CHANGES TO THE STANDARD FOR

ISO 14644 – 1 2015

ISO 14644 – 2 2015

Cleanrooms and Associated Controlled Environments

The newly updated ISO14644-1:2015 has caused some confusion and raised concerns by companies who want to ensure that they are fully compliant.

To address these issues, CVT (Cleanroom Validation Team) share our expertise and have listed some of the most frequently asked questions in the following categories:-

1. **The number of sampling locations is different**

In the 1999 standard the number of locations was equal to the square root of the area in square meters. This has been replaced with a table and more test locations will be required in most cases.

This requirement applies to cleanroom certification but not when cleanroom monitoring is being done. ISO 14644-2 provides guidance for monitoring, but the class limits are established in ISO 14644-1, and as it remains an important standard for monitoring as well.

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 1: Number of sample locations required

2. Elimination of 5um limits for Class 5 and Class 6 locations

The limits were removed for Class 5 and Class 6 locations because there were too few particles to be statistically significant. For general cleanroom applications, this was a valid decision. Nonetheless, elsewhere in the standard it recognises that some applications may still need to monitor these sizes such as in life science which is an application with special need to continue monitoring 5um particles.

The life science industries have focused on 0.5um and 5um because these sizes effectively bracket the range of viable, airborne particles. Viruses, for example, may only be 0.1um in size but they are only airborne in clusters, not individually. The number of 5um particles in a

Class 5 area is typically as few as 1 or 2 in number. A small increase in counts due to viable particles would be lost in the background counts for 0.5 micron particles, but should stand out as unusual in the 5um channel. So, monitoring 5um particles is critical in this instance.

Class 5 areas are not about statistics but about having an early warning of potential microbial colonization in the area. This allows production to be halted before thousands of rand worth of raw materials are wasted pending verification of the problem by viable sampling.

For this reason, and because EU GMP, Annex 1 has not indicated a relaxation of 5um requirements, life science companies should continue to monitor 5um particles in Class 5 areas, as in the past.

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 2: ISO 14644-1:2015 New Maximum Concentration Limits

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

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 ≥ 5um 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 3). This change to the ISO 14644 standard is a major concern for a number of reviewers.

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Table 3

The reasons for the de-emphasis on the ≥ 5 um 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 um make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

3. Removal of the 95% UCL requirement

For 10 locations or more, ISO14644-1 has only required a straight average. For fewer than 10 locations, the standard has required a statistical calculation (95% UCL) that assures with 95% of the areas in the room will not exceed the calculated value, which needs to be less than the room limit to pass.

The problem with the calculation is that it is strongly influenced by the standard deviation. The wider the disparity in the counts between areas in the calculation, the greater the standard deviation and the greater the calculated (95% UCL) number will be.

The standard now avoids the problem altogether by requiring that all individual locations pass and that no 95% UCL is calculated.

The new standard is essentially a relaxation of requirements. Areas that passed before would still pass but for certification more testing time may be required due to the increased number of locations in some instances.

4. Test Frequency based on assessment and monitoring strategy

ISO 14644-2 specifies the requirement of a monitoring plan, based on risk assessment of the intended use. The data obtained must provide evidence of cleanroom or clean zone performance related to air cleanliness by particle concentration.

Emphasis is placed on a monitoring strategy in addition to the initial or periodic classification of a cleanroom or clean zone in accordance with ISO 14644-1:2015,5.1.

Potential benefits gained from monitoring are:-

- Faster response to adverse events and conditions
- Ability to set trends from data over time
- Integration of data from multiple instruments
- Enhanced knowledge of installation and process, which allows for more effective risk assessment
- Improved control of operational costs and product losses

Supplementary policies, requirements and restrictions may be imposed when significant changes have been made to the installation or process requirements.

In the absence of continuous monitoring equipment many end users have elected to adopt the British Standard Institution recommendation as detailed below.

Test parameter/Performance attribute	Maximum time interval between tests
Airborne particle concentrations ≤ ISO Class 5	6 months
Airborne particle concentrations > ISO Class 5	12 months
Pressure differentials	Continuously monitored by frequent manual observation or by automated instrumentation
Installed filter leak test in unidirectional airflow and cleanliness classes ≤ ISO Class 5	6 months
Installed filter leak test in non-unidirectional airflow and cleanliness classes > ISO Class 5	12 months
Airflow velocities in unidirectional airflow	6 months
Airflow volume supply in non-unidirectional airflow	12 months
Containment leak (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content.
Airflow visualization (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content.
Recovery time in non-unidirectional airflow (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content.
Particle deposition rates (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content.
Segregation tests (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content.
a) Temperature b) Humidity c) Electrostatic and ion generator	As required, and in agreement with the cleanroom user.