

Application Note

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***Particle Monitoring in
Pharmaceutical Cleanrooms***

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Particle Monitoring in Pharmaceutical Cleanrooms

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Environmental monitoring is an important aspect of regulatory and quality control in the production of pharmaceuticals. The manufacturing environment must be controlled and monitored during the production of drugs. Final drug products must be sterile and free from contamination.

Terminal sterilization and aseptic processing are the two paths taken to produce sterile drugs. Terminal sterilization is the process of sterilizing materials and containers, done with the material in its containers, with the product in its final form.

In aseptic filling or packaging, the individual components are sterilized separately and brought together in the final form in a sterile environment.

Sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible.

The greatest concern with the manufacturing of sterile drugs is viable microorganisms. With current technology, it is not possible to monitor these in real time. Particle counters play an important part in determining the quality of the air during aseptic processing.

Components of an environmental monitoring program include:

- Airborne nonviable particulate monitoring
- Airborne viable contaminant monitoring
- Viable contaminant monitoring of surfaces
- Viable contaminant monitoring of personnel
- Temperature and humidity monitoring
- Pressure differential monitoring

Cleanrooms and Particle Counting

The production of sterile pharmaceuticals is carried out in various classes of cleanrooms. The most critical operation is during aseptic preparation and filling. Particle counting, microbiological monitoring, temperature, relative humidity and pressure differential measurements must be monitored during the production of these drugs.

Cleanroom Standards:

Cleanrooms are classified by the maximum allowable number of particles per volume unit of air. The volumes typically used are cubic meters (m³) and cubic feet (ft³).

Cleanroom standards also define:

- Minimum sampling volume to gather statistically valid samples (20 particles)
- Minimum number of points to classify an area based upon statistical criteria

The first and most widely recognized cleanroom standard is United States, Federal Standard 209E, also referred to as FED-STD 209E (see Table 1). This standard is obsolete but is still widely used in many cleanrooms.

Replacing FED-STD 209E is the international standard for cleanroom classification, ISO 14644-1 (see Table 2). It is important to note that concentration limits are essentially the same at 0.5 microns as FED-STD 209E, though differences exist for smaller sized particles. ISO 14644-1 has two classifications "cleaner" and one classification "dirtier" than FED-STD 209E. Table 3 shows a comparison between the two standards.

Cleanroom Standards
Table 1: FED-STD 209E

FED-STD 209 Cleanroom Classification											
CLASS NAME		0.1µM		0.2µM		0.3µM		0.5µM		5.0µM	
		VOLUME UNITS		VOLUME UNIT		VOLUME UNIT		VOLUME UNIT		VOLUME UNIT	
S.I.	ENGLISH	(M ³)	(FT ³)	(M ³)	(FT ³)	(M ³)	(FT ³)	(M ³)	(FT ³)	(M ³)	(FT ³)
M1		350	9.91	75.7	2.14	30.9	0.875	10	0.283		
M1.5	1	1240	35	265	7.5	16	3	35.3	1		
M2		3500	99.1	757	21.4	309	8.75	100	2.83		
M2.5	10	12,400	350	2,650	75	1,060	30	353	10		
M3		35,000	991	7,570	214	3,090	87.5	1,000	28.3		
M3.5	100			26,500	750	10,600	300	3,530	100		
M4				75,000	2,140	30,900	875	10,000	283		
M4.5	1000							35,300	1,000	247	7
M5								100,000	2,830	618	17.5
M5.5	10,000							353,000	10,000	2,470	70
M6								1,000,000	28,300	6,180	175
M6.5	100,000							3,530,000	100,000	24,700	700
M7								10,000,000	283,300	61,800	17,500

Table 1 shows FED-STD 209E table for particle concentration limits. Note there are two Class Names (S.I. and English). S.I. refers to System International. Particle concentration limits are expressed in either M³ or FT³.

Table 2: ISO 14644-1

ISO 14644-1 Cleanroom Classification						
ISO Classification Number	0.1µM	0.2µM	0.3µM	0.5µM	1.0µM	5.0µM
	VOLUME UNITS	VOLUME UNIT	VOLUME UNIT	VOLUME UNIT	VOLUME UNIT	VOLUME UNIT
	(M ³)	(M ³)	(M ³)	(M ³)	(M ³)	(M ³)
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1,000	237	102	35	8	
ISO 4	10,000	2,370	1,020	352	83	
ISO 5	100,000	23,700	10,200	3,520	832	29
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	283,000

Table 2 shows the ISO 14644-1 standard for particle concentration limits. The equivalent particle concentrations at 0.5µm to FED STD 209E should be noted.

Table 3 shows a comparison between ISO 14644-1 and FED STD 209E.

Table 3: between ISO 14644-1 and FED STD 209E

ISO Classification Number	Federal Standard 209
ISO 1	
ISO 2	
ISO 3	1
ISO 4	10
ISO 5	100
ISO 6	1,000
ISO 7	10,000
ISO 8	100,000
ISO 9	

With both these standards, the occupancy status is defined in one of three states: As Built, At Rest, Operational.

The occupancy states defined in ISO 14644-1 are as follows:

As built: The condition where the installation is complete with all services connected and functioning, but with no production equipment, materials or personnel present. As built classification can only be done once, when the room is built and before bringing in the equipment.

At-rest: The condition where the installation is complete with equipment installed and operating in a manner agreed between the customer and supplier, but with no personnel present.

Operational: The condition where the installation is functioning in the specified manner, with the specified number of personnel present and working in the manner agreed upon.

Cleanrooms used for the manufacturing of pharmaceuticals have specific environmental standards, addressing the particle concentration (non-viable particles) but the microbial concentration (viable particles) as well. The two most widely used are those published by the European Union and the United States. Though similar, there are some significant differences. In both instances there are two requirements for particle counters.

FDA Guidelines

For the United States, the air quality classification is defined in the Code of Federal Regulations Document 21 CFR Parts 210 & 211. It is also defined in the supporting document "Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice" (see table 4).

Table 4 United States, 21 CFR Part 211 Current Good Manufacturing Practice

Air Classifications				
Clean Area Classification (0.5µm particles/ft ³)	ISO Designation	≥0.5µm particles/m ³	Microbiological Active Air Action Levels ^c (cfu/m ³)	Microbiological Settling Plates Action Levels ^{c,dd} (diam. 90mm;cfu/4 hours)
100	ISO 5	3,520	1 ^e	1 ^e
1000	ISO 6	35,200	7	3
10,000	ISO 7	352,000	10	5
100,000	ISO 8	3,520,000	100	50

a - All classifications based on data measured in the vicinity of exposed materials during periods of activity.

b - ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO particle concentration is equal to class 100 and approximately equals Grade A.

c - Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action.

d - The additional use of settling plates is optional.

e - Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

21 CFR Part 210 & 211 are also referred to as the Current Good Manufacturing Practice. This document is considered non-binding and represents the FDA's current thinking on contamination control.

The FDA references both FED-STD 209E and ISO 14644-1 cleanroom standards for the classification of cleanrooms. By utilizing these standards, such important requirements such as minimum sample locations and sample volumes for this classification are defined by these external documents. Additionally with ISO 14644-2, the frequency of recertification is also defined.

Cleanroom certification and the following re-certification to the standards is important for determining that the cleanroom installation meets the requirements of the cleanroom standard. This is performed at specific intervals and is different than the routine monitoring during the manufacturing process.

Routine particle counting during the manufacturing process provides immediate realization of particle levels when sterile manufacturing is taking place. The location of the particle counter should be such that the data collected reflects on the air quality the materials are exposed to.

The classifications relevant to sterile production are listed in table 4 and refer to 0.5 µm particles and greater. Additionally, microbiological levels for active air sampling and settling plates are defined.

The FDA defines areas for sterile manufacturing as Critical and Supporting Areas.

Critical Areas:

A critical area is one in which the sterilized drug product, containers and closures are exposed to environmental conditions. This area must be designed to maintain product sterility during activities including: aseptic connections, adding sterile materials, filling and closing operations. A critical area is classified as ISO Class 5 or FED-STD 209E Class 100. Referenced also is this classification as equivalent to EU Grade A.

Supporting Clean Areas:

Supporting clean areas have different classifications. These classifications are based upon the functions carried out in these areas. These clean areas are designed to support the aseptic process. The support functions of these areas include handling nonsterile components, formulated products, in-process materials, equipment, and container/closures. The type of activities conducted in a supporting clean area determines its classification. The area immediately adjacent to the aseptic processing line should be at a minimum, Class 10,000 (ISO 7) standard under dynamic (operational) conditions. This area can also be Class 1,000 (ISO 6). An alternative is to maintain the entire aseptic filling room at Class 100 (ISO 5). An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities such as equipment cleaning.

Particle Counting in Critical Areas: Class 100 / ISO Class 5

In critical areas, particle counting locations should be no more than one foot away from the work site and should be with the air flow. Remote particle counters connected to a facility monitoring system are preferred over portables because remotes can be more closely located to the actual work being performed and are less intrusive than the larger portable instruments.

In the instances where the operations generate high levels of particles from the product (powders), then it would not be feasible to count particles within the one foot distance.

Air can be sampled at a greater distance to indicate that the environment is within control.

Facility Monitoring Systems

The FDA also recommends the monitoring of temperature, relative humidity and differential pressure. Facility Monitoring Systems (FMS) can monitor the particle counts and these parameters as well.

European Guidelines

For Europe, the air quality classification for sterile medicinal products is defined in the document: EC Guide to Good Manufacturing Practice Annex 1: (see table 5).

Annex 1 calls out concentration limits for both 0.5µm and 5.0µm particles and references ISO 14644-1 for 0.5 µm particle concentration. This document does not specify the minimum number of sample locations required to classify a cleanroom but does call out a minimum sample volume of 1 M³ for the entire area being classified (during the formal classification / re-classification). This volume is required regardless of area size.

It is important to note the difference between cleanroom certification and routine monitoring, as stated earlier. The EU has requirements for monitoring particles at 0.5µm and 5.0µm. In addition, the EU has classification limits for operational AND at rest periods. The at-rest periods are achieved after 15-20 minutes.

Table 5: EC Guide to Good Manufacturing Practice Annex 1:

Grade	at rest (b)		in operation (b)	
	Maximum permitted number of particles / m ³ equal to or above (a)			
	0.5µM (d)	5µM	0.5µM (d)	5µM
A	3,500	1 (e)	3,500	1 (e)
B	3,500	1 (e)	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	not defined (f)	not defined (f)

Notes:

(a) Particle measurement based on the use of a discrete airborne particle counter to measure the concentration of particles at designated sizes equal to or greater than the threshold stated. A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone and is recommended for the surrounding grade B areas. For routine testing the total sample volume should not be less than 1 m³ for grade A and B areas and preferably also in grade C areas.

(b) The particulate conditions given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations. The particulate conditions for grade A “in operation” given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress due to the generation of particles or droplets from the product itself.

(c) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate terminal filters such as HEPA for grades A, B and C.

(d) The guidance given for the maximum permitted number of particles in the “at rest” and “in operation” conditions correspond approximately to the cleanliness classes in the EN/ISO 14644-1 at a particle size of 0.5µm.

(e) These areas are expected to be completely free from particles of sizes greater than or equal to 5µm. As it is impossible to demonstrate the absence of particles with any statistical significance, the limits are set to 1 particle/m³. During the cleanroom qualification it should be shown that the areas can be maintained within the defined limits.

(f) The requirements and limits will depend on the nature of the operations carried out.

A continuous measurement system should be used for grade A and B areas. Annex 1 does not specify the use of portable particle counters or remote particle counters.

Differences

Some differences exist between the FDA's requirements for cleanrooms and the EU.

- ◆ The FDA does not have requirements for 5.0 micron particle data.
- ◆ The EU has classification limits for operational AND at-rest periods. The at-rest periods are achieved after 15-20 minutes.
- ◆ In addition, the FDA specifies cleanroom classifications using either ISO or FED-STD 209E standards.
- ◆ EU Annex 1 requires (for certification and not routine monitoring) a total cubic meter be sampled per area. This is the total sample volume of all the monitoring points regardless of the size of the area.

Facility Monitoring Systems

Based upon both the US and EU GMP, continuous particle counting is a requirement for sterile manufacturing. With the FDA recommending the use of remote particle counters specifically, Facility Monitoring Systems (FMS) are becoming the preferred method of monitoring sterile manufacturing environments. FMS systems are typically designed to automatically collect data from particle counters. In addition to particle counting data, additional inputs can be used to monitor the environment.

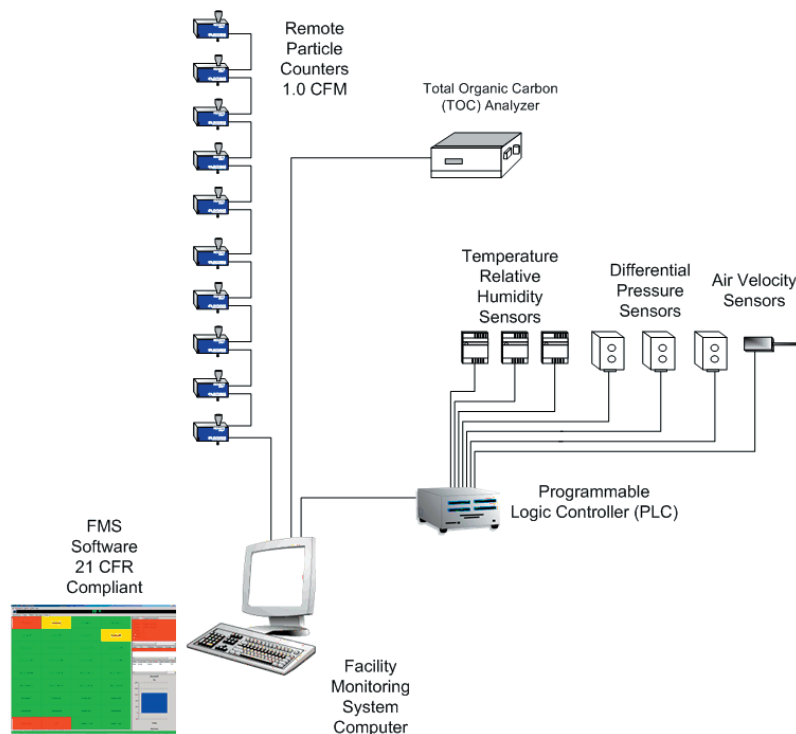
Other parameters that must be monitored and controlled in sterile manufacturing are:

- ◆ Temperature
- ◆ Relative Humidity
- ◆ Differential Pressure
- ◆ Air Velocity and Direction

Figure 1 is an example of a typical FMS system.

A Facility Monitoring System can automate the recording of this data and provide alarming notification for out of tolerance conditions. In addition to alarming and automated recording of this data, specific reports can be generated based upon time of manufacturing or individual batches.

Figure 1: FMS System Diagram



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