Cleanroom Supplies Ltd

OPTIMUM PROTECTION™

Disposable Protective Clothing and Contamination Control

ISO14644 Cleanroom Guide

What Is ISO14644?

ISO 14644 is the international standard used to design, construct, validate and operate a cleanroom. For those new to cleanrooms, take a look at our basic concept of a cleanroom video. The standard was first published in 1999, and replaced the former US Federal Standard 209E in 2001. After a consultation period and amendments, Parts 1 and 2 were updated and revised in December 2015.

What Are The Key Changes To ISO14644-1:2015?

ISO 14644-1:2015 specifies the classification of air cleanliness in terms of concentration of airborne particles in cleanrooms and clean controlled environments. (See page 8 for full list)

The main improvement is in the particle sampling methods. The previous methods were dependant upon an ad-hoc approach in ascertaining the number and location of sampling points. Improved sampling methods in the revised ISO 14644-1 document along with the enhanced guidance for particle counter calibration, provides improved confidence in cleanroom performance .

By increasing statistical accuracy through a larger number of sampling locations, the ISO 14644-1:2015 document also eliminates the need for the upper confidence limit (UCL) calculation for counting between 1 to 9 locations.

The UCL calculation which was previously required for cleanrooms requiring between 2 and 9 sample locations. Provided all sample locations are within the Class or Grade requirements, there is no longer any need to perform the UCL calculation.

The changes to ISO 14644-1 do not necessarily have an impact on the principles of classification however the basis for classification has been changed from ‘Classification by Formula’ to ‘Classification by Table’ (with a formula for intermediate sizes).

ISO 14644-1:2015 Table 1 – ISO Classes of air cleanliness by particle concentration

ISO Class number (*N*)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10*[b]	d	d	d	d	e
2	100	*24*[b]	*10*[b]	d	d	e
3	1 000	237	102	*35*[b]	d	e
4	10 000	2 370	1 020	352	*83*[b]	e
5	100 000	23 700	10 200	3 520	832	d, e, f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9g	c	c	c	35 200 000	8 320 000	293 000

What Are The Implications For EU GMP Cleanroom Operators?

This guide aims to provide a brief overview of the changes, but more importantly, how the changes affect the current Guide to GMP for Medicinal Products – Annex 1 Manufacture of sterile medicinal products and the average pharmaceutical cleanroom. The application and uncertainty of ≥5.0µm particles in Grade A and Grade B environments for classification and monitoring to ISO 5

It will impact on every GMP Pharmaceuticals cleanroom user.

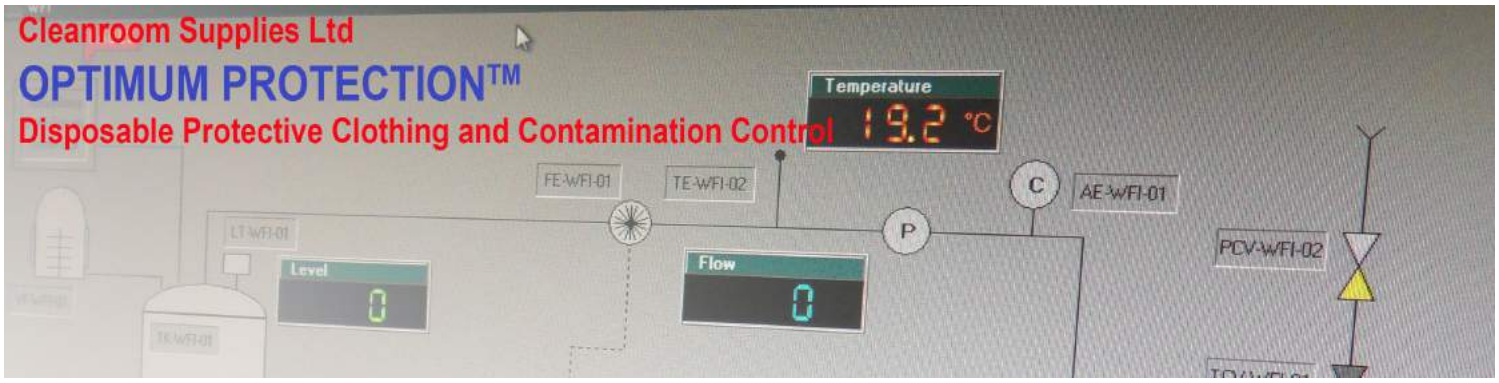
The fundamental changes in the ISO 14644-1:2015 document impacting on the GMP community are:

- Change to the method for calculating number of sample locations for classification or re-qualification
- Elimination of the 95% Upper Confidence Limit (UCL) calculation
- Reference to ISO 21501-4 in the normative* Annex A where the requirements for air particle counters are defined (*normative = must comply with this section)
- Removal of the maximum allowable concentration of airborne particles/m^3 ≥ 5 microns for ISO Class 5 from the Cleanliness Classes table (ISO Class 5 at 5microns is equivalent to GMP Grade B at rest)

All GMP cleanroom users will have to make changes to their cleanroom classification or re-qualification SOPs to incorporate the larger number of sampling points required in the new version of the ISO standard. In some cases a risk assessment may be required to retrospectively investigate the potential impact on product quality if the new classification/re-qualification changes the cleanroom Class or Grade. In some cases where this is the case, the cleanroom owner may have to consider making changes to their cleanroom and air handling systems to bring the cleanroom back into the required Class or Grade.

All GMP cleanroom users will have to ensure that the particle counters used to classify and monitor their cleanrooms are compliant with the requirements of ISO 21501-4, including those counters forming a part of a continuous monitoring system.

All SOPs and qualification protocols in pharmaceutical manufacturing related to the HVAC system and cleanroom operation should be changed accordingly.
Although EU GMP and USA cGMP both define the airborne particle counts/m^3 for each cleanliness class or grade, they do not contain guidance on the cleanroom classification procedure. Instead they point the reader to ISO 14644-1 for the cleanroom classification methodology. As part of the routine periodic review process, the ISO committee responsible for ISO 14644-1 decided that areas of the classification process required revision to improve statistical accuracy.



In ISO 1,2,3 and ISO 5 classes, the particle diameter that could be taken as a reference has been changed. The most significant reflection of it to the industry is that the limit which was 29 particles for 5 microns doesn't exist anymore.

The application and uncertainty of ≥5.0µm particles in Grade A and Grade B environments for classification and monitoring to ISO 5

The removal of the 95% UCL calculations

The increase in sampling locations for most cleanrooms.

Based on the updated ISO class classification table in ISO 14644-1:2015, GMP Annex 1 Maximum Permitted Particles Table now fall outside the ISO classification system and therefore should not be used for formal classification:

Grade	Maximum permitted number of particles/m³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

Macro-particle descriptor

The ISO 14644-1:2015 standard describes any particle with an equivalent diameter ≥5.0µm as a macro-particle. Where a regulatory agency demands consideration of these particles, the counting and sizing of these macro-particles is expressed using the M descriptor in the format.

The pharmaceutical industry will be affected by this change according to GMP Appendix 1 but there is no cause for concern. Firstly, 0.5 and 1 micron particle diameters while preparing reports comply with 14644-1 will be used for ISO Class 5.

By using M descriptor, the 5 micron value within GMP Appendix 1 will be indicated.

ISO *M* (*a*; *b*); *c*

Where:

A. is the maximum permitted concentration of macro-particles (expressed in particles/m^3)

B. is the equivalent diameter of the macro-particles

C. is the specified measurement method (typically Light Scattering Airborne Particle Counter (LSAPC)).

For example, the Grade A at rest concentration of 20 particles/m^3 @ ≥5.0µm would be expressed as:

ISO M (20; ≥5.0 µm); LSAPC

The new M descriptor will be used to define the Annex 1 Grade A and Grade B and by using the existing ISO 14644-1 designation of airborne particle concentration (expressed as *ISO Class number; occupancy state; considered particle size(s)*.

Grade A

ISO 5; at rest, operational; ≥0.5µm
ISO M (20; ≥5.0µm); at rest, operational; LSAPC

Grade B

ISO 5; at rest; ≥0.5µm and ISO M (29; ≥5.0µm); at rest; LSAPC
ISO 7; operational; ≥0.5µm, ≥5.0µm

The Key Changes Can Be Summarized As:

1.Title of the ISO 14644-1 is changed from “Classification of air cleanliness” to “Classification of air cleanliness by particle concentration”.

2. The number of sampling points in the area is no longer calculated as the square root of the surface area formula but it is now taken from a given table A1. (See Appendix A)

3. Formula to calculate the particle concentration (Cn) in respective classification number is no longer used and the value is taken directly from the table.

4. Particles of 5 µm in ISO 5 class have been removed from the limit value table.

5. UCL calculation is not required. There is no need to perform an observation of all measuring points in the room. Each single measuring point is considered individually and has to meet the limit value.

6. The length of tubing used in particle counter should be less than 1 metre.

7. The classification number, the air sample volumes, measuring time as well as the cancellation criterion is not changed and remains as same to the version ISO14644-1:1999.

Cleanroom Construction Design to Validation

Cleanroom design and construction expertise is essential in providing a safe, clean environment. Critical processes such as the assembly of electronic components, manufacture of clinical products, pharmaceutical products and medical devices are carried out in clean room environments. The ISO 14644 and EU GMP standards exist to provide guidance for cleanroom design, construction and operation.

20 Years Of Experience

The design and installation process for a cleanroom or laboratory can be complex - therefore it is essential that you select a reputable company with experience within these environments.

Optimum cleanrooms provide expertise in the design of cleanrooms and laboratories. For more information contact our helpful team at optimum cleanroom

Optimum cleanrooms provide a complete turnkey service from design and build through to construction, commissioning and validation.

If you are refurbishing, expanding or looking to build a new cleanroom or laboratory facility speak to OPTIMUM for a cost effective solution to your laboratory or cleanroom project.

What does the recent ISO 14644-1:2015 update mean for particle counters?

The performance requirements of particle counter have been laid down in the ISO 14644-3 document since its first publication in 2005 and corresponds with ISO 21501-4.

ISO 21501-4 Determination of particle size distribution — Single particle light interaction methods — Part 4: Light scattering airborne particle counter for clean spaces.

In an effort to enhance confidence in the quality of cleanroom environments, the amended ISO 14644-1 document includes performance criteria for particle counters specified in ISO 14644-3 and provides a consistent test method for the calibration of particle counters.

Although many particle counters available in the market are designed for use in low particle concentration environments, some give inaccurate results in low particle concentration environments such as pharmaceutical grade cleanrooms. Therefore, particle counters developed for the less critical industrial applications may not meet the rigorous requirements specified in ISO 21501-4 and ISO 14644-3.

Calibration service should be based upon ISO 21501-4. According to this standard, the frequency and method of calibration should be based upon current accepted practice as specified in ISO 21501-4.
However, the standard also caters for non-compliant particle counters. The notes state:

"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."

ISO/GMP Cleanroom Hand Held Particle Counter

Well designed, compact and easy to configure hand held particle counter. Complete with full validation certificate and carry case.

Complies fully with the latest revision of ISO14644. suitable for ISO and GMP cleanrooms. The Airy Technology P311 stores 8,000 sample records that can be viewed on the unit or on a computer via USB cable. The P311 complies with ISO 21501-4 and includes a one year warranty. With excellent quality and reliable performance, the Airy Technology P311 is the best priced handheld particle counter in the market.

You can view a range of ISO14644 compliant particle counter here.

Appendix A

Table A.1 - Sampling locations related to cleanroom area	
Area of cleanroom (M^2) less than or equal to	Minimum number of sampling locations to be tested (N_L)
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
64	12
68	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
636	26
1000	27
>1000	See Formula (A.1)

Note 1: If the considered area falls between two values in the table, the greater of the should be selected.
Note 2: In the case of unidirectional airflow, the area may be considered as the cross section of the moving air perpendicular to the direction of the airflow. In all other cases the area may be considered as the horizontal plan area of the cleanroom or clean zone

Appendix B

The standard currently:

ISO14644-1	Classification of air cleanliness by particle concentration
ISO14644-2	Specifications for testing and monitoring to prove continued compliance with ISO14644
ISO14644-3	Test Methods
ISO14644-4	Design, construction and Start-up
ISO14644-5	Operations
ISO14644-6	Vocabulary
ISO 14644-7	Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)
ISO 14644-8	Classification of air cleanliness by chemical concentration (ACC)
ISO 14644-9	Classification of surface cleanliness by particle concentration
ISO 14644-10	Classification of surface cleanliness by chemical concentration
ISO 14644-11	DRAFT
ISO 14644-12	DRAFT - Classification of air cleanliness by nanoscale particle concentration
ISO 14644-13	Cleaning of surfaces to achieve defined levels of cleanliness in terms of particle and chemical classifications.
ISO 14644-14	Assessment of suitability for use of equipment by airborne particle concentration.