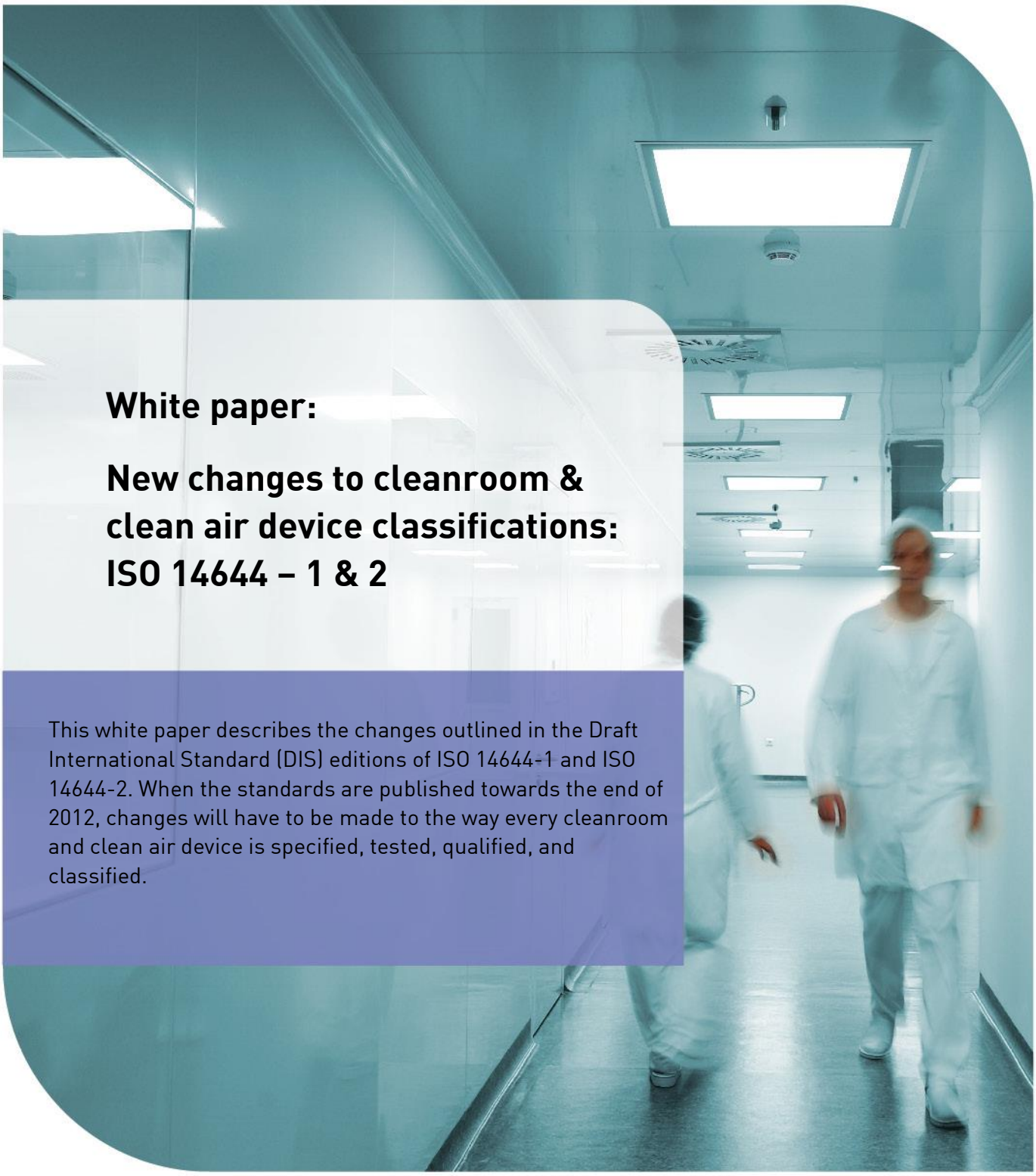

White paper:

New changes to cleanroom & clean air device classifications: ISO 14644 – 1 & 2

This white paper describes the changes outlined in the Draft International Standard (DIS) editions of ISO 14644-1 and ISO 14644-2. When the standards are published towards the end of 2012, changes will have to be made to the way every cleanroom and clean air device is specified, tested, qualified, and classified.

PharmOut®

MKT_TMP200_01_r06

Reasons for the change

On the 2nd May 2011, the draft revisions of the two most important cleanroom standards were approved with comments. This white paper provides a 'heads-up' on the proposed changes to:

- ISO 14644-1:1999 Cleanrooms and Associated Environments – Part 1. Classification of Air Cleanliness
- ISO 14644-2:2000 Cleanrooms and associated controlled environments — Part 2. Specifications for monitoring and periodic testing to prove continued compliance with ISO 14644-1:1999.

All classified cleanrooms and clean air devices will be impacted when the standards are published in 2012.

ISO 14644-1:1999

ISO Technical Committee 209 has been working on the revision of the basic airborne cleanliness classification standard for the last 5 years. The ISO community voted in favour 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 locations).
- Review the classification procedure and make it more applicable to rooms in operation. In this situation, the contamination isn't 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.

ISO 14644-2:2000

The same technical committee has also been working on the revision of the ISO 14644-2:2000 in conjunction with the revision of ISO 14644-1. The ISO community voted in favour of the revision to improve the standard to:

- Simplify and clarify requirements 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.

Details of the changes

Classification limits in ISO 14644-1

Slight modifications have been made to the specification limits for some of the 9 ISO cleanroom classifications, as indicated in the table below.

Table1: The basic classification table proposed in ISO (DIS) 14644-1:2010. Concentration limits in brackets indicate requirements from ISO 14644-1: 1999 that have been removed in the new version.

ISO Classification Number (N)	Maximum concentration limits (particles/m^3)					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
ISO Class 1	10	(2)				
ISO Class 2	100	24	10	(4)		
ISO Class 3	1 000	237	102	35	(8)	
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

Of particular note for the pharmaceutical and related industries is the removal of 5.0□m particle specification limits for ISO 5 areas. While this is a significant shift and one which may have future ramifications for these industries, manufacturers need to be aware that the current PIC/S and EU GMP codes still require assessment of this particle size for both classification and monitoring events.

Classification methodology

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 "N-L = √A" from the 1999 version of the standard. For all room sizes above 6m2, the new table results in an increase in required sample locations.
- The 1999 standard required that sample sizes of 2-9 include a confidence limit calculation. 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 in compliant at a 95% confidence limit.

Table 2: Number of sample locations required with respect to cleanroom area.

Area (m^2) Less than or equal to	Min number of sample locations	Area (m^2) Less than or equal to	Min number of sample locations
2	1	72	14
4	2	76	15
6	3	104	16
8	4	108	17
10	5	116	18
24	6	148	19
28	7	156	20
32	8	192	21
36	9	232	22
52	10	276	23
56	11	352	24
64	12	436	25
68	13	500	26

Semi-random sampling

- Like the 1999 standard, the draft standard requires the room to be divided into the relevant number of sub-divisions. However, the new standard requires that measurements be taken at random from within each sub-division, and that location should be newly randomized at each classification. The 1999 standard allowed the sample locations to be the same at each classification.
- The standard also allows for locations, identified as high risk, which may be sampled in addition to the randomized sample locations.

Acceptance Criterion

Classification according to the 1999 standard passed if the average of all the samples met the specification limits. However, the draft standard requires that all samples meet the limits.

Parameters have been chosen intending to obtain a reasonable balance between the theoretical formulation of the sampling process and practical experience, including the general practice applied with the1999 standard.

The effect of these three changes provides a risk based approach which is statistically superior to the method in the 1999 standard. While it may require a higher level of sampling, it is also simplified and easier to understand than the previous version.

Changes to ISO 14644-2

The changes to ISO 14644-2 include some new requirements, but largely update the standard to conform to current industry best practice. The following key changes are noted.

Requirements

- The draft standard clearly identifies that there is a difference between routine strategic testing and real-time monitoring, which was absent in the 2000 version.
- Formal classification testing must be undertaken annually, as a minimum - except where real-time air cleanliness monitoring and room pressure differential demonstrate ongoing control AND where industry regulation allows longer period (that is, not within the pharmaceutical or related industries).

New guidance annexes

- The draft standard includes new guidance annexes on monitoring which acknowledge and allow for the use of permanent fixed systems as well as portable instruments.
- There is a new guidance annex which lists the aspects that should be considered when specifying a real-time particle monitoring system. The scope of this guidance ranges from identification of critical sample locations, through to how the data collected will be evaluated and reported, and the acceptance/rejection criteria. A similar style of guidance is given for room pressure differential monitoring systems.
- A separate new annex provides guidance on monitoring air volume or air velocity in air treatment systems.

How does this affect you?

Manufacturers who perform their own classification will need to become familiar with the new standard, as existing methodology will no longer be sufficient to comply with the classification requirements.

Where a manufacturer uses a third party for classification, it is still the manufacturer's responsibility to ensure that classification work is conducted according to the current applicable standard. As a result, it is important to work together with contracted parties to ensure that the current standards are applied.

Manufacturers should also review quality management systems, as updates to policies, procedures and specifications may be required as a result of the changes.

References

Hartvig, et al. *Sampling Plan for Cleanroom Classification with respect to Airborne Particles*, European Journal of Parenteral and Pharmaceutical Sciences, 2011, 16(I).

Sources

Links used within this document are prone to change. Please refer to the appropriate source for the most recent information. We endeavour to keep an up-to-date record of information at www.pharmout.net

PharmOut is an international GMP consultancy serving the Pharmaceutical, Medical Device and Veterinary industries. PharmOut specialises in PIC/S, WHO, United States FDA, European EMA, and Australian TGA GMP consulting, engineering, project management, training, validation, continuous improvement and regulatory services.

Our team includes international GMP experts who have previously held leadership roles within regulatory bodies.

For more information please visit www.pharmout.net or contact us at info@pharmout.net.

PharmOut Pty Ltd, ABN: 85 117 673 766, Unit 10, 24 Lakeside Drive, Burwood East, Victoria 3151.
Ph: +61 3 9887 6412, Fax: +61 3 8610 0169, Email: info@pharmout.net Web: www.pharmout.net