

Old	NEW
<p>3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.</p> <p>In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. The “at-rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.</p> <p>The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms.</p> <p>For the manufacture of sterile medicinal products 4 grades can be distinguished.</p> <p>Grade A : The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications.</p> <p>The maintenance of laminarity should be demonstrated and validated.</p> <p>A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.</p> <p>Grade B : For aseptic preparation and filling, this is the background environment for the grade A zone.</p> <p>Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.</p>	<p><i>The existing text of clause 3 remains unchanged up to and including the following:</i></p> <p>Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.</p> <p>3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.</p> <p>In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. The “at-rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.</p> <p>The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms.</p> <p>For the manufacture of sterile medicinal products 4 grades can be distinguished.</p> <p>Grade A : The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications.</p> <p>The maintenance of laminarity should be demonstrated and validated.</p> <p>A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.</p> <p>Grade B : For aseptic preparation and filling, this is the background environment for the grade A zone.</p> <p>Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.</p>

The airborne particulate classification for these grades is given in the following table.

Grade	at rest (b)		in operation (b)	
	maximum permitted number of particles/m ³ equal to or above (a)			
	0.5 µm (d)	5 µm	0.5 µm (d)	5 µm
A	3 500	1 (e)	3 500	1 (e)
B (c)	3 500	1 (e)	350 000	2 000
C (c)	350 000	2 000	3 500 000	20 000
D (c)	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 0.5 µm.

The remaining text of clause 3 up to but not including the following:

Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

and clause 4 is replaced by:

(e) These areas are expected to be completely free from particles of size greater than or equal to 5 µm. As it is impossible to demonstrate the absence of particles with any statistical significance the limits are set to 1 particle / m³. During the clean room 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. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

Examples of operations to be carried out in the various grades are given in the table below. (see also par. 11 and 12)

Grade	Examples of operations for terminally sterilised products. (see par. 11)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations. (see par. 12)
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered.
D	Handling of components after washing.

4. The areas should be monitored during operation, in order to control the particulate cleanliness of the various grades.

4. Clean room and clean air device classification
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. The maximum permitted airborne particle concentration for each grade is given in the following table.

Grade	at rest		in operation	
	Maximum permitted number of particles/m ³ equal to or above			
	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 500	1*	3 500	1*
B	3 500	1*	350 000	2 000
C	350 000	2 000	3 5000 000	20 000
D	3 500 000	20 000	Not defined	Not defined

The maximum permitted number of particles at $\geq 5.0\mu\text{m}$ is established at 1/ m³ but for reasons related to false counts associated with electronic noise, stray light, etc. a limit of 20/m³ could be considered.

For classification purposes, in Grade A zones, a minimum sample volume of 1m³ should be taken. Grade A and Grade B (at rest) is similar to EN ISO Class 5 for particles $\geq 0.5\mu\text{m}$. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size. It should be noted that this will give rise to a sampling time of about 35 minutes at each location when using a particle counter with a sample rate of 28.3 litre/minute (one cubic-foot per minute).

Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles $\geq 5.0\mu\text{m}$ particles in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems.

“In operation” classification may be demonstrated during media fills because of the worst-case simulation required for this.

EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

	<p>5. Clean room and clean air device monitoring Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on formal risk analysis study and results obtained during the initial classification of rooms and/or devices.</p> <p>For Grade A zones a continuous or frequent sampling particle monitoring system should be used, except where justified, e.g. the filling of live virus vaccines. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. Such systems may consist of independent particle counters; or have one particle counter that is linked to a number of sampling ports sequentially via a tubing manifold system. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be validated. The Grade A zone should be monitored at such a frequency that all interventions and other transient events would be captured and alarms triggered if excursions from defined operating norms occur.</p> <p>The sample sizes taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.</p>
	<p>6. In Grade A and B zones, the monitoring of the 5.0 µm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of µm particle counts ≥ 5 µm may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnosis of poor practices during machine set-up and routine operation.</p>
	<p>7. The particle limits 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. It is accepted that it may not always be possible to demonstrate low levels of particles ≥ 5 µm at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.</p>
	<p>8. For Grade D areas in operation, the requirements and limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.</p>

	<p><i>The new clause 9 takes up the existing text of clause 3 at the following point:</i></p> <p>9. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.</p>
<p>5. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.</p> <p>.....</p>	<p><i>The existing clauses from 5 to 41 are unchanged but re-numbered as 10-46.</i></p> <p>10. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.</p> <p>.....</p>