ISO EN 17141 & ISO 14968 Overview Frequently Asked Questions

This FAQ paper is a follow up to the webinar, "**ISO EN 17141 & ISO 14968 Overview**" presented by Giulia Artalli and Mark Hallworth. Many thoughtful questions were asked about viable monitoring requirements in cleanrooms and other applications. Questions submitted during and after the webinar are answered by Giulia Artalli and Mark Hallworth, below. If you have any additional queries for our experts, **submit them directly here**.

Is there any guidance or requirement that applies in a quality control laboratory? Or are they only applicable for cleanrooms in manufacturing areas?

The standard covers different applications, and is designed for all that are designated for use in controlled cleanrooms and where monitoring is performed. Section ISO 17141, *Annex A – Guidance for life science pharmaceutical and biopharmaceutical applications* gives some direction as to what comprises a plan for a clean laboratory, and this points to GMP requirements.

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Is ISO EN 17141 used for working with stem cells in cleanrooms?

Stem cells are part of a new group of products under the label "ATMPs". There are few guidances that apply yet, but this is changing. There is a PDA conference on ATMPs and a breakout group that are writing guidance for the unique needs of these products, including a sub-group for environmental monitoring and controls. As most ATMPs will be under isolator or bio-cabinet conditions, similar monitoring requirements to classic pharmaceutical filling is expected. This increases the protection against product, cross-product, and batch contamination. The guidance should be available by the end of 2021. Until then, classic GMP Grade A/B monitoring is the precedent.

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What is ISO's link to GMP, and where are these standards used?

The quality management system (QMS) for manufacturing is defined in the FDA's 21 CFR for the US and the EudraLex for the EU. The QMS is also associated with ISO 9001 and ICH-10.

In EC GMP Annex 1, the standard for particle concentration is defined by risk-based activities in Grade A, B, and so on. To determine that measurement we are directed to ISO 14644-1, as this gives the technical framework and details of what is required to meet that guidance.

For microbial monitoring of an environment, the limits are given in GMP for establishing a 'system'. The SOPs for routine sampling are based on the guidance from GMP. But, if we look for a little more support on what comprises this 'system', details are few. We are directed to the next level of support and that is ISO 14698-1 & 2, which gives more 'substance' to creating a plan, how to set up a system, choice of most suitable instrument, validation of process, etc. The two (GMP and ISO) are intrinsically linked, so ISO acts as enhanced support for GMP. GMP is the highest anticipated expectation of standard, as it directly applies to drug product, whereas ISO is established in a range of industries.

EN 17141 replaced ISO 14698-1&2 as it felt it did not give sufficient detail with certain elements of both the "Normative" and "Informative" sections. The annexes within EN 17141 direct the reader to GMP for further information relating to limits applied, and offers guidance on technique.

In essence, ISO are a body of reference documents for guidance in establishing a process.

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How do I check the particles in nitrogen gas, and what are the specifications?

The requirement to monitor facilities falls into your plan of identifying the source of potential contamination. Section 4.4.2, copied below, includes compressed nitrogen. To determine the quantifiable impact of the contamination source and how it trends requires testing to ensure it meets a point it is likely to create a contamination issue. There are instruments available that can monitor the compressed gases within a facility, including nitrogen, and this test should be performed as part of your overall Contamination Control Strategy (CCS). See Particle Measuring System's **compressed gas kit**, an accessory for **MiniCapt® Mobile** and **Remote** Microbial Samplers. This page also includes several application notes on how to take the best sample based on use.

*Check out our **microbial samplers** at pmeasuring.com!*

4.4.2 Sources of microbiological contamination

4.4.2.1 General

Sources of microbiological contamination can be prime and derived or associated.

4.4.2.2 Prime sources

The following are examples of prime sources:

— People - A major source of contamination;

— Supply Air - Air supplied into clean controlled environments. (re-circulated or fresh make up);

— Product Materials - Product in solid or liquid form, containers and packaging;

— Utilities - Compressed air, nitrogen, propane, oxygen, WFI;

— Machines - Processing and packaging equipment.

- Taken from ISO EN 17141

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For Grade D oral solid dosage forms production, is it enough to do microbial monitoring once every 3 months?

Frequency of measurement is identified in paragraph (c) of ISO EN 17141. You need to determine the frequency required. Paragraph (b) describes assessing the risk of the process to product. Without fully knowing the risks, it is hard to determine in absolute terms that a 3-month frequency is acceptable. First the initial qualification should show no significant risk point that might allow contamination to go uncontrolled. A more stringent surface monitoring program for high contact areas is recommended as any airborne contaminants might aggregate and cause a more significant failure if left unabated.

4.3 Microbiological contamination control system quality attributes

The microbiological contamination control system shall consider the following steps:

a) identification of all potential microbiological contamination sources and routes of contamination in the clean controlled environment, deemed microorganisms of interest;

b) assessment of the risk from these sources and routes and, where appropriate, introduce or improve microbiological contamination control methods to reduce the identified risks;

c) establishment of a monitoring schedule, with valid sampling methods, to monitor the microbiological contamination source, or their control methods or both;

d) establishment of alert and action levels, and where appropriate target levels, with measures to be taken when required, if these levels are exceeded;

e) verification on a continuing basis, that the microbiological contamination control system is effective and meeting agreed performance parameters by reviewing product contamination rates, environmental monitoring results, risk assessment methods, control methods and monitoring limits and, where appropriate, modify them accordingly;

f) establishment and maintenance of appropriate documentation;

g) education and training of all staff involved with the clean controlled environment.

- Taken from ISO EN 17141

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Is there any guidance or requirement for microbiological monitoring equipment validation?

There is additional information that cover different applications within the standard, and the new standard is designed for all applications that are designated for use in controlled cleanrooms and where monitoring is performed. Section ISO 17141, *Annex A – Guidance for life science pharmaceutical and biopharmaceutical applications* gives direction on a plan for a clean laboratory, and points to GMP requirements.

There is also *Appendix E – Guidance on culture based microbiological measurement methods and sampler verification*, which outlines the process of instrument validation. Particle Measuring Systems offers validation and IQ/OQ tests to demonstrate the instruments capability once on your site.

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What is the required incubation period for microbiological tests? What is the minimum required number of sampling points?

Plates are usually incubated for:

- 2 days at 30 - 35 °C followed by 5 days at 20 - 25 °C, if bacteria must be recovered before fungi
- 5 days at 20 - 25 °C followed by 2 days at 30 - 35 °C, if fungi must be recovered before bacteria

Duration can increase or decrease for endogenic microorganisms. For example, if you have a slow growing microorganism in your environment.

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Why 2 µm and not 1 µm? Does monitoring smaller particle correlate to better performance?

Our instruments do capture particles that are < 2 µm based on the impaction velocity technical reviews. The higher the velocity, the smaller the particle that will be collected. Impaction is a function of volumetric flowrate and orifice size, so either reducing the orifice or increasing flow will collect smaller particles. However there are other considerations:

Maximum impaction velocity – There is concern that too high a velocity may stress the organism so it does not replicate, also known as a viable but not culturable (VBNC) microorganism. The highest impaction is found in slit-to-agar samplers (historically a reference sampler), and can be up to 70 m/s. The MiniCapt 100 LPM (D50 of 1.3 µm on average) has an impaction velocity of 46 m/s, and is a suitable compromise between velocity and stress. High velocities also cause shearing, where a cluster of microbes will tear into smaller elements as they are collected. This could potentially amplify a result if compared against settle plate sedimentation data.

Size of interest – There is data that shows the mean size of a free floating viable organism in a cleanroom environment is between 10 µm – 20 µm (see Whyte's 2007 paper, *Collection efficiency and design of microbial air samplers*, and Ljungqvist, and Reinmüller's 1998 paper, *Active sampling of airborne viable particles in controlled environments: a comparative study of common instruments*). These are usually associated with operators sloughing off particles inside the cleanroom, hence a move to isolators. Sampler performance below this operating range may not describe the process in a cleanroom with any greater degree of visibility of risk than those at 2 µm. Where a D50 at 2 µm will yield a D100 at < 5 µm. Similarly, particle counters can monitor an environment at 0.1 µm, but do not give analytical data for those where this is not a concerning risk value.

One of the factors that also improves the MiniCapt performance is the radial slit design, which is why our ISO 14698-1 testing demonstrates that as air is drawn through the impactor head, the height above the media is adjusted to an optimum height. The 'gap' (X - height) here allows for cross talk between adjacent slits (S). We have very defined flow trajectories. Multi-hole impactors effectively create and buffer a zone of turbulent air below the impactor plane, thus reducing the effective jet velocity of air passing through the hole.

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Do I have to buy a specific model of MiniCapt® to sample compressed gas?

The MiniCapt® Mobile Microbial Air Sampler offers a complete range of accessories that can be used when necessary. Each model is compatible with all accessories. Ensure you select the compressed gas kit or other accessory that pertains to the MiniCapt Mobile's flowrate.

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What single use technology do you offer?

The BioCapt Single-Use combines impactor and agar plate together into a disposable, polystyrene product. Light and easy to install by the operator, the unique design of BioCapt Single-Use reduces the rate of false positives and the cost related to sampling point handling.

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