ISO 14644 Revisions Summary

Abstract

The recent revision of ISO 14644-1 and-2 has introduced several changes for cleanroom classification and monitoring guidelines. This paper will highlight the major changes in the new ISO 14644-1 compared to the previous version, as well as the possible impact on the Pharmaceutical EU GMP Annex 1 and FDA Aseptic Processing Guideline.

Introduction

Over the last five years, the ISO Technical Committee 209 has been working on the revision of the basic airborne cleanliness classification, 14644-1 and -2.
The ISO community voted in favor of the revision to update and improve the standard specifically to:

- simplify the classification process, and if possible, remove the need to evaluate the 95% upper confidence limit (UCL) for low sample location numbers (currently required for 2/9 of cleanroom locations).
- review the classification procedure and make it more applicable to cleanroom operation. In this situation, the contamination is not expected to be evenly distributed; an assumption the current statistical approach makes.
- generally, update the standard as required to current thinking and industry requirements.
- avoid any radical change to the principles of the current ISO cleanliness classes 1÷9.

The same technical committee has also been working on the revision of the ISO 14644-2:2000 (*not analyzed in this document*) in conjunction with the revision of ISO 14644-1. The ISO community voted in favor of the revision to improve the ISO 14644-2:2000 standard to:

- simplify and clarify requirement and guidance tables that specify frequency of testing and monitoring of cleanrooms used to demonstrate continued compliance with the cleanliness classification.
- refine how these intervals may be extended, provided that automated monitoring systems show the cleanroom is under control.
- provide new guidance on aspects that should be considered when configuring a monitoring system for a cleanroom.

On October 29th 2015, during the last voting session, the revised 14644-1 and -2 Standards were approved by a significant majority of the member nations participating in the ISO/TC 209 committee.

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Definitions

To simplify ISO 14644-1:2015, summaries are provided below of sections relevant to the revisions.

ISO 14644-1:2015
Cleanrooms and Associated Environments
Part 1. Classification of air cleanliness by particle concentration

This section specifies classes of air cleanliness for the world's cleanrooms and controlled environments in terms of the number of particles expressed as a concentration in air volume. To determine the class, a specified testing method is required, which includes selection of sampling locations.

ISO 14644-1 Introduction

ISO 14644-1 represents the first chapter of a series of documents, which describe the method, procedures and limits to be applied in the cleanroom design, operation and controls. This standard is used in different industries including Microelectronics, Pharmaceuticals, Aerospace, Medical Devices, Healthcare and Food Production.
It specifies classes of air cleanliness for the world's cleanrooms and controlled environments in terms of the number of particles expressed as a concentration in air volume. To determine the class, a specified testing method is required, which includes a strategic selection of sampling locations.

ISO 14644-1 Scope

The scope of this International Standard is to provide guidelines, specifications and rules to be used for cleanroom certification in terms of airborne particle concentration. ISO 14644-1 addresses all consideration for classification purposes that have cumulative distributions based on threshold (lower limit) sizes ranging from 0.1 µm to 5 µm. Lower particles size concentration limits (nanoparticles), are addressed in ISO 14644-12.

2015 Revision

ISO 14644-1:2015 – New maximum concentration limits

The ISO classification is based on a new table (Table 1), which uses the current and well-known formula for the intermediate decimal classes (Figure 1).

Table 1 Selected airborne particulate cleanliness classes						
ISO 14644-1:2015 Classification Number (N)	Maximum concentration limits (particles/m³)					
	0.1 µm	**0.2 µm**	**0.3 µm**	**0.5 µm**	**1.0 µm**	**5.0 µm**
ISO Class 1	10					
ISO Class 2	100	24	10			
ISO Class 3	1 000	237	102	35		
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	298
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

Table 1: ISO 14644-1:2015 – New Maximum Concentration Limits

$$C_n = 10^N \times \left(\frac{0{,}1}{D}\right)^{2{,}08} \qquad \text{(E.1)}$$

where

C_n is the maximum permitted concentration (particles per cubic metre) of airborne particles that are equal to and greater than the considered particle size. C_n is rounded to the nearest whole number, using no more than three significant figures;

N is the ISO classification number, which shall not exceed a value of 9 or be less than 1;

D is the considered particle size, in micrometres, that is not listed in Table 1;

K is a constant, 0,1, expressed in micrometres.

Figure 1: formula used for the intermediate decimal classes

The foremost concern in the Life Science industry is the removal of the ≥ 5 µm particle concentration in ISO Class 5 clean areas (for classification purpose) when compared to the ISO 14644-1:1999 version.

In the 1999 version, the limit is 29 particles per cubic meter as reported on the table below (Table 2). This change to the ISO/DIS 14644 standard is a major concern for a number of reviewers.

Table 1 Selected airborne particulate cleanliness classes						
ISO 14644-1:1999 Classification Number (N)	Maximum concentration limits (particles/m³)					
	0.1 µm	**0.2 µm**	**0.3 µm**	**0.5 µm**	**1.0 µm**	**5.0 µm**
ISO Class 1	10					
ISO Class 2	100	24	10			
ISO Class 3	1 000	237	102	35		
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	298
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

Table 2

The reasons for the de-emphasis on the ≥ 5 µm ISO Class 5 limit include:

- Sampling and statistical limitations for particles in low concentrations make this classification inappropriate.

- Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

ISO 14644-1:2015 – Sample locations

In order to achieve the goals of the ISO community, the significant changes with ISO 14644-1 are related to revision of the classification method, summarized as follows.

Number of sample locations

- A new table has been developed for the determination of the number of sample locations, replacing "$Location\ Number\ = \sqrt{m^2 room\ area}$" from the ISO 14644-1:1999 version of the standard.

- For all room sizes above 6 m², the new table (Table 3) results in an increase of required sample locations.

- The ISO14644-1:1999 standard required the UCL 95% (Upper Confidential Limit) calculation for sample locations between 2 and 9.

- The new table has been pre-calculated to eliminate the need for this calculation. The new method, when successfully applied, assures that at least 90% of the room is compliant at a 95% confidence limit.

Area of zone [m2]	ISO 14644-1:1999	ISO 14644-1:2015
2	2	1
4	2	2
6	3	3
8	3	4
10	4	5
24	5	6
28	6	7
32	6	8
36	6	9
52	8	10
56	8	11
64	8	12
68	9	13
72	9	14
76	9	15
104	11	16
108	11	17
116	11	18
148	13	19
156	13	20
192	14	21
232	16	22
276	17	23
352	19	24
436	21	25
636	24	26
1000	32	27
>1000	n/a	See Formula A. 1

Table 3: Number of sample locations required

$$N_L = 27 \times \left(\frac{A\ m^2}{1000}\right)$$

Formula A. 1: Formula used to determine the number of sampling locations

The determination of each sampling location will be based on a semi-random sampling technique, based on a "hypergeometric" distribution, which is the statistical model for sampling without replacement.

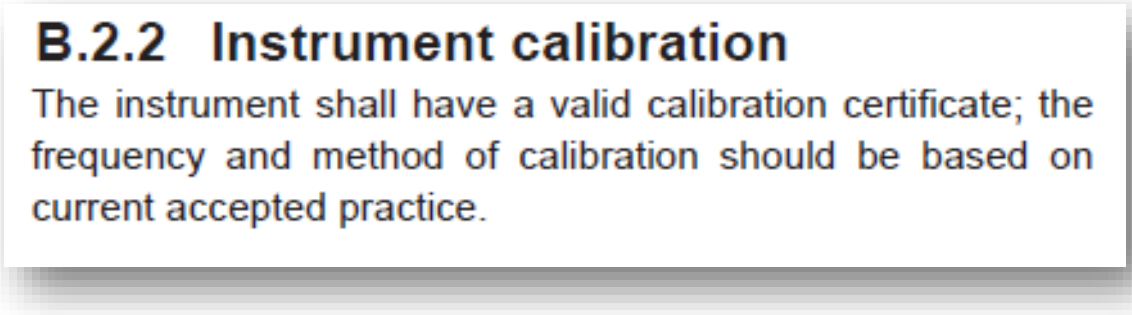
This is a significant change from current practice, and means that each time a zone is classified, the sample locations may be different. If a company has determined through a risk assessment that certain locations need to be examined specifically, then these should be applied over and above the randomly selected locations.

Recognizing that the ≥ 5.0 micron class limit for ISO 5 has been removed in the revised standard, parties wishing to use the standard for classifying the environments EU GMP Grade A, and B "at rest" will have to use the macro-particle limit table retained in the standard.

Instrument calibration

Another important change in the new revised Standard is represented by the need to use ISO 21501-4 compliant particle counters.

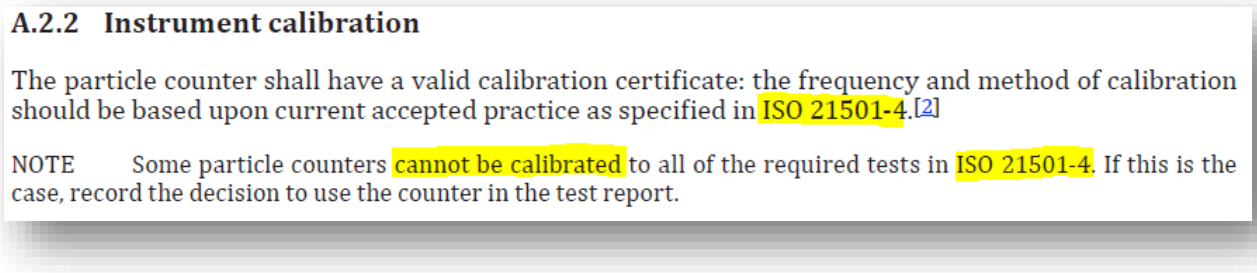
The paragraph B.2.2 of the (previous) ISO 14644-1:1999 required to perform particle counting using “calibrated” instruments, not mentioning any specific calibration technique requirement.



B.2.2 Instrument calibration

The instrument shall have a valid calibration certificate; the frequency and method of calibration should be based on current accepted practice.

The new released version of ISO 14644-1:2015 specifically requires the use of ISO 21501-4 compliant instrument at paragraph A.2.2



A.2.2 Instrument calibration

The particle counter shall have a valid calibration certificate: the frequency and method of calibration should be based upon current accepted practice as specified in ISO 21501-4.[2]

NOTE Some particle counters cannot be calibrated to all of the required tests in ISO 21501-4. If this is the case, record the decision to use the counter in the test report.

As reported in the above note, not all instruments will be able to meet those requirements and the use of non-compliant instruments will require an additional explanation for authorities.
More information about the ISO 21501-4 requirements can be found on a separated application note, available on the Particle Measuring Systems website, Knowledge Page: Understanding ISO 21501-4

Conclusion

The new changes described here will impact cleanroom classifications, and any company that needs to comply with this standard will be required to update their internal SOP in order to meet the new ISO 14644 requirements.

ISO 14644-1:2015 was published on November 1st 2015 and will be effective starting from January 1, 2016. All users who want to be compliant with this standard will be required to take any necessary action before the end of 2016.

All Particle Measuring Systems instruments will have updates applied in order to fully meet these new ISO requirements.

For more information about the new ISO 14644-1:2015, instrument firmware upgrade or expert consultancies, contact your Particle Measuring Systems local representative or navigate our Contacts web page.

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