



# Environmental monitoring program in Pharmaceutical manufacturing facilities

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# Environmental monitoring

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- ☺ A process to assess the clean room and other controlled environments of a pharmaceutical facility
- ☺ Environmental surveillance is a tool utilized to evaluate the effect of controls on the manufacturing environment.
- ☺ It Can serve as an adjunct to the sterility assurance program for the microbial quality of drugs.



# Environmental monitoring

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Comprehensive environmental control program should be supported by:.....

- ☺ Sound facility design and maintenance,
- ☺ Documentation systems,
- ☺ Validated/qualified sanitization / disinfection procedures,
- ☺ Reliable process controls,
- ☺ Good housekeeping practices,
- ☺ Effective area access controls,
- ☺ Effective Training, certification/qualification and evaluation programs,
- ☺ Quality assurance of materials and equipment.



# Environmental monitoring

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Effective environmental monitoring shall consider  
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- ☺ The classification of a clean room based on particulate count limits
- ☺ Microbiological evaluation programs for controlled environments
- ☺ Training of personnel
- ☺ Critical factors in design and implementation of a microbiological evaluation program
- ☺ Development of a sampling plan



# Environmental monitoring

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Effective environmental monitoring shall consider  
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- ☺ Establishment of microbiological Alert and Action levels
- ☺ Methodologies and instrumentation used for microbiological sampling
- ☺ Media and diluents used
- ☺ Identification of microbial isolates
- ☺ Operational evaluation via media fills



# Environmental monitoring

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## Environmental Classification

- ☺ All of the classifications can be applied to particles <sup>3</sup> 0.5 mm, while other particle sizes, e.g., 0.1, 0.2, 0.3 and 5 mm, utilize only some of the classifications.
- ☺ In the United States, the pharmaceutical industry classifies production areas as Class 100, 10,000 and 100,000 (M 3.5, M 5.5 and M 6.5, respectively) based on particles <sup>3</sup> 0.5 mm, the classification reflecting the number of particles per cubic foot.



# Environmental monitoring

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## Environmental Classification

- ☺ Federal European Union, The Rules Governing Medicinal Products in the European Union, (Vol. IV: Good manufacturing practice for medicinal products) include an air classification system in Annex 1 under the heading “Manufacture of Sterile Medicinal Products.”
- ☺ Air quality is classified alphabetically as Grade(s) A through D, with Grade A being the cleanest.
- ☺ Associated with each respective grade is the maximum allowable number of particles per cubic meter.



# Environmental monitoring

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## Environmental Cleaning and Sanitization / Disinfection

- ☺ Implementation of cleaning and sanitization procedures is critical.
- ☺ Environmental monitoring data are used in determining the effectiveness of the cleaning procedures.
- ☺ Validation of established cleaning and sanitization procedures should demonstrate microbial reduction.
- ☺ Procedures also ensure the effectiveness of removal of product and detergent residue.



# Environmental monitoring

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## Environmental Cleaning and Sanitization / Disinfection

- ☺ The goal is to demonstrate that routine sanitization procedures .....
- ☺ To establish the sanitizers effectiveness regularly.



# Environmental monitoring

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Clean room monitoring & control criticality includes……

- ☺ Sample Site Selection
- ☺ Sampling Frequency
- ☺ Established Alert and Action Levels utilization
- ☺ Data Management (Data Collection, Analysis, Approach, and Interpretation)
- ☺ Characterization of findings (Eg. Isolates)
- ☺ Investigations/Corrective Actions taken place when required
- ☺ Documentation maintained



# Environmental monitoring

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VALIDATION / QUALIFICATION MUST  
CONSIDER.....

- ☺ Personnel working
- ☺ Environment / HVAC Systems
- ☺ Utilities
- ☺ Validation of Aseptic Processes – Media Fills (Process Simulation Tests)

# Environmental monitoring

Class 100 Monitoring Table (Max. values are given)

COUNTRY DOCUMENT	U.S. FS 209E	U.S. USP <1116>	EU (at rest, static)	EU (operational, dynamic)	EU (operational, dynamic)	ISO 14644-1
CLASSIFICATION	M 3.5 (100)	M 3.5	A and B	A	B	5
FREQUENCY	Not stated	Each Operating Shift	Not stated	Frequent, using a variety of methods	Frequent, using a variety of methods	Not stated
TOTAL PARTICULATE COUNT	3,500/m <sup>3</sup> (> 0.5 mm) 100/cu. ft.	100/cu. ft. (> 0.5 mm)	3,500/m <sup>3</sup> (equal to or above 0.5 mm) 0/m <sup>3</sup> (> 5 mm)	3,500/m <sup>3</sup> (equal to or above 0.5 mm) 0/m <sup>3</sup> (> 5 mm)	350,000/m <sup>3</sup> (equal to or above 0.5 mm) 2,000/m <sup>3</sup> (> 5 mm)	3,520/m <sup>3</sup> (equal to or above 0.5 mm) 29/m <sup>3</sup> (5.0 mm)
AIRBORNE VIABLES	Not stated	0.1 CFU per cu. ft.	Not stated	<1 CFU/m <sup>3</sup> Settle plate 90 mm <1 CFU/4 hours	<10 CFU/m <sup>3</sup> Settle plate 90 mm 5 CFU/4 hours	Not stated
SURFACE VIABLES (except floors)	Not stated	3 CFU per contact plate*	Not stated	<1 CFU per contact plate (no distinction for floors and walls)	5 CFU per contact plate (no distinction for floors and walls)	Not stated
SURFACE VIABLES (floors)	Not stated	3 CFU per contact plate	Not stated	<1 CFU per contact plate (no distinction for floors and walls)	5 CFU per contact plate (no distinction for floors and walls)	Not stated
PERSONNEL GOWN	Not stated	5 CFU per contact plate	Not stated	Not stated	Not stated	Not stated
PERSONNEL GLOVES	Not stated	3 CFU per contact plate	Not stated	Glove print 5 fingers <1 CFU per glove	Glove print 5 fingers 5 CFU per glove	Not stated
AIR VELOCITY UNIDIRECTIONAL	Not stated	Not stated	0.45 m/s ±20%	0.45 m/s ±20%	Not appropriate	Not stated
FREQUENCY OF ^P Monitoring	Not stated	Each shift	Not stated	Continuous	Continuous	Not stated

# Environmental monitoring

## Class 10,000 Monitoring Table (Max. values are given)

COUNTRY DOCUMENT	U.S. FS 209E	U.S. USP <1116>	EU (at rest, static)	EU (operational, dynamic)	ISO 14644-1
CLASSIFICATION	M 5.5 (10,000)	M 5.5	C	C	7
FREQUENCY	Not stated	Each Operating Shift	Not stated	Not stated	Not stated
TOTAL PARTICULATE COUNT	353,000/m <sup>3</sup> (°0.5 mm) 10,000/cu. ft.	10,000/cu. ft. (°0.5 mm)	350,000/m <sup>3</sup> (equal to or above 0.5 mm) 2,000/m <sup>3</sup> (>5 mm)	3,500,000/m <sup>3</sup> (equal to or above 0.5 mm) 20,000/m <sup>3</sup> (>5 mm)	352,000/m <sup>3</sup> (equal to or above 0.5 mm) 930/m <sup>3</sup> (>5 mm)
AIRBORNE VIABLES	Not stated	0.5 CFU per cu. ft.	Not stated	100 CFU/m <sup>3</sup> Settle plate 90 mm 50 CFU/4 hours	Not stated
SURFACE VIABLES (except floors)	Not stated	5 CFU per contact plate*	Not stated	25 CFU per contact plate	Not stated
SURFACE VIABLES (floors)	Not stated	10 CFU per contact plate	Not stated	Not stated	Not stated
PERSONNEL GOWN	Not stated	20 CFU per contact plate	Not stated	Not stated	Not stated
PERSONNEL GLOVES	Not stated	10 CFU per contact plate	Not stated	Not stated	Not stated
FREQUENCY OF Delta P monitoring	Not stated	Each shift 1 2x/week2	Not stated	Not stated	Not stated

# Environmental monitoring

## Class 100,000 Monitoring Table (Max. values are given)

COUNTRY DOCUMENT	U.S. FS 209E	U.S. USP <1116>	EU (at rest, static)	EU (operational, dynamic)	ISO 14644-1
CLASSIFICATION	M 6.5 (100,000)	M 6.5	D	D	8
FREQUENCY	Not stated	Twice/week	Not stated	Not stated	Not stated
TOTAL PARTICULATE COUNT	3,530,000/m <sup>3</sup> (≥0.5 mm) 100,000/cu. ft.	100,000/cu. ft. (≥0.5 mm)	3,500,000/m <sup>3</sup> (equal to or above 0.5 mm) 20,000/m <sup>3</sup> (>5 mm)	Not defined	3,520,000/m <sup>3</sup> (equal to or above 0.5 mm) 29,300/m <sup>3</sup> (>5 mm)
AIRBORNE VIABLES	Not stated	2.5 CFU per cu. ft.	Not stated	200 CFU/m <sup>3</sup> Settle plate 90 mm 100 CFU/4 hours	Not stated
SURFACE VIABLES (except floors)	Not stated	Not stated	Not stated	50 CFU per contact plate	Not stated
SURFACE VIABLES (floors)	Not stated	Not stated	Not stated	Not stated	Not stated
FREQUENCY OF Delta P monitoring	Not stated	Weekly	Not stated	Not stated	Not stated

# Environmental monitoring

## Airborne Particulate Cleanliness Classes – Comparison

Class Name	Particles equal to and larger than 0.5 $\mu\text{m}$		
	U.S. Customary	(m <sup>3</sup> )	(ft <sup>3</sup> )
M1	—	10.0	0.283
M1.5	1	35.3	1.00
M2	—	100	2.8
M2.5	10	353	10.0
M3	—	1,000	28.3
M3.5	100	3,530	100
M4	—	10,000	283
M4.5	1,000	35,300	1,000
M5	—	100,000	2,830
M5.5	10,000	353,000	10,000
M6	—	1,000,000	28,300
M6.5	100,000	3,530,000	100,000
M7	—	10,000,000	283,000

# Environmental monitoring

Clean room classification requirements as per EU  
GMP

GMP class	Max No. of particles in static ( per m <sup>3</sup> )		Max No. of particles in Dynamic ( per m <sup>3</sup> )	
	0.5 µm	5 µm	0.5 µm	5 µm
A	3,500	1	3,500	1
B	3,500	1	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	ND	ND

# Environmental monitoring

## Limits and Trend Analysis

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- ☺ Limits would be consistent with regulatory & compendial guidelines
- ☺ Alert limits should be set from monitoring histories at the 95% percentile
- ☺ With >98% of the samples taken containing no micro organisms trend analysis is more difficult
- ☺ Reaction should be to consecutive out-of-limit & not individual results

# Environmental monitoring

## Corrective Action in Response to Out-of-limit

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- ☺ The corrective action plans in response to exceeding the alert & action limits need to be written.
- ☺ The development of check lists for systems review & corrective action is helpful.
- ☺ All corrective actions must be completed & documented in a timely fashion.

# Environmental monitoring

## Investigations

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In response to excursions outside the action limits and out-of-trend results the following will be reviewed:

- Identification of the isolates & a determination of their possible origin
- An investigation of the status of the environmental control systems
- The occurrence of atypical activity in the processing area
- Review of product & component sterilization & aseptic filling process
- Microbial monitoring history

# Environmental monitoring

## Investigations

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In response to excursions outside the action limits and out-of-trend results the following will be reviewed:

- Media fill record
- Equipment & facilities maintenance documentation
- Sanitization record
- Training status of the personnel
- Level of supervision

# Environmental monitoring

## Corrective Actions

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- Additional environmental controls
- More intense sampling
- Revision to aseptic practices
- Review of cleaning & sanitization practices
- Determine sensitivity of the isolate to disinfectant
- Enhanced supervision
- Retraining of clean room personnel
- Additional product testing

# Environmental monitoring

## Test Failures

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### Apply Root Cause Analysis / CAPA

- Incorrect application of test methods
- Technician lacking proper training
- Cross contamination / not adhering to GLP's
- Any of the 5 M's
  - Man
  - Measurement
  - Method
  - Material
  - Mother Nature

# Environmental monitoring

## Review List of Test Failures

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- Allows for review of production, control records and investigation reports.
- Initial positive sterility test results and investigations are under highest scrutiny.
- The manufacturer has to do a great deal of explaining and investigating before a valid justification can be made.

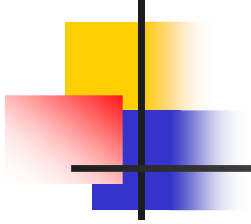


# Environmental monitoring

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## Bibliography:

- ☺ Documents referred are .....
- PDA Technical Report No. 13
- Federal Standard 209E
- Publications of the ISO 14644-1 and 14644-2 documents.
- USP general information chapter <1116> “Microbial Evaluation and Classification of Clean Rooms
- FDA Guideline on Sterile Products Produced by Aseptic Processing



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# Thank you