PARTICLE MEASUREMENT IN CLEAN ROOMS.

PARTICLE MEASUREMENT

Particle measurement in clean rooms.
Content

PARTICLE MEASUREMENT IN CLEAN ROOMS

1 Particle measurement in clean rooms
   1.1 Operational state
   1.2 Pharmaceutical cleanroom classes
      1.2.1 Class A
      1.2.2 Class B
      1.2.3 Class C and D
   1.3 Practice of particle measurement
   1.4 Acceptance criteria

History

Document number: wp1508007-0100-en
Version / Revision: V1R0, 2015-08
Status: Initial version, released

<table>
<thead>
<tr>
<th>History</th>
<th>Version</th>
<th>Date</th>
<th>Comment / Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document number: wp1508007-0100-en</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Version / Revision: V1R0, 2015-08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status: Initial version, released</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>Version</td>
<td>Date</td>
<td>Comment / Note</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>V1R0</td>
<td>2015-08</td>
<td></td>
<td>Initial Version</td>
</tr>
</tbody>
</table>

Table 1: History
1 Particle measurement in clean rooms

In addition to the measurement of air change rates, the best way to verify whether a cleanroom really provides the expected cleanliness class is detecting the particle concentration during active use. This is done by means of a particle counter, which measures the number and size distribution of the particle pollution per unit volume. The size range of interest usually is between 0.1 and 10 µm depending on the purpose of the clean room. In the pharmaceutical industry, only the size classes 0.5µm and 5.0µm are important. In the microelectronic production, however, the smallest particles in the range of 0.1 µm and below can already decide between function and non-function of a wafer. Due to the relatively low volume flow of current particle counter (28,3l, 50l, 100l / min) they can cover only a small proportion of the whole room volume. The measured value obtained thereby is considered representative for the entire room based on the assumption that the particle concentration is distributed fairly evenly. Of course, this assumption is not always true, especially not when particle sources exist at certain locations within the room. Therefore, the particle measurement should always be carried out on the spot - i.e. in immediate vicinity of the product. Depending on the cleanroom class, a regularly recurring "clearance measurement" with mobile particle counters is useful to verify the cleanroom status or a continuous recording of the particle concentration is either necessary or demanded by the relevant guidelines of pharmaceutical production.

1.1 Operational state

The measured particle concentration in clean rooms, however, can be subject to significant fluctuations, depending on their state. For this purpose, the ISO 14644-1 defines 3 states of a clean room:

"As Built": This situation is assumed after the finalization of the clean room, but without staff and installed equipment, and without items in production.

"At Rest" ("hibernation"): All production facilities and equipment have been installed within the clean room, but without the presence of staff.

"Operational" ("In Service"): All production equipment and devices are in use, and the number of people needed for production is working in the clean room.

Considering these different conditions, it becomes clear very quickly that they are also the source of various types of particle contamination. While in the "as-built" state the measured particle concentration largely corresponds to the concentration in the filtered air, a much higher concentration is to be measured in manufacturing facilities of "in-service" ("Operational") state - or when personnel is in the cleanroom. Often, the attained cleanroom class of "In Service" - ("Operational") state is by one or two classes worse than in "hibernation" ("at rest").

The maximum allowed particle concentrations measured in particles per cubic meter in the individual operating states of a clean room are also defined in the ISO 14644-1.
Cleanroom classes according to ISO 14644-1 (particles per m³)

<table>
<thead>
<tr>
<th>Class</th>
<th>&gt;=0,1µm</th>
<th>&gt;=0,2µm</th>
<th>&gt;=0,3µm</th>
<th>&gt;=0,5µm</th>
<th>&gt;=1,0m</th>
<th>&gt;=5,0µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO1</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ISO2</td>
<td>100</td>
<td>24</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ISO3</td>
<td>1.000</td>
<td>237</td>
<td>102</td>
<td>35</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>ISO4</td>
<td>10.000</td>
<td>2.370</td>
<td>1.020</td>
<td>352</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>ISO5</td>
<td>100.000</td>
<td>23.700</td>
<td>10.200</td>
<td>35.200</td>
<td>832</td>
<td>29</td>
</tr>
<tr>
<td>ISO6</td>
<td>1.000.000</td>
<td>237.000</td>
<td>102.000</td>
<td>35.200</td>
<td>832.000</td>
<td>293</td>
</tr>
<tr>
<td>ISO7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>352.000</td>
<td>83.200</td>
<td>2.930</td>
</tr>
<tr>
<td>ISO8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.520.000</td>
<td>832.000</td>
<td>29.300</td>
</tr>
<tr>
<td>ISO9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.320.000</td>
<td>2.93000</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Cleanroom classes acc. ISO 14644-1

1.2 Pharmaceutical cleanroom classes

The current European standards for pharmaceutical cleanrooms is defined in the EU GMP guideline. It defines 4 classes of clean rooms for manufacturing sterile medical products, which apply depending on the nature of the manufactured product and the protected process. In addition to ISO 14644, limits for microorganisms are also defined for pharmaceutically used cleanrooms, which are detected by measurement using contact and sedimentation plates, or microbiological samplers.

1.2.1 Class A

Local zone for high risk processes, e.g. aseptic filling, open ampoules and vessels.

Typically, these conditions are achieved by the use of biological safety cabinets (laminar flow), which produce a laminar flow in the region of 0,36-0,54m / s in the workspace.

1.2.2 Class B

For aseptic preparation and filling. It is mostly used as a surrounding cleanroom class for safety cabinets.

1.2.3 Class C and D

Cleanroom classes for executing less critical processes in the manufacture of sterile products. Table 3 shows the maximum permissible particle measurement values for the respective cleanroom class in the possible operating states.
### Maximum number of particles / m³ equal to or greater than the specified size (particles per m³)

<table>
<thead>
<tr>
<th>Class</th>
<th>&gt;=0.5µm</th>
<th>&gt;=5.0µm</th>
<th>&gt;=0.5µm</th>
<th>&gt;=5.0µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3.520</td>
<td>20</td>
<td>3.520</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>3.520</td>
<td>29</td>
<td>352000</td>
<td>2.900</td>
</tr>
<tr>
<td>C</td>
<td>352000</td>
<td>2.900</td>
<td>352000</td>
<td>29.000</td>
</tr>
<tr>
<td>D</td>
<td>3520000</td>
<td>29.000</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Room classification acc. GMP

### 1.3 Practice of particle measurement

In order to be able to classify a cleanroom accordingly, the particle concentration in a sufficiently large proportion of the air volume per unit of time must be determined by measurement. Since a single particle counter can only measure a limited volume flow per unit time, with larger rooms, use of multiple particle counters is necessary. The ISO 14644-1 defines the following relation:

\[ NL = \sqrt{A} \]

Equation 1:

Where NL is the number of particle measuring points and A is the area of the clean room in square meters.

ISO 14644-1 demands that the particle measuring points are very uniformly distributed within the room and positioned at working height and that depending on the detected cleanroom class, a certain minimum sample volume per unit of time and per measuring point is required in order to obtain statistically trustworthy measurement results. The standard defines in this respect the minimum amount of 20 particles of the largest particle size of the considered cleanroom class. The minimal necessary measurement volume can be calculated as follows:

\[ V = \frac{20}{C} \times 1000 \]

Equation 2: where V is the class limit, the minimum sample volume of a measuring point in liters and C in particles per cubic meter of the largest particle size of the specified cleanroom class.

Other constraints that have to be taken into account are the minimum sample volume of 2L and the minimum sampling time (= measurement time) of 1 minute.
1.4 Acceptance criteria

According to ISO 14644-1, a cleanroom class is considered to be achieved if the following criteria are met:

- The average particle concentration at each measurement point is below the class limit
- At less than 10 measurement points, the calculated 95% upper confidence limit must be below the class limit.
- These cleanroom valuation methods can be explained by way of an example with the following assumptions.

**Cleanroom floor space: 4 x 5 m**

**ISO class 3 @ >=0,1µm**

ISO Class 3 defines as the upper limit 1000 particles / m³ at a particle size of >= 0.1 micron.

On the basis of clean room area, the minimum number of measurement points is calculated with Equation 3

\[ \sqrt{4 \times 5} = 4.47 \]

Equation 3:

The nearest integer \( \geq 4.47 \) is 5, which means that at least 5 measuring points have to be used.

The minimum required sample volume for each measurement point is calculated with Equation 2

Minimum sample volume = \( \frac{20}{\text{class limit on particle size}} \times 1000 = \frac{20}{0.1} \times 1000 = 20 \) liters

When using a particle counter with 28.3l / min, a measurement time of \( \frac{20}{28.3} \times 60 = 43 \) seconds per minute would be sufficient. However, since ISO 14644-1 defines as an additional constraint the minimum measuring time of 1 min, the necessary measuring time is 1 min.

Since, in this case, however, less than 10 measurement points were measured, the calculation of the 95% confidence interval is necessary. The following table shows exemplary measurement results:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Particle Count &gt;=0.1µm/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1: 580 particles</td>
<td>&gt;=0,1µm/m³</td>
</tr>
<tr>
<td>Measurement 2: 612 particles</td>
<td>&gt;=0,1µm/m³</td>
</tr>
<tr>
<td>Measurement 3: 706 particles</td>
<td>&gt;=0,1µm/m³</td>
</tr>
<tr>
<td>Measurement 4: 530 particles</td>
<td>&gt;=0,1µm/m³</td>
</tr>
<tr>
<td>Measurement 5: 553 particles</td>
<td>&gt;=0,1µm/m³</td>
</tr>
</tbody>
</table>

To get the 95% upper confidence limit, the arithmetic average has to be calculated first.

\[ m = (580+612+706+530+553)/5 = 596 \text{ particles } >=0,1µm/m³ \]
The standard deviation is calculated as follows:

\[ s = \sqrt{\frac{(580 - 596)^2 + (612 - 596)^2 + (706 - 596)^2 + (530 - 596)^2 + (553 - 596)^2}{(5 - 1)}} = 69 \]

From the distribution function (table of Bartsch - mathematical formula collection), \( t \) can be determined depending on the number of measurement points:

\[ t = 2,1 \]

The 95% confidence interval can be determined as follows:

\[ 95\% \text{ Vertrauensintervall} = \bar{m} + \left( \frac{t \cdot s}{\sqrt{n}} \right) = 596 + \left( \frac{2,1 \cdot 69}{\sqrt{5}} \right) = 661 \]

Equation 4:

The result means that, the number of particles is less than or equal 661 particles / m³ with 95% probability. Therefore, the class limit of 1000 particles > 0.1 µm / m³ is met.

If the measurement results based on the calculations are subject to a broad diversification e.g.

**Measurement 1:** 926 particles >= 0.1µm / m³

**Measurement 2:** 958 particles >= 0.1µm / m³

**Measurement 3:** 937 particles >= 0.1µm / m³

**Measurement 4:** 963 particles >= 0.1µm / m³

**Measurement 5:** 214 particles >= 0.1µm / m³

the 95% confidence interval would be 1108

Due to the large standard deviation, the result is well above the class limit of 1000 particles > 0.1 µm / m³.

These acceptance criteria and calculation methods are to be used only for single measurements and have no meaning in a continuous particle monitoring, since a much larger number of measurements is carried out in this case, and the statistical uncertainty lowers substantially thereby. In most cases, a single particle counter per cleanroom is sufficient in a continuous detection - only in very large clean rooms and especially in anticipation of unevenly concentrated distribution within the cleanroom, the installation of two or more particles measuring points makes sense.
Niotronic Hard- & Software GmbH
office@niotronic.com, +43 316 698200