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Air sampling at working height in aseptic cleanrooms:

GMP compliance and best practices

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Introduction

In highly sensitive production areas such as biotechnology, pharmaceuticals or stem cell research, cleanliness in aseptic cleanrooms is of crucial importance. In these critical environments, where the smallest impurities can drastically affect product integrity, very strict air quality management is required in accordance with current GMP regulations.

Passive air sampling plays an essential role in maintaining a high level of purity, as the main advantage of this method is the practical implementation of non-invasive, continuous monitoring of microbiological air quality.

The discussion will focus on the importance and methodology of air sampling at working height in these specific aseptic cleanroom environments, focusing on its role in GMP compliance and best practice.

We will look at technical, regulatory, and health aspects, understanding their impact on product quality. Additionally, we will emphasize that this approach goes beyond regulatory compliance – it is a commitment to scientific excellence in critical areas of the healthcare industry.

Our goal is to provide professionals with deeper insight into the development and implementation of effective air sampling strategies. This ensures sterile integrity in cleanrooms, which are critical to the product life cycle and consumer health and safety.

What does the GMP-requirements state?

I. Regulatory framework

In an international context, cleanroom standards are essential for ensuring product safety and quality in the pharmaceutical industry. The performance of particle concentration measurements, including viable particles by active and passive air sampling at working height, is an important component that is already included in the initial qualification of cleanrooms. Various regulatory authorities have established requirements for this in their standards:

ISO 14644

This standard indicates the need for a monitoring plan for cleanrooms based on a three-dimensional definition of measuring points. These measuring points are defined as part of a risk assessment to qualify the cleanroom class [1].

Annex 1:2022

The GMP regulation of the European Medicines Agency specifically refers to the ISO 14644 standard to determine the “minimum number of sampling points and their positioning”. This is particularly relevant for the manufacture of sterile medicinal products, where the measurement of particle concentration is required at critical points or during “high risk operations”, primarily at working height [2], [3].

VDI 2083

Measurement at working height is particularly considered in the area with low-turbulence displacement flow and further refers to the fact that this is “sometimes required by supervisory authorities (GMP area)” [4].

Overall, these regulations underline the importance of adhering to strict cleanroom standards, especially when measuring particle concentration at specified heights, to ensure the sterility and safety of the product through the production environment.

FDA cGMP

The US-GMP regulation currently has no specific consideration of measurement points or height [16] but “FDA has historically recognized the benefits of harmonization with other regulatory authorities” and is already referring to ISO guidelines such as ISO 13485 on some other topics like Quality System Regulation for Medical Devices [15].

II. Definition of air quality

The concentration of airborne particles is a primary indicator of air quality across GMP regulations. Maximum permissible particle counts are defined for various particle sizes such as 0.5 µm per cubic meter of air, which are crucial for preventing product contamination [13].

In addition, microbiological monitoring is required to determine the air quality. For example the FDA states that control systems must be implemented as "necessary to prevent contamination or mixups" [5] and "procedures shall include validation of all aseptic and sterilization processes" [14]. These controls include physical parameters as well as viable and non-viable particulates, as outlined in the documentation provided by the FDA [6].

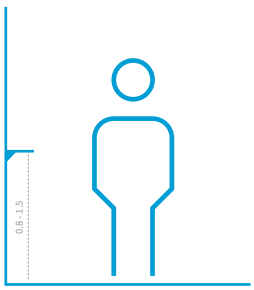
Annex 1 states that the monitoring program must be considered holistically, in order to be evaluated as an indicator of asepsis, as the "reliability of each of the elements of the monitoring system (viable, non-viable and APS [Media-fill]) when taken in isolation is limited" [7].

In the technical literature, "air quality" in aseptic cleanroom environments is defined as a measure that includes detailed monitoring of the "particle concentration in the working area" [17] of non-living but also living particles "in addition to physical parameters such as air exchange rate, temperature and humidity to ascertain that the specified cleanroom standard has been achieved" [9].

This leads to the requirement that measurements of the "microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification" [8].

III. Definition of working height

The “working height” in cleanrooms refers to the height at which most critical activities take place close to the product. Although the definition may vary in different sources, it is a key aspect in monitoring air quality and environmental conditions.



0.8 - 1.5 m

The Chinese specialist Zhonglin Xu suggest a working height range of 0.8 to 1.5 meters above the floor, as referenced in GxP-related literature [18].

For example, although the FDA CGMP guidelines do not explicitly use the term “working height”, the guidelines contextually imply that monitoring of environmental conditions should take place in areas relevant to production processes, which usually implies measurement at working height [5]. Similarly, the ISO 14644 standard does not provide a precise definition of working height but refers to a specific measurement height that should be determined in the course of the risk assessment [1].

However, other relevant GMP regulations go into more detail on the definition of working height:

Specifically, within the draft version of the current revision of Annex 1, the working height was limited to the horizontal level of critical processes and activities close to the product [3].

The Chinese specialist Zhonglin Xu suggest a working height range of 0.8 to 1.5 meters above the floor, as referenced in GxP-related literature [18]. In contrast, more specific guidelines from Scottish GxP specifications define the height precisely at 1 meter above the floor [10]. This specific height is also supported by expert literature on cleanroom monitoring, such as works by William Whyte [11], and discussions on updates to the current Annex 1 revision by Tim Eaton [12].

These guidelines make it clear that the working height is considered a critical point for monitoring air quality in cleanrooms. This is based on the assumption that, in terms of product quality, the greatest risk of product contamination exists at this height and therefore regular and thorough monitoring is required.

Motivation behind the GMP requirements

I. Technical perspective

According to Annex 1 of the EU GMP guidelines, the air velocity in the breathing zone of personnel in cleanrooms must be measured at the working height. The breathing zone is defined as the immediate vicinity of the head and upper torso of the personnel. This is where the air inhaled and exhaled by personnel is most likely to be contaminated.

In addition, this area of the room contains transfer openings, such as procedure gloves, rapid transfer ports (RTP) and production line doors, such as isolators or RABS (Restricted Access Barrier System), which can easily be used by personnel. Therefore, these locations are considered critical locations in terms of the guidelines.

Measuring the air velocity in the breathing zone helps determine the effectiveness of the airflow system in removing contaminated air and maintaining a controlled environment in the cleanroom.

By monitoring the air velocity in this area, the operator can determine if the airflow patterns are directed towards personnel and if the airflow velocity is sufficient to remove contaminants from the breathing zone.

II. Microbiological perspective

The working height is usually described as the average height at which personnel perform their work in the cleanroom environment. The reason for this is that staff are the main source of contamination in a cleanroom, and their breath and skin excrete particles that can settle on surfaces or become airborne.

On the one hand, the level of particle contamination can vary according to height, with higher concentrations typically found near the floor and lower concentrations near the ceiling. Thus, it can be assumed that the working height is statistically and practically the most realistic occurrence of contamination in the room during critical activities during production.

On the other hand, the level of particle contamination can vary due to the distance from the product during the manufacturing process. By carrying out air sampling at working height, it is therefore possible to obtain a more accurate representation of the product contamination that personnel are likely to introduce during their work activities.

This information can be used to determine whether the cleanroom environment meets the desired cleanliness standards or whether suitable measures need to be taken.

III. Occupational safety perspective

In the context of occupational health and safety, air sampling at working height serves as an informative procedure. It ensures the most accurate possible assessment of the particle pollution to which personnel may be exposed during their work.

These contaminants can include a range of potential health risks, including pathogens, hormones, toxins and other potential production particles. Air sampling in the breathing zone accurately assesses the inhalation exposure of cleanroom workers, reducing the risk of adverse health effects.

This proactive approach is crucial to minimize resource losses due to sickness and staff shortages in cleanroom environments.

Conclusion

In the pursuit of achieving excellence in GMP compliance and ensuring this integrity of air quality within cleanrooms, the importance especially of air sampling at the designated working height cannot be overstated.

A preferred measurement height between1 meter up to human breathing zone is in line with some of the current regulations and underlines the critical transition from a historical two-dimensional mapping approach to a mandatory three-dimensional strategy. This transition is critical to avoid potential false negatives when measuring airborne microbial contamination, thereby reducing the need for corrective and preventative actions (CAPA) and finally to avoid jeopardizing product integrity.

To prepare GMP documentation for future compliance, a clear definition of the working height in qualification documentation is strongly advocated. In addition, the use of practical and traceable equipment for air sampling at standardised heights is recommended to demonstrate that measurements are not taken outside the qualified measurement height.

In summary, the adoption of specified devices for traceable and reproducible air sampling, such as floor stands and wall-mounted holders, is integral to the reliable and precise monitoring of air quality at the working height. This practice is essential not only for upholding GMP compliance but also for safeguarding product integrity and the health of personnel involved in the manufacture of pharmaceuticals and sterile medicinal products.

Best Practice for Passive Air Sampling

In this context, two notable solutions emerge: the sedimentation plate stand and the wall-mountable sedimentation plate holders.

Sedimentation Plate Stand

The SPHFS01 model exemplifies a typical floor stand utilized in passive air sampling, particularly effective in central cleanroom areas and near critical points. These stands facilitate GMP-compliant working heights for air sampling. However, considerations include their spatial footprint in cleanrooms and the potential for displacement or toppling, which may necessitate repeated measurements.

Wall-Mountable Sedimentation Plate Holders

The foldable, wall-mountable SPHWM01 model offers a space-efficient solution, particularly suited for areas adjacent to walls. Its shock-resistant build and durable materials make it a reliable option for challenging cleanroom conditions. The design allows for consistent use of qualified measuring points, thereby supporting GMP standard compliance. It is not suitable for room-centered measurements in clean rooms.

Sources

[1] International Organization for Standardization (ISO), 2015 ISO 14644-2:2015 Cleanrooms and associated controlled environments – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration, Section 4.3.5.

[2] European Commission, 2022 EudraLex – The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 1: Manufacture of Sterile Medicinal Products, Section 4.28.

[3] European Commission, 2020 Draft Revision of Annex 1 of EudraLex Volume 4, Section 4.32.

[4] Association of German Engineers (VDI), 2022 VDI 2083 Sheet 3: Cleanroom technology; measurement of particle contamination, Chapter 6.2.2.

[5] U.S. Food and Drug Administration (FDA), n.d. Code of Federal Regulations Title 21, Chapter I, Subchapter C, Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals, Section 211.42.

[6] U.S. Food and Drug Administration (FDA), 2015 Facilities & Equipment: CGMP Requirements. Available at: https://www.fda.gov/media/92841/download (2024-02-01).

[7] European Commission, 2022 EudraLex – The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 1: Manufacture of Sterile Medicinal Products, Section 9.1.

[8] European Commission, 2022 EudraLex – The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 1: Manufacture of Sterile Medicinal Products, Section 4.31.

[9] Whyte, W., 2001 Cleanroom Technologies [1st ed.], JOHN WILEY & SONS, LTD: Chichester, UK. Chapter 9.1.

[10] Scottish Quality Assurance Specialist Interest Group, 2004 Guidelines on Test Methods for Environmental Monitoring for Aseptic Dispensing Facilities, Section 1.5.1.

[11] Whyte, W., 2021 Cleanroom Testing and Monitoring [1st ed.], Euromed Communications: UK. Annex A.3.

[12] Eaton, T., 2023. EU GGMP Annex 1 2022 and Pharmaceutical Cleanroom Classification – Consideration of the changes from EU GGMP Annex 1 2008. European Journal of Parenteral & Pharmaceutical Sciences. Available at: https://www.ejpps.online/post/vol27-4-eu-ggmp-annex-1-2022-and-pharmaceutical-cleanroom-classification-consideration (2024-02-01).

[13] International Organization for Standardization (ISO), 2015 ISO 14644-1:2015 Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration, Section 4.3.

[14] U.S. Food and Drug Administration (FDA), n.d. Code of Federal Regulations Title 21, Chapter I, Subchapter C, Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals, Section 211.113.

[15] Office of the Federal Register, National Archives and Records Administration & U.S. Government Publishing Office (2024) “Medical Devices: Quality System Regulation Amendments”. Federal Register. Available at: https://www.federalregister.gov/documents/2024/02/02/2024-01709/medical-devices-quality-system-regulation-amendments (2024-03-15)

[16] U.S. Food and Drug Administration (FDA), n.d. Code of Federal Regulations Title 21, Chapter I, Subchapter C, Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals, Section 211.42.

[17] Xu, Z. ,2014. Fundamentals of Air Cleaning Technology and Its Application in Cleanrooms, Springer-Verlag: Germany. Chapter 8.5.1.

[18] Xu, Z. ,2014. Fundamentals of Air Cleaning Technology and Its Application in Cleanrooms, Springer-Verlag: Germany. Chapter 14.4.4.3.