CACR

Clean Air and Containment Review

Enhance your knowledge of contamination control

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Reducing cleanroom HVAC energy use

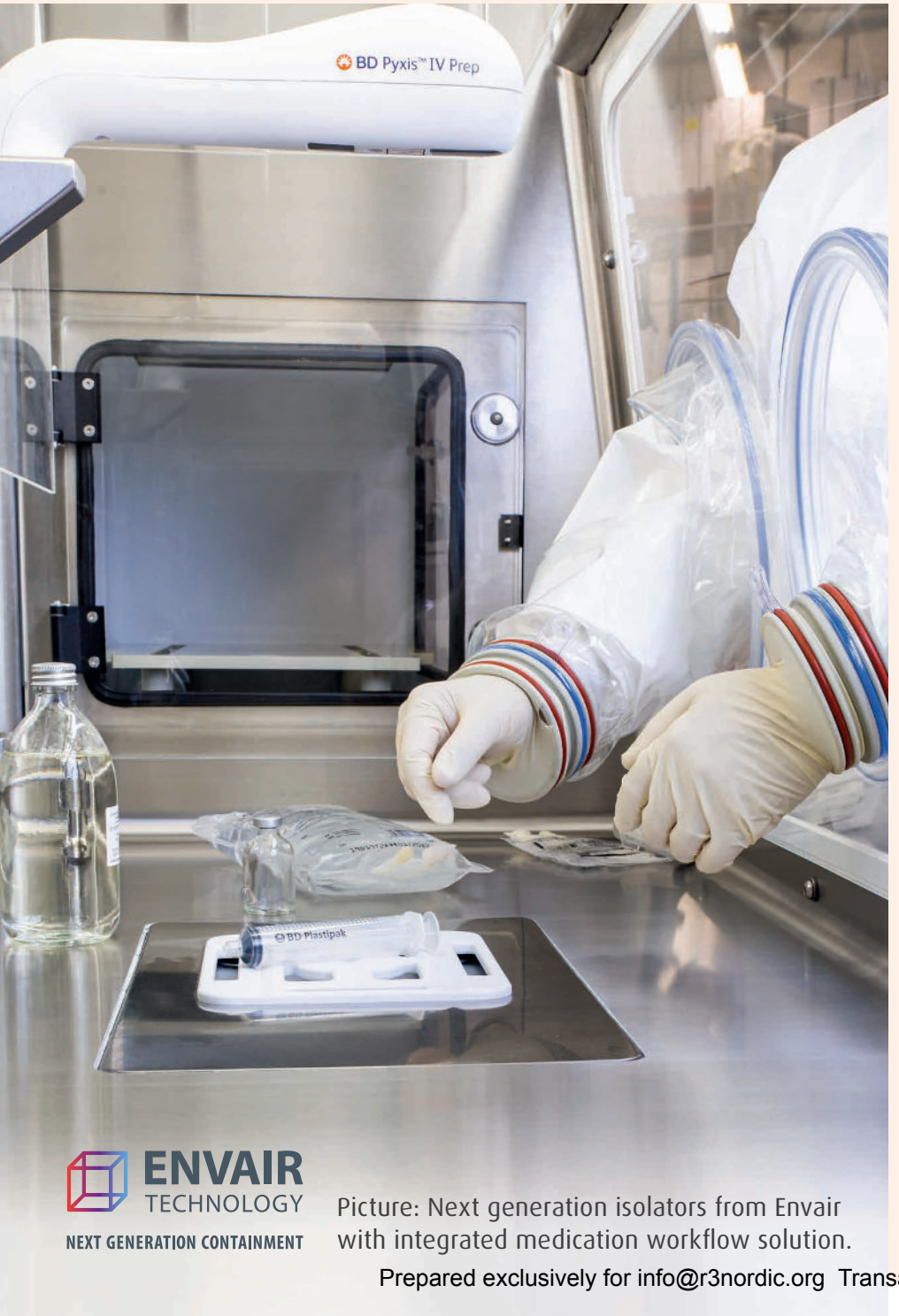
Containment leakage testing

Face masks: Lessons from COVID-19 research

Energy efficiency in cleanrooms and clean air devices: ISO 14644-16

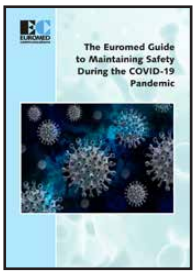
Book review: Advances in Practical Safety Ventilation

Events and Training courses



Picture: Next generation isolators from Envair with integrated medication workflow solution.

EUROMED communications



Clean Air and Containment Review is a quarterly journal aimed at users, specifiers, designers, manufacturers, installers and testers of clean air and containment equipment. It publishes articles of topical, technical and historical interest, updates on standards and regulations, news, views and information on relevant events, especially training.

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Editorial

Welcome to this delayed issue of CACR. The reasons for the delay are medical but I don't propose to have an 'organ recital' here as these are usually rather boring.

CACR44 contains the usual variety of articles as well as a book review and an obituary. However, instead of summarising them in my editorial, as I sometimes do, I have selected some short extracts under the heading 'Pearls of wisdom' (see box below) to intrigue you and maybe tempt you to read the articles themselves.

A feature of every issue is 'Life-lines'. This started as a selection of random quotations that appealed to me. Then I started homing in on quotations of eminent personalities, such as Shakespeare and Einstein, and discovered Yogi Berra (CACR24) who had a wonderful way with words, for example: "The future ain't what it used to be." More recently I have reproduced quotes by Louis Pasteur (CACR43) one of which was: "Gentlemen, it is the microbes who will have the last word." For this issue I have sought out quotations on 'Truth', this being a subject that all of us must have reflected upon recently. We seem to be living in an age where, if you say something loudly enough and often enough, people will believe it. That doesn't appeal to my scientific and, hopefully, open mind which much prefers reasoned argument.

In CACR44 I am sure that the authors of the articles have sought to present the truth but, if there is anything that is disputed, I invite a reasoned response!

John Neiger

Pearls of wisdom

… recently there has been recognition that the amount of filtered air supplied to a cleanroom should be based on a scientific assessment of the potential sources of contamination and their estimated strength and not on a traditionally prescribed air change rate value. This approach has been shown to achieve energy savings of up to 30%.
Nigel Lenegan, page 4

A containment facility requires low leakage construction for two reasons: firstly, to contain any biological aerosols and secondly, to contain any gases used for decontamination.
Joshua Magor, page 8

The origin of cleanroom masks is with surgical face masks, which were introduced to protect patients from wound infection and contamination during surgical procedures in the 1960s. This concept of minimising the number and rate of microbial-carrying droplets was adopted for the production of medicines.
Tim Sandle, page 12

The design of a non-unidirectional airflow cleanroom requires effective airflow design for good performance. Traditional air volume calculations can be improved by the inclusion of a ventilation effectiveness (VE) index in their data.
Dick Gibbons, page 18

The book offers a rich treasury of advice for anyone who works within pharmaceuticals or healthcare and who is seeking advice in relation to strengthening contamination control. There is detailed guidance on all aspects of cleanroom airflow patterns, the mechanics of airflow, and how microbial contamination is carried within the airstream.
Book review, page 20

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Reducing cleanroom HVAC energy use by following a scientific approach

Nigel Lenegan

Abstract

In this article, the author draws on his experience to describe how most organisations in the pharmaceutical sector have already put into effect the simpler, less expensive measures for achieving energy savings, and argues that the time has come to look more carefully at HVAC and, particularly, fan power. For example, US guidance on air change rates has not been revised since 2004. Since then, many aspects of cleanroom operations have improved, contamination risks have been reduced and recently there has been recognition that the amount of filtered air supplied to a cleanroom should be based on a scientific assessment of the potential sources of contamination and their estimated strength and not on a traditionally prescribed air change rate value. This approach has been shown to achieve energy savings of up to 30%.

Introduction

Over the past 10 years, the pharmaceutical sector has been very successful in reducing energy use and carbon dioxide emissions in its facilities. However, I suspect further reductions will be required to to meet new corporate targets to comply with international climate change agreements and to mitigate increased energy use due to rising demand for medicines.

In my experience, energy reduction achievements across the last decade tended to come from quick wins in the supporting utilities, for example: providing inverter drives on fans and pumps, reducing compressed air pressure, fixing leaks, specifying direct drive fans and pumps in place of belt-drive etc. These quick wins, often called "low-hanging fruit", have been picked and the harder to reach opportunities must now be targeted to provide deeper cuts in facility energy use.

In my experience of energy analysis and monitoring of pharmaceutical manufacturing facilities, HVAC energy tends to be 50-75% of the energy demand of a facility, much of this being due to HVAC fan power. Fan power is directly related to airflow and pressure and again, in my experience, GMP classified cleanrooms are renowned for over-performing due to excess airflow. Hence, airflow reduction in classified cleanrooms must be considered in order to deliver the deeper cuts in energy use necessary over the next 5-10 years.

One reason these opportunities are harder to implement is because HVAC systems provide the internal environment required by GMP to assure product quality and patient safety. Hence, I find there is a natural resistance to change by some key stakeholders, who believe that the higher the airflow, the cleaner the room, therefore the safer the product and the lower the risk of patient harm.

From work I have done with pharmaceutical companies and their production and quality departments, when the actual risk to patients arising from airflow reduction is considered, we often find that the change to this risk is small provided a quality assured scientific approach is followed. In these cases, energy savings arising from reduced airflow have been delivered. These projects have yielded energy and carbon reduction of 20-30%, with a return on investment in 12-18 months.

Reasons for excess energy use in classified cleanrooms

When I have investigated these over-performing GMP classified facilities, I found that often, the main reason for excess airflow and associated high energy use was that the end user and their design companies did not consider the actual levels of in-room contamination to be diluted and removed by the HVAC system. Traditionally these rooms were (and still are) designed using air-change rates which have no scientific basis and are just as likely to lead to under-design in some rooms as over-design.

When I have tried to investigate the origins of standard air-change rates, I have found very little in the relevant standards or regulatory guidelines. One source I did identify was the FDA Sterile Drug Products document[1] published in 2004. This states *"Air change rate is another important cleanroom design parameter. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas."*

In my experience, traditionally designed cleanrooms, FDA Class 100,000 / ISO 8 (EU GMP Grade C operational) often run at 20-50 ac/hr and FDA Class 10,000 / ISO 7 (EU GMP Grade B operational) rooms at 50-100 ac/hr. FDA Class 100 / ISO 5 (EU GMP Grade A) are usually ventilated using unidirectional airflow (UDAF) where airflow velocity and not air-change rate is the critical parameter.

However, since 2004, many aspects of GMP cleanroom operation have improved, reducing the risk of product contamination. Such improvements include separative devices to provide a physical barrier, better supply air quality from improved HEPA filters and housings, operator training, cleaning and disinfection efficacy and, perhaps with the most impact, developments in operator garments and more care with operator movements during production. Yet the benefits of these improvements have not been considered when determining the required air change rate and the traditional approach to air-change rates has not been challenged.

What can be done differently?

Instead of specifying traditional air-change rates, a scientific approach should be used to determine or, at least influence, the design airflow rate. Such an approach would look at the source strength of contamination and apply dilution calculations and ventilation effectiveness assessments to determine the level of airborne contamination in the cleanroom. Typically, particle sizes of ≥0.5µm, ≥5µm and MCPs (microbe carrying particles >10µm) would be considered as they are the particles that

feature in regulatory guidelines. This approach would enable filtered airflow supply rates to be determined and likely levels of contamination under steady state and during entry and exit events to be predicted. There are several technical papers written by Whyte *et al*[2–10] which provide information on how to determine the amount of filtered air required in a given cleanroom. ISO14644-16:2019[11] also provides further information.

Where a scientific approach can be applied

This approach is most relevant in facilities where contamination control is critical to product manufacture, namely all EU grade B-D[12] and US FDA ISO 5-8 classified cleanrooms used in sterile (aseptic and terminally sterilised) facilities for injectables or products which are at-risk from microbial contamination including ointments, creams, suspensions and emulsions.

These cleanrooms are internationally regulated, well maintained, regularly re-checked and closely monitored using qualified particle and environmental monitoring systems. Since the introduction of separative devices such as isolators and restricted access barrier systems (RABS), product sterility assurance in EU Grade A / FDA Class 100 / ISO 5 cleanrooms is high. Opportunities for face velocity reduction can be included in a scientific approach. The biggest improvements using this approach are in turbulently ventilated cleanrooms where the dominant source of viable contamination is from people. These rooms are usually background and support rooms (EU GMP Grade B, C and D / FDA Class 10,000-100,000 / ISO 7 and ISO 8 and possibly CNC (Controlled Not Classified) environments where traditional air-change rates may have been used for design.

What are the risks / challenges?

If a robust process is followed as part of a scientific approach, the risks to patient and product quality should be negligible, whereas using a traditional approach which does not consider the levels of contamination is riskier and less predictable.

Final thoughts

I believe that if corporate expectations for reductions in energy use and carbon emissions are to be realised, then the elephant in the room is airflow in classified cleanrooms. To achieve this, I would advocate that a robust scientific approach is applied to the design of new facilities and to energy optimisation of existing facilities. Carried out correctly this will yield reduced plant size, reduced energy use, reduced capital cost, reduced running costs and reduced carbon dioxide emissions – helping the Pharmaceutical sector to be more sustainable.

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Containment leakage testing

Joshua Magor

Abstract

This article discusses why containment facilities require low leakage construction. It is based on experience with the Australian Centre for Disease Preparedness (ACDP) facility and the acceptance criteria set for its testing. Two formulae for calculating the leakage coefficient Beta are compared; one takes into account the room volume while the other only considers the measured air leakage rate regardless of room volume. To aid in the understanding of the effect of different leak rates, a formula is derived to calculate the theoretical concentration of fumigant in a room with respect to time. This formula is used to compare common leak rates discussed in literature, the current leak rates seen at the ACDP and the effect of varying room size. Finally, there is some reflection on the uniqueness of different facilities posing the question - should there be a "one size fits all" approach to setting the allowable leak rates or should these be assessed based on the criticality of the room or facility?

Introduction

A containment facility requires low leakage construction for two reasons: firstly, to contain any biological aerosols and secondly, to contain any gases used for decontamination. At the Australian Centre for Disease Preparedness (ACDP) (formerly known as the Australian Animal Health Laboratory [AAHL]) air leakage testing is conducted for all Physical Containment (PC) levels 3 and 4 animal rooms and PC level 4 laboratories.* During normal operation laboratories operate and are decontaminated at negative pressure with exhaust air directed through a HEPA filter. The only time a laboratory would become positively pressurised is during a malfunction. Low leakage construction contains any biological aerosols in the event a room becomes positively pressurised and it reduces dilution during decontamination when the room is under negative pressure. However, containment leakage testing is typically carried out with the facility at positive pressure.

If it is necessary for a facility to have a low leakage rate, then it is also necessary to validate that the facility is meeting this requirement. Pickering's (1982) Analysis of Containment report[1] developed quantitative measures for the determination of how much leakage could be tolerated at the ACDP and the procedure of how to conduct the measurement of leakage. The Analysis of Containment report presents two methods for determining the leak-tightness of a structure:

Firstly, the direct flow measurement method:

$$\beta = \frac{q}{\Delta p} \quad \textbf{Equation 1.1}$$

Where:

β = Leakage Coefficient for Room $\frac{m^3}{Pa.s}$

q = Air Leakage Rate from Room $\frac{m^3}{s}$

Δp = Pressure Difference Across Barrier Pa

Secondly, the time constant method:

$$\beta = \frac{V}{PT} \quad \textbf{Equation 1.2}$$

Where:

β = Leakage Coefficient for Room $\frac{m^3}{Pa.s}$

V = Volume of Room m^3

P = Atmospheric Pressure taken as $10^5\ Pa$

T = The Time Constant s

$$T = \frac{t}{ln(\frac{p_i}{p_f})}$$

Where:

T = Time Constant s

t = Time to reach p_f s

p_f = Final pressure Pa

p_i = Initial pressure Pa

In this article we will explore the theoretical difference between these two methods to assess which is more effective and investigate the effect that the leak-tightness of a structure has on its ability to successfully contain gaseous decontamination.

"A containment facility requires low leakage construction for two reasons: firstly, to contain any biological aerosols and secondly, to contain any gases used for decontamination."

Current requirements for the leak-tightness of a structure in Australia

Containment facilities in Australia are highly regulated. Both the Australian Department of Agriculture, Water and the Environment (DA) requirements for operating Biosecurity Containment levels 3 and 4 facilities[2] and the Office of the Gene Technology Regulator (OGTR) guidelines for certification of Physical Containment Level 3 and Level 4 facilities[3–5] state that a room should be constructed to have an air leakage rate that does not exceed 120 L/min at 200 Pa on commissioning. Subsequently, an air leakage rate of less than 1200 L/min at 200 Pa should be maintained. These leakage rates are taken from AS/NZS 2243.3:2010 *Safety in Laboratories Part 3: Microbiological Safety and Containment*,[6] and correspond to leakage coefficients of 10^{-5} and 10^{-4} $\frac{m^3}{Pa.s}$ at 200 Pa . These are calculated by rearranging Equation 1.1 below for the direct flow measurement method. AS/NZS 2243.3:2010 is widely used overseas and details the requirements for containment facilities based on the risk group of the

*Physical Containment levels 3 and 4 are broadly equivalent to the World Health Organisation Biosafety Levels 3 and 4.

microorganisms that are used.

The ACDP was built based on Pickering's (1982) report, *Analysis of Containment*, which determined a worst possible failure mode of a positively pressurised room during a 25-year average recurrence interval wind event with a malfunction period of one hour to create a leakage pathway to outside the building. This scenario was used to determine the maximum permissible leakage coefficient of $\beta = 3.2 \times 10^{-7} \frac{m^3}{Pa.s}$ which corresponds to an air leakage rate of 3.84 L/min at 200 Pa. Using this value as the acceptance criteria for rooms would ensure that <1 infective aerosol doses would escape the facility during such a malfunction. As the ACDP facility was a pioneer in the industry, there was no standard to build upon; thus, this study was developed to establish the acceptance criteria. With remote monitoring and other advancements in technology a 1-hour malfunction period producing positive pressure could never occur today.

The difference in the two methods used to determine the leak-tightness of a structure

Air leakage testing at the ACDP is typically performed using the direct flow measurement method, where compressed air is introduced into the space being tested and the pressure is monitored through a digital manometer. An equilibrium is found by adjusting the flow until the pressure stabilises at 500 Pa, the leakage rate being recorded at this point. It should be noted that 500 Pa is not necessarily recommended or achievable for all facilities. For ease of comparison with the current test pressure recommendations in AS/NZS 2243.3:2010, straight-line interpolation is used to calculate the equivalent air leakage rate at a differential pressure of 200 Pa. This method measures the air leakage rate and makes no allowance for the size of the room.

The time constant method is described by Pickering (1982) as pressurising a room to a test pressure, allowing the system to stabilise, and then allowing the pressure to decay. This method incorporates a volume component. To demonstrate the effect that Volume has on the Time Constant calculated by this method, Equation 1.2 is solved using two different values for Volume ($V_2 = 2V_1$) with all other values equal.

$$\beta_1 = \frac{V_1}{P \times T_1} \; and \; \beta_2 = \frac{V_2}{P \times T_2}$$

Let:

$$\beta_1 = \beta_2$$

$$V_2 = 2V_1$$

Substituting in $V_2 = 2V_1$ gives:

$$\frac{V_1}{P \times T_1} = \frac{2V_1}{P \times T_2}$$

Simplifying gives:

$$T_2 = 2T_1$$

This demonstrates that in order to have the same β value, the time required for the pressure to decay would be twice as long. If the volume is doubled and the time to decay is the same, then the air leakage rate must be two-fold higher. Alternatively, if the volume is doubled but it takes the same time to decay, then the β value is half that of the room with the smaller volume, as it reflects a more leak-tight structure.

The effect leak-tightness of a structure on the concentration of fumigant

The effect of leakage on the concentration of fumigant in a room can aid in the visualisation of the leak effect. The following method could be applied to any number of fumigants, including hydrogen peroxide, chlorine dioxide or formaldehyde. When performing formaldehyde decontamination at the ACDP, 5g/m³ of paraformaldehyde is used. Considering the room temperature of 20°C at atmospheric pressure (ignoring the conversion of our reference pressure to the room pressure for simplicity), this would generate:

$$ppm = \frac{mg}{m^3} \times \frac{22.4}{M} \times \frac{(273 + T)}{273} \times \frac{1013}{P}$$

M = Molecular weight of substance

$22.4\ L$ =Volume of 1 mol at 1 atmospheric pressure at 0°C

$273\ K$ =conversion of °C to Kelvin

$1013\ hPA$ = 1 Atmospheric pressure

P =Atmospheric pressure at location

$ppm =$

$$5000 \frac{mg}{m^3} \times \frac{22.4}{30.031 g/mol} \times \frac{(273 + 20)}{273} \times \frac{1013}{1013}$$

$ppm = 4003$

This demonstrates that a typical formaldehyde decontamination at the ACDP produces a concentration of 4003 ppm at the beginning of the 15-hour dwell time. The equation for mass accumulation (Himmelblau 1989, p.106)[7] is used to develop a formula to consider the rate of change of the concentration over time:

$$Accumulation = Input - Output \pm Reaction\ Rate$$

Assuming the absence of decay or reactions occurring in the room:

$$Accumulation = Input - Output$$

Therefore, the rate of change of the concentration can be expressed as follows:

$$Rate\ of\ Change\ of\ Concentration = \frac{dC}{dt} = \frac{(Q_{in} \times C_{in}) - (Q_{out} \times C_{out})}{V}$$

Where:

dC =Change in concentration

dt =Change in time

Q_{in} =Leak rate into the room

Q_{out} =Flow rate out of the room

C_{in} =Concentration of formaldehyde entering the room through the leak

C_{out} =Concentration lost through the exhaust air to maintain negative pressure

V =Volume of the room

Note: units may vary if they are consistent.

The following assumptions are made: C_{out} or the concentration lost through the exhaust valve = Concentration in the room = C

The turbulence in the room, caused by fans, is significant and the exhaust valve feathers every few minutes to ensure that the room remains negatively pressurized. It is therefore reasonable to assume that the leaked air at a concentration of 0 ppm will mix with the gas in the room.

Therefore let:

$$Q_{in} = Q_{out} = Q$$

And,

Concentration entering the room

$$C_{in} = 0\ ppm$$

This gives the following formula:

$$\frac{dC}{dt} = \frac{-QC}{V}$$

Rearrange this in preparation for integration:

$$\frac{dC}{C} = \frac{-Q}{V}dt$$

Setting the bounds of integration as:

$t = 0\ to\ t = t$

And,

Initial concentration= $[C]_0$ and Concentration at time $t = [C]_t$

$$\int_{[C]_0}^{[C]_t} \frac{dC}{C} = \frac{-Q}{V}\int_0^t dt$$

Gives:

$$ln[C]\Big|_{[C]_0}^{[C]_t} = \frac{-Q}{V} \times t\Big|_0^t$$

$$ln[C]_t - ln[C]_0 = \frac{-Qt}{V}$$

Simplification gives:

$$[C]_t = e^{\frac{-Qt}{V} + ln[C]_0}$$

Further simplification gives:

$$[C]_t = e^{\frac{-Qt}{V}} e^{ln[C]_0}$$

$$[C]_t = [C]_0 e^{\frac{-Qt}{V}} \quad \textbf{Equation 1.3}$$

where:

$[C]_t$ = Concentration in the room at time t

$[C]_0$ = Concentration in the room at time 0 or the initial concentration after the generation of gas

Q = Room leakage rate

t = Time to be evaluated

V = Volume

The above relationship shows that the concentration will decay exponentially and asymptotically as it approaches zero. Table 1 demonstrates the results of considering three different leakage rates and two different room sizes and details the concentration of formaldehyde remaining in the room after the 15-hour dwell time. As expected, Equation 1.3 shows that if one room is ten times larger than another room, then the leakage rate can be ten times higher for a given concentration. While Equation 1.3 does not have a pressure component, the leak rates chosen for analysis in Table 1 were measured at a pressure differential of 200 Pa as described earlier in this article.

Table 1

	Q = 20 L/min	Q = 120 L/min	Q = 1200 L/min
V = 100 m³	3343.6 ppm	1359.4 ppm	0.08 ppm
V = 1000 m³	3931.6 ppm	3593.2 ppm	1359.4 ppm

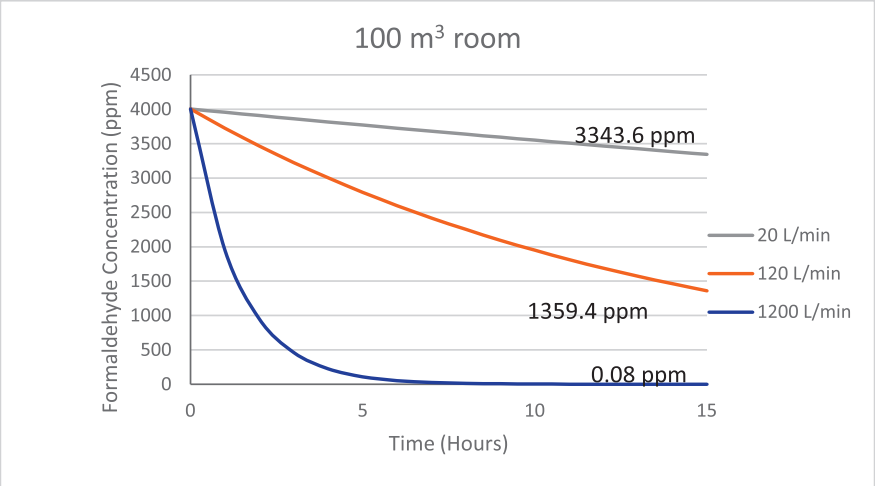

Figure 1: Concentration decay in 100 m³ room

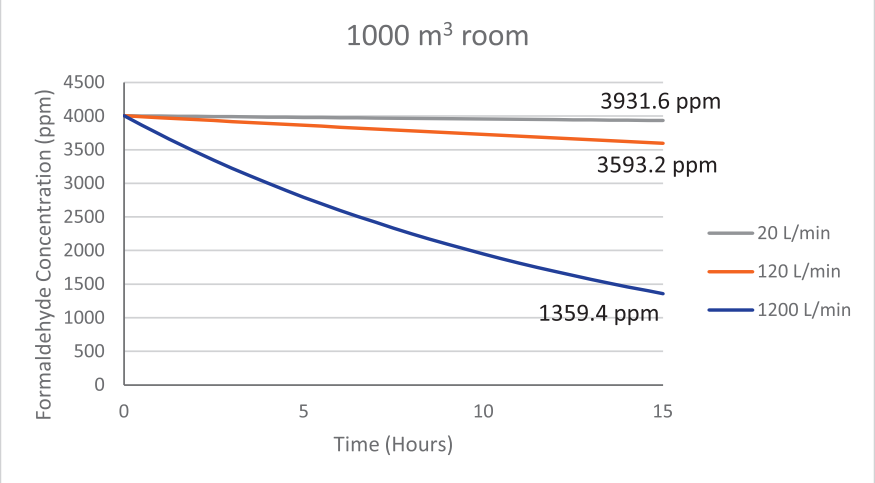

Figure 2: Concentration decay in 1000 m³ room

The variables used to calculate the values in Table 1 are as follows:

$[C]_0 = 4003\ ppm$

$Q = 20\ and\ 120\ and\ 1200\ L/minute$

$t = 15\ hours$

$V = 100m^3$ and $1000m^3$

Note units need to be made consistent.

Table 1 shows the concentration remaining in the room after the 15-hour dwell time.

Figures 1 and 2 show the decay of concentration in two different room sizes over the 15-hour dwell time.

Discussion

The application of Equation 1.3 shows a much larger impact on the concentration of fumigant in a smaller room. Given the long dwell times and the historical use of the fumigation method at the ACDP, dilution has never been an issue for a typical animal room of 100 m³ in volume and a leakage rate of ≤20 L/min. However, if a laboratory was 100 m³ with a leakage rate of 1200 L/min, this would have a significant impact on the efficacy of decontamination. Equation 1.1 shows that the leakage rate is directly proportional to the pressure differential, so structures that are not as leak-tight may be decontaminated at

lower pressure differentials to reduce the effects of leakage on the efficacy of the decontamination. If the fumigant is generated during the decontamination cycle (e.g., with chlorine dioxide), then the flow rate of fumigant should be sized to account for the loss of concentration due to room leakage. The location to which the fumigant is leaked is of major importance from an environmental and health and safety perspective: when more leakage is allowed, more fumigant will be released from the space in a less controlled manner. The nature of the leak will also have an impact, as a leak may be spread over several locations or could be in one location. If it is the latter, there may be efficacy considerations with greater local dilution at the point of the leak.

If one of the objectives of the facility is to contain biological aerosols in the event of an air handling malfunction, then it would be counterproductive to have a permissible leakage rate that considers the volume of the room.

In summary, Pickering (1982) presents two formulae for calculating the leak tightness of a structure. The time constant method includes a volume component, while the direct flow measurement method does not. In the initial stages of construction at the ACDP, the time constant method was used; however, as the laboratory build progressed, the direct flow measurement method was adopted due to the ease of use when leakage rates are very small (Pickering 1982). Considering this, the two formulae will give similar results if the rooms are similar. However, if the rooms are of different volumes, the same β value can be achieved with different leakage rates, which could be misleading. Taken together the results of this investigation suggest that the prescribed leakage rates of 120 L/min and 1200 L/min at 200 Pa should be assessed on an individual basis, considering the unique requirements and risks associated with each laboratory and its fumigation strategy, rather than by a one size fits all approach. If one of the objectives of the facility is to contain biological aerosols in the event of an air handling malfunction, then it would be counterproductive to have a permissible leakage rate that considers the volume of the room. For example, if a larger primary containment animal room had a higher allowable leakage rate than a smaller room, then in a positive pressurisation event, more biological aerosol would be leaked into adjacent spaces. Further research would be required to determine if an animal facility where the structure provides the primary containment should have the same permissible leakage rate as a facility where a separative device provides the primary containment.

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Face masks: Lessons from COVID-19 research

Tim Sandle

Abstract

The 2020 novel coronavirus pandemic has led to a wider interest in the classification, performance and testing of face masks. This article assesses the international standards for face masks and proceeds to examine some recent COVID-19 related examinations of face masks. Some of the outcomes of these studies are pertinent to general cleanroom use and help to inform cleanroom users about the importance of mask selection, mask donning, fitting, expiry time, and post-use handling.

Introduction

The surgical or medical face mask is an established item of cleanroom clothing and essential for many activities, including electronics manufacture, aseptic processing in pharmaceuticals, and surgical procedures. While many aspects of face mask use have been well-documented, it has again become the subject of research focus during the time of the novel coronavirus pandemic.[1] The use of masks has also become a matter of public policy debate, centred on the ability of surgical masks to reduce the transmission of coronavirus in respiratory droplets that fall rapidly near the source, coarse aerosols with aerodynamic diameter >5 µm and fine-particle aerosols with aerodynamic diameter ≤5 µm);[2] and hence whether or not wearing such masks by the general public can contribute to slowing the spread of COVID-19 by infected people.[3] Most studies find that source control, i.e. putting a mask on the infection source is up to 300 times more effective than putting a mask on the potential receiver of the infectious droplets.[4]

This article examines five areas drawn from research studies published during the first few months of the coronavirus outbreak and considers learning points for cleanroom operations. In addition, for readers who have more general concerns about the SARS-CoV-2 virus, there are some pointers of interest in relation to preventative measures and coronavirus transmission. The article starts with a discussion of the key criteria for face masks and the main global standards that apply in order to set the context and to provide guidance on the differences between the U.S. and Europe in terms of face mask specifications.

The origin of cleanroom masks is with surgical face masks, which were introduced to protect patients from wound infection and contamination during surgical procedures in the 1960s.

Face masks

The origin of cleanroom masks is with surgical face masks, which were introduced to protect patients from wound infection and contamination from surgeons (the wearers) during surgical procedures in the 1960s.[5] This concept of minimising the number and rate of microbial-carrying droplets was adopted for the production of medicines. The 'surgical' mask is normally formed from three-layers of material: a melt-blown polymer (typically polypropylene) layer sandwiched between two layers of non-woven fabric. The finished form is pleated, to enable the mask to expand so that it fits the wearer more securely, and is equipped with either elastic straps, to allow the mask to be tied or pulled around the head, or with ear loops.

There are different standards for face masks, which have been subject to periodic update, dating back to a study from 1980 that lays down the foundations for assessing mask efficiency.[6] For the 'surgical style' mask (and most common cleanroom masks) the European standard is EN 14683: 2019.[7] Within this norm there are three classes of mask (Types 1 to 3) based on particle filter efficiency ratings, where masks range between 95% and 98% in relation to the ability to filter particles of 3.0 µm (stated as the 'Bacteria Filtration Efficiency standard'). This test is a requirement for surgical masks. The U.S. equivalent standard is ASTM F2100.[8] The U.S. standard has an identical bacterial filter requirement, although it has an additional 0.1 µm particle filter efficiency rating (for the 'Particle Filtration Efficiency standard'). With both types of filtration this relates to particle capture efficiency, with the bacterial test focused on protection from biological aerosols.

For respiratory masks, the European standard is EN 149:2001[9] and the masks are classed as 'filtering face pieces' (FFP) in the range FFP1 – FFP3. The U.S. standard is developed by the U.S. National Institute for Occupational Safety and Health (NOSH) as 42 CFR 84,[10] where the masks are classed N95, N99 and N100. The respiratory masks are assessed by their ability to filter 0.3 µm particles as this represents the most-penetrating particle size. The requirements for the U.S. masks is tighter. For example, the N95 has a >95% efficiency rating and the N100 a >99.97% rating; whereas the European FFP1 is rated >80% (total inward leakage <22%) and the FFP3 >95% (total inward leakage <2%). Readers with an interest in COVID-19 matters will note that the N95 and FFP3 ratings are equivalent. China has a different norm to both the U.S. and Europe. In addition to the performance ratings, masks used for some cleanroom operations are required to be sterile either through gamma radiation or through ethylene oxide gas, with both processes required to achieve a Sterility Assurance Level of 10^{-6}).

The bacteria filtration efficiency test is of importance to cleanrooms. This test typically uses *Staphylococcus aureus* as the challenge organism. (*Staphylococcus aureus* is an organism of clinical relevance). An alternative involves the application of 0.1 µm latex spheres. The bacterium is challenged against a test mask in an aerosolised form at a flow rate of 28.3 L/m (which simulates the range of normal respiration). The test takes place with the inside of the face mask in contact with the bacterial challenge (to simulate what the wearer may be exhaling). A suitable number of

masks should be tested in order to establish confidence limits concerning product performance (the number of masks to be tested varies according to different standards). For the particle efficiency of respiratory masks, this is assessed using a mildly degrading aerosol of sodium chloride (NaCl) with a maximum test challenge loading of 200 mg.

These days the quality of most face masks is high; however, the COVID-19 pandemic has led to more companies of hitherto unknown origin flooding the market with face masks, some of which may be substandard (especially in relation to ventilation leaks or where there are issues with mask integrity[11]). It is important to obtain appropriate quality certification to assess masks and ideally, at least under normal conditions, to audit the manufacturer of the mask. Problems with some of these defective masks are examined below.

General issues with the use of face masks

Face masks are only effective when carefully handled and when they tightly fit the wearer (a point addressed below). Masks will degrade when subjected to physical, chemical, and thermal stresses. The integrity of the material can also be compromised during use by effects like flexing and abrasion, or when the mask becomes wet (as might occur from water splashes or alcohol sprays) or from excessive perspiration.

2020 research highlights

1. Risks of ill-fitting face masks

For a face mask to be effective, it not only needs to have the appropriate microbial filter efficiency and to maintain pressure during respiration, the mask also needs to fit securely. While most N95 or FFP3 respirator masks are typically face-fit tested the standard cleanroom 'surgical' mask is not, with the mask design aimed at to fit the 'typical face' (which is ill-defined and variable). Where a mask does not fit securely this leads to the phenonomeon of deflection where exhaled air and droplets are directed through a fine gap between the mask and skin, leading to outward leakage around the 'face-seal' perimeter. To examine the effect of an ill-fitting mask, scientists working at the U.S. Department of Energy's Center for Nanoscale Materials user facility at Argonne National Laboratory undertook a series of experiments on face masks.

For the study, an aerosol mixing chamber was used to produce particles ranging from 10 nm to 6 µm in diameter. A fan blew the aerosol across various cloth samples at an airflow rate corresponding to a person's respiration at rest (which averages at 15 breaths per minute[12]), and the researchers measured the number and size of particles in air before and after passing through the fabric. It was found that a 1% gap (of around 1 millimetre) reduced the filtering efficiency of all masks evaluated by half or more. This finding was drawn from assessing the fluid dynamics of face masks and investigating this via analytical and numerical computations, together with a combination of one dimensional-flow models and two and three dimensional-flow simulations. This emphasises the importance of a properly fitted mask and the potential risk to the environment this poses (either viral, in relation to the study, or bacterial in terms of general cleanroom application) on entering the cleanroom, given the tendency for most of the airflow and droplets to pass through such gaps.[13]

2. Maximum wear time for a face mask

The maximum time that a face mask can be worn for is a question often asked by cleanroom personnel (as well as being a question sometimes directed by regulators). A French study which has surgical masks designed for a single use only concluded that the mask must be changed as soon as it becomes wet and at least every 4 hours at the most. This was based on an assessment of standard wear conditions taking into account mask integrity. The assessment was made using surgical masks carrying CE marking and released to the standard EN 14683. After four hours it was found that the medical face mask no longer functioned as an appropriate microbial barrier. For respirators the maximum wear time was assessed as 8 hours.[14] Such findings are useful for cleanroom managers when proceduralising maximum mask wearing times.

3. Time-expiry of face masks

In addition to wear time, manufactured masks will only maintain their integrity for a finite period of time. Face masks are subject to natural ageing and will reach an expiry date beyond which their effectiveness cannot be guaranteed. Research generally indicates a two year expiry, although this will vary between manufacturers and the source material.[15] This leads to considerations for stock rotation within the cleanroom setting to ensure that expired stocks of PPE are not transferred to the changing room where they can be reused.

4. Safe removal of face masks (and other PPE)

Research conducted at Florida Atlantic University's Schmidt College of Medicine has assessed procedures for putting on and taking off personal protective equipment (PPE). This was designed to demonstrate how aerosol-generating procedures can lead to exposure of contamination with improper use of PPE. For the study, the researchers used a nontoxic fluorescent solution, which is only visible under ultraviolet light. A group of healthcare volunteers were then enlisted for the study. The volunteers were requested to put on a headcover, gown, surgical gloves, eye protection, and a face mask. Following the donning of the equipment, the volunteers entered into a room to care for a simulated patient (this was a mannequin sprayed down with an invisible simulated contagion). Following a period of time in the room, the volunteers were taken to another room, where the lights were turned off prior to removing their PPE. Turning off the lights enabled the identification of widespread simulated contagion on the PPE, both on the gloves and gowns from directly touching the simulated patient and on the masks from the aerosolized solution. The researchers used a black light flashlight to examine each health care worker and to identify the presence of any fluorescent solution.

Following the flashlight examination, the volunteers completely removed their PPE. Researchers discovered the presence of fluorescent solution on the skin of the personnel, which represented an exposure to the contagion and indicated that they made an error while putting on or taking off their PPE. The results from the experiment revealed that the most common error made by the health care staff was contaminating the face or forearms during PPE removal. In contrast, those who put on and took off

their PPE according to guidelines had no signs of the fluorescent contagion on their skin or face.[16] This research reinforces best practices, not only during the era of COVID-19, but as a general hygiene measure when exiting from the cleanroom.

5. Reusing masks

Reusing face masks designed for single-use is not normally recommended. In the era of COVID-19, some health agencies have needed to resort to the re-use of face masks. A study backed by the American Chemical Society has reviewed the extent to which higher-grade face masks can be decontaminated without adversely impacting on integrity and bacterial filter efficiency.

Most face masks are formed of polypropylene fibres that form a porous, breathable network (assessed on the basis of mask airflow resistance). To help capture smaller particles that could slip through the holes, the fibres are electrostatically charged. When subject to different environmental factors, the formation of the fibres can weaken. To examine the impact of the disinfection factor, scientists looked at different methods that could reasonably be used to assess how well mask materials hold up to repeated disinfections. For the study, U.S. certified N95 masks were used. It was found that spraying the fabric with an ethanol or chlorine bleach solution drastically reduced the filtration efficiency after only one treatment, from about 96% to 56% (ethanol) or 73% (bleach). A single steam treatment maintained filtration, but five steam treatments led to a sharp decline in efficiency. UV radiation was found to be less damaging and allowed up to 20 cycles of disinfection; however, administering the exact dose of UV that kills the virus without damaging mask materials is not straightforward and the use of UV-C light carries health and safety considerations. In contrast to these methods, the optimal disinfection method was heating. Applying a temperature of 82°C for 20 minutes allowed the fabric to be treated 50 times without loss of filtration efficiency.[17] In addition, a different research group looked at the application of hydrogen peroxide vapour. This study showed that using 35% w/v cycle enable face masks to be decontaminated up to twenty times; after twenty cycles, however, the mask properties were altered to the extent that masks no longer fitted securely.[18]

Care must therefore be taken if masks are to be re-used. The World Health Organisation has warned that the incorrect use and disposal of an infected mask may actually increase the rate of transmission.[19] For cleanrooms, it is not considered good practice to reuse face masks.

Not all surgical facemasks are of the same quality. Variations arise with the materials of manufacture and the method of manufacture, including the melt-blown process for producing the polypropylene fabric and the resulting quality.

6. Variable and substandard facemasks

Not all surgical facemasks are of the same quality. Variations arise with the materials of manufacture and the method of manufacture, including the melt-blown process for producing the polypropylene fabric and the resulting quality. A study from Northeastern University (Boston, U.S.), demonstrated that different commercially available surgical masks removed between 53% to 75% of particles <300 nm from air when worn as designed. Moreover, the overall particle removal efficiency extended to between 28% to 91%. The surgical masks that were deemed to be more effective were those that contained a nylon overlayer. This addition improved particle removal efficiency of many masks by minimizing gaps. The reason such variations arise is because the testing methods used by some manufacturers are limited to testing the fabric only and not the mask as constructed or worn.[20]

The coronavirus pandemic has seen several substandard facemasks flooding the cleanroom personal protective clothing market.[21] Many of these masks are reportedly originating from Asia, including Hong Kong.[22] While mainland China has a standard for surgical masks equivalent to the U.S. and European norms (GB 19083-2010 Technical Requirements for Protective Face Mask for Medical Use), this standard is not applicable to Hong Kong. Advice on spotting substandard or counterfeit masks is not strong within Europe; however the U.S. Centers for Disease Control and Protection (CDC) provides considerable detail on its website.[23]

Since the specialized equipment required to measure filtration efficiency of mask materials for the most penetrating particle size (usually around 300 nm) is not widely available,[24] the purchaser is reliant upon the manufacturer's specification, certification and assessment when evaluating between suppliers. Face masks sold within the European Union should carry a Conformité Européenne (CE) mark (or a UKCA mark for masks sold within the UK from 1st January 2021). It is therefore important to assess the specification for the mask and to confirm that the accompanying certification matches the specification requirements. As well as purchasing from a reputable supplier, it is good practice to undertake periodic supplier audits.

7. Face coverings

While face coverings, rather than facemasks, are not suitable for donning to go into a cleanroom, readers may be interested in face coverings as alternatives to surgical facemasks (for wearing in offices or for non-work activities). Unfortunately, many self-made coverings or coverings manufactured by fashionable brands confer only limited viral capture capabilities. Among the more promising materials, a 2020 study showed that hand-made masks have some effect, provided they are made from cotton materials. The use of cotton is effective in reducing the level of spray generated through everyday speech. However, other self-made face coverings, like bandanas, neck fleeces and balaclavas were found to be ineffective. The study, which was developed to provide useful data during the coronavirus pandemic, took place at the Duke University Medical Center and it set out to assess the relative effectivity of different face coverings.

To reach their conclusions physicists designed a simple test method for mask and face covering effectiveness, based on a box, a laser, a lens, and a cell phone

Table 1: Comparison of materials for fabric masks

Material (source)	Structure	Initial Filtration Efficiency (%)	Initial Pressure drop (Pa)	Filter quality factor, Q (kPa^{-1})
Polypropylene (interfacing material)	spunbonded	6	1.6	16.9
Cotton (sweater)	knit	26	17	7.6
Cotton (T-shirt)	knit	21	14.5	7.4
Polyester (toddler wrap)	knit	17	12.3	6.8
Cotton (T-shirt)	woven	5	4.5	5.4
Cellulose (tissue paper)	bonded	20	19	5.1
Cellulose (paper towel)	bonded	10	11	4.3
Silk (napkin)	woven	4	7.3	2.8
Cotton (handkerchief)	woven	1.1	9.8	0.48
Cotton, gauze	woven	0.7	6.5	0.47
Nylon (exercise pants)	woven	23	244	0.4

camera. The device detects the scattering of water particles, which are generated as a person speaks. With the relative, mean droplet efficiency, the N95 mask had a droplet count below 0.001; a surgical mask around 0.01; a self-made cotton mask of around 0.1; and many other materials close to 1.0 (which was almost identical to wearing no face covering at all). While some masks were evidently better than others, given that around half of COVID-19 infections come from people who do not show symptoms, the wearing of some form of mask does help to avoid viral transmission.[25] Supporting evidence from mathematical models shows that routine facemask use by 50 percent or more of the population reduces COVID-19 spread to an R-number less than 1.0, flattening future disease waves and allowing less-stringent lockdowns.[26] The reproduction or 'R' number relates to the number of people an infected individual passes the virus onto. This needs to stay below 1.0 for a pandemic to slow.

A summary of the findings is presented in Table 1. Here the higher the 'filter quality factor', the better the facemask is at filtering particles.

The filter quality factor is derived from the following formula:[27]

$$Q = -\frac{\log \alpha}{\Delta P}$$

Where:
α (penetration) = 1-E/100
(E is the filtration efficiency (in %)

ΔP is the pressure drop across the filter (in kilopascals).

A maximum Q results from a high filtration efficiency (low penetration) with low pressure drop, which is regarded as suitable for facial coverings.

Caveats with Table 1 are that each mask fashioned from the material is formed of a minimum of three layers: an inner layer touching the mouth and an outer layer that is exposed to the environment. Material should be water-absorbing (hydrophilic) materials combined with an external synthetic material that does not easily absorb liquid (hydrophobic).

Summary

This article has revisited the topic of face masks, drawing on research papers published during the first half of 2020 in relation to the global coronavirus pandemic. A review of these research areas highlights concerns over the fitting and removal of face masks (and provides a reminder that face masks need to be considered as infectious waste, especially in relation to certain types of processing or following surgery). The fitting activity not only extends to the activity of touching the mask since an improperly secure mask will allow for particle release and hence a contamination risk. There are other determinants which affect the efficacy of the face mask, such as environmental airflow in the room. The mask wearer must not be forgotten either; factors like breathability and facial fitness are important so that the user is comfortable and the temptation to adjust the mask once worn is reduced. Important as these are, these factors of mask use do not form part of recent research and therefore they have not been included in the main body of the article.

The review has also looked into the re-use of face masks. While such a practice is not recommended for a GMP setting, in some parts of the global health services, where there is a severe shortage of PPE such measures need to be taken in order to ensure healthcare professionals are adequately protected. With this, heating appears to be the most effective measure and the one that is easiest to execute.

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Energy efficiency in cleanrooms and clean air devices: ISO 14644-16

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This paper is the third in a series of outreach articles that are being produced by ISO/TC 209 Working Group Convenors and leaders to foster promotion and education of the expanding body of ISO/TC 209 Standards. It is reproduced here with the kind permission and encouragement of the ISO/TC 209 Secretariat Team.

Abstract

The ISO 14644 family of cleanroom standards has been at the centre of International cleanroom standards development for many years and covers most facets of cleanroom activity and cleanroom types from large ballroom cleanrooms to isolators and clean tunnels. Historically the series started with information on the testing and measurement of airborne particle concentrations and a classification system for allowable particle concentrations within cleanrooms. Guidance on basic design and practice quickly followed and led to the series of ISO cleanroom standards that is now accepted worldwide. The series is under constant review and is still expanding.

Recent documents that have been released concern the quantification of airborne and surface chemical concentrations, nanoparticles and the selection and testing of equipment used within these rooms. However, apart from some misleading information in the original Part 4 design document, questions concerning the energy demands from air purification processing have been overlooked. Nationally, institutions such as the BSI in UK, DIN- VDI in Germany and IEST in the USA have produced limited information on the topic, but Part 16 is the first standard to be internationally agreed. This article explains the key features of the new standard which was released in May 2019.

Introduction

The new standard was proposed and convened by the UK as a progression of their 2013 cleanroom energy management document, BS 8568[1]. It reinforces the principal established in that guide, that airflow preparation and circulation are the main contributors to cleanroom energy use, demanding up to 80% of total energy in some facilities. Whilst much of its original advice in BS 8568 on basics such as over-engineering, leak prevention, filter selection, management and maintenance is retained in the new standard, the content is expanded and airflow volume assessments replace air change rate calculations. All this has been achieved by the formation of ISO Working Group 13 with cleanroom experts from Australia, China, Europe, Russia, Scandinavia and the USA to share their experience in this field. The working group also agreed that an energy comparison scheme should be part of the new standard, using terminology and metrics developed for ISO 50001, the International energy management systems standard. Experts from France, Holland, and the USA have produced a comprehensive Annex to explain the mathematics of this difficult area which should enable its use worldwide.

Technically the new document focuses on 4 new features:

1. The preparation of an accurate User Requirement Specification (URS) in order to establish the precise user requirement.
This is normal procedure in the pharmaceutical and medical device fields but seems lacking within the mechanical and microelectronic world. Effective design requires an accurate estimation of how many people will work in the room, what type of garments will be worn, the type of materials being processed, the tooling used and the final air and product quality levels to be maintained. Due regard should also be made for the environmental situation outside the facility and seasonal digressions. These considerations should be detailed in the design brief.

2. A practical method for estimating the volume of supply air needed to maintain the specified ISO room classifications in operation.
This requires estimates to be made for the contamination load from the process, from cleanroom people and their garment shedding, and from tooling, in order to factor the contamination load into the new air volume formulae. Investigations into particle concentrations, such as those carried out by Ljungqvist and Reinmüller in Sweden and the International Camfil Farr group are listed for reference in the bibliography.

The design of a non-unidirectional airflow cleanroom requires effective airflow design for good performance. Traditional air volume calculations can be improved by the inclusion of a ventilation effectiveness (VE) index in their data. This index is influenced by the placement of ceiling diffusers and exhaust vents. Part 16 gives two options for its estimation, namely Air Change Effectiveness (ACE) and Contaminant Removal Effectiveness (CRE). The ACE index compares how much clean air a test location receives relative to the average in the cleanroom, whereas CRE, used by the European Heating, Ventilation and Air-conditioning Association (REHVA) and parts of the USA, derives this by comparing the average particle count per cubic metre in the cleanroom and in the exhaust duct.

The ACE theory and the new equations have been developed and production tested by Dr Whyte and colleagues in the UK. Wei Sun's ASHRAE experiments and research work in the US reinforced much of the thinking and introduction of CRE. Several of their papers on the airflow topic are listed in the bibliography.

Note that these indices are not suitable for unidirectional airflow (UDAF) cleanrooms with total ceiling HEPA coverage. Those rooms require

optimisation of airflow speeds, controlled idling set back periods and strict cleanroom discipline, addressed in document sections on adaptive control, education, training and maintenance.

3. Tuning

In non-unidirectional airflow rooms, the air volume flow rate can only be estimated at the design stage since only approximate data on particle generation are available, and a compensation factor is normally applied. Computational Fluid Dynamics (CFD) can be useful in determining the size and positioning of the supply air points and the location(s) of the air extract points. Alexander Fedotov's progressive testing system, developed in Russia, is a pragmatic way of testing the completed cleanroom and ensuring that the compensation factor is not excessive. The process involves progressive testing and relaxation of the air volume until the correct cleanliness level is reliably maintained. This can normally be achieved within 2 or 3 iterations of the test cycle giving rise to the concept of a tuneable process.

A worked example including all the above theory is included in the airflow Annex.

4. Benchmarking

Designated as environmental management tools, the Energy Management Systems standards, especially ISO 50001[2] and ISO 50006[3], contain a wealth of useful information with terminology designed to define the contributing elements of an energy load. They provide ideal tools for comparative process analysis and the experts on the working group reported on how these were adopted and developed in Holland the USA and France for comparative analysis of process fan power between shifts. Additionally an engineering team from ASPEC-ADEME in France worked with the EDF power company to study consumption within their national clean process industries. The study, published in December 2016, compared the annual facility consumption by process, using measurement metrics such as Specific Fan Power (SFP). The study, presented by EDF team and working group member Jean Paul Rignac, makes very interesting reading and shows that these methods can be an excellent indicator of energy power management. Jean Paul was able to share his experience, helping Peter Bertrand and Norman Goldsmith to complete their work on the complex benchmarking Annex for Part 16.

This Annex develops the base line energy performance indicators (EnPIs), used by the Laurence Berkeley National Laboratory with comprehensive formulae to define three main cleanroom related metrics:

1. **Power intensity for contamination removal (PICR)** giving the instantaneous power consumption per square metre of floor surface for the air-handling system to remove contamination. PICR can also be determined from the product of two sub-metrics:
   a. The specific fan power (SFP): the total energy power in kj/m^3 with which the air is moved through all the air handling units serving the cleanroom. This can be calculated by dividing the total electrical power in kW of all the fans by the total airflow rate in m^3/s
   b. The normalized air volume flow rate: the amount of air per square metre in [(m^3/s)/m^2] being used to dilute and displace contaminates in the cleanroom. This can be calculated by dividing the total volume airflow rate in m^3/s by the floor surface area of the cleanroom in m^2
2. **Fan energy intensity for contamination removal (EICR)** is a similar metric to PICR but takes into account energy reduction that occurs during times when the cleanroom is not in operation or in adaptive control mode where the airflow varies according to how much contamination is being generated at the time. This metric is calculated by totalling the energy use of all the fan systems serving a cleanroom, for a period of a year, and dividing by the floor area of the cleanroom.
3. **Energy intensity (EI)** is a basic design metric that is calculated by totalling all annual energy flows to condition the cleanroom in question and dividing by the floor area served. These data are then sorted according to ISO class so that comparisons can be made between facilities, environments, companies and industries for classes 3 to 9 in operation.

We consider that these three metrics establish a host of techniques enabling engineers to compare and optimise energy usage within the cleanroom industry.

The new document also covers the significance of correct gowning, education and training in energy conservation and carries forward the maintenance, leak prevention, filter and motor selection material used in BS 8568. The reduction technique selection tables from 8568 have also been improved to illustrate the benefits or dangers of certain reduction techniques.

Finally I would pay tribute to all our working group members and their professional bodies in China, Germany, Holland, Italy, UK and the US who supported this work by hosting our preparatory meetings. Whilst at 43 pages it is a large document, it is well indexed and provides much new and useful information.

References

1. BS 8568:2013, Cleanroom energy — Code of practice for improving energy efficiency in cleanrooms and clean air devices
2. ISO 50001:2018, Energy management systems — Requirements with guidance for use
3. ISO 50006:2014, Energy management systems — Measuring energy performance using energy baselines (EnB) and energy performance indicators (EnPI) — General principles and guidance

Dick Gibbons, CEng, IMechE, FSEE, has an extensive career in contamination control specialising in the processing of cleanroom product. He has been a major contributor to the work of BSI LBI/30 and ISO TC/209 for many years and is currently convenor of ISO TC 209 Working Group 8 that is revising ISO 14644-8:2013 - Parts 8, 9 and 10. He was convenor of Working Group 13 that has recently completed ISO 14644-16:2019 - Part 16: Energy efficiency in cleanrooms and separative devices.

Advances in Practical Safety Ventilation by Bengt Ljungqvist and Berit Reinmuller

Reviewed by Tim Sandle

Over the course of their careers Bengt Ljungqvist and Berit Reinmuller have produced an array of interesting, and invariably, pioneering papers relating to the design, build and control of clean air, especially where the objective is to protect patients and medicinal products. Both academics have a long association with Chalmers University of Technology (Gothenburg, Sweden). A solid selection of their work has been compiled for a new book: 'Advances in Practical Safety Ventilation – Pharmaceutical cleanrooms and hospital operating room'.

The book offers a rich treasury of advice for anyone who works within pharmaceuticals or healthcare and who is seeking advice in relation to strengthening contamination control. Across 374 pages there is detailed guidance on all aspects of cleanroom airflow patterns, the mechanics of airflow, and how microbial contamination is carried within the airstream.

The primary method for achieving contamination control is through understanding air filtration and air movement and how these influence the dispersal of contaminants, for it is only when particles settle out of the air and onto a surface that the secondary aspect of contamination control comes into play (as cleaning and disinfection). The authors refer to the movement-dispersal principle as 'Safety Ventilation', a neat summation that will hopefully become an established term in the lexicon of cleanrooms.

The book is carefully divided into different sections and the chapters therein balance scientific theory with practical application (such a balance is surprisingly absent from many books relating to the pharma-healthcare area).

It is difficult to select standout chapters from the impressive reading list. In veering towards the personal interests of the reviewer, three chapters are selected. Beginning with Chapter 3, this is remarkably interesting in terms of understanding how a cleanroom operator affects the airflow pattern, especially when acting within a unidirectional airstream. We may understand there is a theoretical risk; however, what Ljungqvist and Reinmuller succeed in doing is modelling this in real settings and diagrammatically present the level of risk based on different locations and the type of operator movement. Of greatest risk is the region around the knee of the operator and it is advised that work in this area is avoided (for any facilities making aseptic connections at this level there is a warning here to seek an immediate redesign). The chapter also explains why convection flows and arm movements from an operator positioned in a vertical unidirectional airflow system has a considerable impact upon the contamination risks at air velocities below 0.4 m/s. To counteract this, the air velocity should be at or above 0.4 m/s in order to achieve an adequate protection efficacy.

The second choice is Chapter 6, which provides a comparison between different models of active air-sampler and advice on how to select the most appropriate sampler. Not all active air-samplers are the same: they differ in terms of collection efficiency and with the size of particles that can be detected at a 50% recovery. The chapter builds upon physical and biological collection efficiencies for the common models (impaction, centrifugal, filtration and so on). Other variables explored, which can influence air-sampler collection efficiency, include environmental conditions, sources, and concentrations of microbial organisms in the environment. Microbial concentration, the majority of which derives from personnel, is in turn influenced by the quality of cleanroom clothing worn by operators. Anyone tasked with purchasing an active air-sampler should draw from the points listed in order to quiz each prospective vendor.

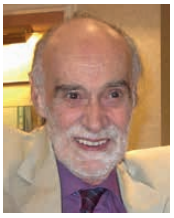
The third choice is with one of several chapters that use quality risk management as a tool for locating contamination risks and providing a basis for using air as a risk mitigation tool. This is captured in what is, in this reviewer's humble opinion, one of the greatest contributions to cleanroom contamination control – the Limitation of Risks (or LR-Method). This pioneering approach makes good use of airflow visualisation together with particle counting, in order to pinpoint those areas within a critical operation (such as aseptic filling) which present the biggest risk. Risks can be compared and relatively assessed by calculating the risk factor. The authors present an effective way for limitation of potential microbial risks. Hence, by running such an exercise, contamination risks to aseptically filled medicines can be first, understood, and second, significantly reduced. While several chapters show the application of the LR-Method, Chapter 12 is especially illuminating, and it offers a form of a road-map that can be deployed in an industrial or clinical setting.

Selecting three chapters is not meant to represent an injustice; this book offers far more: interactions between different clean zones; addressing particle control when using weighing stations; rapid microbiological methods; isolator operations; safety cabinets; the challenges posed by freeze-dryers and autoclaves that open into cleanrooms; the particle complexities of blow-fill-seal; cleanroom clothing (which needs to be considered as a continuous filtration system); the risks posed by people as shedders of microbial carrying particles; and with the patient protection aspects of the hospital operating room. These subjects are examined in great detail across 36 chapters.

'Advances in Practical Safety Ventilation – Pharmaceutical cleanrooms and hospital operating room' is published by Euromed Communications and is available via this link: https://euromedcommunications.com/products/advances-in-practical-safety-ventilation-pharmaceutical-cleanrooms-and-hospital-operating-rooms

Lawrence Whittard: Founder of Cherwell Laboratories

Cherwell Laboratories bids a sad farewell



Cherwell Laboratories, specialist suppliers of environmental monitoring and process validation solutions for the pharmaceutical and related industries, announces with great sadness that its founder, Lawrence Whittard, passed away peacefully at home, on 10th September 2020, he was 83 years old.

Lawrence graduated as a veterinary surgeon from University of Bristol in 1960 and embarked on a career in practice in the West country where he greatly enjoyed rural life. His university year group remained in contact and met each year for a dinner.

An interest in diagnostic work led him to start his own business and he founded Cherwell Laboratories in 1971 as a veterinary diagnostic laboratory. His interests and curiosity meant that new opportunities were never far away and a chance meeting at a laboratory equipment show in 1979 introduced him to Roberto Ligugnana of International PBI, Italy. Cherwell quickly became the UK distributor of their range of media preparation equipment and this started focusing the business on microbiology. Soon afterwards the SAS microbiological air samplers appeared and because of promoting these Cherwell started commercially offering prepared microbiological media to customers; the Redipor® name was born in the early 1980s.

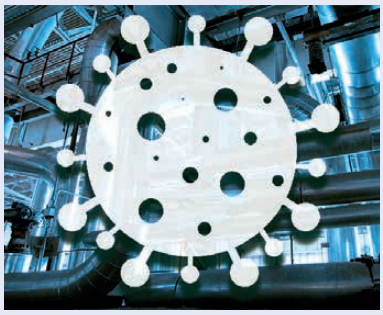
Lawrence's eye for an opportunity never diminished and he helped design and build a Cherwell contact plate filling machine, followed by a system based microbial air sampling system named Multi-SAS. Cherwell grew and by the 2000s had focused on manufacturing prepared media and selling microbiological products primarily to the pharmaceutical sector. As the business continued to grow, more space was required and in 2004 it relocated to its current site, a significant step up but one which has allowed the business to continue to flourish. Lawrence's son Andy had already joined the business and in 2005 became Managing Director.

Lawrence had always been a dedicated family man and welcomed the opportunity for the business to be passed to the next generation. His other son Pete is also a shareholder in the business and sits on the board. Lawrence continued to be an animal lover and had many pets over the years, he was also a keen photographer.

Lawrence's family plan to come together in the future to celebrate his life.

Lawrence's obituary is published online on Cherwell's website: https://www.cherwell-labs.co.uk/cherwell-labs-post/in-memory-of-lawrence-whittard

EECO2 offers COVID-19 HVAC Risk Assessment



With leading knowledge of life science industry HVAC systems, EECO2 is providing solutions to minimize the risks associated with the airborne transmission of the SARS-CoV-2 virus, enabling pharmaceutical manufacturing sites to safely open.

There is a growing body of evidence that the SARS-CoV-2 virus (cause of COVID-19) can be spread through the air, particularly in poorly ventilated indoor spaces. Therefore, ventilation provision, assessment and maintenance in buildings should be reviewed as a priority.

EECO2's expertise ensure changes can be made to the HVAC systems, providing safer environments in the most efficient way, whilst maintaining (or improving) quality and compliance levels.

Each HVAC system and the area it covers will be evaluated with regard to risk to safety and potential improvements to reduce site energy and carbon consumption. EECO2 will support the site with recommendations and solutions. International energy regulations are observed for all system modifications.

For more information about the EECO2 HVAC Risk Assessment, email info@eeco2.com or visit www.eeco2.com

Ecolab helps protect customer facilities, products and people

It is acknowledged that the Covid-19 pandemic has had a significant impact on the way people live, work and think. As a trusted supplier of cleanroom cleaning and disinfection products and services, Ecolab are reinforcing their broader product offering of general cleaning, disinfection and hygiene solutions for less critical areas (such as offices and communal spaces) at customer facilities.

Working with a single supplier for these solutions is an easy way to help ensure whole businesses, and operating costs, are protected. Ecolab Life Sciences can help navigate the many cleaning, disinfection and sanitization needs within customers' operations.

Beyond delivering the appropriate cleaning and hand hygiene products for every situation, Ecolab also shares their expertise to help prevent the spread of infection and provide guidance on maintaining a safe and healthy operation.

www.ecolablifesciences.com

Envair announces new partnership with SmartCompounders

Containment specialist's isolators now available with an integrated compounder solution. Clean air and containment specialist Envair has announced a new partnership with Dutch engineering firm SmartCompounders. The collaboration means Envair will be the only isolator manufacturer in the UK to offer this innovative solution to personalised medication.

Combining the SmartCompounders Chemo automated solution with the Envair CDC F negative pressure isolator can help pharmacy managers quickly and easily increase output for each compounding technician to 20-40 final product containers (IV bags, syringes or elastomeric pumps) per hour, improving efficiency and reducing medication errors.

Commenting on the partnership, Envair Managing Direct Gary Bagshaw said, "With so many clients demanding efficient ways to deliver personalised medicine, we believe the SmartCompounders Chemo integration, which can also connect to prescribing software, is a giant leap forward for hospital pharmacies."

Founder and CEO of SmartCompounders, Sander van Vreeland, added, "With their established relationships with hospitals throughout the UK, we are delighted to be able to add our solution to Envair's portfolio, helping to drive efficiency and improve accuracy in pharmacies and compounding centres."

For more information please contact info@envair.co.uk, visit www.envair.co.uk or download Envair Info Sheet Smart Compounders 601

Cherwell Laboratories Celebrates 50-year Anniversary

Cherwell Laboratories is celebrating 50 years since its founding by Lawrence Whittard in February 1971.

Cherwell's long-standing success can be attributed to its high-quality products and expertise in pharmaceutical industries, along with a strong focus on customer support and service. The implementation of its new Enterprise Resource Planning system is the latest drive to maintain this focus. Providing improved insight on lead times and delivery dates; the system offers enhanced communications and future electronic delivery of key documents such as quality certificates.

Andy Whittard, Managing Director, Cherwell Laboratories, said, "I am very proud of Cherwell's 50-year legacy started by my father Lawrence. We have built our expertise by working closely with customers ensuring we can offer them the best possible cleanroom microbiology solution for the effective management of their controlled environments and processes. Quality is at the core of what we do."

"We are also very proud that our products are contributing to the Covid-19 vaccination program, being used for microbiological QC at some of the vaccine manufacturing sites" Andy added.

Cherwell will be running a series of activities throughout the year, visit https://www.cherwell-labs.co.uk/50-years-of-cherwell for more information.

Andy Whittard

From waste to wipe – Contec adds Sterile Cleanroom Wipe to ReFIBE range of recycled wipes

Sustainable consumable options that are appropriate for cleanrooms are difficult to find. Last year Contec launched ReFIBE, the first sustainable polyester cleanroom wipe that is made from recycled post-consumer plastic bottles.

A sterile version of the knitted polyester wipe has now been added to the range, which makes the wipe even more suitable for life science cleanrooms. ReFIBE wipes are laser-cut with heatsealed edges so very low in particles and fibres.

To make ReFIBE wipes, recycled plastic bottles are collected, then chopped into flake and cleaned. The bottle flake is melted, filtered and formed into chips. These chips are melted and made into yarn. The yarn is then knitted into ReFIBE wipes. Each case of wipes stops at least 480 plastic bottles going to landfill.

For more information or to request a sample, go to www.contecinc.com/eu.

Biosafe – Crowthorne Group's emergency recovery scheme

Keeping business and lab environments clean and industry compliant has been the core objective for the Crowthorne Group since 1986. Providing world-leading servicing, spare parts and validation aimed at maintaining clean air and cleanrooms has allowed the group to become not just service providers but also advisors. Crowthorne's emergency recovery scheme, 'Biosafe' provides a more comprehensive service package to customers with containment level 3/ Hazard group 3 facilities.

biosafe
Part of Crowthorne Group

The program offers 3 levels of cover, ranging from an annual sealability test to a full CL3/HG3 validation and fumigation service, aimed at providing complete compliance to HSE, HTM 03-01 and ACDP guidelines.

The upgraded plan also allows for bespoke service plans, which can be tailored to meet the individual needs of customers.

For further details or to contact Crowthorne Group, please visit https://crowthornehitec.co.uk/biosafe/

ATI's training and certification during COVID-19

Since the beginning of COVID-19, ATI has seen an increase in demand for not only its cleanroom certification equipment (digital photometers and aerosol generators), but also training and certification. Tim Triggs, Director, EMEA took ATI's traditional Academy for Cleanroom Testing curriculum and made it virtual. "Realizing that in-person training was no longer an option during periods of national lockdowns and restricted travel, we had to rethink our way of delivering this content. In creating a virtual classroom experience, we still provide delegates with theory of testing and practical guidance to carry out tests with confidence," said Triggs. The virtual classroom concept has allowed delegates to join who may not have been able to in the past due to budget or time away from the office constraints.

The trainings are delivered from ATI's UK facility and delegates join via Zoom. The typical one or two-day course includes theory, practical demos, Q&A, and testing. Attendance is advised for anyone with a role in engineering, testing, quality, validation, operations, management, or inspections of clean air facilities and equipment. Additional courses have been added during May to meet demand. The full training calendar is posted on ATI's website. Contact Tim Triggs (ttriggs@ATItest.com) to reserve your place.

Particle Measuring Systems releases next generation remote particle counter

New VHP Resistant IsoAir Pro-E remote particle counter for versatile cleanroom monitoring.

The IsoAir® Pro-E Remote Particle Counter from Particle Measuring Systems (PMS) leverages the latest technologies to streamline cleanroom monitoring while meeting global regulations including EU GMP Annex 1, ISO 14644-2, and is part of a 21 CFR Part 11 solution. The robust 316L stainless steel enclosure is liquid resistant with an IP65 rating which protects the unit during cleaning and disinfection activities.

This is the first particle counter with built in vacuum designed for use with the Vaporized Hydrogen Peroxide (VHP) process. Additionally, this cleanroom monitoring instrument is powered by Power over Ethernet (POE) and, with the internal blower, requires very few external connections and supporting equipment.

"Only Particle Measuring Systems provides complete viable non-viable cleanroom monitoring solutions as well as the flexibility to meet the needs of large and small bio-manufacturing processes," said Paul Hartigan, Global Product Line Manager at Particle Measuring Systems. He continued, "The IsoAir Pro-E is an example of how we engineer agile and user-friendly design into our products to meet evolving industry needs."

Managing data is adaptive with easy integration into a variety of PMS or third-party software systems. Additionally, the quick release mounting bracket stores essential sensor data such as the IP address at the point of measurement, reducing the time and complexity of unit installation after calibration or servicing. This remote particle sensor is "plug-n-play" with no complex re-programming before reinstallation into the cleanroom monitoring system – see www.pmeasuring.com

Cleanroom and particle monitoring solutions with EMS Particle Solutions

Established in 1988, EMS Particle Solutions is an industry leader in cleanroom and particle monitoring Solutions. Headquartered in Dublin, EMS operates in both Ireland and the United Kingdom, offering the latest range of innovative products and specialised services to industries including pharmaceuticals/life sciences, semiconductor/microelectronics, aerospace & defence, food & beverage, industrial manufacturing, and research & development.

EMS are the exclusive distributors of Particle Measuring Systems (PMS) products in Ireland and the UK. Particle Measuring Systems is one of the world's leading manufacturers for particle counting instruments, and molecular and microbial monitoring.

EMS offers fully integrated and robust monitoring solutions including:

- Particle counters and microbial samplers (remote and portable);
- Environmental and facility monitoring systems (FMS); and
- Data collection and data management (DM)

In addition to providing expert solutions using the latest technology and products available, EMS offers a complete range of cleanroom and particle monitoring services ranging from cleanroom certification; calibration laboratory (including repairs to manufacturer's specification) and biosafety cabinet and isolator certification services.

EMS Particle Solutions has the experience and expertise necessary to successfully detect, analyse and manage cleanroom contamination to meet regulatory requirements (including ISO 14644-1:2015 and EU GMP Annex 1 while improving overall yield.

For more information, please contact: www.emsparticlesolutions.co.uk, phone: +44 (0) 1223 257 704 or email: info@emsparticlesolutions.co.uk

Events

2021	Event	Location
May 3-6	ESTECH 2021	Baltimore, Maryland
May 25-27	Symposium & Exhibition 2021	Naantali Spa, Finland
June 15-16	Achema	Frankfurt, Germany
July 6-7	Making Pharmaceuticals Exhibition and Conference	Coventry, UK
September 14-15	Cleanroom Technology Conference	Birmingham, UK
September 14-15	Manufacturing Chemist Live 2021	Birmingham, UK
September 28-29	Making Pharmaceuticals Ireland,	Dublin, Eire
November 3-4	Lab Innovations	Birmingham, UK
November 23-25	A3P International Congress	Biarritz, France
November 24-25	Cleanzone	Frankfurt, Germany
December 16-18	EP and Clean Tech China 2021	Shanghai, China
2022	**Event**	**Location**
March 22-23	Making Pharmaceuticals	Milan, Italy
October 11-13	25th International Symposium on Contamination Control, ICCCS'20	Antalya, Turkey

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2021	**Event**	**Location**
May 3 am	Contamination Busters: Get the Dirt Out of the Cleanroom	During ESTECH 2021
May 3 pm	Risk is a Four Letter Word	During ESTECH 2021
May 4	The Unseen Contaminant: Taking Charge of Electrostatic Contamination	During ESTECH 2021
May 5	Stop Contamination in Your Operations with Reusable and Disposable Garments	During ESTECH 2021
May 6	Develop Standard Operating Procedures Using IEST Recommended Practices	During ESTECH 2021

CCN (Contamination Control Network) www.theccnetwork.org		
2021	**Event**	**Location**
March 30	Free webinar on Cleanroom Standards – Application to Projects and Operations	VIRTUAL
November 9-11	CTCB-I Cleanroom Testing Course	Liphook, England

ICS (Irish Cleanroom Society) www.cleanrooms-ireland.ie		
2021	**Event**	**Location**
For a complete list of courses including CTCB-I courses, please see https://www.cleanrooms-ireland.ie/training/		

R3Nordic www.r3nordic.org Safety Ventilation www.safetyventilation.com		
2021	**Event**	**Location**
October 12-14	CTCB-I Certification Course	Gothenburg, Sweden
For courses run by R3Nordic see https://r3nordic.org/		

VCCN (Association of Contamination Control Netherlands)		
2021	**Event**	**Location**
For a complete list of courses including CTCB-I courses, please see http://www.vccn.nl/cursusaanbod		

TTD (Cleanroom Technologies Society of Turkey www.temizoda.org.tr		
2021	**Event**	**Location**
For courses run by TTD see https://www.temizoda.org.tr/en/trainings		

Life-lines

Quotations about truth

There are three truths. There's my truth, your truth and then THE truth. (Chinese proverb)

Truth will ultimately prevail where there is pains to bring it to light. (George Washington)

A lie gets halfway around the world before the truth has a chance to get its pants on. (Winston Churchill)

Truth is like the sun. You can shut it out for a time, but it ain't goin' away. (Elvis Presley)

If you tell the truth, you don't have to remember anything. (Mark Twain)

All truths are easy to understand once they are discovered; the point is to discover them. (Galileo Galilei)

Once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth. (Arthur Conan Doyle)

Truth exists; only lies are invented. (Georges Braque)

Three things cannot be long hidden: the sun, the moon, and the truth. (Buddha)

YOUR BUSINESS IN SAFE HANDS

HAND HYGIENE

FACILITY DISINFECTION

PRODUCT MANUFACTURING

ON EVERY SURFACE IN EVERY AREA

PROTECTING YOUR FACILITIES PRODUCTS PEOPLE

Your partner in cleaning and disinfection, Ecolab Life Sciences provides expert guidance and solutions for every manufacturing facility, every office, every employee.

Find out more here:
www.ecolab.com/staysafe

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