring**: The cleanroom should then be monitored to verify that conditions are maintained.

3. **Data review**: The data accrued from the monitoring must be reviewed in light of the risk to finished product quality.

2009 EU GMP Annex 1

Room Classification, Clause #4

- Cleanrooms and clean air devices should be classified in accordance with EN ISO 14644-1.
- Classification should be clearly differentiated from operational process environmental monitoring.
- Maximum permitted airborne particle concentration for each grade is given in the ISO 14644-1.

ISO 14644-1:2015 2nd Edition
Classes of air cleanliness by particle concentration

Maximum allowable concentrations (particles/m^3) for particles equal to and greater than the considered sizes

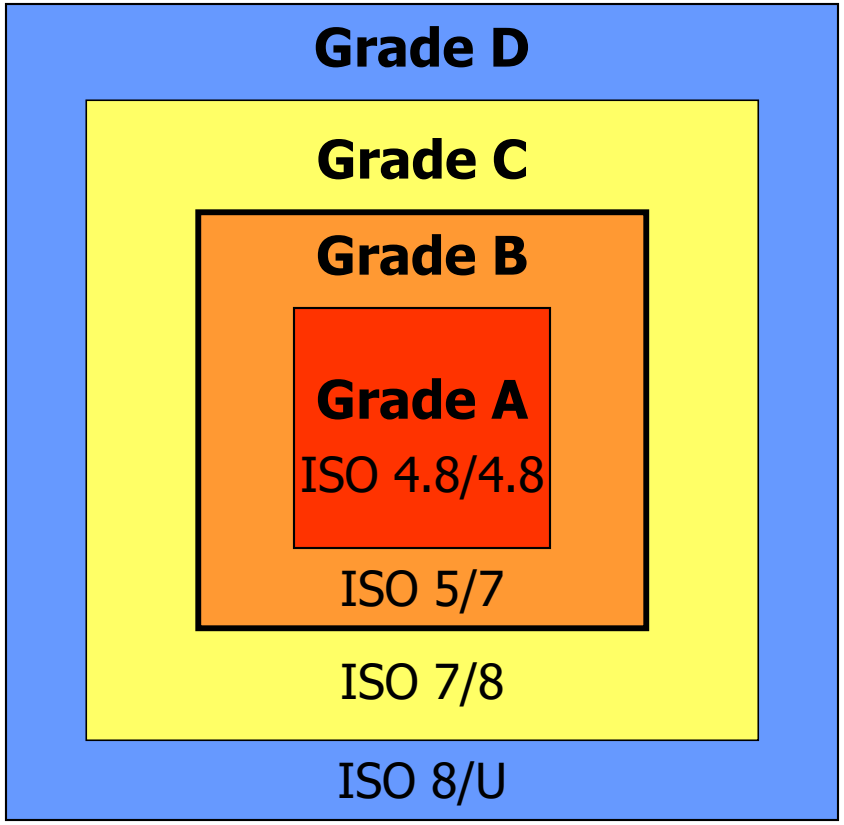
CLASS	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
ISO 1	10					
ISO 2	100	24	10			
ISO 3	1,000	237	102	35		
ISO 4	10,000	2,370	1,020	352	83	
ISO 5	100,000	23,700	10,200	3,520	832	
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO 7				352,000	83,200	2,930
ISO 8				3,520,000	832,000	29,300
ISO 9				35,200,000	8,320,000	293,000

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

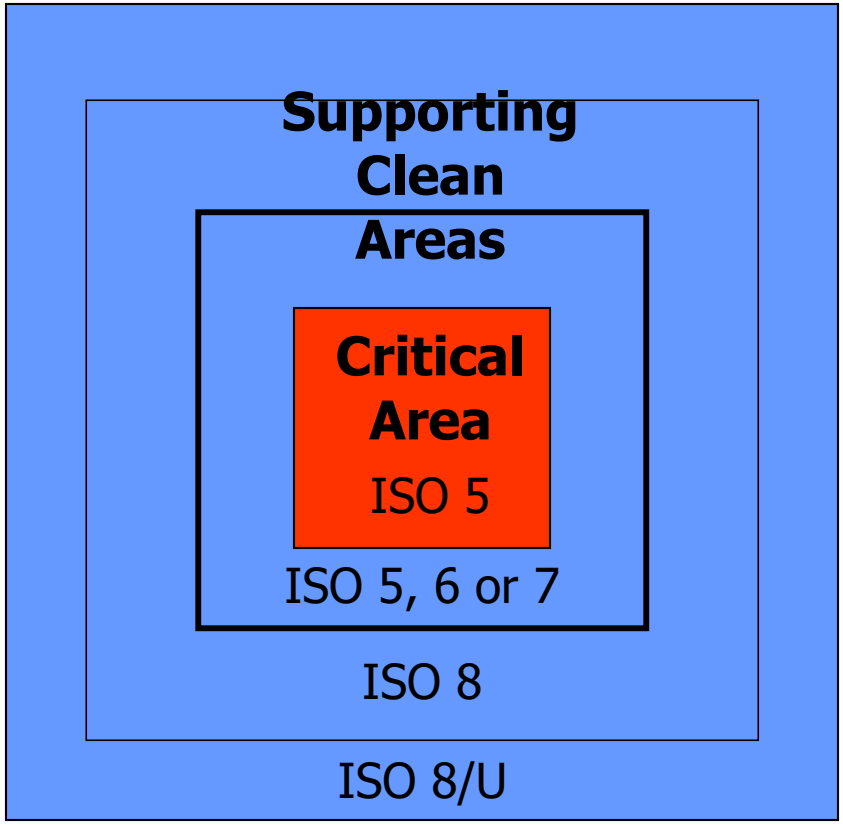
Cleanroom Grades, cont.

EU GMP Annex 1



At Rest / In Operation

FDA Aseptic Guidelines



In Operation

Table summarizing clean area air classifications and recommended action levels of microbiological quality

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. 90 mm; 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

In Operation

2004

EU Classification Table

		AT REST [b]		IN OPERATION [b]	
(ISO)	Grade	Maximum permitted number of particles/m³ equal to or above[a]			
		≥0.5 µm[d]	≥5 µm	≥0.5 µm[d]	≥5 µm
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 2009

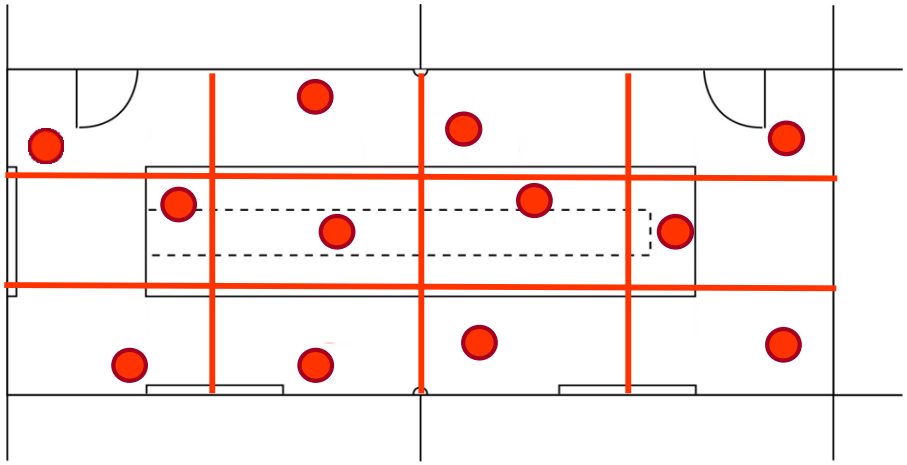
Cleanroom certifications

Certification occurs after facility construction or significant physical changes. Certification guarantees the facility has met the requirements for a statistically-valid maximum concentration of specified-size airborne particles.

Cleanroom certifications may occur in any of three different stages:

- **As Built**: a cleanroom fully constructed and operational, with all services connected and functioning, but has no production equipment or operating personnel
- **At Rest**: a cleanroom fully operational, with production **equipment** installed and operating or operable, but has **no personnel** within the facility.
- **Operational**: a cleanroom in normal manufacturing operations, including **equipment and personnel.**

Sample locations (ISO-14644-1:2015)



Area of Cleanroom (m2) less than or equal to	Minimum number of sample locations to be tested (N_L)
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
64	12
68	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
636	26
1000	27
>1000	See Equation A.1

- 5 m x 12 m = 60 m^2 => 12 locations (from table)
- The cleanroom or clean zone area is divided up into a grid of sections of near equal area, whose number is equal to the number of sampling locations.
- Random location within grid, not necessarily the center and at work height.

Sampling Volume per Location

- The single volume (V_s) per location is determined by using the following equation:

  $V_s = [\ 20\ / C_{n,m}\ ] \times 1000$

  (expressed in liters)

- V_s is the minimum single sample volume per location, expressed in liters.
- $C_{n,m}$ is the class limit (number of particles per cubic meter) for the considered particle size specified for that class.
- 20 is the minimum number of particles needed for a statistically accurate result.

Sampling Volume per Location - Example

- At each sampling location, sample a sufficient volume of air that a minimum of 20 particles would be detected if the particle concentration for the largest considered particle size were at the class limit for the designated ISO class.

- Applying the formula, the single volume (V_s) **per location** is calculated as:

  V_s = [20 / 3520] x 1000 = 5.68 liters (for ISO-5)
  (expressed in liters)

  V_s = [20 / 35200] x 1000 = 0.568 liters (for ISO-6)
  (expressed in liters)

- Minimum Sample Period = 1 minute (28.3L with 1CFM particle counter)

EU and FDA Classification Tables

EU

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

FDA

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)
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

Additional EU Annex 1 Comments on Classification

- Recertification of the cleanroom should follow the guidance given in ISO 14644-2.
  - Once per year for ISO Class 6 and greater
  - Once every six months for ISO Class 5 and cleaner
    - Note: exceptions can apply if using continuous monitoring
- The sample volume for Grade A testing should be 1 m^3 per sample location.
- Portable particle counters with short length or no tubing should be used.
- Isokinetic sampling heads should be used in unidirectional flow zones.

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.”

GMP requirements for Monitoring

- EU and FDA have similar monitoring requirements:
  - LOCATIONS: Risk-based selection of monitoring locations
  - FREQUENCY:
    - Continuous monitoring of critical areas (Grade A/B) (ISO5/ISO7)
    - Routine monitoring of supporting cleanrooms (Grade C/D) (ISO8/ISO9) depending on the nature of activities
  - Microbial and particle monitoring are both required
  - Compressed gases and ambient air must be monitored for microbial and particle contamination. Check filter integrity.

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 temperature, 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 that is followed. The plan details must be rationalized and have good description.

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

FDA Aseptic Guidelines

- **Critical areas**: Continuous monitoring during setup and operation
- **Supporting clean areas**: Frequency of sampling depends on nature of cleanroom activities

Monitoring – sample volume

EU Annex 1

- "It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms"

Not required to have cubic meter samples during continuous monitoring

- 1-minute sample periods are typical during continuous monitoring

Monitoring – special applications

- Powder filling
  - FDA and EU acknowledge difficulty of monitoring close to fill point, but both require monitoring prior and after filling
  - Recommendation:
    - Monitor particles before and after filling. Monitor differential pressure throughout.
    - Monitor surrounding area, with higher frequency depending on the barrier
- Dangerous product (cytotoxic, radioactive)
  - Same as powder filling – monitor particles before and after filling
  - Negative pressure isolator increases the importance of monitoring the surrounding area.

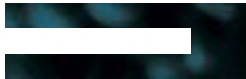
Monitoring – compressed gas

EU Annex 1

- "Non-combustible gases should be passed through micro-organism retentive filters."
- "The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals."

FDA Aseptic Guidelines

- "A compressed gas should be of appropriate purity and its microbial and particle quality after filtration should be equal to or better than that of the air in the environment into which the gas is introduced."
- "We recommend that filters be integrity tested upon installation and periodically thereafter (e.g., end of use)"



Environmental Monitoring Summary

- GMPs require room classification, then monitoring.
- 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 compressed gas.
- Critical areas (Grade A/B, ISO 5) should be monitored continuously.
- Supporting areas (Grade C/D, ISO 7/8) can be tested periodically with portables or manifolds.

Classification And Monitoring Differences

	Classification	Monitoring
Frequency	6 months or annual	Daily, weekly, monthly, or continuous
Number of positions	By formula	Risk Analysis
Sample Volume	By formula	Based on grade of room
Pass/Fail Criteria	By table	By need for trend info or control
Reporting format	By standard	In form needed for rapid understanding
Distribution of counts in a room or zone	Uniform or homogenous	Unique at each sample position

Summary: EU and FDA have similar monitoring requirements

	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 Systems

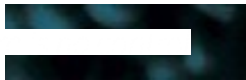
Contamination Monitoring Hardware

Environmental Monitoring Systems

Software & System Integration

System Implementation (Project Lifecycle)

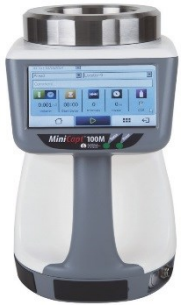
Alarm Limits and Data Interpretation



Contamination monitoring hardware

Portable

Particle Counter



Microbial Sampler (impaction)

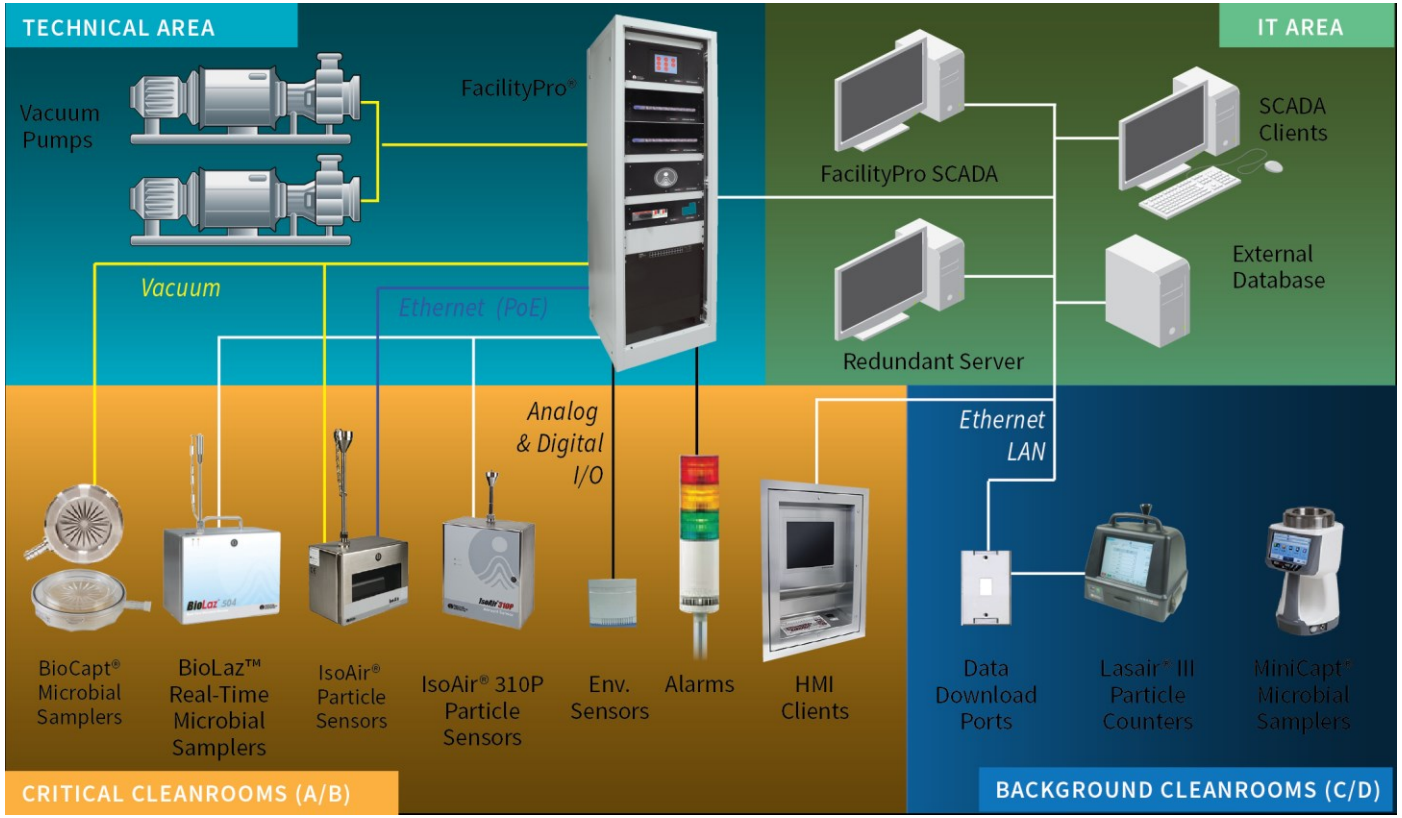
Continuous/Remote

Particle Sensor (internal vacuum)

Particle Sensor (external vacuum)

Microbial Sampler (external vacuum)

System architecture

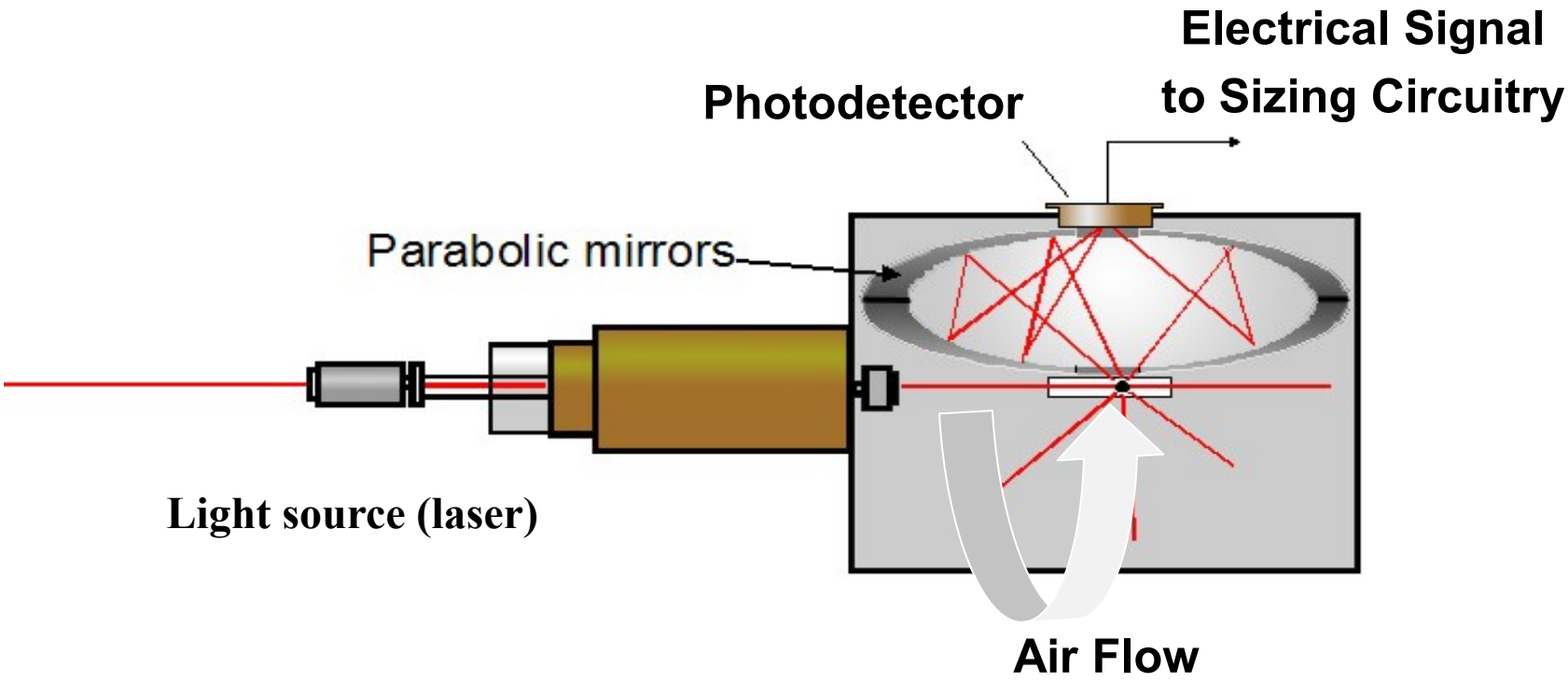


Technologies for Particle Counters

- Extinction *vs*. Scattering
  - **Extinction** particle counters count and size particles by measuring the light extinction caused by a large particle present in the light beam. When a particle is absent, the signal is strong; when a particle is present, the signal decreases.
  - **Scattering** particle counters measure the amount of light reflected in many directions by a particle (*scattered* light)
- Volumetric vs. Non-Volumetric (*In-situ*)
  - **Volumetric** particle counters look at the entire volume of a sample. (Pharma regulated)
  - **Non-volumetric** (*In-Situ**) particle counters look at a small portion of a sample or where the optics are “in position”.

Scattering Particle Counter Detector Technology

Scattered light is directed by mirrors onto a photodetector where it is converted into a pulse of electrical energy.



Applications of Particle Counters

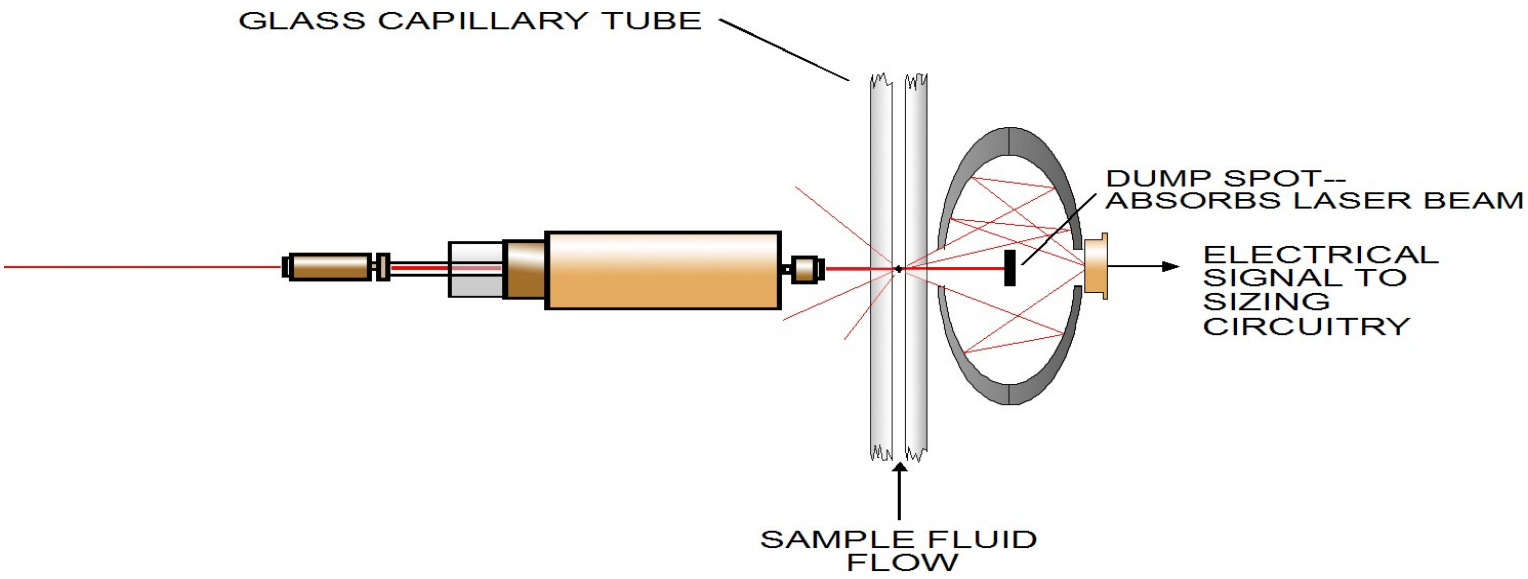
There are three primary categories:

1. Aerosol particle counters
2. Liquid particle counters
3. Solid particle counters (*)

(*) Solid particle counters are used to measure dry particles for various industrial applications.

Liquid Scattering Particle Counter

- Utilize an optically transparent flow cell or capillary to detect particles passing through a laser beam.
- Light scattered from particles traverses air/glass and glass/liquid interfaces.



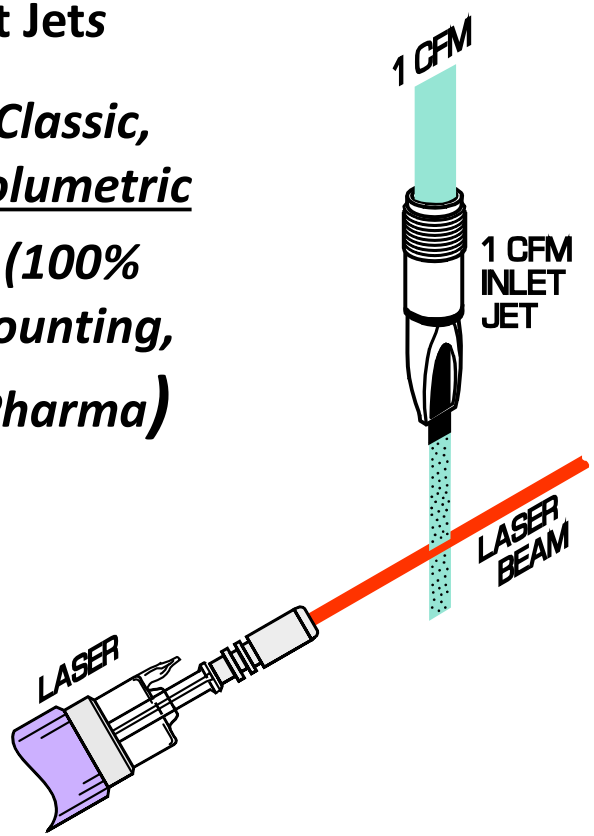
Aerosol Particle Counter

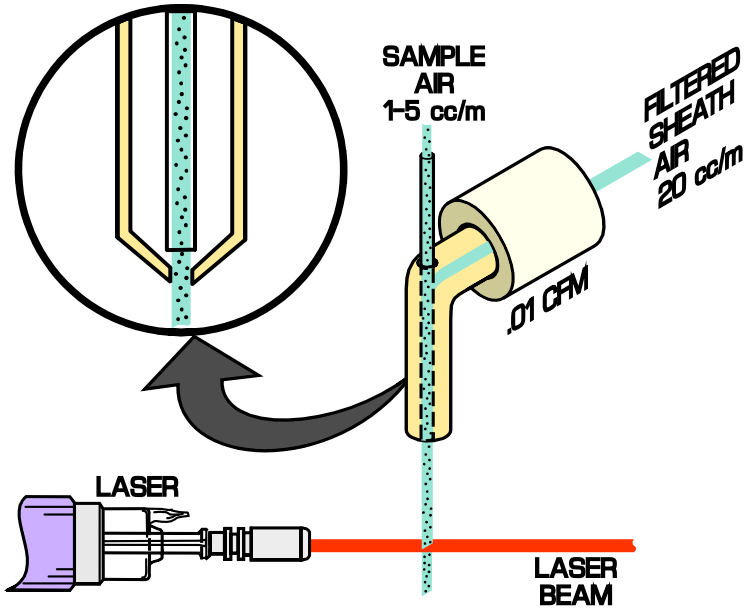
Inlet Jets

Classic,

<u>Volumetric</u>

(100% counting, Pharma)





Dilution type

Monitoring applications

- Sample point positioning
- Filling lines
- Lyophilization
- Grade B background areas
- Blow-fill-seal
- Isolators
- Biosafety cabinets
- Compressed gas

Filling lines

- The required monitoring for critical areas should be continuous and within the zone immediately surrounding the product whenever the product or open container is exposed to the environment.
- The monitoring locations should therefore be as close as possible to the exposed product or semi-stoppered vials. (FDA – 12 inches critical operation)
- Where a significant distance exists between the end of the filling line and semi-stoppering, and the loading door of the lyophilizer, the product should be maintained within an ISO Class 5 environment and monitored at intervals throughout this distance.

Lyophilization

EU Annex 1

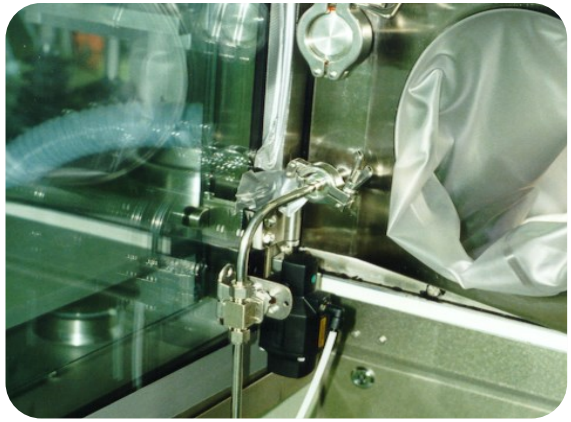
- Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a Grade A environment with a Grade B background or in sealed transfer tray in a Grade B environment.
- Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.
  - Monitor the transfer from filler to freeze dryer
  - Lyo transfer carts – use WiFi communication

Blow-Fill-Seal

- Small area – point placement can be tricky
  - Too close to filter = poor data
  - Avoid smoke from plastic moulding near fill point
  - Find a balance to ensure the area is clean, but data is good
- Consider monitoring of incoming air pipes

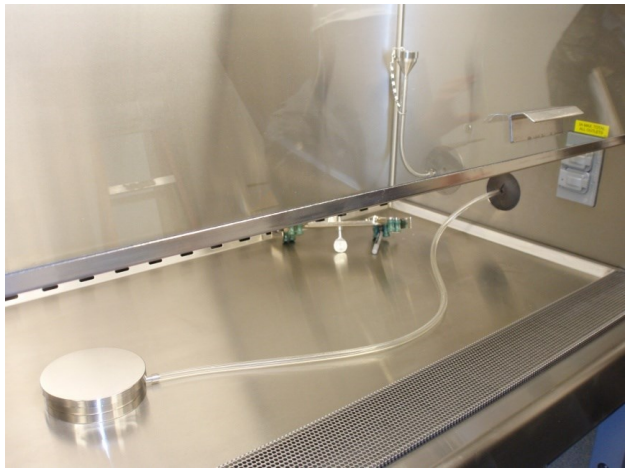
Isolators

- Isolator access is more difficult
  - Install ports to plumb transport tubing inside
  - Bulkhead or tri-clamp sanitary fittings are common
- Mount sensors below or on the side of isolator
  - Directly below is best for particle transport, but less convenient for sensor access



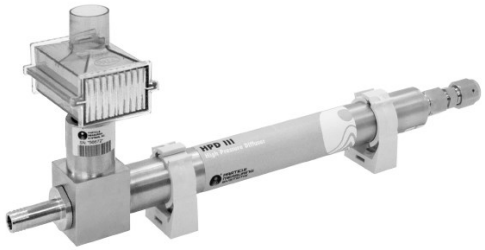
BioSafety cabinets

- Number of points depends on size of cabinet
  - Typically 1 particle and 1 microbial point is sufficient
  - If two filter banks, consider 2 particle and 2 microbial - or a point in the middle
- Mount sensors below or on the side of cabinet
  - Plumb tubing through the side or back wall



Compressed gas

- Monitor routinely at point of use
  - More frequent testing for more critical locations
- Some companies monitor continuously off main lines



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 – Biocontamination 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

Thank You !

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