



Changes to GMP force cleanroom re-classifications

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OVERVIEW

According to both USA cGMP¹ and EU GMP² cleanroom classification should be carried out according to ISO 14644-1. The 1994 version of this ISO standard has been re-written by a group of international subject matter experts and ISO 14644-1:2015⁶ was published on December 15, 2015. ISO 14644-1:2015 contains substantial revisions impacting both the way the cleanrooms are classified and the performance requirements of the air particle counting instruments used to carry out the classification. Cleanroom users claiming compliance to cGMP and/or GMP will have to consider these new rules when next re-qualifying their cleanrooms, potentially purchasing new air particle counters if their existing counters do not comply with the new performance rules and facing the dilemma that the new re-qualification may indicate that their cleanroom is not operating at the grade they had achieved using the old classification process. This paper explains the new rules.

Introduction

Although EU GMP and USA cGMP both define the airborne particle counts/m³ for each cleanliness class/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. At the same time, the ISO committee decided to add a reference in the normative Annex on airborne particle counters to

ISO 21501-4⁵, which provides a calibration procedure and verification method for particle counters, intended to minimize the inaccuracy in the measurement result by a counter, as well as the differences in the measured results from different particle counters. The stringent performance rules in ISO 21501-4 mean that many older air particle counters are no-longer suitable for cleanroom classification/re-qualification according to ISO 14644-1.

Cleanliness Classes/Grades

There are fundamental differences between the USA cGMP and the EU GMP documents for cleanroom classes/grades. The foremost difference is that the EU GMP requires the cleanroom user to classify and subsequently monitor their cleanrooms for airborne particles ≥ 0.5 microns in size and also ≥ 5 microns in size, whereas the USA cGMP only requires the user to classify and subsequently monitor their cleanrooms for airborne particles ≥ 0.5 microns only.

As can also be seen from the tables in Fig. 1 and 2, cGMP does not define airborne cleanliness levels for each cleanroom Class when the cleanroom is at rest, whereas GMP differentiates between these two states.

The third major difference between the two documents is that cGMP has an additional Class between Class 100 (equivalent to GMP Grade A) and Class 10,000 (equivalent to GMP Grade B in operation) and GMP has an additional Grade D, defined as having $\leq 3,520,000$ particles ≥ 0.5 microns at rest.

Clean Area Classification (0.5 μm particles/ft ³)	ISO Designation	$\geq 0.5 \mu\text{m}$ particles/m ³	Microbiological Active Air Action Levels (cfu/m ³)	Microbiological Settling Plates Action Levels (diam. 90mm; cfu/4 hours)
100	5	3,520	1	1
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

Figure 1. Cleanroom Classes as defined in USA cGMP

	Maximum permitted number of particles per m ³ equal to or greater than the tabulated size			
	At rest		In Operation	
Grade	0.5 μm	5.0 μm	0.5 μm	5.0 μm
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

Figure 2. Cleanroom Grades as defined in EU GMP

The Changes to ISO 14644-1

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

1. Change to the method for calculating number of sample locations for classification/re-qualification
2. Elimination of the 95% Upper Confidence Limit (UCL) calculation
3. 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)
4. Removal of the maximum allowable concentration of airborne particles/m³ ≥ 5 microns for ISO Class 5 from the Cleanliness Classes table (ISO Class 5 at ≥ 5 microns is equivalent to GMP Grade B at rest)

The new method for calculating the number of sample locations now relies on a look-up table where the number of locations per cleanroom size is defined as opposed to the current method that calculates the number of locations based on the square root of the cleanroom floor area. In order to achieve a pragmatic level of statistical accuracy, the number of sample locations required for classification/re-qualification has been increased, i.e. cleanroom users will have to increase the number of sample locations for cleanroom classification/re-qualification. As per the ISO 14644-1:1999 document, ISO 14644-1:2015 states that the sample locations should be spaced out evenly across the cleanroom on an equally-spaced grid.

The requirement for the new sample locations could lead to confusion in particle counter users who are used to following the same classification/re-qualification routine, especially for those with multiple cleanrooms and multiple air particle counter users. Cleanroom owners could attempt to mitigate the chances of resultant data errors/miss sampling by choosing to use air particle counters that can be programmed with the new cleanroom sampling program so that the user is prompted to take the correct number of samples using the correct particle counter configuration in each cleanroom Grade. The same opportunity for confusion and potential resultant mistakes would apply to any form of manual data transfer from paper print outs from the particle counters to Excel* or a laboratory information management system (LIMS). Cleanroom owners could choose to mitigate the risk of data transfer errors by choosing particle counters that can transfer the particle count data via wireless Ethernet in Excel readable format straight to their secure data server or LIMS systems (visit <http://www.particle.com/met-one-air-particle-counters/portable/met-one-3400-simply-paperless> for more information on particle counters with these capabilities)

By increasing statistical accuracy through a larger number of sampling locations, the ISO 14644-1:2015 document also eliminates the need for the UCL calculation which was previously required for cleanrooms requiring between 2 and 9 sample locations. Provided all sample locations are within the Class/Grade requirements, there is no longer any need to perform the UCL calculation.

ISO 21501-4 lays down the calibration procedures to ensure that air particle counter sampling measurement inaccuracies are reduced. It also includes a final confirmation of air particle counter performance, the Counting Efficiency test. This compares the performance of the particle counter under test against an instrument with a higher resolution of around 0.3microns. Both the counter under test and the higher resolution instrument are challenged with an air sample containing certified particles at the smallest calibration size for the counter under test, typically 0.5microns for GMP applications. As the certified particles will have an expected Normal (or 'Gaussian') size distribution profile, 50% of the certified particles will be ≥ 0.5 microns and 50% will be ≤ 0.5 microns, hence the counter under test must count and report that 50% of the airborne particles are ≥ 0.5 microns, whereas the instrument with the higher resolution should report 100% of the airborne particles as being ≥ 0.3 microns. Hence the higher resolution counter will count the entire particle population, allowing the ability of the counter under test to accurately report that 50% of the certified particles are ≥ 0.5 microns (see Fig. 3).

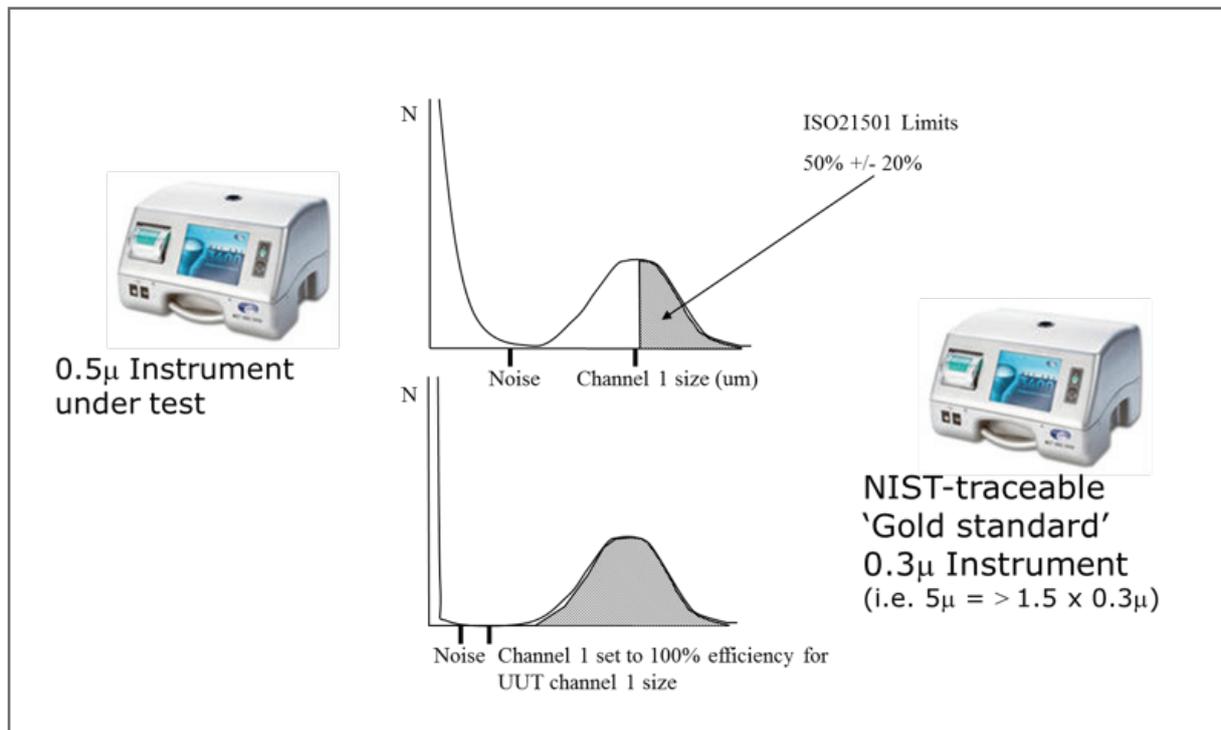


Figure 3. The ISO 21501-4 Counting Efficiency Test

In another move to improve the statistical accuracy of the classification/re-qualification, the international subject matter experts tasked with re-writing the standard decided to remove from the Cleanliness Classes table numbers of particles that were too small to be considered statistically sound. Controversially, this was extended to include the 29 particles/m³ for ISO Class 5 for particles ≥ 5 microns, potentially undermining the EU GMP requirement to measure these particles in Grade A and Grade B environments.

Implications for the GMP Cleanroom Community

Thanks to the undated reference to ISO 14644-1 in the GMP and cGMP documents, to the new ISO 14644-1:2015 will impact on every cleanroom user in the GMP community.

All GMP cleanroom users will have to make changes to their cleanroom classification/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/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.

Conclusion

The changes to ISO 14644-1 represent possibly the biggest change to GMP cleanrooms since the requirement to sample 1m³ at each and every sample location when classifying/re-qualifying Grade A environments was introduced to GMP Annex 1 in 2003. The GMP cleanroom community would be wise to start planning for these changes now rather than waiting 'till they are inspected to the ISO 14644-1:2015 document.. (visit <http://www.particle.com/met-one-air-particle-counters/portable/met-one-3400-simply-paperless> for more information on particle counters designed to support the new ISO 14644-1 and ISO 21501-4 requirements)

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Biography

Tony held the Convenorship of the ISO Working Group revising ISO 14698-1 & -2 for microbial control in cleanrooms and is the UK subject matter expert to the ISO Working Group currently revising ISO 14644-1 & -2 for cleanroom classification at the heart of the aseptic manufacturing chapters of both the European GMP and the USA cGMP documents.

Tony holds a Bachelor's Degree in Electrical & Electronic Engineering and is employed by Beckman Coulter Life Sciences as a Senior Marketing Manager.

Experienced in water system TOC, conductivity and ozone analysis and cleanroom monitoring systems as well as particle characterisation, Tony has spent the last fifteen years in applied metrology for the pharmaceutical and healthcare manufacturing industries. Prior to that, he worked for companies providing process control automation solutions for manufacturing industries.

Tony was joint-editor on the ISPE Guide to Ozone Sanitization of Pharmaceutical Water Systems and was also chief editor of the PHSS Best Practice Guide for Cleanroom Monitoring.

Tony is a well-known international speaker and has provided educational seminars on TOC, liquid particle counting, ozone sanitization for water systems and cleanroom monitoring in UK, France, Italy, India, Malaysia, China, USA, Scandinavia, Ireland, Hungary, Switzerland, Indonesia, Belgium, Greece, Switzerland, Turkey, Egypt, Denmark and most recently Poland and Italy.



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