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Clean up Period and Recovery Time

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Both of the terms "clean up period" (Annex 1) and "recovery time" (ISO 14644-3, informative part B.4) are often used to describe the same procedure but they are completely different from each other. These test methods have no validity with respect to the airborne microbes, which depend greatly upon the number of persons in the room as well as their clothing and activity.

Clean up period according to Annex 1

The particle count limits for the "at rest" condition should be reached for a room free of personnel after a short clean up period of 20 minutes (guidance value) once activities are completed ("in operation" state) (Annex 1 (2022), Item 4.29 iii.; Annex 1 (2008), Item 14 after 15–20 minutes).

The particle limits for the "at rest" state should be achieved within 20 minutes after the completion of operations and any cleaning. Implementation of this recommendation means that:

- The particle measurement would be performed during actual operations. Additional personnel in the room performing the measurement have to be considered.
- After completing operation, the personnel leave the room.
- The measurements are continued. The particle limit for the "at rest" state should be reached within 20 minutes.

The implied conclusion would be that for optimal air flow conditions, the room content should be "flushed out" after 20 minutes. In this case the recommended air exchange rate would have theoretically be 3 (20 minutes).

This makes it necessary to define the critical areas of a cleanroom which are tested. Preferably a programmable particle counter should be used so that a timeframe of more than 20 minutes can be tested with repeated printout or storage of values every minute, for example. The evaluation of the results would show if the result conforms within that timeframe. A resulting clean up period requiring much less than 20 minutes to reach the limit value at rest is a sign that:

- the volumetric air flow rate (or exchange rate) that is (too) high and/or,
- a more than adequate rate of airborne contaminant removal is provided.

It is up to the pharmaceutical manufacturer to assess the actual clean up period and the necessary power consumption to achieve the high air change rates versus the impact to product safety (risk analysis!).

Testing the recovery time according to ISO 14644-3

In the DIN ISO 14644:2020 standard, Annex B.4, the methods for testing the recovery time for units with turbulent airflow are described. Measurement of the recovery time for ISO class 8 (C) and 9 (D), as well as for low-turbulence plug-flow airflows, is not recommended. Measurements should be conducted in any agreed state (preferably in the at rest state), and thus it is a potential test item during operational qualification testing.

This testing is used to determine the ventilation effectiveness at the measurement location and thus the capabilities of the AHU (Air Handling Unit) to achieve the target cleanroom class within a limited time period after loading the room with airborne particles.

The time required to reduce the introduced particle concentration down to 1% of the starting value is determined. When the particles are introduced (e.g. with an aerosol generator), it should be ensured that the initial particle concentration is at least 100 times the target cleanroom class limit value.

In the pharmaceuticals industry defining a grade D not to have limits in the "in operation" state should only be done with adequate justification. And thus, the recovery time for GMP grade D with the specified limit values (in logical consequence: ISO class 9) should be determined and proven.

Practical testing recommendations

The "combination" of both methods, i.e. measuring the recovery time (according to ISO) within 20 minutes (from Annex 1), which is often observed in practice, leads to false conclusions about the effectiveness of air purification and particle removal: For example, the air purity of particles in the "in operation" state can easily be < 15% of the limit value and the recovery time 100:1 according to ISO can be 30 minutes.

One alternative test procedure could take the following form to make a conclusion about the flushing behavior of the AHU possible:

- The room is artificially subjected to a load of 0.5µm sized particles (using an aerosol generator) to the point at which the maximum monitoring limit for "in operation" is met (alternatively with about 30% of the limit). This creates a simulated operating state.
- Afterwards, the aerosol generator is turned off and the time is measured how long it takes for the particle concentration to reach the limit value for the "at rest" status. This particle count level should be reached within a time span of 15–20 minutes.

Example:

- A grade C cleanroom for production is subjected to a particle loading with 0.5µm particles up to a level of 1,050,000 particles/m3 (30% of the "in operation" limit for grade C according to Annex 1 is 3,520,000 particles/m3).
- The aerosol generator is turned off and measurements are conducted with the particle counter until the number of 0.5µm particles falls below 352,000 ("at rest" limit for grade C). The measured time corresponds to the clean up period.

This test simulates the operating condition (setting the maximum particle concentration in the "in operation" state) for the cleanroom. The capability to uphold the recommended "cleanup" of 20 minutes fits the recommendations given in Annex 1 (2022). The ability to meet the requirement to maintain particle concentrations below this artificially created maximum can be proven under normal operating conditions during the

validation phase for the production equipment (APS – Aseptic Process Simulation, formally known as media fills, conformance lots). Additional testing is possible as part of periodic or continual particle monitoring.

In practice, the clean up period and recovery time are often mistaken – people may refer to the clean up period but perform a recovery time measurement or vice versa. From a legal and normative point of view, these measurements should be seen as recommendations, but from the point of view of the authorities, they must be applied.

Truth is: Annex 1 (2022) recommends determining the cleanup period, i.e. the time required to return from "in operation" to "at rest". For grade B that is a factor of 100:1, for grades C and D a factor of 10:1. Annex 1 refers at other locations to the cleanroom requirements given in ISO 14644-3 – in this standard the recovery time measurement is described measuring a 100:1 or 10:1 dilution. According to Annex 1 (2022), the recovery time must also be determined for the qualification.

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