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ALERT AND ACTION LEVELS FOR AIRBORNE PARTICLES IN BIOPHARMA PROCESSES

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Most companies have chosen a harmonized approach using the recommendations from the EU and the FDA, to include applying the most stringent criteria where applicable, although some companies use the most stringent criteria across the board. However, the regulators prefer to see Alert and Action Levels based on historical data once the EM program has been established for a minimum of 12 months.[1]

An "Alert Level" is a particle population parameter set by the user that, when exceeded, gives an early warning of a drift from normal operational conditions, and should result in increased attention or correction action.[2]

An "Action Level" is a particle population parameter set by the user that, when exceeded, requires immediate intervention, including investigation of cause, and corrective action.[3]

Users should select either a single alarm level or a dual approach of alert and action levels. In the life science biopharma industry two levels of alarm – termed alert and action – are employed as a quality control measure and response tool.

The establishment of alert- or action-level alarms requires careful consideration to ensure they provide an effective basis for initiating a response, such as further investigation or increased observation (known as an "alert level"); and trigger a remedial action response (known as an "action level").

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[1] Pharmaceutical Microbiology Forum Newsletter – Volume 11(1)

[2] ISO 14644-2, 3.4; and PIC/S GMP:2014, Annex 1, Glossary

[3] ISO 14644-2, 3.3; and PIC/S GMP:2014, Annex 1, Glossary

The **purpose** of an environmental monitoring program is to provide oversight for foreign particulate matter and microbiological cleanliness of manufacturing operation and document the state of control of the facility.[4]

According to ISO 14644-2 Section B.3.1.1, the **objective** of *particle monitoring* in an *operating* cleanroom is to provide an *indication* that the required level of cleanliness is achieved at critical control points. Risk assessment and evaluation of sample data from formal or clean area classification limits is made in accordance with ISO 14644-1 (Reference Table 1), and should be used to determine the monitoring locations (critical control points). It is important to note, that monitoring locations will generally differ from certification locations as the purpose of certification is to validate an ENTIRE cleanroom, while the purpose of monitoring "critical control points" in the operational state is again to provide an indication that compendial cleanliness requirements of the air *around the process* are satisfied.
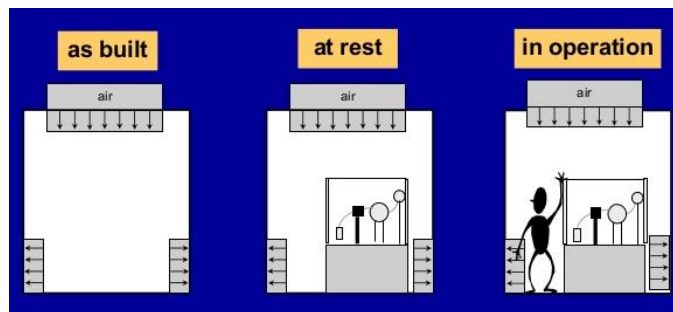

Figure 1: Cleanroom Conditions

Grade A (ISO Class 4.8), B (ISO Class 5), C (ISO Class 7), and D (ISO Class 8) cleanrooms and clean devices should be routinely monitored *'in operation'* and the monitoring locations based on a formal risk analysis study. In order to meet 'in operation' conditions these areas should be designed to reach certain specified air-cleanliness levels in the 'at rest' occupancy state. In Grade A areas a minimum sample volume of 1

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[4] Yang, Zhao, O'day, and Fleming. *Environmental Monitoring: setting alert and action limits based on a zero-inflated model.* PDA Journal of Pharmaceutical Science and technology / 2013; 67 (1).

cubic meter should be taken per sample location.[5] It is also an industry best practice to take full cubic meter samples in ISO Class 5 or Grade B zones.

In Grade A and B areas, the monitoring of the > 5.0 µm particle concentration counts takes on particular significant as it is an important diagnostic tool for early detection of failure. [6]

The alert and action levels identified should provide effective information to allow management of performance changes and identification of deviations from defined acceptance criteria.

Statistical process control principles can be used to set alert and action levels based on analysis of historical data. For example, based on historical data, Alert Levels are set at the 95th percentile (cut-off value approach), or at a tolerance limit of $\gamma = 0.95$ and $P = 0.95$ (non-parametric tolerance limit approach), or at 2 x SD (standard Deviation) from the mean value. Action Levels are typically set at the 99th percentile (cut-off value approach), or at a tolerance limit of $\gamma = 0.99$ and $P = 0.99$ (non-parametric tolerance limit approach), or at 3 x SD from the mean value. Yet, there are companies that have chosen to establish only the Alert Levels based on historical data and keep the action levels based on industry/compendial recommendations. Such approach is also acceptable and these companies have successfully defended their position with the regulatory agencies.[7]

It is important to note that all participants agreed that the rationale for how the Alert and Action Levels are established must be captured in a governing EM SOP or Master Plan.

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[5] PIC/S GMP: 2014, Annex 1, nos. 3, 4, 5, 13, 15; and EU GMP, Annex 1, no. 8, 15

[6] PIC/S GMP: 2014, Annex 1, no. 13; and EU GMP, Annex 1, no. 13

[7] Data from the qualification study should be used to set the **initial operating alert and action levels** for the routine environmental monitoring program.

It is essential to establish appropriate methods to annunciate or indicate when the particle count values reach alert and action levels. Extra care should be taken when considering alert and action levels for ISO Class 5 areas, as low concentration of particles may result in "***nuisance alarms***" due to false counts. Frequent "nuisance alarms" should be avoided as they can lead to alarms being ignored by users. For example, in an ISO Class 5 area it may not be a good practice to set an alarm at 5.0 μm = 1. This may result a large number of nuisance alarms, as it may not always be possible to demonstrate low levels of > 5.0 μm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself (PCI-S, Annex 1, no. 9). Also, zero counting in the 5 μm channel may prove problematic as normal counts will usually vary between 0-2 counts even in non-fill areas.

The duration of a sample period needs to be considered in terms of allowable risk. Setting a longer sample period can smooth data and avoid potential "nuisance alarms," but may conceal an unacceptably high level of airborne particle concentration over a short period caused by an unusual contamination-generating event. This should be of particular concern in Grade A or B areas, where continuous monitoring at low flow rates is the norm. It is generally recommended in these areas to sample at 1 minute intervals.

When sampling two particle sizes (0.5 μm and 5.0 μm) simultaneously and samples taken at 1 minute intervals, setting alert and action levels is more complex.

One-Minute Alarm Strategies:

> Alternate Strategy #1: A trigger threshold value based on a series of consecutive higher readings.   The higher readings trigger a warning based upon the occurrence of a higher level of counts being maintained over a period of time – For example, three consecutive 1-minute readings all above a specified level.

> Alternate Strategy #2: A threshold value trigger based on a high frequency of elevated readings. Sometimes referred to as "x out of y", this strategy records readings that are above a specified threshold; if a sufficient number of readings is a series are above the specified values then an alert or action alarm is

triggered. For example, if 3 out of 10 readings are above a threshold then an alert or action alarm will be triggered. [8]

The above strategies may work well for the > 0.5 μm channel. However, if we expect zero counts in the > 5.0 μm channel, setting an alarm threshold using a frequency methodology may not be wise, and could potentially fail to alarm for an excursion in the larger 5 μm size.

OTHER THINGS TO CONSIDER

When 5 μm is a size of interest, it is an industry best practice to use an isokinetic probe pointed vertically upwards in a turbulent or non-unidirectional airflow system. In unidirectional airflow, an isokinetic probe should be pointed into the laminar flow. Consistency of the physical sampling position and orientation of the isokinetic probe can have an effect on the particle concentration measured from one sample period to the next. The position of the sample should not change substantially without due consideration of the impact on trending history and alert and action levels.
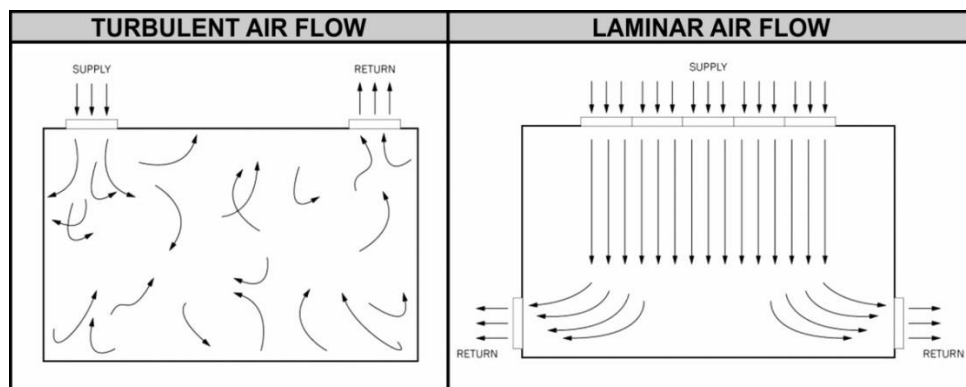

Figure 2: Types of Air Flow in a Clean Zone

With regards to particle counters:

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[8] ISO 14644-2: 2015, Annex B (Informative), Section B.3.4.3

a) The concentration of foreign particulate matter and biological contamination is directly proportional to the level of activity in a cleanroom, the volume of the cleanroom, and the ventilation mechanism and effectiveness.

b) It is an industry best practice to investigation particle count readings that are consistently lower than the expected norms. This may be an indication of a malfunction of the particle counter, its blower, or data-logging apparatus.

c) Typically, the acceptable range of particle concentrations for the "at rest" state may be significantly lower than the "operational" state in non-unidirectional airflow systems.

d) Warning values may need to be different for different sample locations within the same clean zone.

e) Normal activity in a cleanroom may create momentary increases in particle counts that may be acceptable and normal.

ESTABLISH A 'NORMAL OPERATING RANGE'

Measure and record particle counts at sample points over a significant period of time in both "at rest" and "operational" occupancy rates using the intended sample size and time. From this dataset, the expected normal performance of the cleanroom can be determined and become the basis for establishing alert and action levels (Ref. Figure 1). It goes without saying the expected sample values will be well below the ISO threshold class limit AND action level.
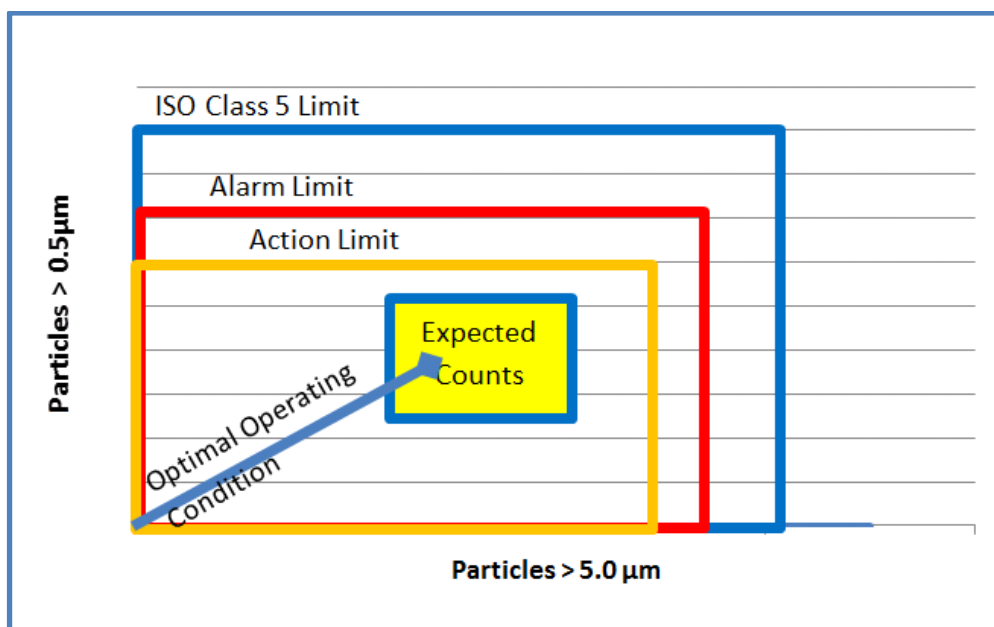
Figure 3: Alert and Action Levels

It is recommended that a period of observation be made when a major change occurs to a cleanroom or clean area design, or if there is a major change to the operation of the installation.

PERIODIC EVALUATION

Most companies re-calculate Alert and Action Levels annually since the FDA expects these values to be based on historical data. One company pointed out that the USP only states that a company must have Alert/Action Levels and reevaluate them periodically. Another company indicated that the Alert Levels were re-calculated annually at 80% of previous and already established level. Regardless of the frequency and method chosen, the expectation is that the calculated levels should go down with time and that adverse trends are timely detected and addressed. [9]

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[9] Pharmaceutical Microbiology Forum Newsletter – Volume 11(1), pgs. 2-3. Available Online

SOURCES

    ISO 14644-1:2015

    ISO 14644-2:2015

    PIC/S GMP, Annex 1

    EU GMP, Annex 1

    Pharmaceutical Microbiology Forum Newsletter – Volume 11(1), Number 1
        January - March 2004