

Environmental Monitoring of Clean Rooms

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Environmental Monitoring of Clean Rooms

- ☞ A manufacturing facility for pharmaceutical products and medical devices must be designed with minimizing the introduction, generation and retention of airborne particles in mind.
- ☞ Other parameters that need to be controlled are: air flow filtration, room pressurizations, air velocities, temperature, relative humidity.

Environmental Monitoring of Clean Rooms

Clean rooms must be designed having in mind:

- Location of the in and out air locks, gowning and de-gowning, door interlocks, visibility, personnel flow, material flow, the introduction of components, location of utilities, location of the equipment inside the clean room.

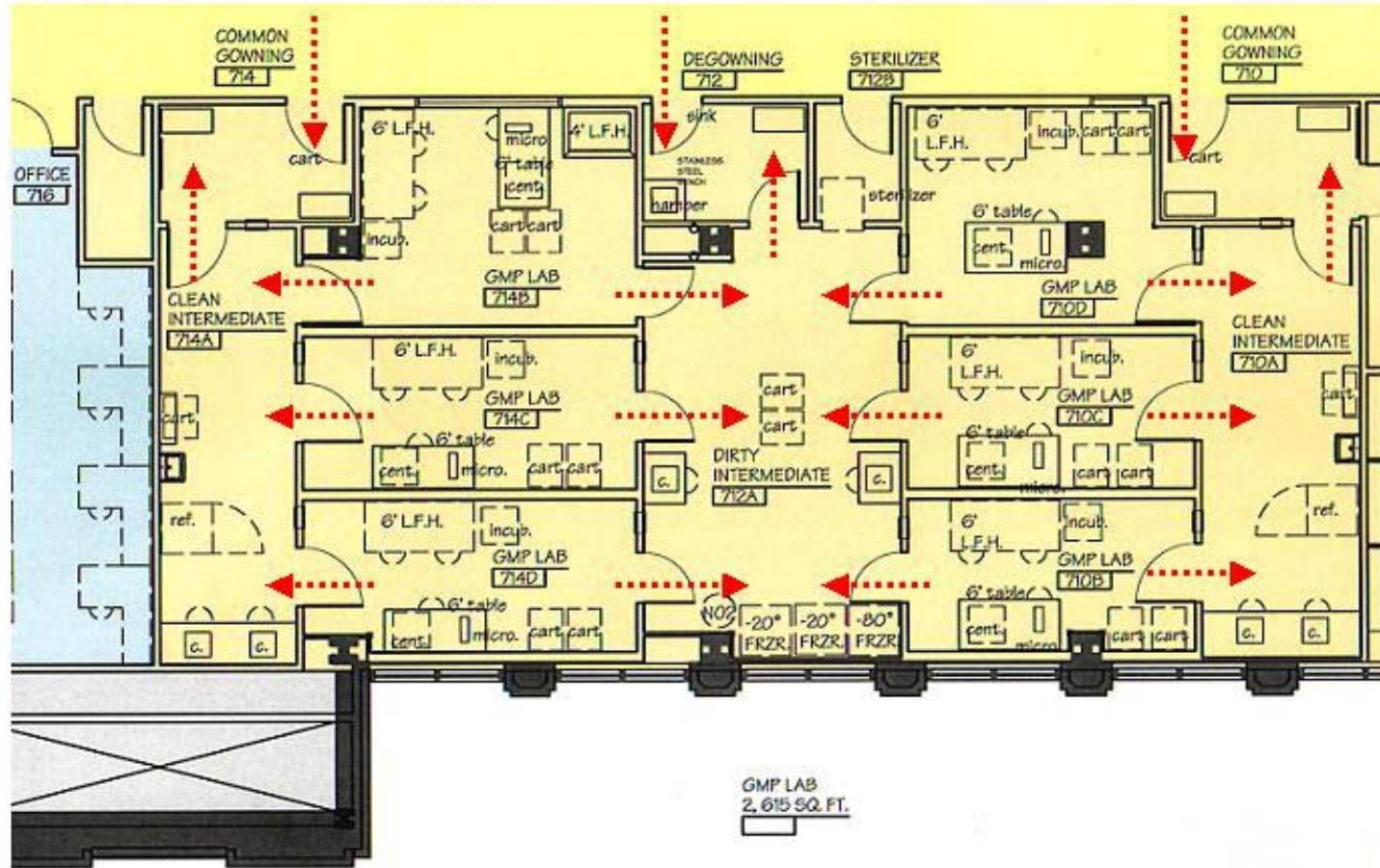
Class 10,000 Clean Room

(GMP facility in an academic center)



Class 10,000 Clean Room

(Airflow Diagram)



Environmental Monitoring of Clean Rooms

Two Standards:

- Federal Standard 209 E
- ISO 14644
- Federal Standard 209 E is easier to understand than ISO 14644
- Many companies continue to test their facilities along Federal Standard 209E

Environmental Monitoring of Clean Rooms

(European Union) EUGGMP 2002

Grade A corresponds to:	Class 100 M 3.5 & ISO 5
Grade B corresponds to:	Class 100 M 3.5 & ISO 5
Grade C corresponds to:	Class 10,000 M 5.5 & ISO 7
Grade D corresponds to:	Class 100,000 M6.5 & ISO 8

Environmental Monitoring of Clean Rooms

Particles in Outdoor Air
Number of Particles / m³ on Outdoor Air

Size in Microns	Dirty	Normal	Clean
>0.1	10,000,000,000	3,000,000,000	500,000,000
>0.3	300,000,000	90,000,000	20,000,000
>0.5	30,000,000	7,000,000	1,000,000

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290E	ISO14644	0.1µm/m ³	0.2µm/m ³	0.3µm/m ³	0.5µm/m ²	1µm/m ³	5µm/m ³
	4						
	CLASS 1	10	2				
	CLASS 2	100	24	10	4		
1	CLASS 3	1,000	237	102	35	8	
10	CLASS 4	10,000	2,370	1,020	352	83	
100	CLASS 5	100,000	23,700	10,200	3,520	832	29
1,000	CLASS 6	1,000,000	237,000	102,000	35,200	8,320	293
10,000	CLASS 7				352,000	83,200	2,930
100,000	CLASS 8				3,520,000	832,000	29,300
1,000,000	CLASS 9				35,200,000	8,320,000	293,000

Environmental Monitoring of Clean Rooms

Maximum permitted number of particles
per cubic meter (cubic foot)

Grade	at Rest		in Operation	
	0.5 μ m	5 μ m	0.5 μ m	5 μ m
A C 100	3,500 (100)	0	3,500 (100)	
B C 100	3,500 (100)	0	350,000 (10,000)	
C C 10,000	350,000 (10,000)	2,000	3,500,000 (100,000)	
D C 100,000	3,500,000 (100,000)	20,000	NOT DEFINED	NOT DEFINED

Environmental Monitoring of Clean Rooms

Physical	Chemical	Biologic	Energy
Dust	Organic Compounds	Bacteria	Thermal
Dirt	Inorganic Salts	Fungus	Light
Grit	Vapor	Spores	Electromagnetic (EMI)
Fiber	Mist	Pollen	Electrostatic (ESD)
Lint	Fume	Virus	Radiation
Fly ash	Smoke	Human Skin Cells	Electrical

Environmental Monitoring of Clean Rooms

Schedule of Mandatory Test to Demonstrate Continuing Compliance in Clean Rooms

Test Parameter	Class	Maximum Time Interval
Particle Count Test	\leq ISO 5	6 Months
	$>$ ISO 5	12 Months
Air Pressure Difference	All Classes	Daily
Airflow	All Classes	12 Months

Environmental Monitoring of Clean Rooms

(European Union) EUGGMP 2002 Recommended Limits for Microbial Contamination

Grade	Air Sample	Settle Plates 90 mm Dia. CFU /m ³	Contact Plates 55 mm Dia. CFU / m ³	Glove Prints 5 Fingers CFU / Glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Environmental Monitoring of Clean Rooms

GRADE	CLASS	TYPE OF ASEPTIC OPERATIONS
A	100	Aseptic Preparation and Filling
B	100	Room Conditions for Activities Requiring Grade A
C	10,000	Preparation of Solutions to be Filtered
D	100,000	Handling of Components after Washing

Environmental Monitoring of Clean Rooms

Clean Room Environmental Monitoring

TEST

- Particle Monitoring in Air
- HEPA Filter Integrity Testing
- Air Change Rate Calculation
- Air Pressure Differentials
- Temperature and Humidity
- Microbial Monitoring by Settle plates and /or Swabs in Aseptic Areas

FREQUENCY

6 Months

Yearly

6 Months

Daily

Daily

Daily, and at
Decrease
Frequency
in other Areas

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Air Classification by FDA Guideline on Sterile Drug Products

CLEAN AREA CLASSIFICATION	<0.5µm Particles		Microbiological Limits	
	ft ³	m ³	ft ³	m ³
100	100	3,500	<1	<3
1,000	1,000	35,000	<2	<7
10,000	10,000	350,000	<3	<18
10,0000	100,000	3,500,000	<25	<88

Environmental Monitoring of Clean Rooms

Special Requirements for ISO Class 3 (290E Class 1) Clean Rooms

Air Quality	Total Hydrocarbons <1PPM; Na <0.1 $\mu\text{g}/\text{m}^3$
Fresh Air Intake	0.5 m^3 / min per m^2 of Clean Room Area
Vibration	<0.1 μ (Building); <0.01 μ (Equipment) Rooms
Noise	<55 dbA
Temperature	0.1 Degree C
Humidity	<2%
Magnetic Field	<1mG
Static Charge	<50 v

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Clean Room Industry Design Rule of Thumb

ISO Class	Controls	Air Velocity fpm	Air Changes per Hour	HEPA Coverage
1	Stringent	70-130	>750	100%
2	Stringent	70-130	>750	100%
3	Stringent	70-130	>750	100%
4	Stringent	70-130	500-600	100%
5	Stringent	70-90	150-400	100%
6	Intermediate	25-40	60-100	33%-40%
7	Intermediate	10-15	25-40	10%-15%
8	Less Stringent	3-5	10-15	5%-10%

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Air Particle Counting

- Federal Standard 209E calculates a minimum of 12 locations
- ISO 14644 calculates a minimum of 9 locations

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Air Particle Counting Base Line

- ☞ Take three one-minute, one-CFM (28.3 liters) samples per location for better statistical reliability.
- ☞ Test Laminar Flow work stations and Barrier isolators the same way.
- ☞ Testing should be done every six months or after any repairs, or renovations.
- ☞ When sampling, test for viable organism at the same time.

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Elements of a Microbial Monitoring Program

- Sampling Methods
- Media & Incubation Conditions
- Sampling Locations
- Frequency of Sampling
- Alert & Action Limits
- Trend Analysis
- Out of Limits Investigations
- Corrective Action

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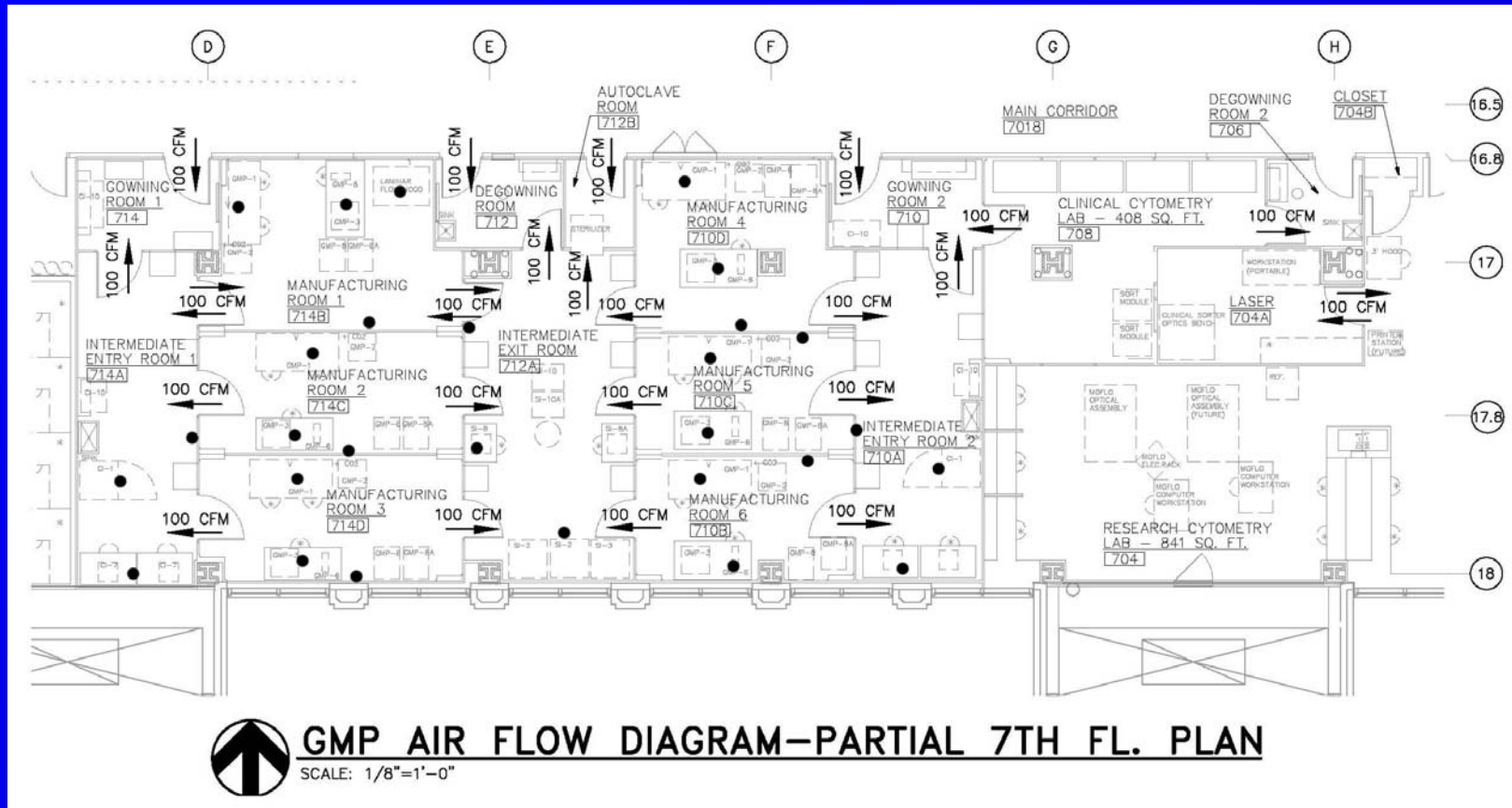
- ☞ The selection of sampling locations depends on the room classification, design, layout of the manufacturing process.
- ☞ Each process should be evaluated in order to identify the actual and potential sources of contamination.

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- ➔ A diagram of the sampling locations must be done as well as documenting the procedure of collecting, incubate and analyze samples.

Class 10,000 Clean Room

Touch Plate Sampling Points



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- ☞ Sampling must occur at the same location each time and at the same time of the day.

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Air Sampling - Microbial

- Sieve Impaction – Sieve to Air Samplers
- Centrifugal Impaction – Reuter Centrifugal Sampler Plus
- Filtration – MD-8 Air Sampler
- Slit Impaction – Slit to Agar Air Sampler
- Settling Plates

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Microbial Air Samplers Basic Principals

- ➔ Microbial Air Samplers collect a predetermined volume of air and impact microorganisms against agar-based growth medium. Once that sample has been collected and the medium incubated, the results are expressed in colony forming units per cubic meter.

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Microbial Air Samplers

The most common impaction portable air samplers are:

- ➔ Centrifugal Impaction: It utilizes a rotor device in the head of the air sampler to draw air and microorganisms in and onto a special strip containing growth medium. The centrifugal force causes particles and microorganisms to impact the medium at a rate dependent on the size of the particle.

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Microbial Air Samplers

- ☞ Sieve Impaction: Is based on the aspiration of air through small holes at the top of the sampler.

A Petri dish containing growth medium sits in a holder and a perforated lid locks in place over the medium. A fan mechanism is placed below and draws air through the lid. The air directly impacts the Petri dish, forcing the microorganism to stick to the surface of the Agar.

The impaction speed as well as particle size efficiency is a function of the holes in the perforated lid and the fan speed. This allows particles as small as 1 micron in diameter at a single flow rate.

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Surface and Personnel Sampling

- Surface Rinse Method
- RODAC Plate Method
- Swab Method
- ATP Bioluminescence Hygiene Monitoring Method

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Microbial Monitoring Frequency

- Air, Surfaces and Personnel Monitoring Should be done Frequently During Aseptic Operations
- Product Contact Surfaces Should be Monitored at the End of the Aseptic Operation

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Monitoring Sites

- ☞ Air monitoring should be done adjacent to the filling location.
- ☞ Product contact surfaces areas, non contact areas, open vials, stopper track, etc.
- ☞ Personnel monitoring should be done at the sleeves and gloves.

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Air Monitoring Limits

- Class 100 and Class 1,000
- Critical processing areas for product and containers
- Less than 3 cfu per cubic meter of air or 0.1 cfu per cubic foot.
- Frequency: Each shift

Environmental Monitoring of Clean Rooms

Air Monitoring Limits

- Class 10,000
- Less critical processing areas for product and containers.
- Less than 20 cfu per cubic meter of air or 0.5 cfu per cubic foot.
- Frequency: Daily

Environmental Monitoring of Clean rooms

Limits Air Monitoring

- Class 100,000
- Controlled support areas
- 100 cfu per cubic meter of air or 2.5 cfu per cubic foot
- Frequency: Twice per week

Environmental Monitoring of Clean Rooms

Surface Monitoring Limits

- Class 100 and 1,000
- Critical processing areas for product and containers
- 3 cfu per 30 square centimeters or 2 square inches
- RODAC plate.
- 5 cfu per 30 square centimeters or 2 square inches
- RODAC plate for the floor.
- Frequency: Each shift

Environmental Monitoring of Clean Rooms

Surface Monitoring Limits

- Class 10,000
- Less critical processing areas for product and containers.
- 5 cfu per 30 square centimeters or 2 square inches
- RODAC plate.
- Frequency: Daily

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Note:

- ☞ Personnel involved in the manufacturing, packaging processes generally contribute with most of the viable contamination.

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Personnel Monitoring Limits

- Class 100 and 1,000
- Critical processing areas for product and containers
- 3 cfu per glove (30 square centimeters)
- 5 cfu per gown (30 square centimeters)
- Frequency: Each shift

Environmental Monitoring of Clean Rooms

Personnel Monitoring Limits

Class 10,000

- Less critical processing areas for product and containers
- 10 cfu per glove (30 square centimeters)
- 20 cfu per gown (30 square centimeters)
- Frequency: Daily

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Setting Limits

- ☞ Limits should be consistent with regulatory and compendial guidelines.
- ☞ Alert limits should be set from monitoring history

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Corrective Action

- ☞ The corrective action plan must be written
- ☞ A check list must be developed for systems review and corrective action.
- ☞ All corrective actions must be documented in a timely fashion.

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Conclusions

- A well designed and executed monitoring plan is a must.
- The monitoring plan has to be designed using good Judgment so that it can be defended during a compliance audit.

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Thank You



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Thank You



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