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Semiconductor Manufacturing Facility Design

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- Cleanrooms have a dirty little secret

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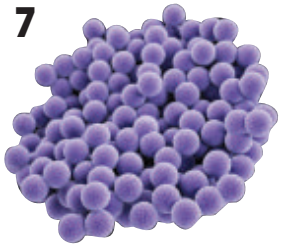
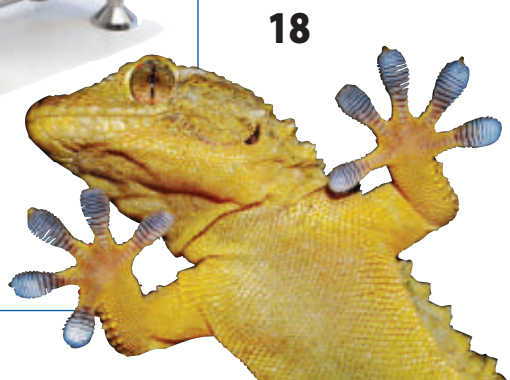
Texas Instruments' Richardson Fabrication Facility (RFAB). Credit for this image and cover image: Texas Instruments





The Implications of ISO/DIS 14644-1.2

How does this standard affect biopharma monitoring of clean areas?

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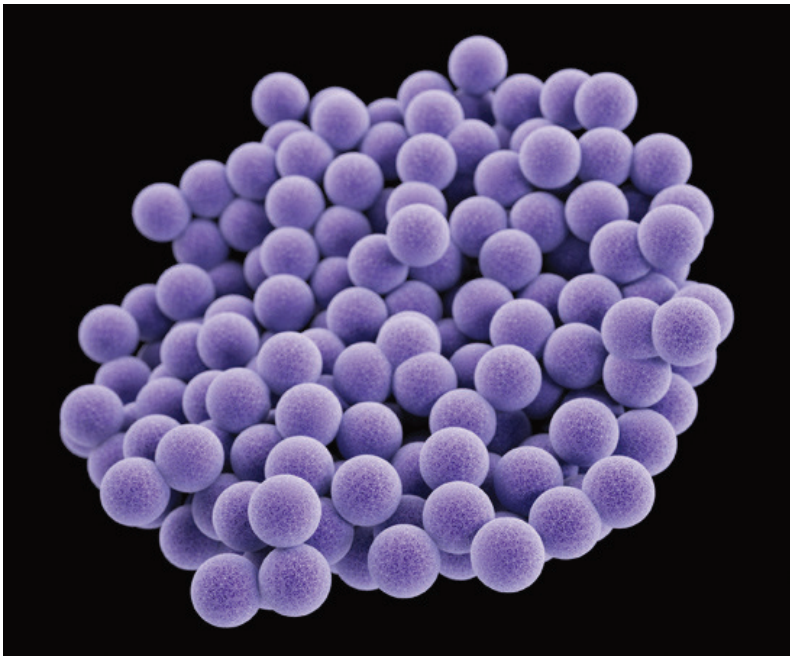
The International Standards Organization (ISO) has published a Draft International Standard (DIS) for clean areas. Quality control managers in the pharmaceutical and biotechnology industries are curious about how this will impact their monitoring and compliance requirements.

Of foremost concern in the life science industry is the apparent removal of the > 5 µm particle concentration in ISO Class 5 clean areas when compared to the 1999 version. In the 1999 version, the limit is 29 particles per cubic meter. This change to the ISO/DIS 14644 standard is a major concern for a number of reviewers.



***Staphylococcus aureus* bacteria cluster > 5 µm. Credit: Centers for Disease Control and Prevention**

The reasons for the de-emphasis on the 5 µm ISO Class 5 limit include:

Sampling and statistical limitations for particles in low concentrations make classification inappropriate; and

Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

According to Farquharson (2012), "Once the DIS standard is ratified, and assuming the concentration limit for the 5 µm column for ISO Class 5 is blank, then without further clarification this particle size cannot be used for classification in accordance with the ISO 14644-1." He continues, "However, monitoring may be a different matter."

In the life science industry, this change presents a unique dilemma on how to support regulatory requirements set out in the European Union Good Manufacturing Practice (EU GMP) Annex 1. It is even more sensitive due to the replication of the EU GMP Annex 1 requirements in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP Annex 1 No. 4, the World Health Organization (WHO) GMP for sterile pharmaceutical products Annex 6 No. 4.6.1, and the Chinese GMP regulations.

We know that in 2011 to 2012, experts were working on wording to be included in the standard that would allow the pharmaceutical industry regulatory authorities to provide their own guidance outside the boundaries of the standard.

Regardless, the ISO/DIS 14644-1.2 has a third footnote that is often lost in the minutiae, and many erroneously presume that monitoring of the > 5 µm particle is no longer required. The DIS standard states (in footnote f):

"In order to undertake classification at this particle size, use of the macro-particle descriptor M should be considered for > 5 µm."

The above references ISO/DIS 14644-1, Annex C, entitled "Counting and sizing of airborne macroparticles." Per ISO/DIS 14644-1.2 section C.1:

"In some situations, typically those related to specific process requirements, alternative levels of air cleanliness may be specified on the basis of particle populations that are not within the size range applicable to classification."

ISO14644-1 pertains to classification of cleanrooms. Contrary to some claims, Annex C was strengthened in revision 1.2 of the draft standard, which was released in 2014. This new version of the ISO 14644-1.2 does not eliminate the 5 µm classification where there are specific process requirements. These are generally found in phar-

maceutical, biotechnology, and life sciences.

Quality control personnel need to know why they are monitoring certain particle sizes. This is of paramount importance in the life science industry whose products affect public safety and therefore company reputations and business continuity. No doubt, environmental monitoring of clean areas in the life science industry is a mission critical application, and the one single activity that has the most impact on quality control.

The reason we monitor > 5 µm particles in the biopharma industry is twofold. First, to provide an early warning that a potential problem may be occurring. Indeed, most ISO Class 5 clean zones have counts of zero or one on the > 5 µm channel.

Moreover, viable microorganisms whose individual sizes are generally less than 1 µm tend to form in pairs, chains, and clusters. These colony forming units together often have a size greater than 5 µm. Therefore, a laser scattering aerosol particle counter (LSAPC) is metaphorically the canary in a coal mine, because it provides an early warning of a potential problem.

This is confirmed in the EU GMP Annex 1, No. 13, which again provides the most common sense approach to monitoring in the Life Science industry:

"In Grade A [ISO Class 4.8] and B [ISO Class 5] zones, the monitoring of the > 5 µm particle concentration count takes on particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of > 5 µm particle counts may be false counts due to electronics noise, stray light, coincidence, etc. However, consecutive or regular counts due to low levels are an indicator of a possible contamination event and should be investigated."

This clause in the EU GMP is supported in the new draft ISO/DIS 14644-1.2 standard, Annex C, section C.2.1, which states:

"If contamination risks caused by particles larger than 5 µm are to be assessed, sampling devices and measurement procedures appropriate to the specific characteristics of such particles should be employed.

The measurement of airborne particle concentrations with size distributions having a threshold size between 5 µm and 20 µm can be made in any of two defined occupancy states; at-rest and operational." (Emphasis added.)

Given the EU GMP provides a table for particle counts in clean zones "at rest" and "in operation" (see Table 1), the statement above shows that ISO/DIS 14644-1.2 draft standard is in harmony with EU GMP Annex 1.

Table 1: EU GMP:2008, Annex 1, No. 4 and 5

		Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
EC GMP	ISO	At rest		In operation	
Grade	Class	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	4.8	3,520	20	3,520	20
B	5	3,520	29	352,000	2,900
C	7	352,000	2,900	3,520,000	29,000
D	8	3,520,000	29,000	not defined	not defined

Additionally, 14644-1.2 section C.2.2 includes an example of how to describe a measurement of a particle count of 29 particles > 5.0 µm using a particle counter. This size limit of 29 particles > 5.0 µm is the current standard for an ISO Class 5 clean area, according to ISO 14644-1.

Therefore, contrary to what others may be suggesting, the > 5 µm particle size should continue to be an important element of risk assessment and monitoring in the life science industry.

Monitoring is about control. When we understand why we are monitoring, then it is clear that class limits in a table do not define all aspects of

control and risk assessment. Class limits are an important measure of environmental control, but if the only concern is passing the location then there could still be exposure to unseen risk. And, in this case, a risk that directly correlates to product quality and public safety.

Regardless of what changes may be made to ISO 14644-1, every indication is that it is unlikely EU GMP Annex 1 will follow suit. EU GMP Annex 1 was introduced to provide better guidelines for the life science industry and to address shortcomings of an ISO standard that focused on generic cleanroom requirements. ISO/DIS 14644-1.2, Annex C recognizes needs beyond what is included in the standard, as it specifically addresses those processes where particles greater than 5 µm (macroparticles) are important.

Certification and monitoring of the > 5 µm channel will continue to be an important element of control and risk assessment in the life science industry. This thesis is broadly supported among all international GMP standards that specifically relate to pharmaceutical and biotechnology sterile production. From a risk management perspective, is it prudent to give up a tool that focuses attention on changes in the environment that may serve to alert personnel of a potential problem that could affect the quality or safety of the product? If using a conservative model when making a risk assessment, most will conclude, based on past experience and an understanding of microbiological organisms, that dispensing with 5 µm monitoring in the life science industry is simply imprudent and not worth the risk.

References

- ISO 14644-1: 1999
- ISO 14644-2: 1999
- ISO/DIS 14644-1.2:2014
- ISO/DIS 14644-1.2:2014
- EU GMP Annex 1, Nos. 4, 5 (page 3), No. 13 (page 4)
- Farquharson, Gordon J., "Revision of ISO 14644-1:1999 — A progress report and explanation of some of the key issues and principles," June 2012.

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