Classification, Qualification and Monitoring According to EU GMP Annex 1 Rev 12

The latest Annex 1 draft has some new definitions and guidance regarding Cleanroom Classification, Qualification, and Monitoring.

Cleanroom Classification

Annex 1 provides essentially the same cleanroom classification definition as ISO 14644-1: 2015, which is a "method of assessing the level of cleanliness against a regulatory specification for a cleanroom or clean zone."[1] Annex 1 also defers to ISO 14644-1:2015 definitions for the various cleanroom standards and specifications. In Annex 1, Revision 12, nothing has changed regarding the association between pharmaceutical grades and the ISO classes:

- Grade A and B cleanrooms must comply with the ISO 5 requirements in at-rest occupancy state.
- Grade C cleanrooms must comply with ISO 7.
- Grade D cleanrooms must comply with ISO 8.

To classify a cleanroom, the total number of particles is measured for both at-rest and in-operation states. Annex 1 and ISO 14644 also align regarding classification. Annex 1 follows the ISO 14644 table with one adjustment: Grade A and B surrounding locations should consider all critical processing zones with a documented risk assessment. This is not the same Cleanroom Risk Assessment (RA) as a Cleanroom Monitoring RA, which is for studying processes. The purpose of the RA for cleanroom classification is to ensure that all critical zones with processes are covered.

Which particle sizes should be measured?

A significant change in Annex 1 from ISO 14644 is that in Grades A and B (ISO 5), only airborne particulates ≥ 0.5 µm* need to be monitored. This is because of the low concentration of macroparticles in these areas. Annex 1 adds that we should also consider counting particles ≥ 1 µm.

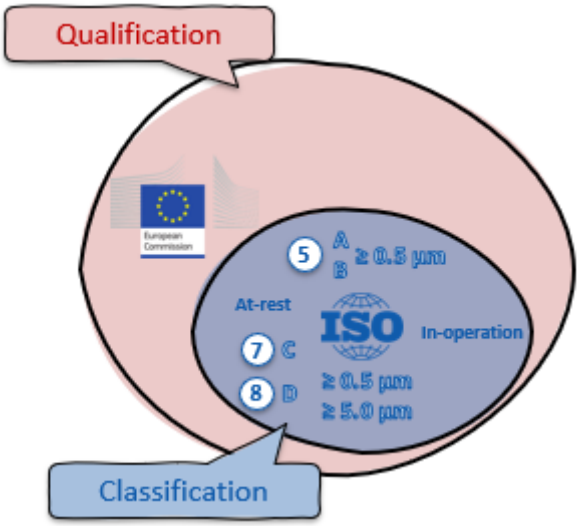
The requirements for Cleanroom Grades C (ISO 7) and D (ISO 8) have not changed. Airborne particulates should be measured at both ≥ 0.5 µm and ≥ 5.0 µm.

TABLE 1 Maximum permitted airborne particulate concentration during classification

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5.0 µm/m³	
	At Rest	In Operation	At Rest	In Operation
A	3,520	3,520	-	-
B	3,520	352,000	-	2,900
C	352,000	3,520,000	2,900	29,000
D	3,520,000	-	29,000	-

Cleanroom Qualification

Defined as “the overall process to assess the level of compliance of a classified cleanroom with its intended use"[1], cleanroom qualifications include room classification. Qualification methodologies are identified in EU GMP Annex 15 and all verification must comply with the testing methodologies in ISO 14644-3:2019.

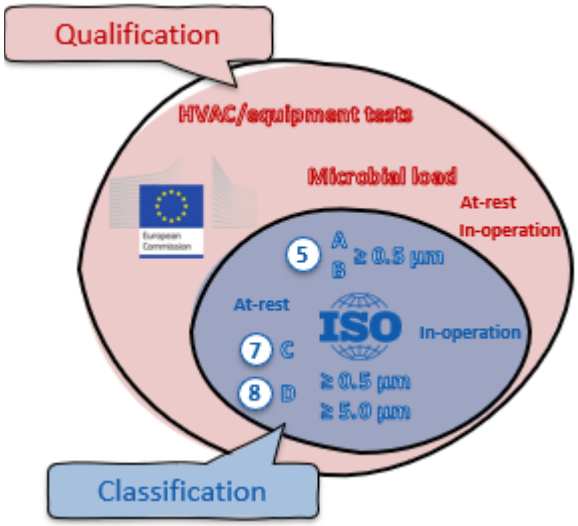


Cleanroom Qualification Verification

The next item to consider is which verifications are needed for cleanroom classification. First, it is important to understand that microbial contamination for airborne and surface must be measured both at-rest and in-operation states.

Next, the number and location of sampling points should be based on a documented risk assessment. This is not the same RA for microbial monitoring. This RA is to create a microbial map that characterizes the cleanroom.

Cleanroom Requalification



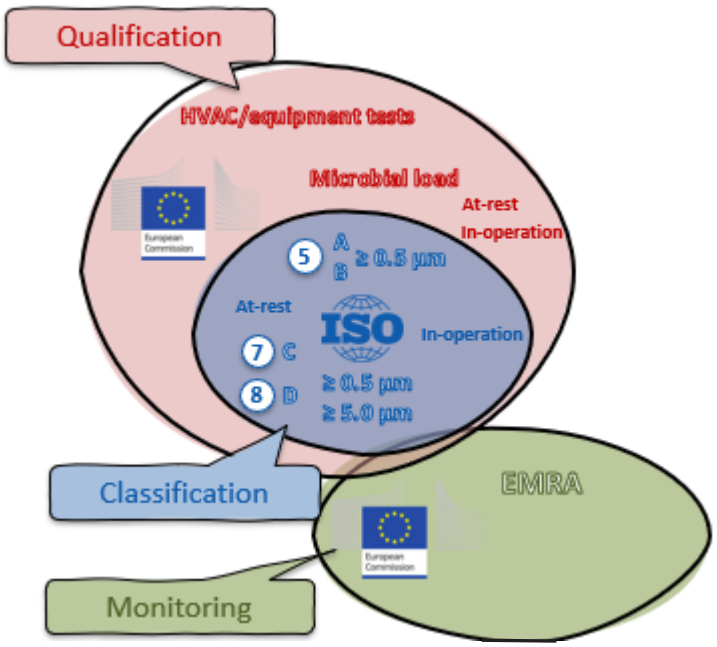
Requalification must be carried out at a minimum of:

- At least every 6 months for Grades A and B
- At least every 12 months for Grades C and D

The new Annex 1 draft also specifies the requalification tests needed, and that after changes or an extraordinary event the cleanroom must be requalified.

Cleanroom Monitoring

There is little overlap with cleanroom monitoring, qualification, and classification:



The goal of cleanroom monitoring is to assess the potential contamination risk of the product. The key location focus of monitoring is at the manufacturing processes. The only connection with Cleanroom Qualification is that, as a secondary purpose, we also provide evidence of the performance of a cleanroom from the process point-of-view.

Because monitoring the manufacturing process is critical, it is important to decide where to sample within the environment. There are many variables to consider, including:

- Product
- Process
- Facility
- Equipment
- Operations
- Historical data
- Qualification data
- Microbial flora

To effectively create a monitoring plan, it is important to do a comprehensive risk-based analysis and consider what was previously found in the classification and qualification phases.

Cleanroom Monitoring Verification

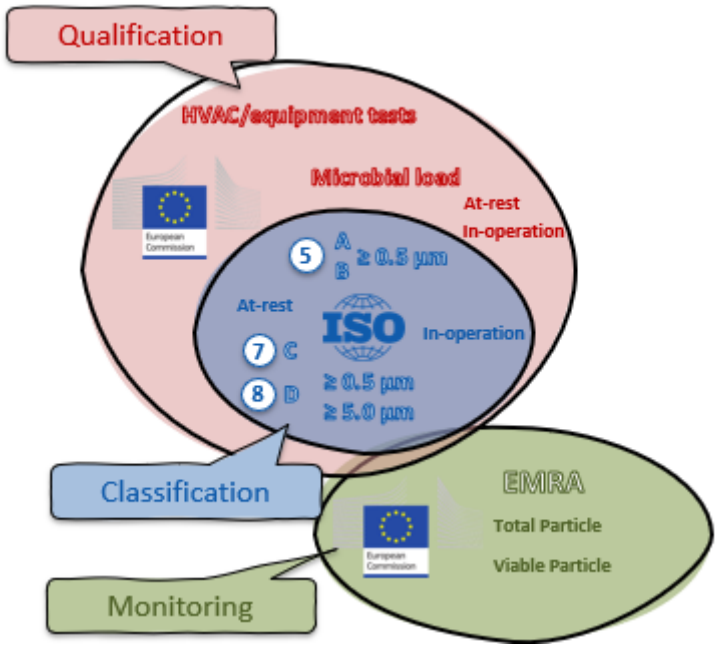
There is nothing new in Annex 1 regarding cleanroom monitoring methods. All grades must monitor total airborne particles at both ≥ 0.5 µm and ≥ 5.0 µm.

TABLE 2 Limits for airborne particulate concentration for the monitoring of non-viable contamination

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5.0 µm/m³	
	At Rest	In Operation	At Rest	In Operation
A	3,520	3,520	-	-
B	3,520	352,000	-	2,900
C	352,000	3,520,000	2,900	29,000
D	3,520,000	-	29,000	-

Regarding viable particles, the newest draft confirms what was presented in earlier Annex 1 revisions, which is the use of a combination of methods:

- Settle plates
- Volumetric air sampling
- Gloves, gown, and surface sampling with swabs and/or contact plates



Solution: Particle Measuring Systems' Contamination Control Advisory Team

Our Contamination Control Advisory Team can support you throughout the RA and application of all items above Our experts are highly specialized in the application of risk analysis tools, and the team has a wide combination of experience in the pharmaceutical world. We can support you with an Environmental monitoring risk analysis service to define sampling points, sampling frequency, and the sampling methodologies and provide you with the rationales to mitigate risk.

Other services on these topics are available including microbial load risk assessment, which is (as discussed above) fundamental during the qualification phase.

The **PMS Advisory Team** can support you through this process, providing you with professional support to identify:

- Sampling points
- Sampling frequency
- Sampling methodologies
- Risk mitigation activities

Cleanroom classification, qualification, and monitoring are at the core of Particle Measuring Systems' solutions. The **FaciltyPro® Environmental Monitoring System** helps you to continuously monitor your environment during the manufacturing process so you can simplify your operation, minimize the risk of contamination during the sampling of critical areas, and react to and control contamination, improving the quality of your product and ensuring the integrity of the data.

The integration of Facility Pro with **PharmaIntegrity™** creates a complete contamination monitoring solution, giving you control of environmental data from material preparation, to on-field sampling, to data analysis and trending.

Only Particle Measuring Systems has a complete solution to provide you with particle counters, **microbial cleanroom monitors**, **education** and **advisory services**, as well as the systems you need.

References

1. EU GMP Annex 1 Revision: Manufacture of Sterile Products (Draft). Rev 12. 396-397, 420. Feb 20, 2020.

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