Calculation of product contamination and required cleanroom class

Air change rate for cleanrooms with non-unidirectional airflow

Ensuring the air supply rate to a cleanroom complies with the EU GGMP and ISO 14644-3 recovery rate requirements

Update on the ISO 14644/14698 series of standards – April 2016
Editorial

With the recent publication of ISO 14644-1:2015 and ISO 14644-2:2015, standards are currently on everybody’s mind. BSI has organised a conference on these two new revisions of existing standards, as well as on the new cleanroom energy management standard currently under development. ESET is including a training course on the new standards at its annual ENTECH Technical Conference, and training organisations everywhere are providing their own courses, some of which are listed on page 32 of this journal.

The focus on these new standards is very desirable. Cleanroom practitioners will re-examine and improve their present practices. The number of contaminated products produced in cleanrooms will hopefully reduce. And the energy management standard, when it is published, will hopefully lead to meaningful energy savings.

But when I think about standards in general, I recall a conference in Italy, some years ago, at which I had been asked to argue the case for negative pressure isolators for the preparation (compounding) of cytotoxic drugs in hospital pharmacies, as widely used in the UK. The other speaker was arguing the case for using open-fronted Class II safety cabinets for this application, as being more widely used in mainland Europe. The other speaker was first. His case was largely based on the safety cabinets being compliant with the relevant standards, especially BS EN 12469:2000 and having been extensively tested by recognised testing establishments in several different countries. When it came to my turn, I realised that I wasn’t going to mention a single standard in my presentation. I was relying on a sound technical case as well as the fact that the isolator I was talking about had been developed with senior hospital pharmacists, i.e. the users. Neither of us ‘wore’ the argument but the occasion emphasised for me that, actually, standards aren’t everything. Blind compliance is just as dangerous as standards aren’t everything. Blind application of standards that are too tightly written can stifle progress.

Coming back to particles, at the time of writing, a New Work Item Proposal is being voted on in ISO. This is for a deposition standard which will become ISO 14644-17 if it goes ahead. The logic of this standard is that particles in the air do not damage the product until they reach the product and deposit on it. In support, this issue of CACR contains the third part of a series of articles by Bill Whyte, Koos Agricola and Martin Derks reporting on the work that they have done on the subject, see page 4.

This issue also contains two distinct articles about airflow, by Alexander Fedotov and by Bill Whyte. The important thing to remember when reading these is that for calculating the steady state concentration, it is the airflow rate, not the air change rate that removes the particles that are dispersed in the cleanroom, and that for calculating the recovery time, it is the air change rate not the airflow rate that is used for the calculation.

The final main feature in this issue is a summary of the status of every standard in the ever-growing ISO 14644 series. The key standard in the series is of course ISO 14644 Part 1, ‘Classification of air cleanliness by particle concentration’. According to ISO, a cleanroom cannot be called a cleanroom unless it is classified in accordance with ISO 14644 Part 1. There are other cleanliness attributes including air cleanliness by chemical concentration, air cleanliness by nanoscale particle concentration, surface cleanliness by particle concentration and surface cleanliness by chemical concentration which can be used alongside air cleanliness by particle concentration, but it must be alongside, not instead of. Unfortunately, ISO 14649 Parts 1 and 2 have not progressed thought the normal periodic review process and do not include ‘levels’ of air and surface cleanliness by microbial contamination, so there is no way, within this ISO series, of specifying microbial cleanliness attributes. CEN (the European Committee for Standardisation) has now picked up this work and hopefully, within a reasonable period of time, we will be able to have cleanrooms with defined microbial cleanliness levels.

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Airborne particle deposition in cleanrooms: Calculation of product contamination and required cleanroom class

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Abstract
This is the third and final article in a series that discusses the deposition of airborne particles onto critical cleanroom surfaces. This article explains a method for calculating the amount of particle or microbe-carrying particle deposition onto cleanroom surfaces, such as product, and a method for calculating the airborne particle cleanliness class, or airborne microbial concentration that is required to obtain a specified and acceptable amount of product contamination.

Introduction
Previous articles in this series
In the first article of this series, Whyte, Agricola and Derks (2015) reviewed the various mechanisms of surface deposition of particles in cleanrooms and concluded that the important mechanisms were gravitational settling, turbulent deposition, electrostatic attraction and, for particles less than about 0.5 µm, Brownian diffusion. Experiments were carried out with particles ≤1µm which showed that over 80% of the deposition was by gravitational sedimentation.

In the second article, Whyte, Agricola and Derks (2016) described an investigation in a cleanroom into the relationship between the airborne particle concentration and particle deposition rate (PDR). These two quantities are related by the deposition velocity of particles through the air, which allows the PDR to be calculated from the airborne concentration, and vice versa. Most particle sampling methods in cleanrooms report the concentration of ‘cumulative’ counts, which includes all particles above a considered size. Deposition velocities were not previously known for a range of cumulative counts but these were obtained in our second article by experimental and theoretical investigations supplemented by previously-published results.

Particle deposition rate (PDR)
The PDR is obtained by measuring the number of particles that deposit over a standard time onto a standard surface area, and is obtained using the following equation:

Equation 1
\[ \text{PDR}_\text{D} = \sum \frac{D}{C_t} \times \text{t} \]

where, \(\text{PDR}_\text{D}\) is the particle deposition rate of particles of a size D µm, \(C_t\) is the initial surface concentration, and t is the time of exposure. The units of measurement of PDR used in our previous two articles were number/m²/hour but airborne particle concentrations in cleanrooms are usually reported per m³ and, to simplify the calculations, the PDR units used in this article are mainly number/m³, or occasionally number/m²/hour. An analogous expression that can be used with airborne microbe-carrying particles (MCPs) in the microbial deposition rate (MDR), which is calculated by use of the following equation:

Equation 2
\[ \text{MDR} = \frac{n}{\text{Surface}} \]

where, n is the number of MCPs deposited on a standard area surface.

The MDR is determined by expose a settle plate for several hours, incubating the plate, and counting the microbial colonies. The nutrient agar surface of the plate will be sterile and therefore the initial count need not be ascertainment, as in Equation 1. The number of MCPs that deposit onto a standard area such as m², in a standard time such as one second, is then calculated to determine the MDR.

Relationship between PDR, airborne particle concentration, and deposition velocity
The relationship between the PDR and airborne particle concentration is given by the following equation:

Equation 3
\[ \text{PDR} = \frac{C}{v_D} \times \text{t} \]

where, \(C\) = airborne concentration of particles of a size D µm and \(v_D\) = deposition velocity of particles of a size D µm.

If the PDR is known, the number of particles that will deposit onto a surface can be calculated by use of the following equation:

Equation 4
\[ \text{Number of particles deposited} = \frac{\text{PDR} \times t}{\text{Surface} \times \cos^2(\theta)} \]

where, a = area of exposed surface, and t = time the surface is exposed to airborne contamination.

If the surface area slopes at an angle of \(\theta\) to the horizontal, an ‘effective horizontal area’ may be used to produce a more accurate result. This is obtained by calculating the horizontal surface area by \(\cos^2(\theta)\).

By substituting the value of PDR, given in Equation 3 into Equation 4, the following equation is obtained that allows the number of particles deposited onto a surface to be calculated from the airborne concentration.

Equation 5
\[ \text{Number of particles deposited} = \frac{\text{PDR} \times t}{\text{Surface} \times \cos^2(\theta)} \]

If MCPs are considered, a set of analogous equations to those given above can be used, where MDR is substituted for PDR, and MCPs for particles.

Cleanroom airborne cleanliness classifications
Classification according to the PDR
A cleanroom can be classified according to its PDR by the method given in the VCCN Guidelines 9 (2014). In these guidelines, the Particle Deposition Class (PDC) of a cleanroom is determined by the following equation:

Equation 6
\[ \text{PDC} = \log_{10}(\text{PDR} + D) \]

where, \(\text{PDR}\) is the maximum permitted PDR (number/m³/h) of particles that are equal to, or larger than, the considered particle size, D (µm).

Classification according to airborne particle concentration
The airborne cleanliness of a cleanroom is classified by ISO 14644-1 in terms of the concentration of particle sizes in the range between a0.1 µm and a5µm, and use of the following equation:

Equation 7
\[ C = 10^6 (D_100)^{1/3} \]

where, \(C\) is the maximum permitted concentration of airborne particles that are equal to, and greater than, the considered particle size, N is the ISO class number, and D (µm) is the considered particle size.

Rewriting Equation 7 in terms of the cleanroom class (N) gives the following equation, which allows the ISO Class (N) to be calculated from a concentration of particles of a considered cumulative size:

Equation 8
\[ N = \log_{10} \left( \frac{C}{100} \right) \]

where, \(C\) is the concentration of particle sizes in the cleanroom air. However, it was found that the PDR was obtained in the cleanroom experiments reported in the second article of this series (Whyte, Agricola and Derks, 2016) and given as a percentage of the total count of all particles ≥5µm. Also shown is an extrapolation of the particle size concentrations of ISO 14644-1 calculated by Equation 7. It can be seen that these diverge from the actual concentrations at about 20µm, and by about 30% at 50µm. This is about 10 times greater. Therefore, for more accurate calculations it is better to use sizes above 20µm.

Deposition velocity of particles
The deposition velocity of particles is their velocity through air towards a cleanroom surface. The deposition velocities of ‘discrete’ sizes of particles have been obtained both theoretically and experimentally by various researchers, and this information is discussed in our second article. However, the normal method of measuring particles in a cleanroom is by cumulative counts, where all particles above a considered size are measured, but the deposition velocity of cumulative counts have not been previously available. These were determined in our second article, and given in Table 1 in c/m/s.

The cumulative deposition velocities given in Table 1 can be used in Equation 3 to calculate PDRs from knowledge of the cumulative particle concentration in the cleanroom air. However, investigations reported in our second article showed that to calculate the most accurate PDRs, the following restrictions should apply.

1. The calculations should only be applied to ‘operational’ conditions in a cleanroom i.e. during manufacturing, and not in ‘at rest’ conditions.

2. The calculation of PDRs for particles above about 0.1µm should be avoided as the cumulative size distribution, and therefore the deposition velocity, is affected by variations in surface cleanliness and redispersion of particles by activity.

3. With the exception of particles ≥0.3µm, the deposition velocities given in Table 1 were obtained from observations in an ISO Class 8 room. However, it was found that the PDR increased as the particle concentration decreased. This was considered to be caused by lower particle concentrations being associated with higher air supply rates, where smaller particles would be quickly swept from the cleanroom with little time to deposit, but larger particles would still be deposited by gravity. This effect was expected.
to increase as the average residence time of the air reduced. An increase in the turbulent intensity of the air was also thought to be a contributing factor. For larger particles between about 0.1 µm and 0.5 µm, the deposition velocities would be expected to increase by about 1.7-fold if it applied to an ISO Class 7 cleanroom, about 3-fold if it applied to an ISO Class 6 cleanroom, and about 5-fold if it applied to an ISO Class 5.

4. Particles 0.1µm or 0.5µm were expected to be less influenced by gravity, and the same deposition velocity applied over the range of cleanroom cleanliness classes.

The main, and usually only, source of MCPs in cleanroom air is personnel. Micro-organisms grow on the skin of personnel and, during activity, micro-organisms are dispersed into the air on skin cells, or fragments of skin cells. MCPs have various shapes, and it is normal to consider particle movement in air and deposition onto surfaces, in terms of equivalent aerodynamic diameter, which is the diameter of a sphere of unit density that settles at a rate equal to the particle being considered. The equivalent aerodynamic particle diameter is not the same as the equivalent optical particle diameter, the latter being used for the sizing of particles by optical particle counters. The average equivalent aerodynamic diameter of airborne particles has been estimated by Noble et al (1963) and Whyte and Hejab (2007) to be about 12µm.

The deposition velocity of the average size of airborne MCPs in different cleanliness conditions in cleanrooms has been recently investigated by Whyte and Eaton (2016), and reported in an article to be published soon. It was found that the deposition velocity increased as the cleanliness of the cleanroom increased, in a similar way to particles, and the results of the study are given in Table 2.

The purpose of this article is to explain calculation methods that can be used for the following purposes:

1. Establish the contamination rate of products manufactured in a cleanroom, when the PDR or airborne particle concentration is known.
2. Establish the maximum airborne cleanliness class, in terms of PDR or airborne particle concentration, for an acceptable and specified amount of product contamination.
3. Repeat (a) and (b) for MCPs.

Before discussing the methods used to carry out these three objectives, it is necessary to consider how the PDR or MDR, and airborne concentrations of particle and microbial contamination, should be sampled to ensure accurate results.

Measurement of airborne contamination in cleanrooms
It has been demonstrated that particle concentrations will vary about a cleanroom. In non-unidirectional airflow cleanrooms, Whyte et al (2010) have shown that the airborne particle concentration can vary about a cleanroom, depending on the performance of the air supply diffusers, temperature difference between supply and room temperature, position of the air extracts, and position of sources of contamination. Carr (1994) also reported that the particle concentrations in a unidirectional cleanroom will vary by up to 10-fold between locations. It is therefore important to ensure that sampling is carried out as close as possible to the product, or other critical surface, so as to reflect the actual airborne contamination adjacent to the surface.

Figure 2 shows the airborne concentration of particles 10µm measured during an experiment reported in the second article in this series. It can be seen that the airborne concentration varied by more than 10 times, and if particle deposition is to be accurately predicted, sampling must be carried out at the same time as products are exposed to deposition, and include periods of low and high activity. Sampling should also be carried out over a suitably long period of time, or if only short manufacturing times occur, by multiple sampling.

Calculation of the number of airborne particles deposited onto product
The number of airborne particles that may deposit onto a product, or another critical surface, can be calculated from knowledge of either the PDR or the airborne particle concentration. Both these methods are now considered by use of the following example:

A product has a horizontal upper surface area of 2 cm² (0.0002m²) that is exposed for 10 min (600s) to airborne contamination in a non-unidirectional ISO Class 8 cleanroom. The reliability of the product is known to be affected by contamination with particles greater than 10µm, and the likely number of these particles that will be deposited onto a product is required.

Table 2: Deposition velocities (cm/s) of MCPs in relation to airborne concentrations

<table>
<thead>
<tr>
<th>Concentration of MCPs/m³</th>
<th>Deposition velocity (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>0.5</td>
<td>1.61</td>
</tr>
<tr>
<td>5</td>
<td>2.04</td>
</tr>
<tr>
<td>10</td>
<td>3.68</td>
</tr>
<tr>
<td>50</td>
<td>8.02</td>
</tr>
<tr>
<td>100</td>
<td>16.01</td>
</tr>
<tr>
<td>200</td>
<td>32.01</td>
</tr>
<tr>
<td>500</td>
<td>79.99</td>
</tr>
</tbody>
</table>

Deposition calculated by means of the PDR: A witness plate, or instrument that measures PDR in real time, is placed adjacent to product, and sampling carried out for a period of several hours. The PDR of particles ≥10µm was found to be 6.0×10⁻⁶dm³/h (60/m³h). The number of particles deposited onto a single product can now be calculated by means of Equation 4.

Number of particles deposited onto product = PDR*τ*a* 0.0012 x 60² ÷ 2.03

This calculation shows that about 2 particles ≥10µm may be deposited on each product.

Deposition calculated by means of the airborne particle concentration: Product contamination can be calculated as follows:

1. The airborne concentration of the critical size of particles ≥10µm is measured adjacent to the product. Sampling losses of particles into the airborne particle counter are minimised and, therefore, no sampling tube used. The air is sampled during normal manufacturing and measured over a sufficiently long period of time to obtain a reliable average concentration, which was 2500m⁻³.

2. The PDR is determined by Equation 3 from the airborne particle concentration. The cleanroom was known to be an ISO Class 8 and, therefore, the deposition velocity of particles ≥10µm, obtained from Table 1, is 0.9 cm/s (0.009 m/s).

Therefore, PDR (nm/s) = c ≥10µm 2500 x 0.089 = 22.5

3. Knowing the surface area of product exposed to airborne contamination is 2 cm² (0.0002 m²) and the time exposed is 10 min (600 s), the product contamination can be determined by Equation 4.

Number of particles deposited onto product = PDR*τ*a* 22.5 x 0.0002 ÷ 60² × 2.7

This method of calculation shows that each product will be contaminated by an average of 2.7 particles ≥10µm. This value is greater than obtained by the PDR method of calculation but a variation between the two methods should be expected, and caused by differences explained in our second article.

Calculation of maximum airborne particle class in a cleanroom
Cleanrooms are costly to build and run, and, if a cleanroom is cleaner than required, the expensive supply of clean air will be costly and wasteful of energy resources. If the cleanroom design produces insufficiently-clean conditions, then an unacceptable amount of product contamination may occur. It is, therefore, best that the cleanroom class is matched to a specified and acceptable amount of airborne product contamination, and the method to obtain this is now illustrated by an example.

It is considered that the critical size of particles that causes a malfunction when a product is contaminated is ≥10µm, and particle contamination should not be greater than one particle in a hundred products. The horizontal area of product exposed to deposition of particles ≥10µm (0.0002 m²) and it is exposed for 10 minutes (600s).

Calculation of the maximum PDR class: The PDR required for the specified level of product contamination (1 in 100 products) from particles ≥10µm can be calculated by use of the rewritten Equation 4:

PDR = number of particles deposited per product ÷ area of product ÷ deposition time

The Particle Deposition Class (PDC) can then be found by reference to VCCN Guidelines 9 (2014) where it will be seen that, for particles ≥10µm, the upper limit of a PDC Class 4 cleanroom is 10000 m⁻³h. Therefore, a PDC of 4 is required.

Calculation of maximum airborne particle class requirement: The maximum airborne particle concentration for an acceptable amount of product contamination from particles ≥10µm can be obtained by firstly calculating the required PDR. This was found in the previous paragraph to be 0.083 m/s². The required particle concentration is then calculated by using the deposition velocity of particles ≥10µm.

Therefore, PDR ≥10µm = c ≥10µm 2500 x 0.83 = 21.25

Using the rewritten Equation 4, the maximum particle concentration can be calculated as follows:

N = log (1 ÷ 100) = 1.7

Therefore, the ISO Class of required cleanroom to maintain an airborne contamination rate of 1 in 100 products is just over ISO Class 5. However, a second step will improve the accuracy of the calculation, as the deposition velocity was assumed to apply to an ISO Class 8 cleanroom, whereas the required cleanroom was closer to Class 5. The deposition velocity used in the calculation was assumed to be 3 times greater i.e. 2.7 cm/s (0.027 m/s). The previous calculation is now repeated using a deposition velocity of 0.027 m/s and the maximum airborne particle concentration found to be 3.1 m⁻³, and the calculation must now be repeated in Table 1 to uncertainties associated with particle measurements, ISO 14644-1:2005 requires that ISO Class should be given in increments no greater than 0.5. Therefore, the maximum ISO Class is 5. It has been previously shown that the concentrations of cumulative counts of particles ≥0.1µm that the cleanroom found in cleanrooms diverge at about ≥10µm from the particle counts expected by extrapolation of the particle size.

Using the rewritten Equation 8, the maximum particle concentration can be calculated as follows:

Maximum airborne particle concentration (≥10µm) = PDR ≥10µm ÷ 0.009 × 9.2 m⁻³

A concentration of 9.2 m⁻³ is, therefore, the maximum airborne concentration of particles ≥10µm that the cleanroom should achieve. However, it is normal practice to design a cleanroom in terms of an ISO 14644-1 class. The maximum concentration of airborne particles is defined in ISO 14644-1 for particles between 0.1 µm and 10 µm, and had the critical size been in that range, reference to the classification Table 1 given in ISO 14644-1 would have given the maximum class of cleanroom that was required for the calculated particle concentration. However the particle size (≥10µm) is above that size range and it is therefore necessary to calculate the ISO Class by means of Equation 8 as follows:

N = log (1 ÷ 100) = 1.7

Therefore, the ISO Class of required cleanroom to maintain an airborne contamination rate of 1 in 100 products is just over ISO Class 5. However, a second step will improve the accuracy of the calculation, as the deposition velocity was assumed to apply to an ISO Class 8 cleanroom, whereas the required cleanroom was closer to Class 5. The deposition velocity used in the calculation was assumed to be 3 times greater i.e. 2.7 cm/s (0.027 m/s). The previous calculation is now repeated using a deposition velocity of 0.027 m/s and the maximum airborne particle concentration found to be 3.1 m⁻³, and the calculation must now be repeated in Table 1 to uncertainties associated with particle measurements, ISO 14644-1:2005 requires that ISO Class should be given in increments no greater than 0.5. Therefore, the maximum ISO Class is 5. It has been previously shown that the concentrations of cumulative counts of particles ≥0.1µm that the cleanroom found in cleanrooms diverge at about ≥10µm from the particle counts expected by extrapolation of the particle size.

Using the rewritten Equation 8, the maximum particle concentration can be calculated as follows:
Calculation of number of MCPs deposited

To calculate the surface contamination of products, or other critical surfaces, the microbial-carrying particles (MCPs), similar methods are used to those described for particles in the previous sections of this article. These methods are based on a count obtained from either a) settle plates that determine the microbial deposition rate (MDR) or b) an airborne microbial sampler that ascertains the concentration of MCPs in the cleanroom air. The methods are illustrated by the example used in the previous two sections, in which a settling time of 5 min and a surface area of 2 cm² (0.0002 m²) is exposed to airborne deposition of MCPs for 10 minutes (600 s).

Calculation of microbial deposition onto product by use of settle plate counts

The method of calculating the product contamination from the deposition rate of MCPs onto settle plates has been previously discussed by Whyte (1986). This method is analogous to measuring the PDR by witness plates, and is likely to be a more accurate method than that involving the air concentration of MCPs obtained by microbial air samplers. Settle plates are Petri dishes that contain nutrient agar, and when exposed in a cleanroom, MCPs will deposit from the air onto their surface. Settle plates with a diameter of 90mm are commonly used, but 140mm diameter plates are more accurate for use in the low airborne concentrations found in cleanrooms; multiple settle plates are also more accurate. After sampling, the settle plates are incubated at a suitable temperature and time, so that MCPs grow into microbial colonies. The colonies can be counted and used to find the number of MCPs that have deposited onto the settle plate in a given time. Settle plates should be laid out adjacent to product to ensure that the same deposition rate of MCPs is likely to occur on these plate as on product, and should be exposed for several hours. The calculation of microbial deposition is illustrated by an example.

A settle plate of 14cm diameter (area = 0.0154m²) was laid out adjacent to a product for 3 hours during manufacturing. To obtain an accurate result, the measurement was repeated several times and the number of MCPs deposited was found to average 3 per plate. The microbial deposition rate (MDR) was calculated by means of Equation 2 as follows:

\[
\text{MDR} = \frac{\text{number of MCPs deposited on a product} \times \text{time of exposure}}{\text{exposed surface area} \times \text{time}}
\]

This MDR is then used to calculate the product contamination. As the product has an exposed horizontal area of 2cm² (0.0002m²) and MCPs have 10 minutes (600s) to deposit, the product contamination rate is as follows:

\[
\text{Number of MCPs deposited on a product} = \frac{\text{MDR} \times \text{time of exposure} \times \text{exposed surface area}}{\text{time}} = \frac{0.0002 \times 600 \times 0.0002}{10} = 0.018
\]

This is equivalent to a contamination rate of 1 in 518 products.

Calculation of the maximum MCP deposition rate for a specified product

Calculation of the maximum airborne microbial concentration, for a specified product contamination rate

MCP contamination has been calculated above for calculating the maximum airborne cleanliness class of cleanroom, and for acceptable product contamination rate of particles. A similar method can be used with MCPs, and is demonstrated by use of the same manufactured product whose horizontal area is 2 cm² (0.0002m²) and exposure time to airborne contamination is 10 minutes (60 s). The acceptable microbial product contamination during manufacturing is set at 1 product in 1000.

Calculation of maximum microbial deposition rate

The maximum MDR for a specified contamination rate of 1 in 1000 products can be calculated from the rewritten Equation 3.

\[
\text{Maximum MDR} = \frac{\text{number of MCPs deposited on product} \times \text{exposed surface area}}{\text{time}} = \frac{0.0003}{(0.0002 \times 600) \times 0.0002} = 0.0083/\text{m}^3
\]

This MDR can be used to obtain the required clearance rate of the cleanroom in terms of the maximum number of microbes deposited on a settle plate. If the settle plate used to sample the air is 14 cm diameter (surface area 0.0154 m²) and exposed for 3 hours (360s), the maximum microbial count on the settle plate is calculated as follows:

\[
\text{Maximum number of MCPs on a settle plate} = \text{MDR} \times \text{time of exposure} = 0.0083 \times 0.0154 \times 3 = 0.0003
\]

This result of 1.4 per settle plate is the number of MCPs that should not be exceeded if the specified product contamination rate of 1 in 1000 products is not to be exceeded.

Calculation of maximum airborne concentration of MCPs

The maximum airborne concentration of MCPs in a cleanroom can be calculated in a similar way to that previously described for airborne particles, and illustrated by an example. To start the calculation, it is necessary to have an estimate of the possible deposition rate of the MCPs (as determined by a first estimate, the cleanroom is assumed to be a non-UDAF type with an airborne concentration of 50ml/m³, and by consulting Table 2 it can be seen that the deposition velocity of the average size of MCPs at that airborne concentration is 0.24m/s (0.0042 m/s). The maximum MDR has been calculated in the previous section and, knowing it is 0.0083/m³, the maximum MCP concentration is calculated as follows:

\[
\text{Maximum MCP concentration} = \text{MDR} = \frac{0.0083}{0.0042} = 1.96/\text{m}^3
\]

The calculated concentration of 1.98/m³ is lower than the concentration first estimated at the start of the calculation (50/m³). This is the result of the calculation should be repeated using a more accurate estimate of the deposition velocity. By consulting Table 2 it can be seen that the deposition velocity for a air concentration of 1.98/m³ would be closer to 1.5 cm/s i.e. 0.015m/s. Using this deposition velocity, the maximum MCP concentration is re-calculated and found to be 0.055/m³.

\[
\text{Maximum MCP concentration} = \text{MDR} = \frac{0.0083}{0.015} = 0.55/\text{m}^3
\]

Discussion

This is the third and last article of a series that discusses the deposition of airborne particles onto critical surfaces in a cleanroom. The Introduction to this present article discusses the inter-relationship between the concentration of airborne contamination, the particle or microbial air sampler (PDR or MDR), and the deposition velocity of particles and MCPs moving through air under the influence of deposition forces, which has been described in previous articles. We have also shown that these investigations, and the conclusion drawn from them in our second article (Whyte, Agricola and Dersch, 2016) that microbe-carrying particles (MCPs) can cause contamination when these particles settle onto product surfaces can be calculated from knowledge of the outcome of these investigations, the present method will give useful results, especially as no method is presently available to calculate the expected rate of product contamination. A method is also given in this article for calculating the maximum airborne particle concentration, and a method of estimating product cleanliness class of cleanroom. A new method has been introduced that calculates the maximum airborne concentration of airborne contamination of either a specified product or airborne particle, and illustrated by an example. To start the calculation, it is necessary to have an estimate of the possible deposition rate of the airborne contamination, and the maximum airborne concentration of airborne contamination is by the PDR or MDR as this is the lowest concentration which will cover all ventilation conditions in a cleanroom. As the deposition rate and airborne concentration of contamination should be measured adjacent to the product, and over air contamination rate at the product exposure area of product exposed to deposition, and time of exposure. Instruments have been available for some time to measure the PDR onto cleanroom surfaces such as silicon wafers, but it is only recently that relatively inexpensive and portable instruments have become available (Agricola and Dersch, 2016). This article presents a method, where an instrument to measure PDR is not available, the airborne concentration of particles above the critical size can be measured by an airborne particle counter, and the PDR calculated by knowledge of its corresponding deposition velocity for cumulative counts.

Table 1 gives the deposition velocities of cumulative counts of a range of particle sizes. However, the deposition velocities may vary from those given in the table if the test method has been demonstrated to be a method that matches an accepted and specified contamination rate of product to a maximum cleanliness class of cleanroom. An example is given to show how this can be calculated for the PDC (according to VCCN 9), and airborne particle class (according to ISO 14644-1).

It is accepted that the calculation of the maximum ISO class for a cleanroom using the methods suggested in this article is unlikely to be accurate, but should give a good indication of the type of cleanroom required e.g. non-uni-directional with a high or low air supply, with a low or high airflow, or the requirement of separate devices, and should be a considerable advance over the present method of using an informed guess. This often leads to cleanrooms that are much cleaner than needed, with unnecessary noise and energy costs. Occasionally, and more seriously, cleanrooms can be built that are not clean enough to avoid excessive airborne contamination. To avoid these problems, a method is required that matches an acceptable and specified contamination rate of product to a maximum cleanliness class of cleanroom. An example is given to show how this can be calculated for the PDC (according to VCCN 9), and airborne particle class (according to ISO 14644-1).

To obtain the most accurate results from the equations given in the Introduction, the deposition rate and airborne concentration of contamination should be measured adjacent to the product, and over air contamination rate at the product exposure area of product exposed to deposition, and time of exposure. Instruments have been available for some time to measure the PDR onto cleanroom surfaces such as silicon wafers, but it is only recently that relatively inexpensive and portable instruments have become available (Agricola and Dersch, 2016). This article presents a method, where an instrument to measure PDR is not available, the airborne concentration of particles above the critical size can be measured by an airborne particle counter, and the PDR calculated by knowledge of its corresponding deposition velocity for cumulative counts.

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Agricola K (2015). Practical contamination control in cleanrooms. Calculations should be a useful tool in the prevention of product contamination. These could be used to determine the maximum deposition velocity. A method is also described that calculates the maximum deposition of MCDs on settle plates, or the airborne concentration, for a specified and acceptable amount of product contamination. These calculations should be a useful tool in contamination control in cleanrooms.

References
Air change rate for cleanrooms with non-uni-directional airflow

Alexander Fedotov

Abstract

Air change rate (ACR) is widely used in the specification of cleanrooms, partly by tradition and partly to compare different cleanrooms or designs. Recommended ACRs have also been a feature of guidelines and standards over the years, notwithstanding the fact that it is volume flow rate and not ACR that is directly related to the removal of airborne contamination. This article describes how ACR can be determined for cleanrooms based largely on equations developed by Camfiil starting in the 1990s. It also shows practical ways of using analytical calculations and describes a flexible approach for determining ACR through the design, testing and operation stages to avoid oversizing and to save energy. Practical examples are included for illustration.

General

Air change rate (ACR) has a key influence on energy consumption in cleanrooms and efforts to reduce it are important. ACR in the steady state depends on five factors (Figure 1):

a. outdoor air required for breathing, according to occupational health standards;

b. compensation for air loss through local exhausts, e.g. safety cabinets used for the elimination of harmful matter;

c. maintaining pressure differentials;

d. elimination of heat loads;

e. maintaining pressure differentials.

Airflow rates for purposes other than to maintain the specified air cleanliness class i.e. factors a) – d) should be kept to a minimum. Normally they should be less than the airflow rate needed to provide the specified air cleanliness class (factor e) if a non-analytical approach with the use of tables, recommendations or ‘rules-of-thumb’ is used.

The first question to ask is what is the ACR appropriate for achieving a specific cleanliness class? This is a difficult question that has no simple answer because the cleanliness class doesn’t just depend on the ACR. It can vary for the same cleanroom depending on characteristics of surfaces, materials, equipment and, more than anything, on people: on how they follow cleanroom procedures regarding operation, behavior, hygiene rules, selection of clothes etc.

Cleanliness class also depends on the cleanroom occupancy state, (as-built, at-rest, operational). A cleanroom with an ACR of 20 h⁻¹ can be ISO class 4 at-rest but it will barely achieve ISO class 8 in the operational state if personnel wear poor clothes that were last washed a long time ago or if cardboard boxes are used in the cleanroom. That is why it is normally assumed that all cleanroom procedures are properly followed when determining ACR.

An important point is that in non-uni-directional airflow cleanrooms the concentration of airborne contamination is controlled by mixing and dilution, i.e. it depends on the rate of generation of contamination in the cleanroom and the volume flow rate of clean air entering the cleanroom (which is equal to the volume flow rate of mixed air leaving the cleanroom). This is why the parameter ‘room volume’ is included in the equations for deriving ACR shown later.

The specification of ACR for cleanrooms has its own history:

1950s: US standards for operating rooms in hospitals:

• 12 h⁻¹ for existing operating rooms;

• 25 h⁻¹ for new operating rooms.

1960: early versions of Fed. Std. 209:

ACR = 20 h⁻¹.

1977: FDA Aseptic Guide repeated ACR = 20 h⁻¹.

1988: 20 h⁻¹ for class 100 000 (ISO 8) was removed in Fed. Std. 209D.

1990: Prof. J. Gustafson from Camfiil offered a general dilution equation and software for cleanliness class calculations [1–2].

2004: the revised version of FDA Aseptic Guide retained 20 h⁻¹.

2014: the author offered a flexible approach for determining and adjustment of ACR at different stages (design – testing – operation) [3].

2015: ISPE Guide offered very broad limits for ACR and specific methods for calculation [4].

A general trend can be observed:

• in the beginning standards were rather strict in their requirements for ACR,

• the worst (highest) value of ACR was used to size the HVAC system.

• requirements for ACR become more strict in some cases (see below);

• then number values were withdrawn from some documents (US Fed. Std. 209D), or became more flexible in other documents as knowledge in cleanroom technology increased;

• certain regulatory authorities retained the old rigid standards in their GMP rules where they have remained till the present;

• the flexible approach offered by the author provides a solution. This combines approximate calculations at the design stage with more precise measurement and verification at the testing and operational stages as more actual data on particle generation is acquired.

The Non-analytical approach

A number of standards and guides give recommendations on ACR based on tables, with limits or ranges for different cleanliness classes [4–7 and others]. These ranges can be too broad and ineffect, in e.g. ‘rules-of-thumb’. One should be very careful when using these recommendations because they can give values that are too high or too low.

IEST Recommended Practice

The new IEST Recommended Practice PR-CC-012.3, 2015 “Considerations in Cleanroom Design” [4, item 5.2.3] recommends ACR limits for cleanrooms in operation:

• 2 – 20 h⁻¹ for ISO class 8;

• 20 – 200 h⁻¹ for ISO class 7 etc.

There is no advice on how to select ACR values within these ranges. The numbers probably reflect experience in some way. ACR depends on many factors and such wide ranges do not provide proper recommendations at all. The upper limits are too high and following them would lead to a huge energy overconsumption. The authors of this guide understood this and described the approach quite honestly as ‘rules-of-thumb’. The guide also presents analytical models for ACR calculations that consider different factors.

EU GMP

Until 1997, the EU GMP guideline editions recommended 20 h⁻¹ ACR for Grade C and Grade D areas. This was taken from US Fed. Std. 209B (1973) and cancelled in the EUGMP in 1997. The responsibility for determining the necessary ACR for a given cleanroom was left to designers.

FDA Aseptic Guide

This Guide recommends 20 h⁻¹ ACR for class 100 000 cleanrooms (ISO 8) in operation, equivalent to Grade C in the EU GMP 2003 edition.

ISPE Baseline

Many practitioners follow the ISPE Baseline [6]. This recommends 20 h⁻¹ ACR both for terminal sterilization and aseptic processes.

WHO Report

The WHO Report [7, Annex 5 item 4.1.6] says that ACR should normally be between 6 h⁻¹ and 20 h⁻¹. The lower value can be considered a step forward, but it is nullified by the severe standards for recovery time (20 min in item 4.1.10 and even 15 min in item 8.2.14, Table 3 of the same report).

The WHO Report gives 6–20 h⁻¹ ACR without explaining how to select the value, but the worst thing is that it advocates 20 h⁻¹ for the manufacture of non-sterile medicinal products!

ISO 14644-4:2001

This standard recommends ACRs for different applications. These rates are too high and the standard is currently under revision.

USP Pharmacopeia

The monograph 1116 of 35th USP, 2012, gives recommendations for ACR in cleanrooms “in operation”, see Table 1.
To sum up:
• The old conservative value of ACR for cleanrooms (~20 h⁻¹) still appears in normative documents and is confusing (Table 2).
• There are no ACR requirements for non-sterile products (except in the WHO report), but some designers prefer to use 20 h⁻¹.
• Sometimes an ACR of 20 h⁻¹ is applied in the at-rest state, as well as the operational state, when a lower figure would be sufficient.
• The FDA Aseptic Guide specifies class ISO 8 for the operational state only; whereas Grade D in the EU GMP is equivalent to ISO 8 for the at-rest state and limits for the in operation state for particle concentration are not specified.

Thus guidelines are not only different, they are contradictory and unexplainable, as can be seen from Table 2.

A question arises:
• Why does the ISPE Baseline Guide go even further extending this ACR argument to an external sterilized products before sterilisation? Risk analysis shows this makes no sense.

The answers are clear: nobody has given any thought to these questions, and the established ‘rules-of-thumb’ have continued to be applied. This was understandable in the 1950s and 1960s when there was lack of experience, but now there is a wealth of knowledge available on cleanroom operations. The ‘rules-of-thumb’ approach is an anachronism now and should not be accepted.

Unfortunately the strict application of these standards and guidelines can lead to impractical solutions, excessive capital expenditure and energy over-consumption. ACR calculations should be done properly at the design stage, taking into account the anticipated particle generation from people and equipment and the potentially positive contributions of directional airflows and air curtains as well as other local air cleaning devices, which normally have HEPA filters.

Table 2: Comparison of guides

<table>
<thead>
<tr>
<th>Guide</th>
<th>Sterile products</th>
<th>Aseptic processes Before sterilizing filtration</th>
<th>Aseptic processes After sterilizing filtration</th>
<th>Terminal sterilized products</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Aseptic</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EU GMP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ISPE</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>WHO</td>
<td>-</td>
<td>6-20</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Noting:
1. ISO Class 8 is equivalent to EU GMP Grade C, ISO Class 7 to EU Grade B and ISO Class 5 to EU Grade A, all “in operation”.
2. USP and FDA Aseptic Guide do not deal with cleanrooms that are equivalent to EU Grade D.
3. ISO Class 5 (EU Grade A) areas have unidirectional airflow with air velocity specified, but not ACR. ISO Class 5 can be achieved in isolators with non-unidirectional airflow with an ACR much less than 180 h⁻¹.

Table 1: Recommendations for ACR from USP <1116>

<table>
<thead>
<tr>
<th>Class</th>
<th>ISO 8</th>
<th>ISO 7</th>
<th>ISO 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR (h⁻¹)</td>
<td>20</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Notes to table:
1. ISO Class 8 is equivalent to EU GMP Grade C, ISO Class 7 to EU Grade B and ISO Class 5 to EU Grade A, all “in operation”.
2. USP and FDA Aseptic Guide do not deal with cleanrooms that are equivalent to EU Grade D.
3. ISO Class 5 (EU Grade A) areas have unidirectional airflow with air velocity specified, but not ACR. ISO Class 5 can be achieved in isolators with non-unidirectional airflow with an ACR much less than 180 h⁻¹.

It is not possible to make universal recommendations for the ‘in operation’ state because the number of personnel and the type of clothes significantly affects the cleanliness level and ACR required. Nor can such recommendations and standards take into account other factors such as equipment heat loads, numbers of personnel, local exhaust volumes etc. that might be dominant in ACR calculations under certain circumstances.

Analytical methods

General

Analytical methods for ACR calculations can be carried out using:
• general equations;
• dilution equations that do not consider all the parameters of the general equations;
• specific models [4].

All these methods require knowledge of particle generation inside the cleanroom. This can only be very approximate at the design stage as explained later in the article.

Modes of cleanroom operation

Generally modes of cleanroom operation include:
• a transitional period from the relatively clean at rest state to the rather dirtier in operation state;
• a transitional period from the relatively dirty in operation state to the at rest state, or, in the case of a recovery test, a transitional period during which a deliberately high particle concentration is reduced by a defined amount;
• the steady state, which may be in operation or at rest.

For purposes of this article and ACR calculations the first case is not discussed. The transitional period during which the particle concentration or contamination level decreases from its initial level and approaches the steady state contamination level asymptotically (Fig. 2). Cvar is the constant component of the particle concentration that refers to the steady state.

A short recovery time may require a much bigger ACR than is necessary to maintain a steady state. The difference can be in orders of magnitude and is often the reason for over-design.

The variable part cste can be used for estimating the recovery time. The constant part cvar should be the basis for determining of ACRs and airflow rates for the steady state (i.e. normal operation).

General ventilation equation [with acknowledgement to Camilli [11], [12]]

The general equation for the particle concentration C in cleanroom air at time t is:

\[ C = \frac{20}{\kappa_1} \left( t \right) \left( \frac{C_{\text{in}}}{\frac{1}{2} \kappa_2} \right) \]

where

Equation 1

C = Cvar + Const.

where Cvar is the variable component of the particle concentration. This describes

the transitional period during which the particle concentration or contamination level decreases from its initial level and approaches the steady state contamination level asymptotically (Fig. 2). Cvar is the constant component of the particle concentration that refers to the steady state.

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The variable part Cvar can be used for estimating the recovery time. The constant part Cconst should be the basis for determining of ACRs and airflow rates for the steady state (i.e. normal operation).
For cleanrooms \( N_\text{G} = 0 \) and equation (7) becomes simpler:

Equation 8
\[
Q = \frac{G_{\text{out}}}{\epsilon_{\text{G}}}
\]

Ventilation efficiency depends on air distribution and location of sources of contamination and \( \epsilon_{\text{G}} \geq 0.7 \) can be assumed for cleanrooms with non-unidirectional airflow and good air distribution (as assumed in Camfil J. Gustavsson, software for ACR calculations).

Simplified general equation for cleanrooms
So the following simplification can be done for cleanrooms without compromising the sense:
\[
Q = \frac{G_{\text{out}}}{\epsilon_{\text{G}}}
\]

Equation 9

If
\[
\epsilon_{\text{G}} = 0.7 \leq \epsilon_{\text{G}} \leq 1
\]

And equation 2 becomes much simpler:

Equation 10
\[
C = \left( \frac{G_{\text{out}}}{\epsilon_{\text{G}}} \right) \cdot \left( \frac{S_{\text{out}}}{S_{\text{in}}} \right) \cdot \frac{1}{V}
\]

Equation 10 can be used for calculation of both the transitional period and the steady state of a cleanroom and can be supported by a computer calculation program that readily gives curves of particle concentration in the air starting from the dirty state through recovery to the clean state [1, 2]. It is convenient to draw such curves for different cases such as occupancy states, numbers of personnel, clothes, particle generation by equipment and so on.

Steady state and simple dilution equation for cleanrooms
Variable part of Equation 10 can be ignored for steady state and particle concentration can be described by much simpler formula known as the balance equation or dilution equation

Equation 11
\[
C = \frac{C_{\text{out}}}{\epsilon_{\text{G}}}
\]

All equations above are valid for airflow rate in m\(^3\)/s. Transfer to m\(^3\)/h is needed to calculate ACR N:

Equation 12
\[
3600 \cdot Q = \frac{\text{m}^3}{\epsilon_{\text{G}}} \cdot N \cdot V, \text{or}
Q = \frac{3600 \cdot S_{\text{out}}}{\epsilon_{\text{G}} \cdot S_{\text{in}}}
\]

where
\[
S = \text{particle generation in a cleanroom, particles/m}^3;
N = \text{air change rate, ACR, h}^{-1};
C = \text{particle concentration in cleanroom air, particles/m}^3
\]

ACR that is necessary to satisfy limit for particle concentration, \( C_{\text{G}} \), will be:

Equation 13
\[
N = \frac{3600 \cdot S_{\text{out}}}{\epsilon_{\text{G}} \cdot S_{\text{in}}}
\]

where
\[
C_{\text{G}} = \text{class limit for particle concentration, particles/m}^3;
N_{\text{alert}} = \text{alert limit for particle concentration, particles/m}^3, \text{to maintain cleanliness class reliably, it should be lower than} C_{\text{G}} \text{with a reasonable safety margin.}
\]

The impact of a unidirectional airflow zone should be taken into account if there is such a zone in the cleanroom.

Examples of ACR calculations are given below.

Microbiological contamination
The ACR that is necessary for cleanrooms with a specified limit of microbiological contamination can be calculated by estimating the rate of generation of microorganisms from people and equipment as the starting point. If the generation of microorganisms by equipment and their penetration into the cleanroom from the surrounding space is negligible, then the concentration of microorganisms per m\(^3\) of air is equal to:

Equation 14
\[
N = \frac{S_{\text{out}}}{N_0 \cdot V}
\]

where
\[
N_0 = \text{number of personnel and kind of equipment, number of personnel and kind of equipment,}
V = \text{cleanroom volume, m}^3;
N = \text{air change rate, h}^{-1};
60 = \text{number of minutes in 1 hour,}
\]

Testing of the cleanroom provides data which will give a more precise minimum ACR to avoid overspecification. Tests with different ACRs should be done with the cleanroom in the operable state and particle concentrations recorded. It is not necessary to carry out too many tests, just enough to obtain sufficient data to verify the extent that \( N_1 \), can be reduced with confidence to \( N_2 \) with a worthwhile saving in energy use.

Operation stage
\( N_1 \) should be the ACR adopted for the cleanroom in operation.

Lifecycle controls should be arranged to be sure that cleanliness levels are not compromised.

Continuous monitoring of particle concentration can be arranged to detect sudden increases in particle concentration and to switch the HVAC system on to full capacity accordingly.

For personnel, equipment and procedures of cleanroom operation should be in full compliance with cleanroom requirements (see ISO 14644-5).

Safety margin
The use of a safety margin provides some redundancy of ACR at the design stage. Determination of safety margin is arbitrary and should be estimated for each application. It can be from \( 30\% \) for processes where the particle generation by equipment is very low, up to \( 100\% \) when these data are unknown (from 3.3 to 4).

The methods of calculating ACR shown above can be used to obtain an approximate estimate of ACR. At the design stage a reasonable safety margin should be added.

Flexible procedure for ACR estimation
The procedure for estimating ACR (N) increases in precision as more data on particle generation becomes available through each stage of the project, namely the design stage, then the testing stage and, finally, in operation. This is shown diagrammatically in Figure 3 [3].

Stage 1

Design stage
(initial estimation of ACR)

Design stage
(initial estimation of ACR)

Test:
At different values of ACR to determine how particle concentration is affected by ACR

Calculate

\[
N_1 = S_{\text{out}} \cdot N_0
\]

Design stage
(initial estimation of ACR)

Find a reduced \( N_2 < N_1 \)
which will give the required cleanliness level

Verify \( N_2 \) gives the required cleanliness level

Testing stage

(initial estimation of ACR)

Stage 2

Testing stage

(initial estimation of ACR)

Operation stage

(initial estimation of ACR)

Stage 3

Operation stage

(initial estimation of ACR)

Personnel, equipment and procedures of cleanroom operation should be in full compliance with cleanroom requirements (see ISO 14644-5).

Safety margin
The use of a safety margin provides some redundancy of ACR at the design stage. Determination of safety margin is arbitrary and should be estimated for each application. It can be from 30% for processes where the particle generation by equipment is very low, up to 100% when these data are unknown (from 3.3 to 4).

As a safety margin in terms of ventilation efficiency, say \( \epsilon_{\text{G}} = 0.6 \) or even lower if he air distribution is deemed to be poor.

As a safety margin for ACR, expressed as the safety margin factor, e.g. \( \epsilon_{\text{G}} \approx 1.3 \) or 2 etc.

Particle generation in cleanrooms
Personnel and equipment (in some cases) are the main sources of contamination in cleanrooms [5, 10, 12]. Other sources can be ignored for correctly designed, constructed and operated cleanrooms.

Figure 3 – Sequence of actions to determine ACR (N)
Personnel
Particle generation depends on quality of clothes and for particles ≥ 0.5 µm can be estimated approximately as [10]:
• ≥ 1 000 particles/s for cleanroom clothes (shirt and trousers) – see also Table 5;
• ≥ 1 000 particles/s for good cleanroom clothes (overall).
For other particle sizes and types of clothes particle generation per second can be estimated for cleanroom clothes as shown in Table 5 [2].
The number of particles generated varies greatly depending on activity and type of clothes. It is possible to reduce the number of particles by a factor of 10 or 100 with suitable clothes and operating procedures.
Equipment
Particle generation by equipment is often not known, but some data are available [11], see Table 6:

Table 6: Particle generation by equipment

<table>
<thead>
<tr>
<th>Type of machine or equipment</th>
<th>Emission rate of particles ≥ 0.5µm (particles/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial filling machine A</td>
<td>3.3 ∙ 10^3</td>
</tr>
<tr>
<td>Vial filling machine B</td>
<td>5 ∙ 10^3</td>
</tr>
<tr>
<td>Blow-fill-seal (BFS machine)</td>
<td>Between 10^3 and 10^4 depending on type of BFS machinery</td>
</tr>
<tr>
<td>Six-axis robot:</td>
<td></td>
</tr>
<tr>
<td>- unmodified</td>
<td>Unmodified</td>
</tr>
<tr>
<td>- modified to reduce emission</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 7: Reduction of particle concentration in air, particle size 0.5µm, in a function of ACR during time t for the at-rest occupancy state

<table>
<thead>
<tr>
<th>Time t, min</th>
<th>Particle concentration in air for ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 h^-1</td>
<td>1.0 ∙ 10^10</td>
</tr>
<tr>
<td>10 h^-1</td>
<td>1.0 ∙ 10^10</td>
</tr>
<tr>
<td>15 h^-1</td>
<td>1.0 ∙ 10^10</td>
</tr>
<tr>
<td>20 h^-1</td>
<td>1.0 ∙ 10^10</td>
</tr>
<tr>
<td>30 h^-1</td>
<td>1.0 ∙ 10^10</td>
</tr>
</tbody>
</table>

Figure 5 – Particle concentration ≥ 0.5 µm in air for two different qualities of clothes at ACR = 10 h^-1.

The starting particle concentration is taken as C_0 = 3 000 000 000 = 10^10 particles/m³.

Figure 5 shows the results of calculations using Equation 10.

Table 8: Particle generation of different sizes by personnel with different kinds of clothes, particles/s

<table>
<thead>
<tr>
<th>Particle size</th>
<th>Cleanroom clothes</th>
<th>Normal clothes</th>
<th>Hard working</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 µm</td>
<td>10 000</td>
<td>100 000</td>
<td>1 000 000</td>
</tr>
<tr>
<td>0.3 µm</td>
<td>20 000</td>
<td>80 000</td>
<td>400 000</td>
</tr>
<tr>
<td>0.5 µm</td>
<td>10 000</td>
<td>50 000</td>
<td>200 000</td>
</tr>
</tbody>
</table>

Recovery time
The variable part C_{ow} of Equation 2 describes the transitional period, when a cleanroom is reaching its cleanliness class
1. after switching on,
2. after an incident of increased particle concentration or
3. after completion of operations (i.e. transition from the in-operation state to the at-rest state).

This transitional period will decrease if the ACR is increased and can be estimated from the recovery time T_r. According to ISO 14644-3 recovery time is the time for the initial particle concentration to reduce to 1/100 of its original value. The steady state starts at the end of the transitional period and C_{ow} becomes negligible. The transitional period is not the same as the recovery time which is a measure of the ability of the cleanroom to recover. The recovery time may be shorter depending on circumstances. Particle concentration at the steady state gives the cleanliness class.

It is useful to draw graphs using Equation 10 that show how particle concentration reduces with time (Figures 4 and 5) through the transitional period up until the steady state is achieved. These graphs enable the ACR and airflow rate to be determined at the design stage if the particle concentration limit is specified. Recovery time can be specified at the design stage using:
• normative documents or
• agreement between customer and supplier or
• URS.

Some normative documents specify 15–20 min recovery time. Applying a recovery time to applications that are not covered by standards or regulations leads to huge overconsumption of energy. The specification of recovery time must be soundly justified, whether it is necessary at all or if it is possible to specify longer recovery times (e.g. 30, 40, 50 min etc.). Short recovery times should be avoided in the interests of energy conservation, unless they are specified in the relevant industry standards or required by the process.

Specification of recovery time after start-up should be based on the working schedule of the cleanroom and the possibility of switching the cleanroom into its operational mode well before the start of work. Particle monitoring can serve to detect increases of particle concentration and to switch the HVAC system onto full power to eliminate contamination quickly.

Examples of air change rate calculation
The two examples that follow show how the equations are used to calculate the air change rate.

Example 1
To calculate the air change rate required for effective clean-up in an EU GMP Grade B cleanroom with the following parameters:
• volume V = 100 m³;
• considered particle size s ≥ 0.5 µm;
• cleanliness class limit in the operational state is ISO 7 = 3 500 000 particles/m³;
• high efficiency cleanroom clothes – shirt/trousers, particle emission rate 10^3 particles/s (particles ≥ 0.5 µm);
• low efficiency cleanroom clothes – cleanroom coverall, particle emission rate 10^2 particles/s.

It is assumed that personnel follow standard hygiene, behavior, garments changing and other requirements.

The cleanroom has the following parameters:
• volume V = 100 m³;
• considered particle size s ≥ 0.5 µm;
• cleanliness class limit in the operational state is ISO 7, i.e. C_{ow} = 3 500 000 particles/m³.

For other particles sizes and types of clothes particle generation per second can be estimated for cleanroom clothes as shown in Table 5 [2].

The cleanroom has the following parameters:
• volume V = 100 m³;
• considered particle size s ≥ 0.5 µm;
• cleanliness class limit in the operational state is ISO 7, i.e. C_{ow} = 3 500 000 particles/m³.

EU GMP requires the at-rest state to be achieved 15–20 minutes after operations cease. Table 7 and Figure 4 show how to achieve this at ACR = 30 h^-1 for the given particle generation. At ACR ≥ 20 h^-1, t ≥ 25 minutes. It is possible to reduce ACR to 15 h^-1 if the recovery time can be specified at 40 min or if it is not specified at all. Lower ACRs do not achieve the required at-rest state in less than one hour.

Example 2
To show how the quality of clothes affects air cleanliness in a cleanroom where ACR = 10 h^-1. The number of personnel is 4 and two types of cleanroom clothes are considered in the example [10]:
• normal cleanroom clothes – shirt/trousers, particle emission rate 10^3 particles/s (particles ≥ 0.5 µm);
• high efficiency cleanroom clothes – cleanroom coverall, particle emission rate 10^2 particles/s.

It is assumed that personnel follow standard hygiene, behavior, garments changing and other requirements. The cleanroom has the following parameters:
• volume V = 100 m³;
• considered particle size s ≥ 0.5 µm;
• cleanliness class limit in the operational state is ISO 7, i.e. C_{ow} = 3 500 000 particles/m³.

The starting particle concentration is taken as C_{0} = 3 000 000 000 = 10^10 particles/m³ because a 100:1 reduction in particle concentration gives an alert limit of 10 000 = 10^10 particles/m³. Figure 5 shows the results of calculations using Equation 10.
Main feature

High efficiency cleanroom garments allow a cleanliness level of ISO Class 7 to be achieved for an air change rate of 10 h⁻¹ and a recovery time (for a 100:1 reduction in particle concentration) of 40 min (if there are no other sources of contamination). For normal cleanroom clothes ISO class 7 can also be maintained but the safety margin is too low. So normal cleanroom clothes cannot be recommended for ISO Class 7 cleanrooms if \( N = 10 \) h⁻¹.

The author would like to express his highest appreciation to John Neiger, CACR Editor, for his significant editorial contribution.

References


Dr. Alexander E. Fedotov has more than 40 year experience of work in research and industry. His primary specialty is automatic control systems. For the last 30 years he has been involved in cleanrooms, latterly in GMP areas too. He is Managing Director of Invar-project, a private company located in Moscow, Russia. The company is active in cleanroom design and testing for different areas of application, especially for the pharmaceutical industry and hospitals. Dr. Fedotov was one of the founders of the Russian Association of Engineers for Contamination Control (ASENMCO) in 1991. He is currently President of ASENMCO and editor of the magazine 'Cleanrooms' in Russian. He is also the editor of three books: 'Cleanrooms' in 1998, 2003 and 2015, 'Basics of GMP' in 2012 and 'Manufacturing Sterile Medicinal Products' in 2012 (all three in Russian) and has contributed two chapters to 'Cleanroom Management in Pharmaceuticals and Healthcare' (Euromed), 2012 in English. He is Chairman of the Russian Technical Committee for standardization TC 184 ‘Industrial cleanliness’ and Russian delegate to several working groups of ISO TC 209 ‘Cleanrooms and associated controlled environments.’

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TEST TEMPERATURE

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35° C

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Ensuring the air supply rate to a cleanroom complies with the EU GGMP and ISO 14644-3 recovery rate requirements

W Whyte1, N Lenegan2 and T Eaton3

1 School of Engineering, University of Glasgow, Glasgow G12 8QQ, 2 Energy and Carbon Reduction Solutions, Ashton-Under-Lyne, Lancashire, OLS 6RE, 3 AstraZeneca, Macclesfield, Cheshire, SK10 2NA

Introduction

Annex 1 of the EU GGMP covers various aspects of sterile products manufacturing, including contamination control. It suggests that manufacturing cleanrooms will quickly recover from the generation of high concentrations of airborne particles, provided the cleanroom should ‘clean up’ in 15 to 20 minutes (guidance value) after completion of operations, to the particle limit stated for the ‘at rest’ state. This applies to cleanrooms designated Grade B and Grade C, which have non-unidirectional airflow, but not to Grade A cleanrooms which have unidirectional airflow, or to Grade D which has no specified ‘operational’ particle concentration. Achieving this ‘clean up’ time is considered to demonstrate that the cleanroom has a ventilation effectiveness that cannot be guaranteed by a simple air supply rate specification which provides the required airborne contamination in the steady-state condition.

According to the EU GGMP, a Grade B cleanroom should have a maximum concentration of particles ≥5μm during operation of 352,000/m3 and in the rest condition of 3520/m3, therefore the required maximum drop in the concentration of particles during ‘clean-up’ is 100 fold. In a Grade C room, the maximum ‘operational’ condition is 3,520,000/m3 and the ‘at rest’ condition is 352,000/m3, which is a 10 fold reduction.

The concentrations of airborne particles will be lower than actually occurs, because of particle deposition onto cleanroom surfaces caused by gravity (ISO 14644-3:2005 gives two recovery test methods).

The decay relationship between the concentration of particles in the cleanroom air and time is exponential, and the recovery rate is usually determined by Equation 1:

\[ n = -2.3 \times 10^{-1} \times \log_{10} \left( \frac{C}{C_0} \right) \]

Where, \( n \) = recovery rate, \( C \) is the time elapsed between the first and second measurement, \( C_0 \) is the initial concentration, and \( C_0 \) is the concentration after time t.

The recovery rate and recovery time both measure the particle decay and one test result can be easily converted to the other.

No required recovery rate or recovery time is specified in ISO 14644-3, but the EU GGMP requirement of a 100 fold particle concentration reduction in less than 20 minutes is often applied to cleanrooms not regulated by the EU GGMP.

When a non-unidirectional airflow cleanroom is being designed, the air supply rate has to be determined. However, it is usually unclear whether this air supply rate is sufficient to ensure the ‘clean up’ requirements given in the EU GGMP. If the calculated air supply is insufficient the recovery time will be longer than desired and the recovery rate slower. It is not until the cleanroom is built and manufacturing starts that testing can be carried out, and it would be useful if a method was available to predict what air supply rate is necessary to ensure a specified reduction in particle concentration in a given time.

Carrying out a recovery test provides a qualification test that gives confidence that the airflow in the non-UDAF cleanroom is well designed and will provide effective particle removal.

The concentrations of airborne contamination in non-unidirectional airflow rooms can be calculated by a set of equations known as the ‘ventilation equations’, their application to cleanrooms has been discussed by Whyte, Whyte and Eaton (2012). These equations can determine the concentrations of particles or micro-carrying particles (MCPs) in cleanroom air as the particle concentration (a) builds up when activity starts, (b) remains relatively steady during manufacturing, or (c) decays when activity stops. The decay equation can be used to determine the air change rate required to satisfy the EU GGMP ‘clean up’ requirements, or another specified recovery time or rate of particles measured by the ISO 14644-3 recovery test methods.

Decay and recovery rate equations

When people leave a cleanroom and machinery is turned off, the concentration of particles in the cleanroom air will decay. Similarly, when the introduction of test particles is stopped during the ISO 14644-3 recovery test, there will be a decay of particles over time. These decays occur in a random way that is predicted by the Equation 2, and in the manner shown in Figure 1.

\[ C = C_0 e^{-nt} \]

where, \( C \) = airborne concentration of particles after a given decay time, \( C_0 \) = initial airborne concentration of particles, \( N \) = room air change rate, \( t \) = decay time.

It is important to note that in Equation 2 the ‘air change rate’ that affects the decay rate and not the ‘air supply rate’. This is different from the steady-state condition, where the particle concentration in the operational supply air for a cleanroom manufacturing is determined by the air supply rate. The air change rate and the air supply rate are related as shown below.

\[ \frac{C}{C_0} = e^{-nt} \]

The ventilation effectiveness at a location in a cleanroom can be determined by measuring the air change rate at the test location and comparing it to the overall cleanroom average (Whyte et al, 2014). The ratio of the air change rate at the test location to the overall cleanroom average is called the Air Change Effectiveness (ACE) index. It is calculated as follows.

\[ ACE \text{ Index} = \frac{\text{air change rate at location}}{\text{overall air change rate}} \]

If the air mixing is perfect, the ACE index will be 1 but if the test location receives more clean air, the ACE index will be higher than 1. Locations that receive less clean air will have an ACE index lower than 1. When the ACE index is 1, the recovery time of between 15 and 20 minutes is given in the EU GGMP as a ‘guidance’ time but 15 minutes is used as it is the most stringent requirement. Equation 5 is used, as follows, to calculate the required air changes per hour.

\[ N = \frac{2.33}{t} \log_{10} \left( \frac{C}{C_0} \right) \]

or, when logarithms to the base 10 are used.

\[ N = \frac{2.3}{t} \log_{10} \left( \frac{C}{C_0} \right) \]

It is interesting to note that the right hand side of Equations 1 and 5 are identical, and therefore the recovery rate (e) is equal to the air change rate (N) at the test location.

Equations 4 and 5 can be used to calculate the room air change rates (N) required by a cleanroom to comply with the EU GGMP or other recovery times or rates. How this is done is illustrated by the following example, which calculates the air change rate for EU GGMP Grade B and C cleanrooms, and can be used for all Grade B and Grade C cleanrooms as long as air mixing is effective.
The air change rate required to produce the correct 'clean up' in an EU GGMP Grade B cleanroom with perfect air mixing was previously calculated as 18.4/h. Applying an ACE index correction factor of 0.7, the minimum air change rate per hour to ensure the correct clean-up should be increased from 18.4 to 26.3. For a Grade C cleanroom, where a 10 fold reduction within 15 minutes is required, the air change rate per hour should be increased from 9.2 to 13.

The air supply rate should now be checked in the example to make sure that it is sufficient. In the example, an air supply rate of 3.33 m³/s, which is equivalent to an air change rate of 40 air changes per hour, was thought to be appropriate. This is greater than the required air changes for the clean-up, and the proposed air supply rate is therefore sufficient.

Discussion and Conclusions

It is necessary when designing non-unidirectional airflow cleanrooms to ensure that the air supply rate will be sufficient to (a) achieve the correct particle concentration in the cleanroom in the steady-state condition, (b) control the heat gains in the cleanroom (c) compensate for room air leakage and process air exhaust, and (d) provide the correct 'clean up' performance. The correct air supply rate will be that which is needed to provide for the most demanding of the four parameters. It has been previously difficult to calculate the air supply rate needed for the clean-up requirements of Annex 1 of the EU GGMP, or another recovery rate or time. This article describes a method to calculate the clean-up requirement.

If the cleanroom has to comply with the EU GGMP and be capable of reducing the airborne concentration in a Grade B cleanroom by a 100 fold in 15 minutes, then, if there is perfect mixing of supply and room air, an air change rate per hour of 18.4 is sufficient. If the cleanroom is a Grade C, an air change rate per hour of 9.2 is required. These two air change rate assumptions that the supply and room air are perfectly mixed and that no location within the cleanroom receives less clean air than other locations. Good air mixing can be achieved by means of efficient air diffusers and low level extracts around the cleanroom. Poor air mixing will require more air to be supplied to the cleanroom but when efficient air diffusers filters and low level extracts are used, an ACE index of 0.7 will compensate for non-uniform air mixing.

The calculations in the previous paragraph assume the airborne concentration during operational conditions is the maximum acceptable by the EU GGMP and the shortest decay time of 15 minutes. However, it would be unusual to find that the airborne concentration in the operational condition was as high as the maximum allowed by the EU GGMP and, therefore, the required drop in particle concentration would be less than 100 fold. This would require a lower air change e.g. a 10 fold drop instead of a 100 fold would halve the air change rate. Similarly, if a 'clean up' time of 20 minutes instead of 15 minutes is acceptable, then the air change rate can also be reduced. The air change rate for these less stringent requirements can be calculated by the method described in this article.

Cleanrooms that are not regulated by the EU GGMP may have similar clean-up requirements to those that are regulated, or may have different clean-up requirements, or may specify a required particle decay in terms of recovery time or recovery rate. Where the specification differs from that of the EU GGMP, Equations 4 or 5 can be used to calculate the required air change rate, and an example of how this is carried out is given in this article.

References


Full biographical notes for W (Bill) Whyte are on page 10.

Tim Eaton, B. Sc. (chemistry), is Sterile Manufacturing Specialist at AstraZeneca. His full biographical notes may be found in CACR20 (October 2014) on page 9.

Nigel Lenegan, B.Eng., C.Eng., MCIBSE, is founder and managing director of Energy & Carbon Reduction Solutions. His full biographical notes may be found in CACR18 on page 13.
Update on the ISO 14644/14698 series of standards – April 2016

John Neiger

The ISO 14644 series of cleanroom standards has taken a major step forward with the publication last December of ISO 14644-1:2015 and ISO 14644-2:2015. These two standards were described in an article by Gordon Farquharson in the previous issue of this journal. Now is an appropriate time to review all the standards in the series and this is done in Table 1.

Before we look at Table 1, it might be useful to take an overview including how the standard development process takes place and the ground covered by these particular standards.

The ISO Technical Committee that is responsible for these standards, ISO TC 209 was formed in 1993 with the objective of developing an international standard for particle cleanliness that could supersede all the national standards that were in existence at the time, including the UK’s BS 5295 and US Federal Standard 209E. (I have always been told that the allocation of the number 209 to the new TC was pure coincidence). With a common international standard for particle cleanliness, everyone would be talking the same language.

The role of the national standards bodies changed at the same time. Eihberto they had been responsible for producing national standards. Now they became bodies whose main responsibility was to discuss the national view on international standards and to appoint technical experts and nominate convenors to the ISO working groups. You can see from Table 1 that TC 209 has almost as many working groups as there are ISO members. (The hoped for online vocabulary (constantly continued compliance with ISO 14644-1. See also article by Gordon Farquharson in CACR25 (January 2016).

ISO 14644-1:2015
WG1
Part 1: Classification of air cleanliness by particle concentration
New standard published in December 2015. Note that there is a new definition for ‘cleanroom’. See also article by Gordon Farquharson in CACR25 (January 2016).

ISO 14644-2:2015
WG1
Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration
New standard published in December 2015. Note new title and focus on monitoring. The UK version of this standard, published by BSI, has a National Forward and an additional Annex with recommendations for periodic tests to demonstrate continued compliance with ISO 14644-1. See also article by Gordon Farquharson in CACR25 (January 2016).

ISO 14644-3:2005
WG3
Part 3: Test methods
Being revised. CD has now been approved for registration as DIS. The revision will cover tests for supporting attributes (airflow velocity, pressure etc.) but not tests for cleanliness attributes.

ISO 14644-4:2001
WG4
Part 4: Design construction and start-up
Systematic review is now proceeding following the appointment of convenor. The revised standard will consider cleanliness by particle concentration and by other cleanliness attributes. An important element will be guidance on airflow rates based on dispersion rates. Much of this work has already been done by WG 13 in connection with Part 16 and it hoped that this will transfer into Part 4, although there is a timing problem as Part 16 is a long way ahead of the revision of Part 4.

ISO 14644-5:2004
WG5
Part 5: Operations
Current

ISO 14644-6:2007
WG6
Part 6: Vocabulary
Withdrawn. The hoped for online vocabulary (constantly updated) for committee use does not yet exist. Definitions are already included in the individual Parts but there is no central control.

ISO 14644-7:2014
WG7
Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments
Current

ISO 14644-8:2013
WG8
Part 8: Classification of air cleanliness by chemical concentration (ACC)
Current

ISO 14644-9:2012
WG9
Part 9: Classification of surface particle cleanliness
Current

ISO 14644-10:2013
WG8
Part 10: Classification of surface cleanliness by chemical concentration
Current

ISO 14644-12
WG10
Part 12: Classification of air cleanliness by nanoscale particle concentration
This standard has passed its DIS stage. TC 209 has decided that it should be a monitoring standard. The latest DIS does not include a table of classes.

ISO 14644-13
WG12
Part 13: Cleaning of surfaces to achieve defined levels of cleanliness in terms of particle and chemical classifications
The three month DIS ballot has been initiated. Not everyone is enthusiastic about this standard as most of the cleaning methods listed are applicable to components rather than cleanroom surfaces, so it is more a process standard than a cleanroom standard.

Table 1: Summary of the status of all the standards in the ISO 14644 series of cleanroom standards

<table>
<thead>
<tr>
<th>Standard/WG No</th>
<th>Title: Cleanrooms and associated clean environments</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO 14644-2:2015</td>
<td>Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration</td>
<td>New standard published in December 2015. Note new title and focus on monitoring. The UK version of this standard, published by BSI, has a National Forward and an additional Annex with recommendations for periodic tests to demonstrate continued compliance with ISO 14644-1. See also article by Gordon Farquharson in CACR25 (January 2016).</td>
</tr>
<tr>
<td>ISO 14644-3:2005</td>
<td>Part 3: Test methods</td>
<td>Being revised. CD has now been approved for registration as DIS. The revision will cover tests for supporting attributes (airflow velocity, pressure etc.) but not tests for cleanliness attributes.</td>
</tr>
<tr>
<td>ISO 14644-4:2001</td>
<td>Part 4: Design construction and start-up</td>
<td>Systematic review is now proceeding following the appointment of convenor. The revised standard will consider cleanliness by particle concentration and by other cleanliness attributes. An important element will be guidance on airflow rates based on dispersion rates. Much of this work has already been done by WG 13 in connection with Part 16 and it hoped that this will transfer into Part 4, although there is a timing problem as Part 16 is a long way ahead of the revision of Part 4.</td>
</tr>
<tr>
<td>ISO 14644-5:2004</td>
<td>Part 5: Operations</td>
<td>Current</td>
</tr>
<tr>
<td>ISO 14644-6:2007</td>
<td>Part 6: Vocabulary</td>
<td>Withdrawn. The hoped for online vocabulary (constantly updated) for committee use does not yet exist. Definitions are already included in the individual Parts but there is no central control.</td>
</tr>
<tr>
<td>ISO 14644-7:2014</td>
<td>Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments</td>
<td>Current</td>
</tr>
<tr>
<td>ISO 14644-8:2013</td>
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<td>Part 9: Classification of surface particle cleanliness</td>
<td>Current</td>
</tr>
<tr>
<td>ISO 14644-10:2013</td>
<td>Part 10: Classification of surface cleanliness by chemical concentration</td>
<td>Current</td>
</tr>
<tr>
<td>ISO 14644-12</td>
<td>Part 12: Classification of air cleanliness by nanoscale particle concentration</td>
<td>This standard has passed its DIS stage. TC 209 has decided that it should be a monitoring standard. The latest DIS does not include a table of classes.</td>
</tr>
<tr>
<td>ISO 14644-13</td>
<td>Part 13: Cleaning of surfaces to achieve defined levels of cleanliness in terms of particle and chemical classifications</td>
<td>The three month DIS ballot has been initiated. Not everyone is enthusiastic about this standard as most of the cleaning methods listed are applicable to components rather than cleanroom surfaces, so it is more a process standard than a cleanroom standard.</td>
</tr>
</tbody>
</table>
Standards

<table>
<thead>
<tr>
<th>Standard/WG No</th>
<th>Title: Cleanrooms and associated clean environments</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO 14644-14</td>
<td>Part 14: Assessment of suitability of equipment and materials for cleanrooms by airborne particle concentration</td>
<td>The FDIS is awaited for formal approval (voting).</td>
</tr>
<tr>
<td>ISO 14644-15</td>
<td>Part 15: Assessment of suitability of equipment and materials for cleanrooms by airborne chemical concentration</td>
<td>The DIS is awaited for formal approval (voting).</td>
</tr>
<tr>
<td>ISO 14644-16</td>
<td>Part 16: Code of practice for improving energy efficiency in cleanrooms and clean air devices</td>
<td>Work is proceeding apace and the DIS is being prepared. Airflow calculations are likely to be moved to Part 4.</td>
</tr>
<tr>
<td>ISO 14644-17</td>
<td>Part 17: Specification of requirements for particle deposition monitoring</td>
<td>Proposal for new project has been received (NWIP) and is being voted on.</td>
</tr>
<tr>
<td>ISO 14698-1:2003</td>
<td>Biocontamination control. Part 1: General principles and methods</td>
<td>The NWIP for revising this poorly used standard was rejected but the work is being picked up by CEN 243 WG 8. At the moment the scope in CEN is wider than just cleanrooms and includes hospitals, biotechnology and the food industry. The working title is ‘Biocontamination control.’</td>
</tr>
</tbody>
</table>

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Air Techniques International acquires DOP Solutions and the Academy for Cleanroom Testing

Letchworth Garden City, UK, 9 March 2016 – Air Techniques International (ATI) announces that it has acquired DOP Solutions, a United Kingdom based manufacturer of aerosol photometers and generators and the Academy for Cleanroom Testing (ACT), a provider of training and education services. With these acquisitions, ATI expands the breadth of its cleanroom testing products and services and strengthens its position in Europe to support customers and partners in the region.

Since 1988, DOP Solutions has been a leader in clean air testing with a range of aerosol detection and measurement instruments and accessories including positive injection pumping systems, aerosol injection ports, sparge pipes and smoke generators. The Academy for Cleanroom Testing grew from a heritage of providing theory and practical training for cleanroom testing based on proven techniques and industry standards such as ISO 14644 and EN 12469/NFSP-49.

Tim Triggs, co-owner and director of DOP Solutions and ACT will lead ATI’s business operations in the geographic region from Europe to India. “By combining with ATI we gain the support and experience of a highly-respected global company, reinforcing our growth initiative in our core business. We also look forward to helping our customers benefit from ATI’s product range including filter testing and Chembio defense,” said Triggs.

“ATI has an exciting period of new growth and expansion,” said Ron Adkings, President of ATI. “We will bring innovative new products and services to our global customers and expand our application expertise to better serve their needs. The acquisition of DOP Solutions and ACT supports this strategic direction. We believe there is a strong fit, and our combined capabilities will create significant value for our customers.”

To learn more about the new ATI, please visit www.atitest.com. For more information about DOP Solutions and ACT, please visit www.dopsolutions.com, e-mail timtriggs@dopsolutions.com or call +44 (0) 1462 676446.

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Fumigation of safety cabinets and containment laboratories has been under the microscope recently. The most commonly used agent, formaldehyde, has been confirmed as a carcinogen by the HSE and both it and its most likely long term replacement, hydrogen peroxide, are both affected by EU Biocidal Products Regulations restricting their sale.

In the immediate term, you can continue to use formaldehyde for cabinet and room fumigation, although in the longer-term its use is likely to be banned. With increased scrutiny of fumigations, this will be a “hot topic” during HSE inspections over the next year or so, so it is best to be prepared. Therefore now is the time to review your fumigation procedures, protocols, risk assessments, staff training, training records and calibration records for monitoring equipment. If you need assistance with regard to regulations compliance or conducting your review, Crowthermore Hi-Tec Services can help, contact us on +44 (0)1252 372333 or sales@chts.co.uk.

Clean Room Construction Ltd follows up at University of Leeds

CRC has been awarded the construction phase for three new Transmission Electron Microscopy (TEM) rooms in a £6 million fast-track scheme at the university. Work has started on site and the contract follows CRC’s successful completion of an Electron Beam close control room for the university.

Richard Rowe, CRC’s Projects Director, said: “CRC has a successful track record of designing and building leading-edge facilities for top universities and we are proud to be working with Leeds on this prestigious project.”

CRC has appointed Barry Haines as Projects Manager. Barry, 36, was formerly the Contracts Manager at WLTair Ltd.

Managing Director Steve Lawton, said: “Barry’s appointment after another record-breaking year for CRC enables us to plan for future growth while maintaining our commitment to quality and first class customer service which has earned us this success to date.”

For more information about CRC, visit www.crc-ltd.co.uk

Cleanroom Guangzhou 2016 set up ready to go

Sponsored by Guangdong Association of Cleanroom Technology (GACT) and supported by Chinese Contamination Control Society (CCCS) and International Confederation of Contamination Control Societies (ICCCS), 2016 Guangzhou International Cleanroom Technology & Equipment Exhibition (Cleanroom Guangzhou 2016) will take place in Poly World Trade Center Expo (PWTC Expo) during 13th-15th, May. It is a free to attend show and registrations are invited online.

In February 2016, the Organizing Committee invited two well-known professionals in cleanroom technology, Koos Agriola, Chairman of the ICCCS Standard and Education Committee, and John Neiger, Editor of United Kingdom Clean Air and Containment Review, to be official advisors to the exhibition. Koos and John both wish the organisers every success for the 2016 exhibition.

Mae Law, Overseas Organiser for the exhibition, reports that over 100 exhibitors will be displaying at the exhibition, at least 10% of whom are either from overseas or represent overseas companies. Attendance is expected to surpass last year’s total of 3,600 visitors.

Mae writes “The 2016 exhibition will be more wonderful with your participation.”

For more information on Cleanroom Guangzhou 2016 please visit http://www.cltc.com/index.php/eng-
Events

<table>
<thead>
<tr>
<th>Dates</th>
<th>Event</th>
<th>Organiser</th>
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<tbody>
<tr>
<td>2016</td>
<td></td>
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<tr>
<td>April 21-23</td>
<td>Cleanroom Technology, Maintenance and Equipment Exhibition, Istanbul, Turkey</td>
<td>antespo</td>
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<tr>
<td>May 2-5</td>
<td>ESTECH '16, Glendale, Arizona</td>
<td>IEST</td>
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<tr>
<td>May 13-15</td>
<td>Cleanroom Guangzhou Exhibition 2016, Guangzhou, China</td>
<td>Guangzhou Grandeur International Exhibition Group</td>
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<tr>
<td>June 9</td>
<td>Sterile Products Manufacture, Nr: Manchester Airport, UK</td>
<td>PHSS</td>
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<tr>
<td>September 5-6</td>
<td>SYMPOSIUM 2016, The 45th R3 Nordic Symposium and Exhibition, Copenhagen, Denmark</td>
<td>R3Nordic</td>
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<tr>
<td>September 6</td>
<td>PHSS Annual Conference 2016 in association with UCL, Q3P, London, UK</td>
<td>PHSS</td>
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<tr>
<td>September 17-23</td>
<td>23rd International Symposium for Contamination Control, ISCCBRZIL2016 “Treading new paths,” São Paulo, Brazil</td>
<td>RCCCS</td>
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<tr>
<td>November 8-9</td>
<td>Cleanzone 2016, Frankfurt, Germany</td>
<td>Messe Frankfurt</td>
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</tbody>
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Training courses

**IEST (Institute of Environmental Sciences and Technology): www.iest.org**

<table>
<thead>
<tr>
<th>2016</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>May 2</td>
<td>Cleanroom Basics: What is a Cleanroom and How Does it Work?</td>
<td>ESTECH Glendale, Arizona</td>
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<td>May 3</td>
<td>Understanding the Changes to ISO 14644-1 and ISO 14644-2</td>
<td>ESTECH Glendale, Arizona</td>
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<tr>
<td>May 4</td>
<td>Basics of Particle Mechanics for Contamination Control in Cleanrooms</td>
<td>ESTECH Glendale, Arizona</td>
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<tr>
<td>May 5</td>
<td>The Unseen Contaminant: Taking Charge of Electrostatic Contamination</td>
<td>ESTECH Glendale, Arizona</td>
</tr>
<tr>
<td>May 5</td>
<td>Cleanrooms, HVAC System Design, and Engineering Fundamentals</td>
<td>ESTECH Glendale, Arizona</td>
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**ICS (Irish Cleanroom Society): www.cleanrooms-ireland.ie**

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<thead>
<tr>
<th>2016</th>
<th>Event</th>
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<tbody>
<tr>
<td>April 19-21</td>
<td>CTCB-I Cleanroom Testing</td>
<td>(South Africa)</td>
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<tr>
<td>May 10</td>
<td>CTCB-I Cleanroom Technology</td>
<td>Letchworth, UK</td>
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<tr>
<td>June 21-23</td>
<td>CTCB-I Cleanroom Testing</td>
<td>Letchworth, UK</td>
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<tr>
<td>July 13</td>
<td>Particle Counting to ISO 14644 with Examination (ICEB accredited)</td>
<td>Letchworth, UK</td>
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<tr>
<td>November 8-10</td>
<td>CTCB-I Cleanroom Testing</td>
<td>Dublin, Ireland</td>
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<td>November 21</td>
<td>CTCB-I Cleanroom Technology</td>
<td>Letchworth, UK</td>
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<tr>
<td>November 22</td>
<td>HEPA filter testing</td>
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<tr>
<td>November 23</td>
<td>Airflow Measurement and Testing</td>
<td>Letchworth, UK</td>
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<tr>
<td>November 24-25</td>
<td>Microbiological Safety Cabinet Testing</td>
<td>Letchworth, UK</td>
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**Life-lines**

*Courtesy of Susan Rogers*

War doesn’t determine who’s right, just who’s left.
A fine is a tax for doing wrong.
A tax is a fine for doing well.
The early bird gets the worm, but the second mouse gets the cheese.
Isn’t Disney World a people trap operated by a mouse?
The best advice for teenagers is, leave home now while you still know everything.
How is it possible to have a civil war? The 50-50-90 rule: Anytime you have a 50-50 chance of getting something right, there’s a 90% probability you’ll get it wrong.
The things that come to those that wait may be the things left by those who got there first.
Logic is the art of going wrong with confidence.
The definition of insanity is doing the same thing over and over again, but expecting different results. (A. Einstein).
Do you design, build or use cleanrooms?

The international standards governing cleanroom classification and monitoring have been updated.

The revisions introduce important improvements to cleanroom and clean device classifications and update operational monitoring guidance and requirements.

- BS EN ISO 14644-1:2015 Cleanrooms and associated controlled environments – Part 1 Classification of air cleanliness by particle concentration and
- BS EN 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 are essential reading for:
  - cleanroom facility users
  - cleanroom testing companies
  - facility design professionals and consultants
  - facility construction professionals and
  - sellers of cleanroom technology components.


www.cleanairandcontainment.com

Helapet are dedicated to supplying sterile and non-sterile consumable products used in the aseptic production of medicines and pharmaceuticals.

Our quality service provision is supported by free sampling and our experienced account management team, committed to providing the best level of one-to-one customer care, advice and support.

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This is What Safety Looks Like...

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You can't put a price on a life. But you can improve your transfer disinfection processes to protect that life.

With regulations requiring the use of sporicidal agents when introducing components into aseptic areas, transfer disinfection is a major challenge to manufacturers and end-users alike.

Klercide Sporicidal Alcohol, the new patented* formulation from Ecolab, provides a range of potentially life saving benefits, including rapid flash-off and sporicidal efficacy in two minutes (EN 13697**).

REFERENCES

* patent pending
** modified EN 13697 sporicidal surface test - log 2 reduction achieved

Scan here to see the full story of how safety starts with new Klercide Sporicidal Alcohol

TO FIND OUT MORE ABOUT OUR UNIQUE SOLUTION FOR TRANSFER DISINFECTION, PLEASE CONTACT YOUR ECOLAB CONTAMINATION CONTROL EXPERT, EMAIL US AT INFOCC@ECOLAB.COM OR CALL +44 (0)2920 854 390

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Brunel Way, Baglan Energy Park
Neath SA11 2GA UK
www.ecolabcc.com

REFERENCES

* patent pending
** modified EN 13697 sporicidal surface test - log 2 reduction achieved

USE BIOCIDES SAFELY. ALWAYS READ THE LABEL AND PRODUCT INFORMATION BEFORE USE.