**TECH TALK** Cleanroom Metrology

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# Facts and Fiction in Cleanroom Metrology

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This article discusses a number of cleanroom qualification parameters in terms of their proper specification. A critical analysis reveals that the useful operating range of some parameters is not appropriately considered by some early standards and guidelines, which are still used by regulatory authorities (the US Food and Drug Administration (FDA) and the European Union (EU)) and industry professionals. In practice, the windows of safely controlled cleanroom operation prove to be considerably larger than anticipated by existing regulations, especially with regard to unidirectional airflow velocity, pressure difference, and other parameters. Many measuring techniques, such as installed HEPA filter integrity testing and recovery time testing, are also regulated more strictly than necessary. Modern cleanroom testing requires more carefully defined targets and more flexibility in using advanced test procedures.

**Keywords**
Cleanroom testing, qualification, pressure difference, airflow velocity, recovery time, HEPA filter testing

## Pressure Difference

ISO Standard 14644-4[1] provides two different concepts for controlling cleanroom segregation: the displacement concept (low pressure differential / high airflow) and the pressure differential concept (high pressure differential / low airflow). For the displacement concept, a minimal pressure differential, causing > 0.2 m/sec (0.656 ft/sec) unidirectional ("displacement") airflow, may be sufficient for efficient cleanroom segregation. For the pressure differential concept, however, a difference of 5–20 Pa is recommended and used for safeguarding constant room pressurization. The displacement concept is suitable for "open" cleanrooms and clean zones, with a large airflow volume from the cleaner area to the less clean area, while the pressure differential concept is the proper solution for "closed" rooms, with a small airflow through closed doors, walls and equipment openings.

While the displacement concept offers almost constant operation, one specific problem of the pressure differential concept is the opening of doors to ancillary areas, such as changing rooms between cleanrooms, disturbing the target values of room pressurization. Care should be taken to avoid "false" pressurization caused by heating, ventilation, and air conditioning (HVAC) control systems re-establishing the target values—for example, by neglecting pressure loss due to a door remaining open for a given time. Another means to avoid "false" pressurization is given by "overflow" concepts, specifically when room pressurization by HVAC control is less suitable due to small room size. "Overflow" may reduce the pressure differential of two- or three-compartment

changing areas between cleanrooms (see Figure 1). In this example of a pressure cascade, two production rooms—the support room and the sterile room—are segregated by a pressure differential of 20 Pa, each with a tolerance of ± 5 Pa. For each of the air locks between the two rooms, the pressure cascade is maintained by the overflow from the adjacent rooms, i.e., by a self-adjusting pressure differential between two HVAC-controlled cleanrooms. Suppose this pressure differential for each of the two air lock compartments (Air lock 1 and Air lock 2 in Figure 1) is about 5 Pa; it is still satisfactory for establishing an airflow velocity of > 3.5 m/sec (11.483 ft/sec; equivalent to a 5-Pa pressure differential) against the contamination airflow. Overflow-protected areas need lower pressure differentials than HVAC-controlled areas. High pressure differences between adjacent areas may adversely affect constant product flow between these areas.

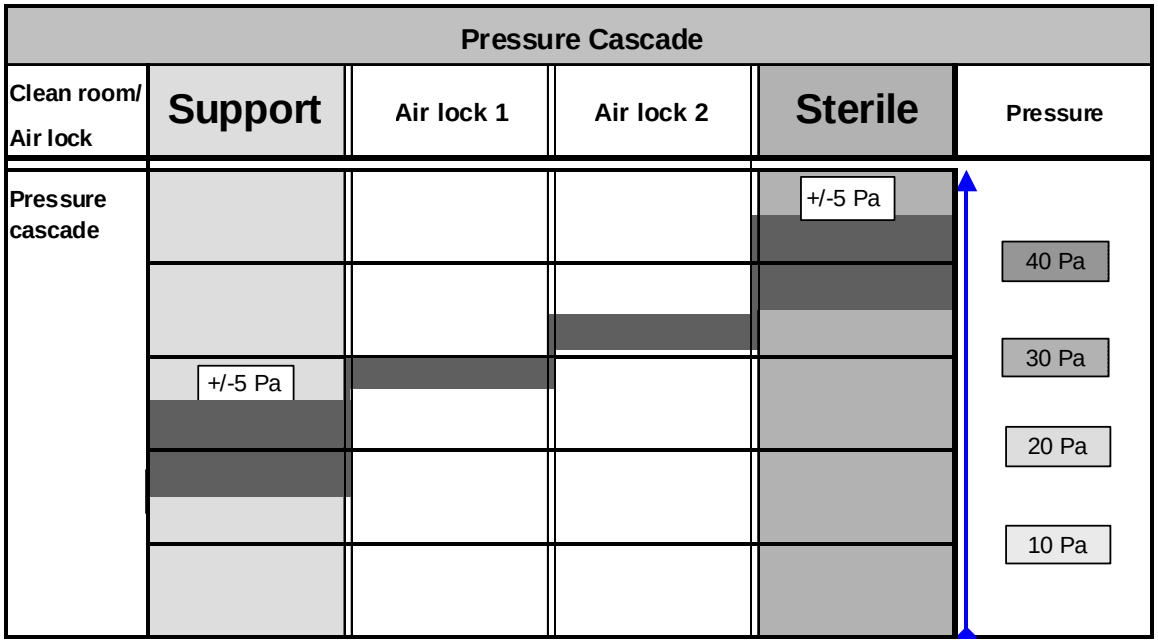

Figure 1—Pressure cascade demonstrating pressure differential segregation and overflow concept.

The effectiveness of these different solutions proves that cleanroom protection against airborne contamination from adjacent areas does not depend on a precisely determined level of pressure difference. Thus, both the European Commission (EC) Good Manufacturing Practice (GMP) recommendation[2] of 12.5 Pa and the US FDA recommendation[3] of 10–15 Pa should be understood as guidance, not as a minimum requirement. For setting pressure-level tolerances, control requirements should be carefully considered. More important than guidance values is the ISO Standard recommendation: "…Flow visualization, either experimentally or by computation, can be used to demonstrate both the effectiveness of the displacement flow concept and the pressure differential concept."

## Airflow velocity / airflow distribution

The requirement for unidirectional airflow with 0.45 m/sec (1.476 ft/sec) ± 20% air velocity (in reference 3) receives great attention in modern cleanroom technology. Authorities and users assume that observing this value greatly affects the quality of cleanroom operation.[3] The definition of this parameter is derived from the original specification[4] of 90 ft/min (0.457 m/sec) air velocity. Even though it has been proven that safely controlled displacement airflow can be established with an air velocity—depending on heat sources—of 0.2 m/sec (0.656 ft/sec; see reference 5 and Figure 2), the traditional specification of 0.45 m/sec (1.476 ft/sec) is taken as a standard for

"laminar flow" or "unidirectional airflow." Higher velocities are required to compensate for disturbances such as those caused by heat sources.

On the other hand, in spite of the precisely defined airflow velocity provided in the EC GMP[2] and the US FDA regulations,[3] some uncertainties remain. Frequently asked questions:

- Is the airflow velocity definition relevant only for first air—below the filter outlet—or also for the working level?
- Are tolerances for operational time, measuring points, and measuring technique included?
- How to specify appropriate tolerance levels?
- What about average airflow velocities and averaging measurement techniques?

Local variations of airflow velocities make it difficult to monitor airflow velocities with satisfactory precision. Hence, re-qualification of airflow averages should be avoided. It is much more suitable to use precisely fixed measurement points. Direct current (DC), motor-driven blowers—offering simultaneous measurement and control of the airflow by evaluating fan speed, power consumption and fan characteristics—seem to be the optimal solution for almost perfectly constant, controlled airflow volume/airflow velocity.

Hence, the airflow of 0.45 m/sec (1.476 ft/sec) ± 20% is more precise than required and seems to offer more guidance than it actually does. The ranges of safely controlled, unidirectional airflow prove to be considerably larger than traditionally assumed, since even below 0.45 m/sec (1.476 ft/sec) unidirectional airflow can be established. Thus, users have not only to focus on standard specifications but to develop operation-specific target values, considering particular installations and measurement equipment. Flow visualization proves to be a suitable means to demonstrate unidirectional airflow, which is more valuable than demonstrating that standard airflow values are being met.

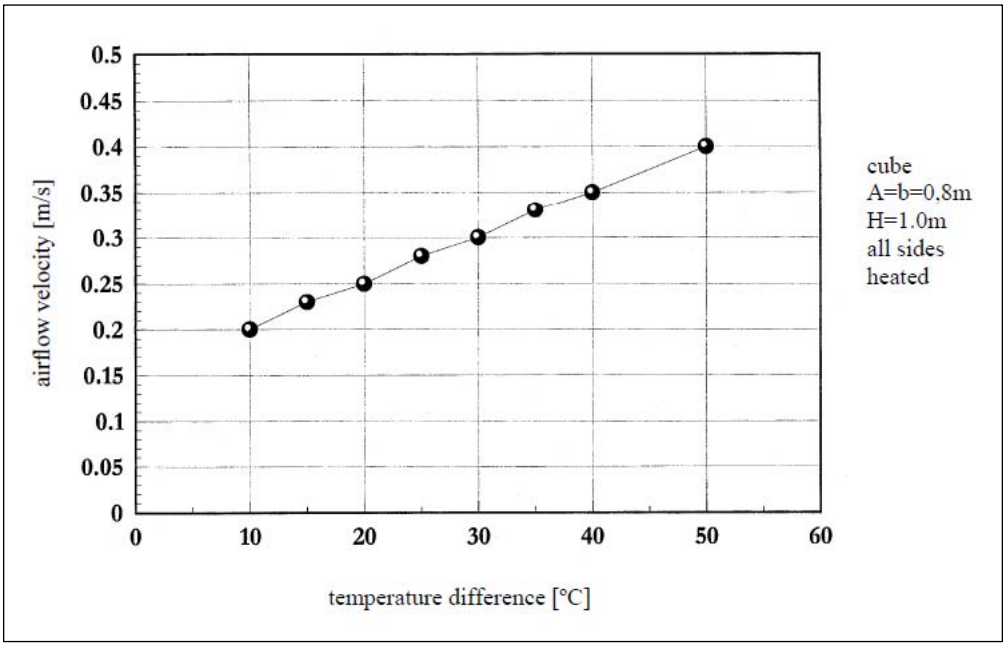


Figure 2—Minimum airflow velocity depending on temperature difference to avoid disturbance of unidirectional airflow.

## Installed HEPA filter leak testing

Current GMP recommendations specify the traditional photometer method (AP)[3] for leak testing and use of dioctyl phthalate (DOP) as a suitable test aerosol. Consequently, there is lack of guidance for using alternative methods and aerosol materials.

Less toxic aerosol materials have been studied by D. R. Moore et al., demonstrating satisfactory correlation between the use of DOP and poly-alpha-olefin (PAO).[6] Their "controlled leak-test method" has been used to demonstrate that di(2-ethylhexyl) sebacate (DEHS) offers better specification and availability and can be used for the same purpose, i.e., replacing DOP[7] (see Figure 3).

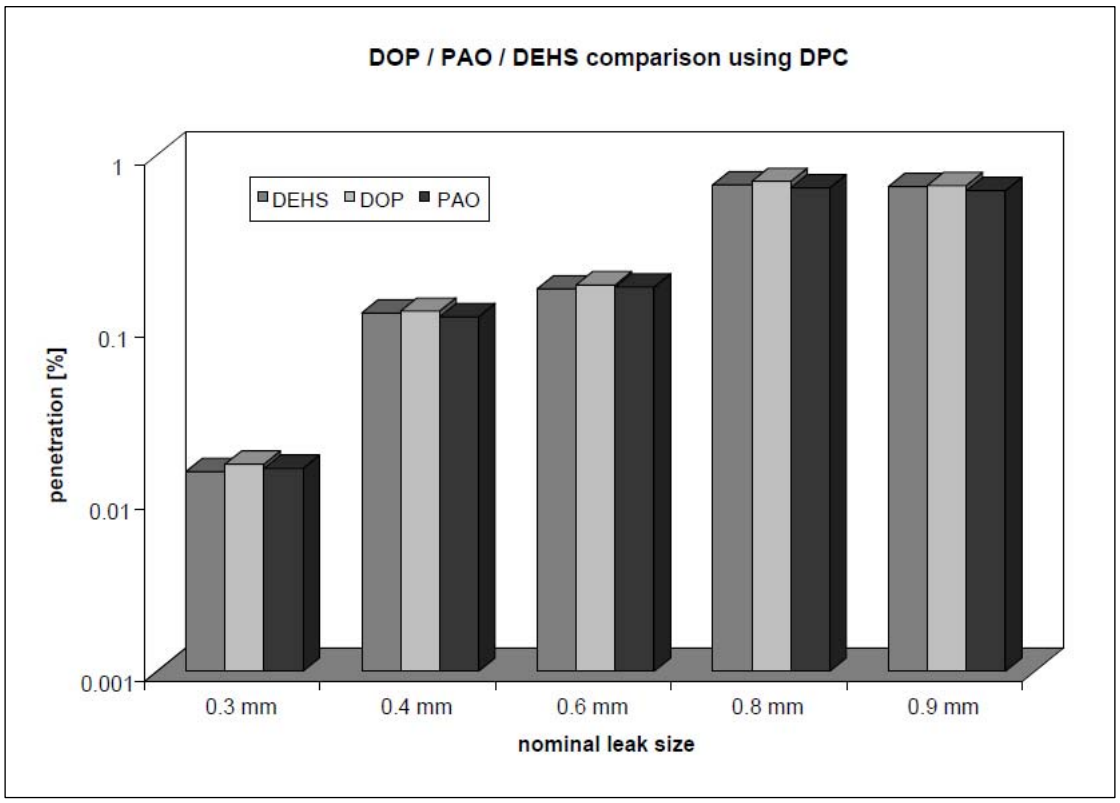


Figure 3—Comparison between using DOP, PAO, and DEHS for installed HEPA filter leak testing with a discrete particle counter.[7]

Because the US pharmaceutical industry prefers the AP method and the EU prefers the DPC (discrete particle counter) method, correlation of both methods has been studied and confirmed, verifying a better resolution for the DPC method[7] (see Figure 4).

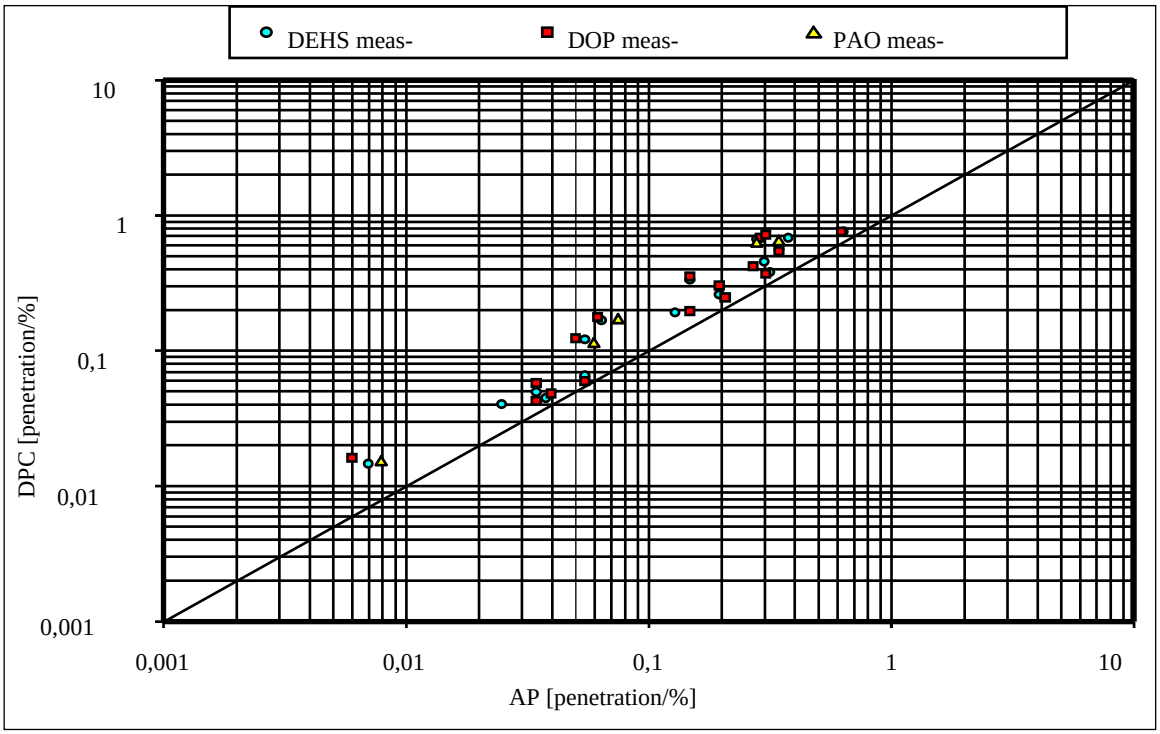


Figure 4—Correlation between aerosol photometer and discrete particle counter detection of nominal leaks in HEPA filters.[7]

Consequently, the physicochemical properties of the investigated aerosol materials do not affect the measuring results of installed HEPA filter leak testing. Both test procedures, the aerosol photometer and the discrete particle counter method, as specified by ISO 14644-3 (B.6),[8] can be used for HEPA filter leak testing.

## Recovery time

"Recovery time" has been specified as the time required to reduce an (artificially increased) initial particle concentration in a cleanroom by a factor of 100. This definition is used by ISO 14644-3, Annex B.12, which ideally matches the requirements of ISO Class 7 non-unidirectional flow cleanrooms. For such cleanrooms with > 20 air changes/hr, a recovery time of less than 20 minutes can be expected.

However, clause 14 EC GMP Annex 1[2] provides a different specification: "the particle limits given for the 'at rest' state should be achieved after a short 'clean-up' period of 15–20 minutes (guidance value) in an unmanned state after completion of operations."

The ISO definition offers the advantage of a precisely specified range for recovery—a useful procedure for testing HVAC installation performance. However, by defining the time for achieving the at-rest state, EC GMP Annex 1 proves to be more flexible, e.g., for determining recovery time in ISO Class 8 and ISO Class 9 cleanrooms, where a reduction factor of 100 is not truly required.

There is no doubt that both specifications may provide useful information. Hence, users may strive to combine the two procedures. In this case, for simulating an operating ISO Class 7 cleanroom, one starts with an initial particle challenge: > 352,000 particles > 0.5µm/m³. The 100:1 recovery rate of ISO is achieved, after this initial concentration is reduced by a factor of 100. The clean-up time of EC GMP can be determined as the time of the particle concentration decay from 352,000 (ISO Class 7 "operational") to the limit value of 3520 (ISO Class 5 "at-rest") particles > 0.5µm/m³ (see Figure 5). The decay of the "original state" is caused by dead volumes in a

changing room; the decay "after improvement" was measured after elimination of the dead volume. Hence, particle counting below the at-rest limit particle concentration may produce additional information on disturbing factors. ISO 8/ISO 9 cleanrooms are characterized by smaller relative variations of the airborne particle concentration and concentrations of a factor of 100 above ISO Class 8 and ISO Class 9 are difficult to realize. Consequently, if recovery time measurement is understood as simulating the transition between the operation state and the at-rest state (or any airborne contamination and decontamination cycle), for ISO Class 8 and ISO Class 9 rooms a ratio of 10:1 is by far more realistic than a 100:1 ratio.

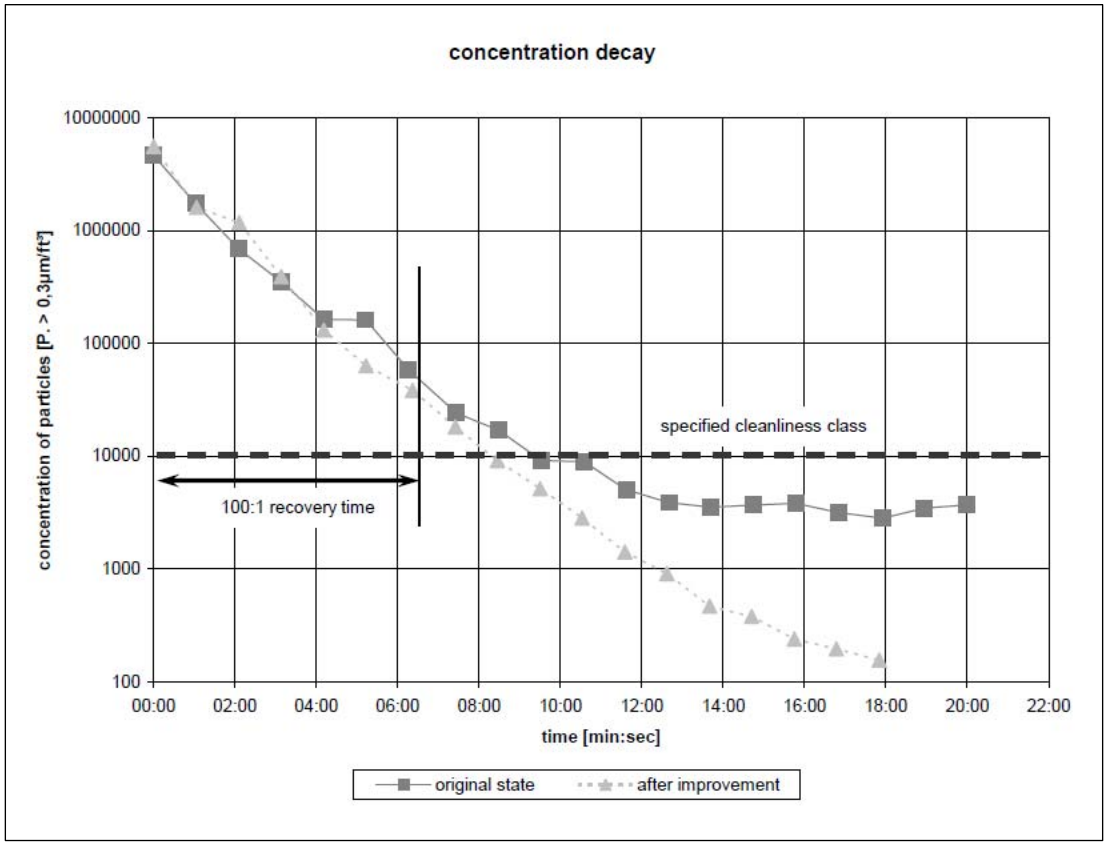


Figure 5—Particle concentration decay during recovery time testing.

## Controlling 5-µm particles in an ISO Class 5 cleanroom environment

EC GMP,[2] requiring the detection of 5-µm particles with a sample volume of at least 1 m³ for ISO Class 5 classification and monitoring, overlooks some essential facts:

- 5-µm particle counts in an ISO Class 5 environment should be avoided in principle due to background noise level and poor resolution. The poor reliability of 5-µm particle counts cannot be fully compensated by increasing the measuring time.
- 5-µm particle determination proves to be about 10 times more expensive and time-consuming than 0.5-µm particle counts.
- Currently there is no scientific evidence that 5-µm particle detection offers any improvement for cleanroom hygiene control.

- EC GMP regulation impedes international harmonization of cleanroom qualification and monitoring procedures.

Even with the latest development of particle counters that offer substantially higher sampling flow rates, the situation does not improve: Areas of ISO Class 5 normally are as small as possible. A particle counter with high sample flow rates cannot be placed in that area since the high sample flow is withdrawn from a small volume. In small areas such as pass-throughs, when the sample flow air is returned into the environment, the pressure differential may be affected; when the sample flow air is returned into the measured area, the air change rate may be affected.

Hence it is most doubtful that controlling 5-µm particles in ISO Class 5 cleanrooms can be justified. In this respect, the relevant EC GMP Annex 1 procedures should normally be ignored. On the other hand, considering the importance of EC GMP Annex 1 regulations, at least many EU pharmaceutical professionals feel obliged to carry out the counting of 5-µm particles in an ISO Class 5 environment.

In this case, the overall expenditure associated with this procedure might be reduced by following the ISO 14644-1 recommendations on "sequential sampling."[9] These recommendations were originally developed to shorten measurements, so that the final results can be assessed by consideration of interim results. Since the basic idea of increasing the sampling volume in EC GMP Annex 1 is to extend the limits of detection sensitivity and not to extend the measuring time, the ISO procedure is definitely applicable.

## Conclusions

The topics discussed here illustrate how authority recommendations and regulations dealing with cleanroom parameters frequently cover only a limited area of application. Hence, users should carefully examine the applicability of such rules, taking into consideration performance data of their installation, and if necessary, considering additional qualification/verification procedures and international standards, such as ISO 14644. One reason for the gap between current regulations and application seems to be that current regulations insufficiently consider technical progress and knowledge documented by international standards. Since it has long been proved that the "windows" of safely controlled cleanroom operation are considerably larger than anticipated by existing regulations, it is reasonable to consider implementing more flexible design, qualification, and operation concepts.

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