New Support for ISO 14644-1

Changes in ISO 14644-1 to improve confidence in quality for critical life-science applications.

Tony Harrison, UK Subject Matter Expert to ISO TC209 Working Group 01, April 2012
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Introduction
ISO 14644-1, Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness is under revision as part of the normal ISO periodic review cycle. An international working group of subject matter experts, ISO TC209 Working Group 01, has been meeting to review the current ISO 14644 document and make recommendations for improvements. Consulting with expert statisticians, the working group is proposing changes to the classification method and also improving the document by incorporating the essential elements of ISO 14644-3, Cleanrooms and associated controlled environments — Part 3: Test methods, to help improve confidence in the quality of results.

Changes in classification method
The current ISO 14644-1 document relies on an ad-hoc method for determining the number and location of sampling locations for cleanroom classification. This ad-hoc method is not based on any statistical sampling method and does not take into account any risk-based assessment. The expert working group has consulted with statisticians and is now proposing a randomized sampling location selection method combined with a risk-assessed fixed-location sampling method.

The randomized sampling method is based on the Hypergeometric statistical model and improves confidence that the sample selection delivers 95% confidence that the

Highlights
• ISO 14644-1 is undergoing re-write
• The new ISO 14644-1 standard will deliver improved confidence in cleanroom performance for critical applications
• A new sample location method is proposed delivering improved confidence in results
• The expert working group has reviewed the normative reference to ISO 21501-4 for particle counter calibration and agreed that it supports the requirements for particle counter performance being moved from the existing ISO 14644-3 into the next version of ISO 14644-1
• As ISO 21501-4 was published in 2007, the ISO working group decided at their February 2012 meeting that users have had sufficient notice to upgrade any non-compliant particle counters
results are representative of 90% of all locations in the room.

The additional, risk assessed, fixed sampling location method allows the cleanroom user to select the locations where their product is most at risk; for example in the filling zone for aseptically prepared drug formulations. These locations are sampled when the cleanroom is initially classified and again every time the room is re-qualified.

These two methods, when used together, deliver a much higher confidence that the cleanroom is working as intended and is suitable for delivering the correct quality controlled environment for critical life science applications and is much improved compared to the method in the current ISO 14644-1 document.

**Improving confidence in quality**

Not all airborne particle counters are designed for the same applications. As well as cleanroom classification and monitoring applications for life-critical applications such as pharmaceutical and life sciences industries, some particle counters are designed for use in less critical industrial applications; for example indoor air quality in offices and public buildings and car paint booths.

![Diagram showing categorization of applications](image)

**Fig. 1. Particle counters can be designed for different applications**

Although some air particle counters are designed to be used in all three application areas, some just cannot cope with the high particle concentration in the industrial applications and others simply cannot give accurate, repeatable results in the low particle population environments found in life-critical cleanroom applications. Hence, particle counters designed for the less critical industrial applications are less likely to meet the exacting requirements laid down in ISO 14644-3 and ISO 21501-4.

In order to improve confidence in the cleanroom environment quality, the revised ISO 14644-1 document will include the particle counter performance criteria currently specified in ISO 14644-3 and
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ISO 21501-4 was originally published in 2007. In addition, the normative reference to ISO 21501-4 in the revised document has been widely publicized by particle counter size manufacturers, industry bodies and national standards agencies since the first draft of the revised ISO 14644-1 was first published in December 2010. Hence the expert working group considered that, by the expected publication date of the revised ISO 14644-1 document in 2013, the industries using ISO 14644-1 will have had six years’ notice, which is ample notification of the requirement to comply with the ISO 21501-4 calibration method and to upgrade any non-compliant particle counters.

Before its publication in 2007, there were no internationally recognized calibration standards for airborne particle counters resulting in widely varying performance from particle counting instrumentation. Since 2007, most international manufacturers of particle counters designed for use in critical life science ISO 14644 applications have adjusted their particle counter designs so that they can now meet the more demanding expectations of this new calibration standard. Cleanroom users can now achieve a much higher level of confidence that their cleanrooms are delivering the required level of quality controlled environment for their processes.

**Content imported from ISO 14644-3**

Particle counter performance criteria has been specified in ISO 14644-3 since its initial publication in 2005 and is matched in ISO 21501-4.

<table>
<thead>
<tr>
<th>Item</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity/Resolution a</td>
<td>Chosen between 0.1 µm to 5 µm with ≤ 10% size resolution</td>
</tr>
<tr>
<td>Uncertainty of measurement</td>
<td>±20% of concentration error at the size setting</td>
</tr>
<tr>
<td>Calibration interval</td>
<td>12 months maximum or specified performance verification</td>
</tr>
<tr>
<td>Counting efficiency</td>
<td>(50 ± 20)% at minimum size threshold and (100 ± 10)% for particles greater than or equal to 1.5 times the minimum threshold size</td>
</tr>
<tr>
<td>Lower concentration range</td>
<td>False count rate is insignificant in comparison to actually expected minimum</td>
</tr>
<tr>
<td>Upper concentration range</td>
<td>Two times greater than the upper limit of the installation cleanliness class concentration at point of use, and no more than 75 % of the manufacturer’s maximum recommended concentration</td>
</tr>
<tr>
<td>a Apparatus with particle sizing resolution greater than 10% can produce particle count results that can vary up to one order of magnitude.</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Specifications for the light-scattering discrete-particle counter from ISO 14644-3

The International Standards Organization Technical Committee ISO TC 209 has decided that, in order to improve clarity, particle counter performance criteria and methods to achieve classification should...
be incorporated into each individual ISO 14644 standard. Hence the particle counter performance requirements specified in Table C.1 of ISO 14644-3 will appear in the revised ISO 14644-1 document. The table contains a warning that “Apparatus with particle sizing resolution greater than 10 % can produce particle count results that can vary up to one order of magnitude”, emphasizing the importance of selecting the correct particle counter for classifying and monitoring critical life science cleanrooms.

Publication timeline
The first Draft International Standard (DIS) DIS ISO 14644-1 was published for public comment in December 2010, triggering much international publicity and debate. Around 200 technical questions and comments were received from the international community relating to this DIS. The ISO expert working group has reviewed the comments and intends to publish a revised draft DIS document sometime in 2013. Meanwhile, ISO Technical Committee TC209 suggests that users wishing to take advantage of the improvements contained in the 2010 DIS ISO 14644-1 document may use it as it stands in place of the 1999 version of this standard, as long as users are aware that the text may change in the final published version.

Conclusion
The improved guidance for particle counter performance and calibration combined with an improved sampling method in the new ISO 14644-1 document will deliver more confidence to the cleanroom user that their cleanroom is delivering the required level of environmental quality control for critical life science applications. Copies of the new draft standard are available from each nation’s national standards body.

Author Biography
Author: Tony Harrison is a subject matter expert to the UK British Standards Institute (BSI) cleanroom mirror group and one of the UK subject matter experts on ISO TC209 Working Group 01 tasked with revising ISO 14644-1 and -2. He is also Convenor of ISO TC209 Working Group 02 tasked with the revision of ISO 14698-1 and -2 for the classification of the cleanroom environment by microbiological cleanliness. Tony is employed by Hach Company as a Senior Product Manager.

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