

Understanding ISO 14644-1/2:2015 and Becoming Compliant

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Particle Measuring Systems

- What is ISO 14644?
- ISO 14644-1:2015 Cleanroom certification revision summary
 - Notable areas of changes
 - ISO 21501-4 Instrument Implications
- ISO 14644-2:2015 Cleanroom Monitoring revision summary
 - Monitoring Plan Alternatives
 - Risk Assessment
 - Alert and Action Limits
 - How to chose the right strategy
 - Learn from FDA 483 Warning Letters



- The recent revision of ISO 14644-1 and-2 has introduced several changes for cleanroom classification and monitoring guidelines.
- The ISO community voted in favor of this revision on October 29th, 2015.
- This presentation discusses those changes and how they affect you.
- Questions will be addressed at the end, but feel free to voice them as they come to mind.

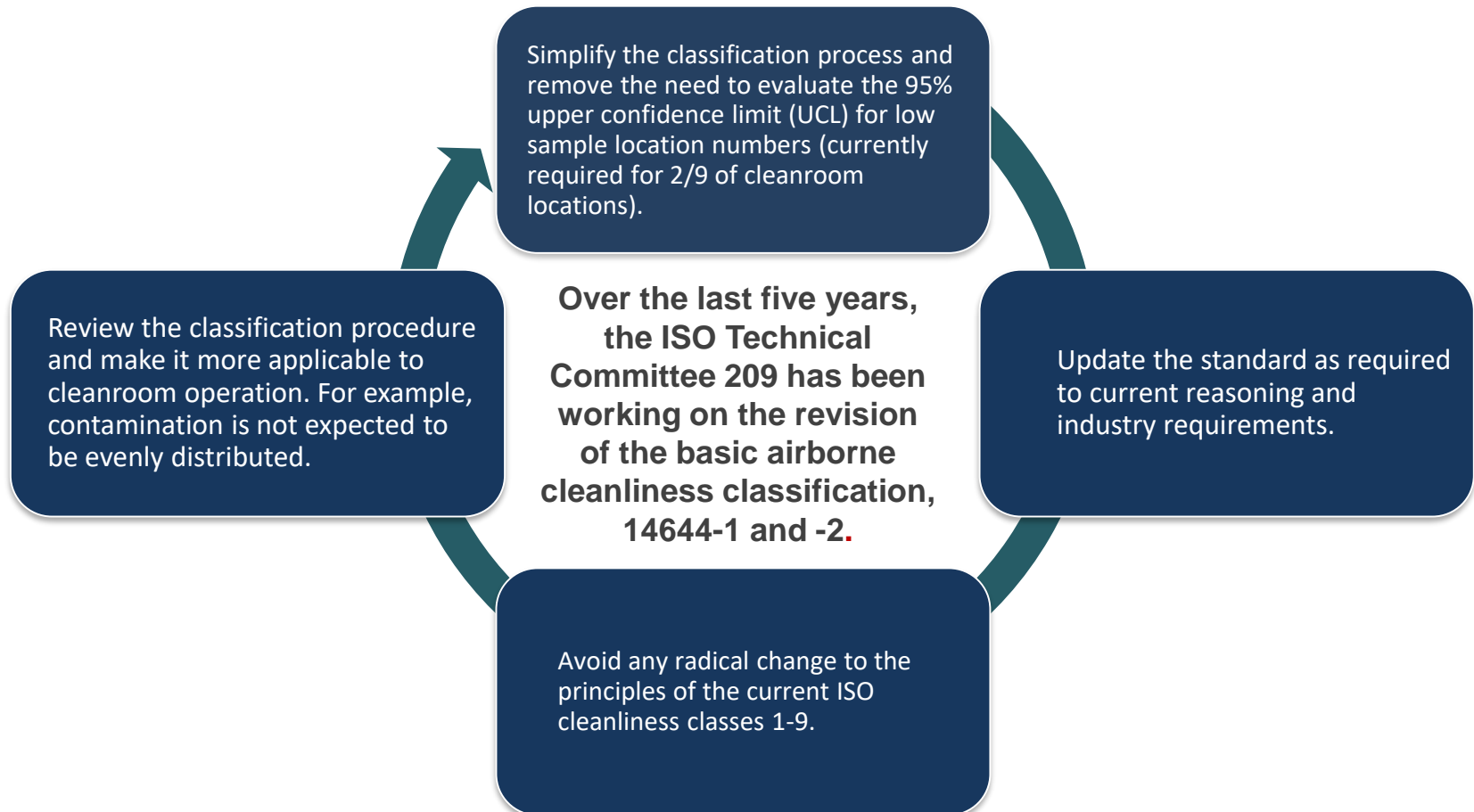
ISO14644 consists of the following parts:

- Part 1: Classification of air cleanliness by particle concentration
- Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration
- Part 3: Test methods
- Part 4: Design, construction and start-up
- Part 5: Operations
- Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)
- Part 8: Classification of air cleanliness by chemical concentration (ACC)
- Part 9: Classification of surface cleanliness by particle concentration
- Part 10: Classification of surface cleanliness by chemical concentration

ISO14644-1 is one of the most used standards in Pharma and Electronics controlled environments

- ISO 14644-1 specifies classes of air cleanliness in terms of the number of particles expressed as a concentration in air volume.
- It also specifies the standard method of testing to determine cleanliness class, including selection of sampling locations.

ISO14644-1:2015 Revision and Purpose



New 14644-1:2015 Revision Summary and Purpose



Notable areas of change:

- Number of Sample Locations
- Particle Concentration Limit
- Particle Counter Calibration

How to determine the number of sample locations:

- A new table has been developed for the determination of the number of sample locations, replacing
“Location Number = $\sqrt{m^2 \text{ room area}}$ ”
from the ISO 14644-1:1999 version of the standard.
- For all room sizes above 6 m², the new table results in an increase of required sample locations.
- The ISO14644-1:1999 standard required the 95% UCL (Upper Confidence Limit) calculation for sample locations between 2 and 9.
 - No longer required for the 2015 revision

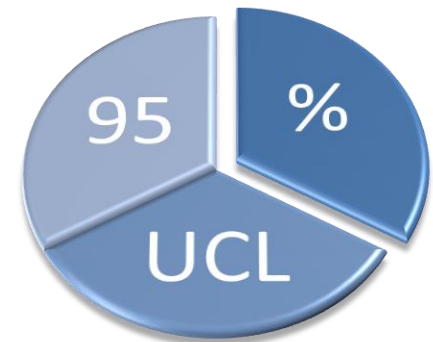
What this means to you:

- Sample location number calculations are now unnecessary.
- For all rooms smaller than 1000m² use the table.
- For all rooms larger than 1000m² use Formula A.1.

$$N_L = 27 \times \left(\frac{A \text{ m}^2}{1000} \right)$$

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

- 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 compliant at a 95% confidence limit.




The selection of each sampling location within each section shall be based on a location that is “representative of the characteristics” of each section.

Table 1 Selected airborne particulate cleanliness classes

ISO 14644-1:1999 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					
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	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

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Primary reasoning for the de-emphasis of the $\geq 5\mu\text{m}$ ISO Class 5 limit includes:

- Sampling and statistical limitations for particles in low concentrations make classification inappropriate.
- In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor 'M' may be adapted and used in conjunction with at least one other particle size.
- Sample collection limitations for both particles in low concentrations and sizes greater than $1\mu\text{m}$ make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

B.2.2 Instrument calibration

The instrument shall have a valid calibration certificate; the frequency and method of calibration should be based on current accepted practice.

14644-1:1999

A.2.2 Instrument calibration

The particle counter shall have a valid calibration certificate: the frequency and method of calibration should be based upon current accepted practice as specified in **ISO 21501-4**.^[2]

14644-1:2015

NOTE 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.

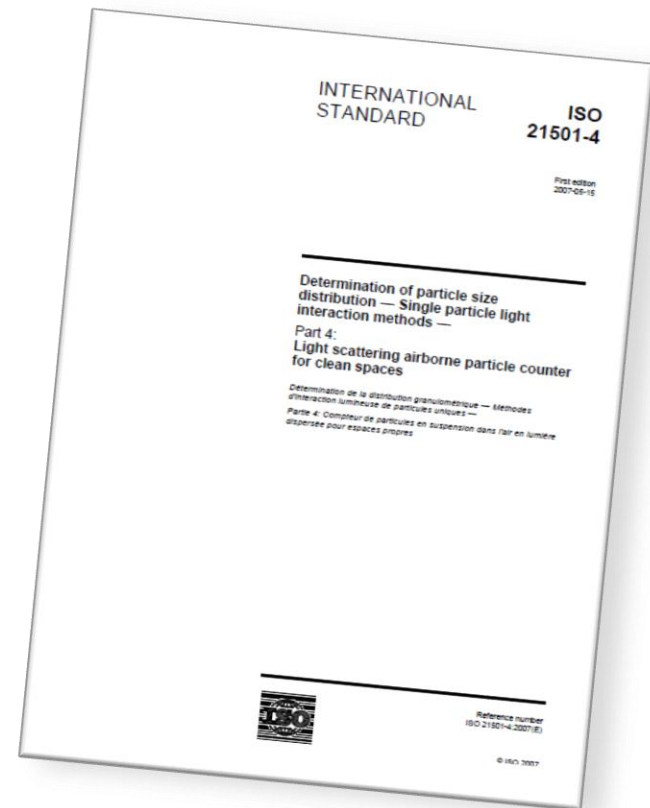
What this means to you:

You are expected to have instruments calibrated in accordance with ISO requirements.

Use of non ISO21501-4 compliant instruments will require additional and undesirable explanations to authorities.

What is ISO21501-4?

- The ISO 21501-4 is the worldwide-recognized standard for optical particle counter calibration.
- This standard was introduced by the ISO organization in 2007, and it is based on the following purpose --



ISO21501 Purpose:

- “...to provide a calibration procedure and verification method for particle counters, so as to minimize the inaccuracy in the measurement result by a counter, as well as the difference in the results measured by different instruments.”
- Four parts: ...-2 (LSLPC), -3 (LELPC), -4 (LSAPC) (LSAPC: Light Scattering Airborne Particle Counter)



Why is ISO21501 Important?

- The ISO 14644-1:2015 introduces the need of ISO 21501-4 particle counters, which assure all cleanroom certification is based on verified data accuracy and reliability.
- Cleanroom users shall then look to ISO 21501 as a method to meet cGMP, EU GMP, ISO 14644-1, and other requirements.
- This change to the ISO 14644-1 represents an important step in improving the accuracy of clean room contamination evaluation and aseptic process control.



- GMP guidance refers to ISO standards, making the standards a part of GMP guidance.
- The 2008 Annex 1 of the EU GMP and US FDA's 2004 Aseptic Processing Guidance refer to ISO 14644-1 and ISO 14644-2 without any specific date or revision. **This means the latest version always applies.**
- It is up to the GMP authorities to inform applicable parties of the grace period and implementation date of the revised standards.
- Users of cleanrooms should have a clear policy of migration to the new standards.



Where -1 describes how to certify, -2 describes how to monitor --

- ISO 14644-2 specifies the requirements of a monitoring plan based on risk assessment of the intended use. The data obtained provides evidence of cleanroom or clean zone performance related to air cleanliness by particle concentration.
- This revision of ISO 14644-2 emphasizes the need to consider a monitoring strategy in addition to the initial or periodic execution of the classification of a cleanroom or clean zone in accordance with ISO 14644-1:2015.

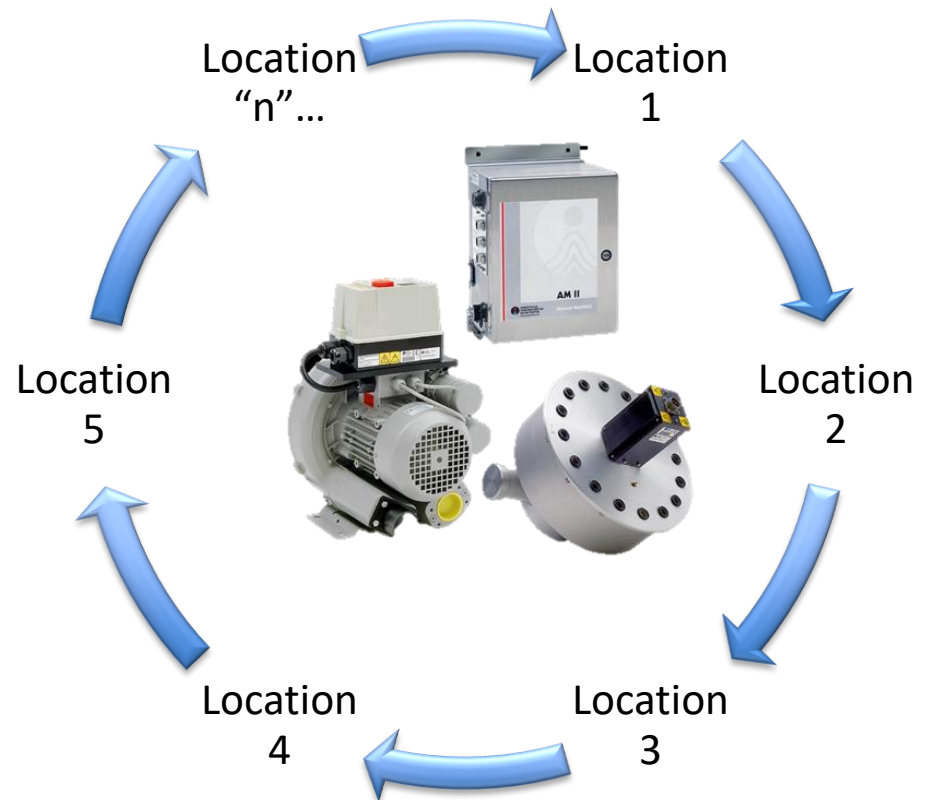
Monitoring

- Monitoring is an observation of the process made in accordance with a specific method, able to provide clear evidence of cleanroom performance.
- Monitoring can be “continuous”, “sequential” or “periodic”.



Sequential

- Performed using sequential multiplexing systems.
- Generally unacceptable for pharmaceutical industry
- High risk of particle loss in long tubing while measuring particles greater than $1\mu\text{m}$



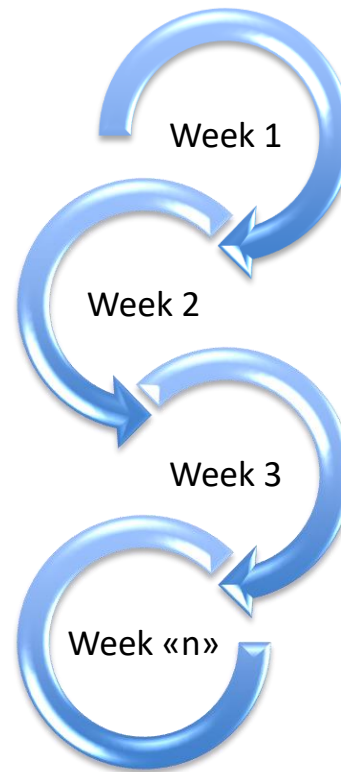
Continuous

- Uses multiple particle counters, one for each individual location
- Continuous flow of data over time
- Immediate evaluation of unexpected contamination events



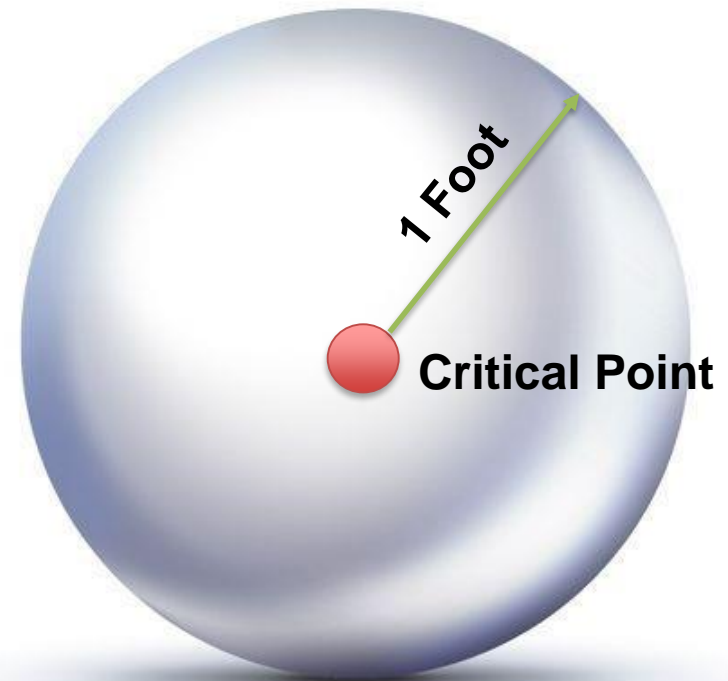
Periodic

- Scheduled particle monitoring frequency (i.e. once per week)
- ISO 14644-2:2015 requires the test frequency to be defined and clearly specified



Sample Point Location

- Understand the contamination sources and their impact on the activity in the cleanroom
 - Based on formal risk assessment
 - Locate particle counter probes as close as possible to critical zones
- Maximum allowed distance
 - 1 foot = 30cm



Instrument Selection

- Airborne particle collection efficiency, suitability to monitor the selected particle size(s), and accessibility for maintenance, calibration, and repair
- Potential adverse impact of the sampling system on the process
- Air sample flow rate and volume
 - 1 cfm / 28.3 lpm commonly used



Risk Assessment

- A formal risk assessment is an essential requirement for implementing a compliant monitoring plan

Goals

- Correctly understand:
 - the process
 - critical areas/locations
 - possible sources of contamination
 - elements that may compromise
 - cleanroom performance or
 - product quality

A typical risk assessment looks at:

- Operator movement
- Previous cleanroom certifications
- Areas where the product is particularly at risk



Action Level

Alarm level at which, when exceeded, will require immediate intervention, root cause investigation and corrective actions



Alert Level

Alarm level defined to provide early warning of a drift from normal conditions.

This level should be used to prevent action level conditions.



How to choose the right strategy

- ISO 14644-2:2015 states the importance
 - long term evaluation
 - yearly assessment of limits, method and frequency
- Yearly assessment does not always mean yearly change!
- Frequently question whether monitoring plan is still applicable and consistent with the cleanroom's actual performance and activities.

How to choose the right strategy

The standard provides some important recommendations, as well as an applicable strategy to keep in mind when setting alert and action limits. One with high significance is provided in the paragraph B.3.1.2, quoted below:

- ...it is important to be sensitive to the high variability of airborne particle concentrations with time and at different locations ... Frequent “nuisance” alarms should be avoided as they can lead to alarms being ignored by users.

483 Letter Extract

...Regarding the increased non-routine surveillance monitoring performed to further evaluate the Building “123456” manufacturing facility, there was no plan in place specifying the locations to be tested, method of sampling, and actions to be taken when microbial contamination was noted...

Comments

Monitoring results are considered insufficient if they don't support and link to a clear and approved plan.

483 Letter Extract

*...the alert and action limits
established for the
manufacturing areas are
not based on historical
data taken from the EM
Program...*

Comments

This warning letter, dated 2001, requires the cleanroom user to proactively and critically review the sampling historical data, as it must be referenced to correctly set up the appropriate alert and action levels.

- The new changes described here will impact cleanroom classifications and monitoring. Any company that needs to comply with this standard is required to update their internal SOP in order to meet the new ISO 14644 requirements.
- ISO 14644-1/2:2015 are not only a new standards to be compliant with, but are also beneficial tools to use in achieving mature cleanroom environmental control.
- ISO 14644-1/2:2015 were published on December 15th, 2015. All users who want to be compliant with this standard are required to take necessary action immediately.