EU GMP Annex 1—Impact on Air Monitoring Program for Medical Devices Manufacturers

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After the latest revision to EU GMP Annex 1 in 2020, Eric Clement Arakel, Global Product Manager, and Myriam Gueye, Segment Marketing Manager, Applied Industries at Sartorius, explain the effect the newest form of the guidance has on both medical device and pharmaceutical manufacturers.

The first version of the guidance dates back to 1971 and though there were multiple revisions up until 2010, this was the year when everyone took stock on what the guidance should look like. The document has expanded over the years, from 16 to over 50 pages and was finalized in August 2022 by the European Commission. So, how does it affect medical device manufacturers?

Though it is a European guide for manufacturing, EU GMP Annex 1's impact is global. As soon as a sterile medicinal product is imported into Europe having been manufactured elsewhere, the same practices must be adopted in these manufacturing facilities too.

What drives the spirit of EU GMP Annex 1 is Quality Risk Management and Contamination Control Strategy. Though it is mostly directed at the manufacturer of sterile medicinal products, it's also important to remember there are a lot of useful aspects for non-sterile manufacturing—including prompts and recommendations.

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The Annex 1 contains several major revisions with many references to the implementation of Quality Risk Management as a more proactive approach rather than reactive. The document also highlights the importance of a contamination control strategy and covers 16 different elements, including cleanroom design and qualification, environmental monitoring, and several other areas.

Section 4, concerning the facility, stipulates that the manufacture of sterile products be carried out in appropriate cleanrooms. The environmental monitoring of viable particles and cleanroom qualification is therefore essential. The focus in the EU GMP Annex 1 tends to be on Grade A cleanroom environments—the most stringent standards under which sterile medicine products are manufactured, where in many cases the products cannot be sterilized.

Annex 1 states that a manufacturer should use a combination of different methods, contact plates, settle plates, and volumetric air sampling and not rely merely on one method or the other.

It also recommends that all Grade A monitoring must be continuous and capture the entire duration of operation—a full manufacturing shift. The air handling units in cleanrooms turn over significantly large volumes of air and therefore sampling only 1 cubic meter is not truly representative. This is one of the reasons why Annex 1 calls for continuous viable air monitoring, not sequential monitoring or sampling miniscule volumes over an extended period of time.

Strictly speaking, continuous viable air monitoring in the Grade A zone can only be achieved through volumetric air sampling. Whether passive sampling using settle plates delivers adequate monitoring is open to debate, but the door has been left open in the document. But bear in mind, it is the use of a combination of different methods that has been recommended.

The EU GMP Annex 1 specifically mentions that monitoring should be for the full duration of critical processing and also recommends monitoring cleanrooms even when operation has stopped.

The document clearly specifies that all interventions caused by the environmental monitoring operation be avoided at all costs. One of the most common interventions is the routine retrieval of impaction plates from volumetric air samplers to avoid dehydration. This is where the MD8 Airscan® from Sartorius comes into its own. Paired with gelatine membrane filtration, cleanrooms can be monitored for a tested period of eight hours, typically the length of an entire manufacturing shift. By circumventing routine intervention, the technology is fully compliant with the requirements of the Annex 1 and stays true to its intended spirit.

It is also worth mentioning that both Grade A and Grade B cleanrooms must be requalified every six months with an aseptic process simulation repeated twice a year, taking into consideration all human interventions that typically occur during production. Care has to be taken, therefore, to minimize all possible interventions, to avoid the introduction of contamination during sterile manufacturing. Routine interventions also typically lead to increased microbiological samples from personnel monitoring.

One of the other key requirements of Annex 1 in terms of environmental monitoring is that the sampling method should not introduce the risk of secondary contamination. By being Vapor Phase H_2O_2 (VHP) compatible, the MD8 Airscan® facilitates complete decontamination when built in-line with the airflow path in advanced aseptic processing systems. Sterile and individually packed gelatin membrane filters, with the retentive capacity of a HEPA filter, are capable of retaining the smallest of viruses. The filters are hygroscopic in nature and prevent the desiccation of retained microbes by forming a protective capsid, enabling long-term continuous monitoring.

Though much of the guidance applies to pharmaceutical products, there is the effect on medical devices too.

Sterile integral drug delivery devices such as single-use pre-filled syringes, inhalers, and transdermal patches can be considered as medicinal products that include a medical device. As the principle intended action is achieved by the drug contained within the device, it is designated as a medicinal product and

therefore falls under the guidance. Implants containing medicinal products whose primary purpose is to release the medicinal product also fall under EU pharmaceutical legislation.

In July 2021, the European Medicines Agency (EMA) adopted a guideline for medicinal products when used with a medical device. This guideline considers the three different configurations of medicinal products (integral, co-packaged, or referenced) and also the impact of the device on the critical quality attributes (CQA) and overall control strategy in the medicinal product dossier.

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