ISO 14644-1:2015 Revision Frequently Asked Questions

The newly updated ISO 14644-1:2015 has caused some confusion and raised concerns by companies who want to ensure that they are fully compliant. To address these issues, Particle Measuring Systems is sharing our industry expertise and have provided an ISO 14644-1:2015 summary paper, an on-demand webinar, and are now providing you with answers to many of the questions that our customers frequently ask. If you have further questions, please reach out to us directly.

Questions have been organized into the following topics:

TOPIC: SAMPLING LOCATIONS

How is the number of sampling points calculated? Why is the number of sampling points predefined when the zone area is less than 1000 m^2?

The new Table A.1 is pre-calculated to eliminate the need for evaluating the UCL 95%.

This approach results in a general increase of sample locations required for most cleanrooms, which consequently results in a lower impact of the old UCL factor listed in the T-Student table available in the FS209E standard.

The new approach allows each location to be treated independently with at least a 95% level of confidence that at least 90% of cleanrooms will comply with the maximum particle concentration limit.

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What is the rationale for the adjustment of sampling locations in the new standard?

In general, the increase of the sampling points required by the new regulations causes the correction factor UCL, present in the T-Student table of the old FS-209E and ISO 14644-1:1999, to be greatly reduced .

In fact, with the increase of sampling points, the correction factor decreases to one for sampling rates greater than 9 points.

This evaluation allows the reduction and simplification of calculations for particulate sampling assessment, thanks to the removal of the 95 % UCL. This is at the expense of an increase in sampling points.

Another important factor that determines the increase in points is related to a more “mature “ approach to particle contamination assessment that is in the new standard. It is no longer recognized as homogeneous inside the cleanroom, but variable. It follows that there is a need of more significant sampling for the general evaluation of the class.

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If I am working within a cabinet, is the sample area size based on the size of the cabinet?

Yes, the sample point selection in an air flow cabinet uses the same approach, with a complete evaluation of the cabinet area to define the number of sample points.

A risk analysis of specific operational conditions can help determine the correct number of sample locations, based on the activities performed and their associated risk.

You must meet or exceed the standard requirements by using either the recommended number of sample locations required, or more. You may not use less.

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Suppose the room requires 10 locations to be sampled. Does a cubic meter sample need to be taken at every location?

The single sample location volume may be different based on the cleanroom class you select and the particle size you want to control.

The ISO 14644-1:2015 standards provide a specific formula for calculating the correct sample volume in the paragraph labeled *A.4.4 Establishment of single sample volume and sampling time per location*.

The single sample volume, V_s, per sampling location is determined by using Formula A.2:

$V_s = (20 / C_{n,m}) \times 1000$

where:

V_s is the minimum single sample volume per location, expressed in liters (see Annex D).

$C_{n,m}$ is the class limit (number of particles per cubic meter) for the largest considered particle size specified for the relevant class.

20 is the number of particles that could be counted if the particle concentration were at the class limit.

The volume sampled at each location shall be at least 2 L, with a minimum sampling time of 1 min for each sample at each location. Each single sample volume at each sampling location should be the same.

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Is the report of particles per cubic meter for each of the required sample locations sufficient for compliance? What other data must be reported?

The ISO 14644-1:2015 lists the minimum required information for a compliance test report (see Section 5.4).

In order to provide detailed particle numbers, it is required to clearly report the concentration level in particles per cubic meter for each single location and, for multiple locations sampled, required to average the total concentration.

Single location values and averaged results should not exceed the value reported in Table 1, used for classification.

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Does the new guideline include changes in the length of the sampling pipe?

The ISO 14644-1:2015 provides the following recommendation:

For sampling of particles larger than and equal to 1 µm, the transit tube length should not exceed the manufacturer's recommended length and diameter, and will typically be no longer than 1 m in length.

You can find several documents and application notes related to this topic on our website, including an evaluation of particle loss in tubing.

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What steps are required when a location fails in the cleanroom several times?

In the case of a repeatedly failing particle test, it is recommended to investigate the possible source of contamination with the performance of additional tests, as described in ISO 14644-3.

For example, you should investigate the efficiency of HVAC systems, filters, etc, to eventually understand why the particle concentration is exceeding the expected limits.

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How is the new hypergeometric sampling distribution executed?

Hypergeometric sampling distribution is one of the most significant changes in the new standard. The standard adopted a more consistent statistical approach to the selection of the sample location number and the evaluation of data collection.

The adoption of a hypergeometric sampling model technique means that samples are drawn randomly, despite the previous ISO 14644-1:1999 where the assumption was that particle concentration followed the same normal distribution across the room.

With this more "mature" approach in mind, the cleanroom or clean zone area is divided up into a grid of sections of near equal area, whose number is equal to the number of sampling locations derived from Table A.1.

A sampling location is placed within each grid section, so as to be representative of that grid section. Locations are chosen representatively. A "representative" location (see A.4.2) means that features such as cleanroom or clean zone layout, equipment disposition, and airflow systems should be considered when selecting sampling locations.

Generally, the selection of sample points should also be supported with a formal risk analysis.

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TOPIC: RISK ANALYSIS

What is the procedure for conducting a risk analysis to determine the sample locations and classification of a cleanroom? Who is responsible for its completion?

A good resource detailing the correct approach and management of risk assessment is the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline, *Quality Risk Management*, Q9.

Click here to directly access this document.

Also, another helpful document is available on our website, where you can find some suggestions for selecting the best non-viable location for monitoring purpose.

A risk analysis can be performed by the company's Quality Assurance team or with the help of an external consultant company. Particle Measuring Systems also offers worldwide consultancy to help customers meet their standard requirements (including ISO, GMP, FDA, etc.).

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Is it possible to have less than the number of sampling locations specified by the new guidelines with justification/rationale performed in a risk assessment?

The number of sampling locations in the classification process must be equal to or greater than the new number reported in the ISO 14644-1:2015 table.

Additional sample points can be measured if necessary, but any number less than the specified sample locations is not allowed with the ISO standard.

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Should a risk analysis be added to existing systems to show that sample points are now and were previously in the right spots? What if it shows that they were not in the past?

Normally, any decision for location, procedure, evaluation etc. should be supported with a risk analysis.

The previous standard did not specifically require the location of sample points in a representative manner. The new standard requires the support of a rational risk assessment for any future decision in the cleanroom classification process.

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TOPIC: CLEANROOM MONITORING, CLASS AND LIMITS

When monitoring the clean area, which limits need to be used (like EU/ISO)?

The monitoring guidelines are reported in ISO 14644-2:2015.

The ISO standard does not provide specific limits for monitoring of particle concentrations, and instead is used for classification purposes.

Alert, warning, and action limits need to be established as described in ISO 14644-2, Annex B, and are generally based on trend contamination analysis and risk assessment.

The evaluated level should not exceed the ISO 14644-1 cleanness class limits.

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What are the limits for particle counts at rest and dynamic conditions?

Classification limits for At Rest and Operational states are equal. The limit table is unique for all the three allowed scenarios: As Built – At Rest – Operational.

For monitoring, the ISO 14644-2:2015 standard requires the At Rest limit to be considerably lower than the Operational occupancy state limit.

Per ISO 14644-1, the air cleanliness class by particle concentration of air in a cleanroom or clean zone shall be defined in one or more of three occupancy states: “as-built”, “at-rest” or “operational”.

You are not obligated to measure every condition for the classification, but it is recommended to keep the particle contamination impact of operators under control.

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What is the limit for 1.0 µm and 5.0 µm in ISO Class 5?

The ISO 14644-1 standard does not necessarily require the use of more than one particle size for classification purposes, except when verifying the particle contamination at 5 µm. In this case, at least one other size must be selected and reported.

Particle sizes at 5 µm can be evaluated using the M-descriptor with the methodology described in the ISO standard’s Appendix C.

In order to continue evaluating large particle contamination, you can refer to Appendix C of the standard and define your specific particle limits if applicable.

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Is the cleanroom ISO class determined with the average of single location concentrations or should the average number of particles in each location be considered?

It is required to clearly report the concentration level in particles per cubic meter for each single location and, in case of multiple locations sampled, you are also required to average the total concentration.

Single location values and averaged results shall not exceed the value reported in the classification Table 1.

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Is it mandatory to consider 5 micron particles for a ISO class 6 cleanroom?

The ISO 14644-1 standard do not specifically require which channels to be sampled for the specific ISO class.

It is up to the clean room user to evaluate and determine which particle size may interfere with the quality of production and then include it in the formal particles contamination control.

ISO class 6 provides limits for particle sizes at 0.1, 0.2, 0.3, 0.5, 1.0, and 5.0 microns, so you should select one or more sizes and compare the sample results to the provided limits.

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If I need to compare the GMP Grade A to ISO Class 5 for 5 micron particles, will I need to take two different counts?

The ISO 14644-1 standard eliminates the 5.0 micron particle limit in the new 2015 standard.

In order to continue evaluating large particle contamination, refer to Appendix C of the standard and define your specific particle limits if applicable.

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Should I re-perform a qualification for existing cleanrooms based on the new standard?

An existing cleanroom shall be certified using the new standard in accordance with your actual control plan. Until the next scheduled control process, you can consider the previous cleanroom qualification (normally performed within the last 12 months) valid.

The new ISO 14644-1:2015 shall be applied from the next certification activity you perform in 2016.

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How is the M-descriptor used?

The Macro particle descriptor is used when the particle size is greater or equal to 5 µm, representing a considerable risk for the specific environment.

In this case, the cleanroom user must establish a particle concentration limit in accordance with a risk assessment for the control of the cleanroom.

Additional information and examples for the Macro descriptor are available in ISO 14644-1:2015, Appendix C.

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When should an intermediate class be applied (found in Annex E, Table 1)?

There is no specific scenario where the intermediate classes are required.

This method can be applied to demonstrate higher cleanroom performance, if the particle concentration is unsuitable for the immediate lower class in addition to reaching a higher range.

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TOPIC: ISO 21501 AND CALIBRATION

Can a particle counter calibrated in a previous way still be used for monitoring?

No, the ISO14644-2:2015 which describes the monitoring guidelines, also requires the use of an ISO 21501-4 compliant particle counter for monitoring as well.

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In the ISO 21501, there is a test on concentration limit. Is the destructive test on the particle counter considered?

The maximum allowed concentration limit test is performed at the instrument design and development stage. As required by the standard, this is not repeated for each instrument as long as the same hardware components are used for any single particle counter.

The additional reason why this test is not replicated at each calibration is due to the risk of optical cell contamination, with requires it be opened for cleaning.

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What is the counting accuracy of an aerosol particle counter?

It is described in the instrument specification sheet and must be compliant with the ISO 21501-4.

For example: Sizing error must be within 10%.

Additional information is available in the Particle Measuring Systems “Understanding 21501-4” application note (Life Science and Electronics versions).

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Are P/FT³ particle counters ISO 21501-4 compliant ?

The ISO 21501-4 compliance of a particle counter is not related to flowrates or particle normalization methods, but to the calibration methodology used.

You can find additional information about the ISO 21501 with this link.

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What technical performance improvements have been made to the newest particle counters (calibrated to ISO 21501-4) that make them superior compared to older units?

The ISO 21501-4 compliant particle counters incorporate modern technology for light scattering control. PMS particle counters also incorporate better flowrate sensor accuracy using volumetric evaluation instead of mass flow readings and, as required by the standard, they incorporate a PHA (Pulse Height Analyzer) which provide a more accurate evaluation of particle pulses.

Additionally, all the ISO 21501-4 compliant instrument are calibrated using the same approved standard and specific tolerance as to minimize the inaccuracy of the instruments.

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TOPIC: ISO TECHNICAL COMMITTEE TC-209

Is the TC-209 still active following the most recent revision of ISO 14644, and if so, what is their current focus?

The ISO committee TC209 works for ISO 14644 standard updates and will continuously work for harmonization of standards included in the 14644 documents. The next meeting is scheduled for September 2016. Click here for more information about the active projects of the ISO TC 209 committee.

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Are there still companies operating under the Federal Standard 209E and is there a significant cost difference to them converting to the ISO 14644?

The FS209E was canceled on November 2001 and replaced by the ISO 14644-1/2.

Below if the official notification extract.

NOTICE OF CANCELLATION FED-STD-209 NOTICE 1

November 29, 2001

FEDERAL STANDARD

AIRBORNE PARTICULATE CLEANLINESS CLASSES

IN CLEANROOMS AND CLEAN ZONES

Federal Standard 209E dated September 11, 1992 is hereby canceled and superseded by International Organization for Standardization (ISO) Standards. International Standards for Cleanrooms and associated controlled environments, ISO 14644-1 Part 1: Classification of air cleanliness; and ISO 14644-2 Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1. Application for copies of ISO Standards 14644-1 Part 1, and 14644-2 Part 2; may be addressed to the Institute of Environmental Sciences and Technology (IEST), 940 East Northwest Highway, Mount Prospect, IL 60056-3444. Phone: 847-255-1561, Fax: 847-255-1699, Web site: www.iest.org, E-mail: publicationsales@iest.org.

Preparing Activity: GSA-FSS

FSC 3694

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TOPIC: PARTICLE COUNTERS

Is there new firmware for the Lasair II that is compliant with the new standards?

The Lasair II is not compliant with either ISO 21501-4 nor with the new ISO 14644-1:2015.

The ISO 21501-4 requires additional tests and hardware features not included in the Lasair II instrument family. This is because it was developed 10 years before the introduction of this standard. Unfortunately, this gap cannot be covered with just a firmware upgrade.

Moreover, the Lasair II is an obsolete instrument and actually out of its service date, so the Lasair II will not receive any further upgrade and support.

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How does the recent Lasair III firmware update work with the EU GMP classification for Grade A areas with the corrected ISO standard?

EU GMP Annex 1 provides specific particle concentration limits for specific cleanroom classes (Grade A, B, C and D). The Lasair III Aerosol Particle Counter, when used with GMP statistical mode, will refer to the GMP maximum concentration table.

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Is the current Lasair III model capable of tracking 1.0 µm? Will it require a firmware upgrade?

Each Lasair III particle counter is capable of tracking 1.0 µm particles without any additional upgrade or modification.

Make sure you have the instrument configured with all 6 channels active using the system configuration menu.

Alternatively, in order to have the new ISO standard statistical mode, including the new limits and sample point table, you will need the firmware upgrade available from our Service Labs.

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Can the Lasair II 550L be upgraded to be compliant with ISO 21501-4?

The Lasair II 550L cannot be upgraded to the new ISO certification requirements. This product has been obsolete since 2009 and it is recommended to upgrade to the fully compliant Lasair III. We can provide a quotation if you are interested in a new unit.

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*The **Lasair III**: Compliant with **ISO 14644-1:2015** and **ISO 21501-4.***

Learn how you can improve your highly regulated cleanroom monitoring.

TOPIC: APPLICATIONS

Does ISO 14644-1 apply to a solid dose facility?

Yes, ISO 14644-1 can be applied to this type of manufacturing area. You should verify which class and standard your cleanroom must be compliant with.

ISO 14644-1 is applicable for any type of cleanroom, including Pharmaceuticals.

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Has the new ISO had an affect on the number of the stationary particle counters (for monitoring) in a filling machine?

No, the number of continuous sample locations is not affected by the ISO14644-1. Monitoring control guidelines are available in the ISO14644-2 standards which clearly require a risk assessment based approach for the evaluation/selection of the sample location.

Use this document for suggestions in selecting the best non-viable location for monitoring purposes.

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Has ISO started to discuss the use of technologies to differentiate between biologic particles and non-biologic particles?

Absolutely, this is an ongoing process which will certainly become an official standard in the near future.

Particle Measuring Systems is actively working with the ISO technical group in order to create a suitable standard for this upcoming real-time microbial control technology.

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