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Picture: Envair + ONFAB are specialist containment engineers

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 CACR42!

This issue, inevitably, features coronavirus in two of the main articles and also in the News section.

The first article, by Luke Mintz, a features reporter for the Daily Telegraph, appeared recently on Daily Telegraph online and when I saw it I thought it was an easy read with some good points and nice illustrations. It is reproduced here with the kind permission of the Telegraph Media Group. The late Dr Bill Newsome, when he was chairman of the BSI microbiological safety cabinet standards committee, on which I was privileged to serve, said something at one of our meetings that has stayed with me ever since. This was that "microbes always go to work on a bus" i.e. skin flakes or liquid droplets, all rather larger than the microbe itself. I have since realised that this was a bit of a generalisation, firstly because some liquid droplets in an aerosol can be quite small – a point well made in in the Telegraph article, and some organisms, such as spores can exist on their own. An article around this topic could be very interesting for readers of CACR. There is also a blog from ImagineMD Physician Group in America that I found most informative – see https://imaginemd.net/blog/coronavirus-april-2020-part-6/. A number of myths are dispelled. The blog is one of a series, all well written and relevant.

The next article, by Tim Sandle, is on the impact of coronavirus on cleanroom operations. Yes – it is necessary, even in cleanrooms, to recognise the risks and to take appropriate precautions against coronavirus.

Andrew Watson continues his 'known-unknown' series with his observations on the positive-negative debate, especially in relation to products that are both toxic and have to be handled aseptically. His are firmly on one side of the argument.

The Innovations section resumes after a gap of several issues with an article by John Cobb on the new PMT Active Air Sampler. This is a new rotating slit to Agar sampler that has the capability, in conjunction with a new vacuum source and control panel, to sample continuously for four hours to meet the requirements of the latest draft of EU GMP Annex 1.

We, in CACR, like to keep readers up to date with the latest developments in ISO standards. Steve Ward, the UK's SME (subject matter expert) on the ISO 209 Working Groups considering ISO 14644 Parts 3 and 4 has written about both these standards. Part 3 was published in 2019 and will be republished in 2020 with some editorial errors corrected. Part 4 is at the beginning of its periodic review and, as Steve writes, "now is the best opportunity for the working group to challenge all the technical elements in the document."

CEN (the European Committee for Standardization) has a Technical Committee, TC 243 that has been shadowing ISO TC 209. With the ISO standards for Biocontamination control, ISO 14698 Parts 1 and 2 (which are also part of the ISO 14644 Cleanrooms and associated controlled environments series of standards under ISO TC 209) having had limited application, CEN TC 243 therefore commissioned a new standard to replace ISO 14698 (which will be withdrawn shortly anyway). This is EN 17141 which will be published in the near future. Conor Murray, convener of the Working Group that has prepared EN 17141, explains what has been going on and the differences between the one new EN standard and the two old ISO standards.

Finally there is a discussion article, this time by Tim Coles on bio-decontamination using hydrogen peroxide.

I would like to record my enormous appreciation to all the authors who make this journal possible … and to invite anyone, who feels they have something to say, to submit articles, letters etc. for consideration.

John Neiger

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The science of airborne viruses: how particles move and what you can do to protect yourself

Luke Mintz

Introduction

As a new study suggests that coronavirus particles could linger in the air for longer than previously thought, we unpick the science. A cough sends droplets into the air – but scientists are yet to prove that coronavirus then lingers.

How long can coronavirus particles survive in the air? It sounds like a simple question, perhaps one that should have already been answered, three months into the biggest medical crisis of a century, which is now responsible for more than 4 million infections and 279,000 deaths across the world.

But it is actually one of the issues on which virologists are most uncertain. Here, experts explain what we do know – and what still remains a mystery.

What happens when coronavirus particles leave your mouth?

When you cough or sneeze, you emit thousands of droplets, like rain. They are essentially tiny drops of saliva – scientists only call them droplets because they are invisible to the naked eye.

These droplets contain particles. The largest and heaviest of the particles will fall straight to the ground, whilst the smallest – known as aerosols – will continue to float about in the air for some time, see Figure 1.

If you have Covid-19 (even if you are not showing symptoms) then your droplets will contain particles of the SARS-CoV-2 virus – a member of the coronavirus family, responsible for the Covid-19 disease.

Scientists generally agree that the most likely route of transmission for the coronavirus is if somebody coughs or sneezes in your close vicinity, and their droplets land on a wet part of your face – your eyes, nose, or mouth.

The droplets can fly about three feet before dropping to the ground, or six feet if the cough is particularly forceful, scientists say.

Another way is if you touch a common-handled object that somebody has recently coughed onto, like a doorknob or mobile phone, and then touch a wet part of your face.

But can they linger in the air?

Virologists have generally been working on the assumption that, unlike other droplets in your breath, SARS-CoV-2 particles cannot linger in the air for hours after somebody coughs. Indeed, an analysis of 75,000 cases in China conducted by the World Health Organisation found no evidence for this sort of airborne transmission.

But that assumption is now being challenged. A study published this week in the journal *Nature Research* looked at two hospitals in Wuhan, China.

By setting up 'aerosol traps' around the buildings, researchers found bits of the virus's genetic material floating around indoor toilets, as well as a room in the hospital where medical staff removed their masks, gowns, and gloves, see Figure 2.

Led by Ke Lan of Wuhan University, the researchers say their findings support the idea that SARS-CoV-2 particles might be able to hang around in the air for hours, highlighting the importance of good indoor ventilation.

The study did not try to answer whether those virus particles were actually causing infection – they might have been dead or degraded particles.

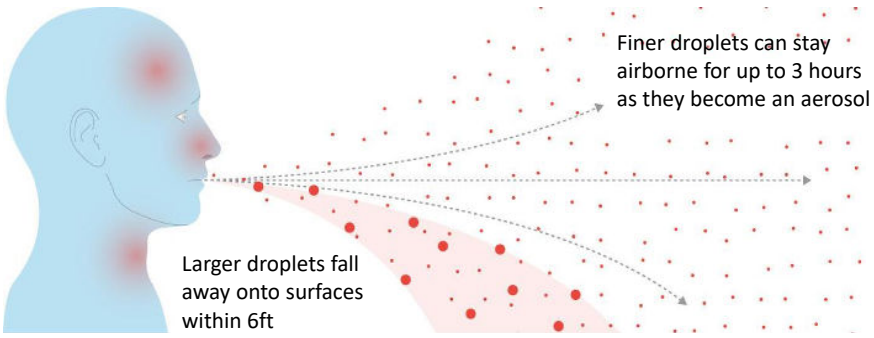

Figure 1: The trajectory of larger droplets and finer droplets

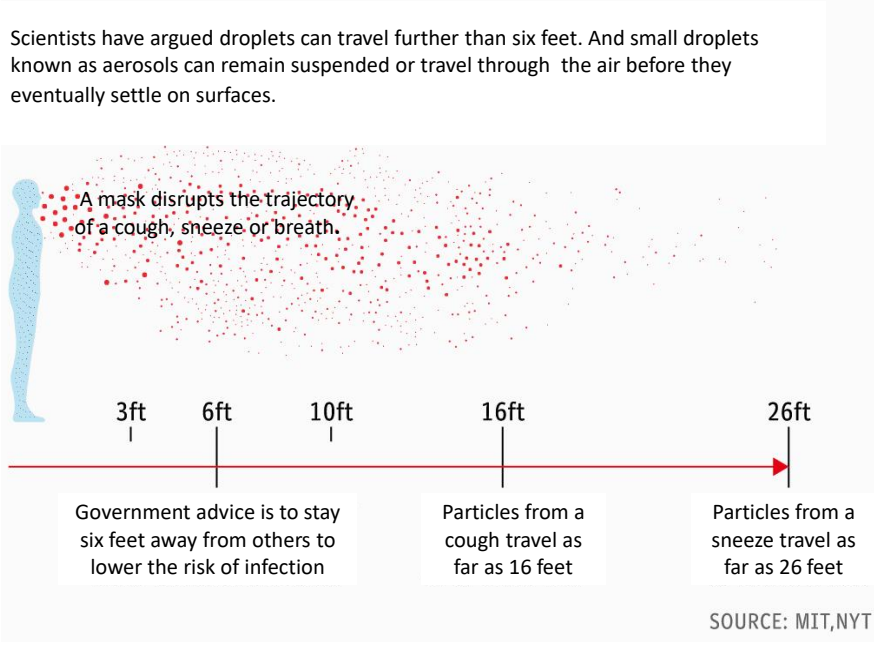

Figure 2: How masks and social distancing could be crucial

Another investigation of a restaurant in Guangzhou, China, found traces of SARS-CoV-2 in the air conditioning system – suggesting that particles of the virus were being blown about the restaurant. The restaurant became the target of investigation after one diner was found to have infected nine others while eating there.

These are only small studies, of course, but scientists stress that there is still a huge amount we don't know about how coronavirus is transmitted. Prof Lawrence Young, a professor of Molecular Oncology at the University of Warwick, says the Wuhan study shows that the virus can contaminate rooms in hospitals where medics remove their PPE, but adds: "Detecting the virus genetic material with a very sensitive test is not the same as detecting infectious virus. Dead or degraded virus would still be detected with this technique."

He adds: "We still don't fully understand how the new coronavirus spreads, but we're learning more every day."

Where are the hotspots?

Because it is seen as unlikely that SARS-CoV-2 can linger in the air for hours, there has been very little public information on how you can protect yourself from these small, airborne particles. Television and bus stop adverts produced by Public Health England (PHE) tend to focus on regular hand washing, for example, which provide little protection against airborne particles.

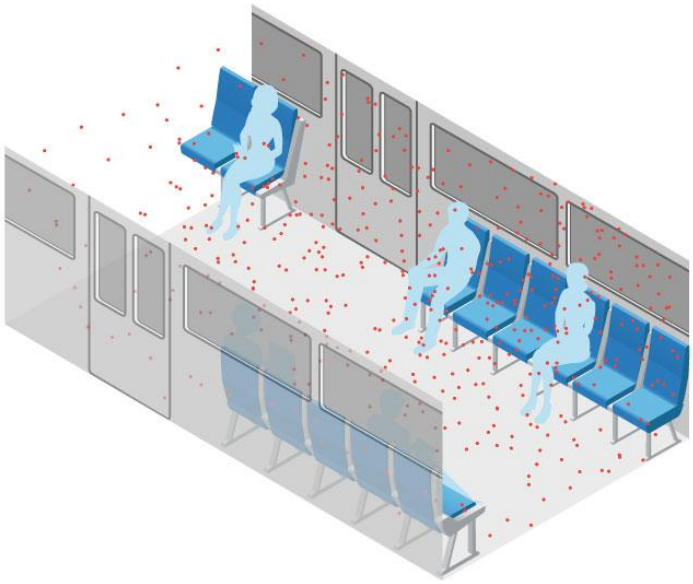

Figure 3: Poor ventilation in underground train carriages means they are a hotspot for lingering small aerosol droplets

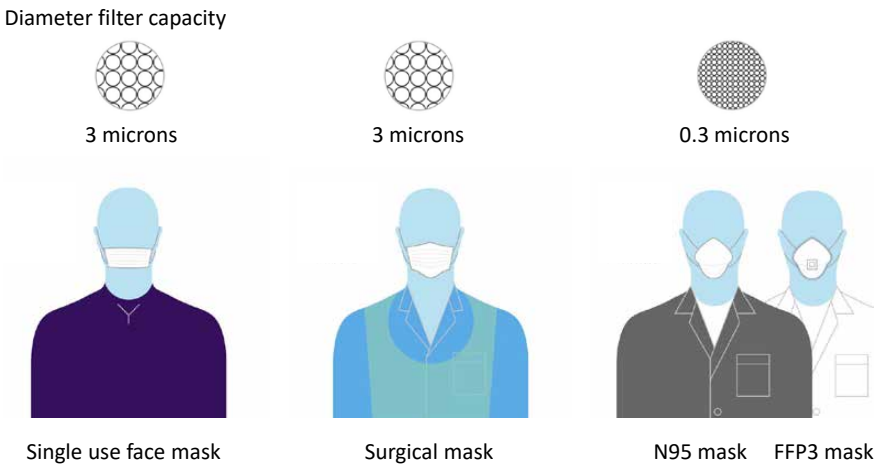

Figure 4: Face masks and their effectiveness against coronavirus

But if the novel virus *can* linger in the air, where is it most likely to gather?

Kevin Bampton, CEO of the British Occupational Hygiene Society, says that direct sunlight does a good job of killing virus particles. The ultraviolet rays break down its fatty outsides, he says, and "it's not going to survive long" – so it's generally better to be in a sunny outdoor environment than a stuffy, indoor one.

And if you are inside, much depends on the level of ventilation. "A mechanically ventilated area – somewhere that has lots of air blowing through it – is less problematic than an unventilated area."

He says that poorly-ventilated train and bus carriages are likely to be particularly vulnerable to airborne particles, as are lifts, see Figure 3.

"Obviously a lift doesn't have a particularly strong ventilation system, you tend to have lots of people in them, you tend to be in close proximity, so it's this sort of area which might be more problematic."

Handily, REHVA, the Federation of European Heating, Ventilation, and Air Conditioning Associations, has released specific guidance[1] on how best to ventilate a building in the era of coronavirus: leave the mechanical ventilator switched on for longer than usual, they say, and avoid "recirculation sectors" which re-pump the same air back into the room.

Which facemask is best?

The most effective facemask for filtering out those tiny, airborne particles is an FFP3 mask. These are fitted with a filter at the front which filters out 99 percent of particles, "and certainly catch those tiny particles, so even if [SARS-CoV-2] was airborne, an FFP3 would catch it," says Bampton.

This is why the British Medical Association recommends that all front-line health workers wear these FFP3 masks, see Figure 4.

At the next rung down is the FFP2 mask, sometimes known by the American name N95, which filters out about 95 percent of particles. These masks are unlikely to protect you from the very smallest airborne particles, says Bampton, see Figure 5.

1. COVID-19 Guidance, April 3 2020 – see https://www.rehva.eu/activities/covid-19-guidance

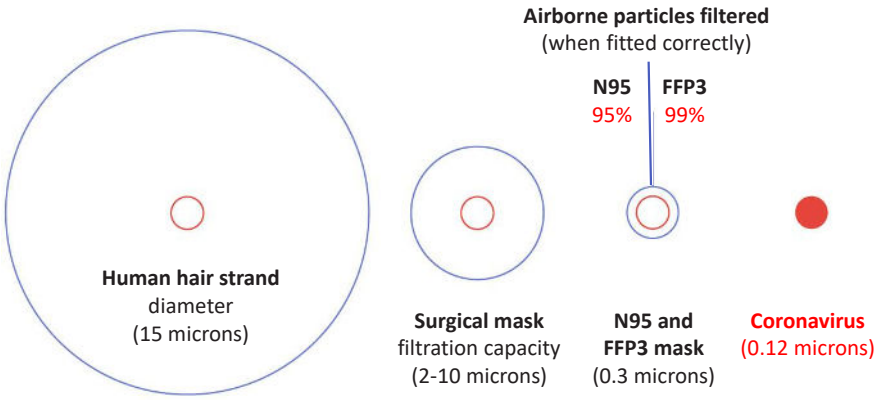

Figure 5: The virus is usually transmitted through droplets during sneezing or coughing. Many of the droplets are less than 1 micron (0.001mm) across.

Below that are surgical masks, which filter out about 20 percent of particles, and homemade cloth masks, which filter out somewhere below 20 percent. These masks are not designed to protect you from airborne particles – their purpose is to stop *you* from infecting others, by preventing your cough droplets from spraying onto those in your vicinity. This is why the U.S. Centers for Disease Control – the American equivalent of PHE (Public Health England) – recently told all Americans to wear cloth masks in public places.

Luke Mintz is a features reporter for the Telegraph and has written a number of relevant articles on aspects of the coronavirus pandemic – see https://www.telegraph.co.uk/authors/luke-mintz0/

Impact of novel coronavirus SARS-CoV-2 in cleanroom operations

Tim Sandle

Abstract

The novel coronavirus SARS-CoV-2 is causing problems globally. This includes cleanroom users. The virus can be passed in the air and it survives on surfaces for prolonged periods of time. While existing protective measures should minimise air risks (such as HEPA filters, air change rates, wearing masks and gloves) the surface risks, due to prolonged survival times, require careful selection of appropriate agents (primarily either alcoholic products at 61 to 71% concentration or hydrogen peroxide at 0.5% or higher).

Introduction

The 2020 coronavirus pandemic is of global concern and it is impacting upon all sectors of the economy. This includes industries which are reliant upon cleanrooms, including the pharmaceutical and healthcare sectors.

This article looks into some of the risk factors relating to cleanrooms, assessing air vector risks as relatively low, as well as the survival of the virus on surfaces (where the risks are greater due to the virus having been recovered after several days from different surface materials). In relation to the higher risk, the article examines the latest research into the most appropriate disinfectants for inactivating the virus on both hands and inanimate objects.

Novel coronavirus

The coronavirus responsible for the 2020 pandemic is named SARS-CoV-2. The virus is a 'sister clade'[i] to the original SARS virus that made headlines in 2003. 'SARS' in relation to both viruses stands for 'severe acute respiratory syndrome-related' virus. The disease caused by the SARS-CoV-2 virus is called COVID-19 ('CO' from corona; 'VI' for virus; and 'D' for disease; with '19' indicating the year for the first reported case in 2019).[1] The disease primarily affects the upper respiratory tract, causing fever, muscle fatigue and breathing difficulties. From injection, the mean incubation time is 6.4 days.[2]

The viruses are named 'coronaviruses' due to the presence of spike-like proteins protruding from the surface, where the proteins have a 'crown-like' appearance. The virus infects through the protein spikes binding to a receptor on human cells termed angiotensin-receptor enzyme 2 (or ACE2). The virus membrane then fuses with the cell membrane, enabling the virus to insert genetic material into the cell.

The virus spreads primarily via water or mucus droplets, passed person to person.[3] A secondary means of transmission is on surfaces. Here the virus can survive for several days on plastic and steel (survival is affected by temperature and humidity, with higher temperature and higher relative humidity linked to lower survival rates).[4] A possible, but as yet unsubstantiated, third means of transmission is potentially by lingering aerosols[5] (where the viral RNA could remain stable for a period of time).[6] It should be noted there is not yet reproducible scientific evidence around this vector in relation to SARS-CoV-2 specifically.

Cleanrooms and risk factors

There are two features of note with the coronavirus, which are of relevance to cleanrooms. The first relates to the relative ease of spreading within the indoor environment relative to the outdoor environment (based on initial reports relating to viral infectivity).[7] The second area of risk is the ability of the virus (or at least viral RNA) to survive on surfaces for prolonged periods of time.

In addressing air as a vector of transmission first, existing aspects of cleanroom design and personnel garments will help to minimise the risk of viral transmission relative to a non-cleanroom indoor environment.

With cleanroom design, HEPA filtered air and far faster air exchange rates compared with non-cleanroom environments will decrease viral transmission. Studies into the first SARS virus indicate that coronaviruses do not pass through H14 HEPA filters, therefore viruses are unlikely to pass into a cleanroom via the external air.[8, 9] This leaves other routes being people and transfer of items. With people, faster air exchange rates are designed to remove particles from cleanrooms at a relatively rapid rate (in the context of most cleanrooms having air change rates above 15 air changes per hour, evidence suggests lower transmission of viral infections under conditions of 20 air changes per hour).[10] This will apply to viruses as much as other microscopic inert particles and bacteria, although room dimensions and items within the room will always present unknown variables. To assess viral load from air, virologists use biosamplers of the appropriate aerosolization efficiency.[11] Further protective measures are provided through cleanroom garments and associated apparel.

With cleanroom garments, the use of a suit, masks, gloves, and goggles each help to reduce viral transmission (albeit that not all cleanroom operations require each of the items to be worn). With suits, these are unlikely be carrying the virus being packaged under clean conditions, wrapped and, depending on the required cleanroom grade, sometimes irradiated. Cleanroom gowns are typically disposed of each day or each operating shift (either as disposable gowns or despatched for re-laundering), reducing the risk of day-to-day transmission. With gloves, these are also supplied clean or sterile in wrapping, are only worn for one work session, and typically subject to regular hand disinfection (which is discussed below).

With goggles, these help to protect the eyes of the operator, reducing the

i. A clade is a related organism descended from a common ancestor.

risk associated with one of the two ways that viral particles can enter the human body (which is via the eyes or through the nasopharynx). For masks, although surgical facemasks are designed to prevent the wearer from contaminating a product (cleanroom facemasks tend to be surgical masks, which protect the patient from the medic, and protect the medic from splashes of bodily fluids) masks will partially reduce the viral transmission.[12, 13] For example, with a normal cough the air dispersion distance is 68 cm; wearing a surgical mask, this drops to 15 cm.[14] With nasal dispersion this can be up to 100 cm (still below the UK government guidance on 2 metre social distancing). It is important that masks worn by operators who may have or subsequent develop symptoms of COVID-19 are disposed of as infected waste items.

A further factor is with temperature and humidity; with the virus infectivity lower at temperatures above 24°C and humidity above 50%.[15] Whereas cleanrooms tend to have lower temperatures (to maintain operator comfort), most have some form of relative humidity control which prevents dryer air supply circulating within the cleanroom. As with advice given to the general public, a further risk reduction factor is with social distancing. Where possible, cleanroom operators should keep apart, at 2 metres, where practicable.

It is important to emphasise that cleanrooms most probably reduce infectivity, but outside of biosafety level 4 containment laboratories or clean air devices no single measures will categorically protect an individual, although a combination approach will lower the opportunities for viral transmission.

Surface survival

Earlier research into other coronaviruses demonstrates how these types of viruses can remain infectious for between 2 hours and 9 days on different types of materials, based on standard 'room temperature' (approximately 20°C) conditions.[16] A higher temperature, such as 30°C or 40°C, is associated with a shorter persistence of coronaviruses (coronaviruses appear to be inactivated at temperatures of 60°C and higher). There is a greater concern at lower temperatures, where studies reveal that at 4°C the ability of coronaviruses to survive on surfaces increases to ≥ 28 days.[17] The current coronavirus of concern, SARS-CoV-2 will reside on surfaces in a similar way to other coronaviruses. Moreover, the viral challenge to a surface can be considerable. For example, one study shows that 1 mL of sputum contains approximately 10^8 viral copies.[18]

According to a summary of literature relating to coronaviruses in general (shown in Table 1 for selected surfaces as might be found in a cleanroom), the survival times differ according to surface type.[19, 20, 21, 22, 23, 24] It should be noted that across the different studies cited, the viral load varied (from 10^3 to 10^8), and there are some interesting variations with temperature. With the Table, the worst-case survival times have been used. While the data relates to all coronaviruses (with most studies relating to SARS and MERS), it is probable that the results are similar to the novel coronavirus given the genetic similarities.

The overall finding from the literature review as presented in Table 1, is that RNA from human coronaviruses are recoverable from inanimate surfaces at room temperature for up to 28 days (for stainless steel, although the typical maximum time is 5 days). However, each of the detection methods were for the presence of coronavirus RNA and the detection of RNA does not necessarily mean the viral material remains infectious. However, for operator safety the findings suggest that any of the surfaces could potentially be contaminated, through viral material remaining on the surface for a substantial period of time. Hence, regular, and perhaps additional, cleaning and disinfection is required for cleanroom surfaces as part of contamination control measures.

Cleaning and disinfection strategies

Given the potential survival of the novel coronavirus on surfaces found within cleanrooms practicing regular cleaning and disinfection is important. Cleaning, which involves the use of anything from water to detergents, is effective at removing material from surfaces and for disassociating micro-organisms from surfaces. Disinfectants, on the other hand, inactivate viruses (as well as killing bacteria) directly. Killing viruses on surfaces presents a challenge since once dried on inanimate surfaces, viruses are less susceptible to disinfection than when hydrated in suspension. This susceptibility is further reduced by the presence of organic soil and viral clumping (hence the emphasis on pre-cleaning).

While information about the SARS-CoV-2 virus is only beginning to emerge, two research papers have looked at the survival of SARS-CoV-2 on surfaces and present some initial studies in relation to this specific coronavirus in terms of virucidal inactivation.[15, 25] The consensus from research papers is:

- Alcohol is effective at inactivating the coronavirus, with inactivation achieved in 30 seconds. The optimal alcohols are ethanol or iso-propyl alcohol (IPA), with a concentration of between 61% and 71%. These alcohols are appropriate for surfaces as well as gloves and skin.

Table 1: Survival of coronaviruses on different surfaces, subject to different temperatures

Surface	Temperature	Survival
Steel	4°C	28 days or greater
	20°C	3 to 28 days
	30°C	4 to 96 hours
Aluminum	20°C	2 to 8 hours
Other metal	20°C	5 days
Paper	20°C	4 to 5 days
Glass	20°C	4 to 5 days
Plastic	20°C	6 to 9 days
PVC	20°C	5 days
Silicon	20°C	5 days
Latex	20°C	8 hours

- With hand sanitization products, the alcohols should be blended with a moisturizer to avoid dermatitis from developing. Benzalkonium chloride-based hand sanitizers have been found to have less reliable activity against coronavirus than either of the alcohols.
- In addition to alcohol-based disinfectants, hydrogen peroxide in liquid form at a concentration of 0.5% or greater has also shown to be effective against SARS-CoV-2, again with less than one-minute contact time.

These emerging studies on the novel coronavirus are supported by earlier literature on other types of human coronaviruses.[26, 27]

By contact time, this refers to the time that the disinfectant needs to be in contact with the surface. The surface needs to remain wet for this period of time (that is the user should not attempt to dry the surface before the contact time has elapsed and if the surface appears to dry before the contact time has been reached, reapply the disinfectant).

Given the potential for survival, whether cleaning and disinfection frequencies need to be increased to lower the possibility of coronavirus infection will depend on the level of personnel gowning (which will be dependent on the cleanroom grade, with operators in higher grade cleanrooms being subject to tighter controls). The risks around main areas of personnel transit and cross-over, such as with corridors and changing rooms, could well be higher and here consideration of additional disinfection could be prudent under the current pandemic.

Summary

In the context of the SARS-CoV-2 novel coronavirus pandemic there are concerns for cleanroom operators and cleanroom operations. This article has considered the risks from air as a vector of transmission and from surfaces (as with surface to person transfer). While the risks from air appear lower, based on current cleanroom design factors, the risks from surfaces are more problematic. SARS-CoV-2 may be shed into the environment and be transferred from environmental surfaces (either fixed within the cleanroom or from items transferred in) to hands of operators. Once contaminated from the environment, hands can then initiate self-inoculation of the mucous membranes of the nose, eyes or mouth. Contamination can also carry forward to new gloves if glove changes are not carried out correctly.

Consequently, infection prevention and control measures need to be adhered to in relation to hand hygiene, personal protective equipment, and surface disinfection, in order to minimise self-contamination and to protect against inoculation of mucosal surfaces and the respiratory tract.

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Cleanroom – known unknowns: 3. Positive pressure versus negative pressure

Andrew Watson

Abstract

This article continues the exploration of known unknowns in cleanroom and containment design. This time we examine the application of positive and negative pressure regimes to an installation according to the materials that are processed within it. Ordinarily, a black and white approach is adopted – if it's toxic, infectious or genetically modified, then it must be processed in a room that is negatively pressurised in relation to the surrounding environment. Otherwise, positive pressure is fine. However, when you look at the mechanisms whereby contamination is distributed, there are compelling reasons for always staying positive.

Why negative – why positive?

The use of a positive or negative pressure or a net outward or inward flow of air, is a well-established tool for contamination control. The choice of positive or negative pressure is generally based on a need to keep things in or keep things out. Where protection of the product is paramount, then a positive pressure is generally chosen. If toxic materials, or infectious or genetically modified organisms are involved, then a negative pressure is applied. Regulations and standards typically take a similar black or white approach.

However, there are some processes where there is a conflict. Aseptic or low bioburden processes that use materials that are toxic, infectious or genetically modified pose a situation where you want to both keep contamination in AND out.

The preparation of chemotherapy is a key example. Facilities for the preparation of these materials are found in hospitals all over the world and a range of standards and guidelines are available that recommend a contrast of pressure regimes. Two examples are an American guideline, USP 800[1] and an Australian Standard, AS 2252.5.[2] In terms of the facility pressure specification, they are very different.

USP 800 states that the secondary engineering control (C-SEC) that houses the primary engineering control (C-PEC), must:

"Have a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas." Section 5.3

USP 800 has similar requirements for a negative pressure for areas of receipt (Section 5.1) and storage (Section 5.2)

AS 2252.5 however has a very different requirement:

The cleanroom shall be maintained at a positive pressure to ambient pressure, with 10 Pa pressure to be considered optimal. (Clause 8.5.4) Note that this is further protected by a bubble airlock (30 Pa) that prevents a direct outward flow of air from the manufacturing cleanroom.

AS 2252.5 goes further to describe the rationale for recommending a positive pressure:

"This provides sufficient pressure to prevent the leakage of outside air into the aseptic environment, but low enough pressure to minimise the flow of contaminated air into uncontrolled spaces if there is a breach of the cleanroom."

Chemotherapy preparation poses some unique challenges. Some of the molecules of the active ingredient are quite small and can volatilise in the event of a spill. These and other active ingredients, are also highly toxic, and generally there is no threshold safe exposure documented. Modern manufacture provides the following mitigations (other than a positive or negative room pressure):

- Materials being processed are generally in solution.
- The active, highly toxic materials are generally prepared from small volumes (<100ml). Prepared materials can be larger, but are more dilute
- Materials are prepared in a containment device such as a Class II Biological Safety Cabinet (BSC), a Cytotoxic Drug Safety Cabinet (CDSC) – like a Class II BSC, but with a HEPA filter underneath the work surface to protect the cabinet internals from contamination – or a pharmaceutical isolator.
- The activities that occur in the containment device are generally closed processes, with very little opportunity for the release of materials. Release outside the containment device is generally due to an accidental release, such as a spill.
- For open cabinet preparations, there is a high level of Personal Protection Equipment (PPE) that protects both the products from the people and the people from the products.

Contamination can be found in many areas where chemotherapy is prepared and on the surfaces of materials that come from related industries. The irony is, if designed and operated correctly, the manufacturing suite will probably be the most uncontaminated place in the facility.

As discussed, control of microbial contamination is also important. Preparations are generally administered within 24 hours of manufacture, so there is no time for a sterility test and environmental data will not arrive until several days after. Unfortunately, many patients have a suppressed immune system and are susceptible to a range of sources of infection. Identifying a contaminated IV solution as the reason for patient injury or death is not always possible. Therefore, the level of assurance we need that our environment is capable of aseptic manufacture is very high indeed.

The facilities that we build for these operations all leak to some extent. Those rooms under positive pressure leak air outwards and those under negative pressure draw air in. Generally, most air transfer occurs through controlled locations, such as under doors, often from other cleanroom areas. However, where there is a pressure difference air will also move through the myriad of gaps and cracks in the walls, floors and ceilings.

Airborne viable contamination in Grade D (ISO 8 at-rest) cleanrooms and controlled-not-classified (CNC) areas generally are in the order of 10 to 50 CFU/m^3. Air from ceiling spaces and

wall cavities will be significantly more. If we assume that we have a net inflow of air of around 10 l/s of outside air for a well-built, but not pressure-tested cleanroom, then we have upwards of 500 CFU entering the cleanroom every hour.

Contrast this to the opportunity of hazardous material to escape a facility under positive pressure. Spills do happen, but they are generally cleaned up quickly, with little time for those specific drugs to volatilise. Additionally, most spills occur in the containment device, rarely in the cleanroom.

Then there is the actual mechanism whereby contamination makes its way out of the facility. 10 l/s is less than 1% of the supply air that moves through a typical chemo suite. Molecular contamination will be well below detectable level. Gaps will most likely be at working height through to ceiling level, therefore contaminated particles and droplets will be hard-pressed to find an air current of sufficient velocity to carry them to a point of escape. Contrast this to air leaking through a gap in a light fitting. Air will have passed over all number of particulate and potentially viable organisms while making its way into the facility.

So, what are we comparing when choosing a room under positive or negative pressure?

- Positive pressure – an undefined chance (but, probably pretty low) of air with an undefined concentration of a toxic substance (but probably undetectable) that may (but may not) escape to an unclassified and populated environment. Not monitored, and probably unmonitorable.
- Negative pressure – a reasonably defined level of air leakage into the room, with a reasonably defined level of microbial contamination. Monitored.

Or in simple terms – probably nothing versus probably something.

Pressure and pharmaceutical isolators

Pharmaceutical isolators are similarly operated in either a negative or positive pressure format. Those that have the ability to be pressure tested actually provide us with a definable level of leakage. ISO 10648-2 provides a pressure testing method that classifies isolator to four levels, looking at the hourly leak rate. Pharmaceutical Isolators used for chemotherapy are generally Class 3 which equates to 1% loss of volume in an hour at the testing pressure. Where a good cleanroom leaks around 10 l/s, for an isolator we are talking leakage rates several orders of magnitude lower. Note that the air change rate is significantly higher and there is a range of further filters, alarms and other safety mechanisms, such as specific glove leak tests, that provide significantly more containment and protection than an open cabinet in a cleanroom. Similarly, we have the chance of egress of toxic material versus ingress of microbial contamination, with similar levels of uncertainty.

There are a couple of other issues that complicate the decision of what pressure regime to use for a pharmaceutical isolator:

1. For negative pressure isolators, due to the risk of microbial ingress, some regulators insist that these units are located in cleanrooms with a Grade B (ISO 7 in-operation) background. This makes for a cleanroom that is very expensive to set up and operate. Positive pressure isolators (particularly those that have an automated decontamination entry process) can be located in a cleanroom with a Grade D background.
2. For positive pressure isolators there can be a perception issue with staff that they are subjected to a higher level of exposure than for an isolator under negative pressure.

In response to issue 2 above, the MHRA commissioned a study of external contamination surrounding both positive and negative pressure isolators and found that there was no difference between the two.

Biological containment

There is an increasing trend in the use of bacteria, viruses and genetically modified versions of these two in immunotherapy preparations. In addition, there is the use of autologous material, both locally and internationally sourced. These materials are generally stored, grown and manipulated in containment facilities, usually governed by standards and regulations relevant to, or derived from research facilities. These new treatments often cannot be terminally sterilised and therefore must be prepared aseptically. Often these processes take days or weeks, with occasional opportunities for both microbial ingress and spills or aerosolization of biological material.

Again, we are faced with the dilemma with maintaining the pressures of these facilities either at positive or negative to the surrounding environment. Ingress of microbial contamination into the process zone under negative pressure is under the same mechanisms as the previous examples. Defining the risk of aerosolised biological material escaping a positive pressure facility is more difficult. The assumption seems to be that it is probable, even likely – but is it really? These 'bugs' need transport to both move and, if in liquid droplets, to remain viable. The ability to lift and transport these particles sufficiently to find their way out of a well-designed and probably pressure tested room, should be almost impossible. But who has really looked at this in any detail?

It is worth exploring this, as I think that a definitive position on the positive – negative debate for enclosures of aseptic processes would have great benefits.

My position – positive pressure with the attendant safety features discussed in this paper will deliver safer products to patients and very little extra risk to the safety of staff and the general public. However, we need more research and discussion on the movement of aerosolised particles. No better time than the present!

References

1. USP General Chapter <800> *Hazardous Drugs – Handling in Healthcare Settings*. 2017
2. AS 2252.5:2017 – *Controlled environments Part 5: Cytotoxic drug safety cabinets (CDSC) – Design, construction, installation, testing and use*

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An innovative Active Air Sampler for continuous viable air monitoring with minimal plate changes

John Cobb

Abstract

The EU Manufacture of Sterile Medicinal Products Annex 1 version 12 Revision is, as of 20 February 2020, undergoing a targeted three month consultation process. The proposed changes include the requirement for "continuous viable air monitoring in the Grade A zone to be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and filling operations."

In addition to this it is also a requirement to investigate any microbial counts and for any organisms isolated to be investigated and identified down to species level. Furthermore their potential impact on product quality for each batch affected and the overall state of control during sterile manufacturing should be investigated, as part of a documented system.

We consider now a new design of active air sampler that is capable of a very high, industry leading, Biological Efficiency, which can be used for an interval sample of 1 cubic metre of air. More importantly this new air sampler can be employed for up to 4 hours on a single plate of TSA (Trypticase Soy Agar) irradiated agar, at critically assessed risk locations in Grade A environments, with minimum human interventions.

This method of active air sampling can supplement or replace settle plates for more accurate microbiological sampling over an entire production run, providing a greater understanding of the level of microbiological control in the Grade A zone.

Introduction

Clean environments are used to control and limit microbial contamination where there is a risk to product quality, patient or consumer.

In Grade A clean zones, like in cleanrooms, isolators or RABS (Restricted Access Barrier Systems), the need to establish and maintain microbial control requires an understanding of the sources of contamination.

Selecting the most appropriate methods for assessing the presence of microbial bioburden with associated risks should be studied in depth for individual processes and facilities. Then the carefully selected best option should become part of a documented and validated Environmental Monitoring (EM) programme.

As part of this EM programme, recent regulatory perspectives need to be considered, especially around microbial monitoring during an entire sterile production process. From a microbial risk perspective, the Pharmaceutical Industry traditionally performs "snap-shots" when looking for presence/absence of bioburden. However, shouldn't we carry out microbial monitoring over an entire production run to gain a more reliable understanding of our critical areas?

Continuous microbial monitoring with an accurate, validated method is far more meaningful and can provide you with a far clearer understanding of microbial presence and potential risk to your product during sterile manufacturing.

Let's look at certain areas in a little more detail:

- Current Standards concerning the choice of the most appropriate AAS (Active Air Sampler) as part of an EM programme.
- Different AAS designs/methods.
- Pros and cons to consider when designing an AAS for Grade A and the plated media used.
- Introducing a new slit-to-agar design with initial validation results.

Current standards concerning the choice of the most appropriate AAS as part of an EM programme.

There are 3 main Standards/Regulations most relevant to consider:

ISO 14698-1:2003[1]

This Standard is in the process of being superseded by CEN 17141. However, a central part regarding AAS's is included. This ISO standard describes the need for a sampler to capture viable particles efficiently on an appropriate culture medium, from both biological and physical efficiency perspectives. A validation method for each is described.

Biological efficiency – is the ability of an AAS to collect microbe-carrying particles efficiently, with minimal drying out or shearing of microbes by the velocity of the air coming though the collection slit or sieve. Also, the drying effect on the chosen culture media needs to be considered. Is no growth present because you are in control, or because the medium has dried out?

Physical efficiency – is the ability of an AAS to collect microbe-carrying particles of different sizes efficiently. Multiple factors affect the physical efficiency including: the geometry of the head, the length and width of the slit or the diameter and number of holes in the impactor sampling head, depending on the method. Another important factor to consider is the velocity of the impacted air and the accuracy of the gap between the sampling head and the surface of the agar plate.

Also, within ISO 14698-1 are some clues (but no specific designs) on what an AAS should include into its specification when considering how to make a suitable AAS for Grade A, some key pointers being:

- Should be able to sample sufficient air in a reasonable time (interpreted as a minimum of 1 cubic metre of air sampled in several minutes at the fastest AAS level and up to 4 hours at the slowest)
- Should have the ability to sample efficiently down to particles of 1 µm. This can be expressed as the need for the Grade A AAS to have a d_{50}[2] value of 1µm (or smaller). Note that a d_{50} value of 1µm is the cut-off value at which 50% of 1µm particles are collected in the sampler and 50% are not collected.
- The exhaust should not disrupt the unidirectional airflow of the room, i.e. the exhaust air should be piped away from the vicinity or dissipated gently.

- The AAS should not contaminate the surrounding area, i.e. the exhaust air should be piped away or passed through an appropriate HEPA filter.

EN 17141: 2020[3]

When published in the very near future, this European standard will replace ISO 14698 in Europe. It takes into account modern developments and practices. In particular, regarding AAS's, it emphasises the importance of biological efficiency and the need to have an appropriate collection efficiency for the area being tested. An important point to consider is the significance of this when read in connection with Annex 1. In principal this can be interpreted as meaning that to recognise "no growths" accurately, an AAS will need to have a d_{50} cut-off value of better than 1 (i.e. smaller than 1 µm) in conjunction with a high Biological Efficiency, otherwise there is a risk of only having at best a 50% chance of collecting any 1 µm particles.

EU GMP Annex 1: Manufacture of Sterile Medicinal Products (Revision 12 under final consultation as of 20th February 2020)[4]

Sections 9.24 to 9.33 entitled "Environmental and personnel monitoring – viable particles" are relevant to EM and the choice of appropriate methods.

Of specific interest are Sections 9.27, 9.29 and the Table 7 in 9.30 which are quoted here in full:

9.27 Continuous viable air monitoring in the Grade A zone (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and filling operations. A similar approach should be considered for Grade B cleanrooms 1977 based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided.

9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. The recovery efficiency of the sampling methods chosen should be qualified.

9.30 Action limits for viable particle contamination are shown in Table 7 [of Annex 1].

Table 7: Maximum action limits for viable particle contamination

Grade	Air sample cfu/m³	Settle plates (diam. 90 mm) cfu/4 hours (a)	Contact plates (diam. 55mm), cfu/plate (c)	Glove print, Including 5 fingers on both hands cfu/glove
A	No growth (b)			
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

a. *Settle plates should be exposed for the duration of operations and changed as required after 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used). Individual settle plates may be exposed for less than 4 hours.*

b. *It should be noted that for Grade A, any growth should result in an investigation.*

Note (a) above, provides the opportunity to consider replacing settle plates with an AAS that can sample for 4 hours on a single plate, giving a sample time equivalent to a normal exposure on a settle plate, but with a considerably better Collection Efficiency (consistently more than 10 fold) than a settle plate (see later).

Different Active Air Sampler (AAS) designs/methods

There are a number of different AAS methodologies which have evolved. The most commonly seen ones are:

a. Centrifugal – employs strips of agar. This sampler causes excessive turbulence and the strips require manipulation from the instrument for incubation. Not relevant to Grade A.

b. Filtration – employs a gelatine filter membrane to capture particles from the environment. After sampling, the gelatine membrane needs to be aseptically removed onto a petri dish of Trypticase Soy Agar (TSA) and allowed to dissolve releasing trapped particles onto the medium for incubation. This manipulation means this method is not suited for Grade A.

c. Sieve Sampler – employs a fixed sampling head positioned (typically) 2.5mm over the surface of a TSA plate. May be a sieve plate with usually 300 small holes or a number of radial slits, the orifice dimensions being designed to give sufficient velocity to give a d_{50} value down to about 1 µm or slightly over. There are a number of airflow rates available by different sieve samplers, ranging from 1 cubic foot per minute (equivalent to 28.3 litres per minute), which takes 35 minutes 20 seconds to sample 1 cubic metre, to 100 litres per minute which takes 10 minutes to sample a cubic metre. Even faster AAS's are available that will sample a cubic metre in just a few minutes. Beware though, as some sieve sampler designs are a lot less efficient with significantly higher d_{50} values (e.g. >10 µm) and these should only be employed for trending where significantly higher counts are anticipated.

A sieve sampler is an "interval sampler" and the media plate needs to be changed after each and every cubic metre of air.

As the air impacts onto the same fixed positions on the agar surface, there is a natural drying out of the media at those points and particles impacted can be desiccated, reducing the Biological Efficiency.

As a technique, it needs careful qualification if the intent is to use a sieve sampler in Grade A. However, the sample is only a snap-shot of the air at the time of the sample being taken. A positive result for growth is significant, but a negative result can be misleading, as there may well be long intervals where no samples are taken.

For areas where slightly higher numbers of organisms are anticipated, like C, D or unclassified areas, it is a good method for trending.

Sieve samplers can be battery or mains operated or can be built into a

facility. They can also be positioned with the head at the chosen sample point, with the controls and vacuum source located away at a safe position.

d. Slit to Agar sampler – Optimal method for the most critical, risk assessed areas in Grade A. These samplers have a fixed radial slit in the sampling head, positioned over an agar plate which rotates up to 360 degrees over a user selected time. Air is impacted on to a fresh part of the agar surface continually and so a d_{50} value of better (smaller) than 1 can be maintained throughout. These AAS's come with the added advantage of an excellent Biological Efficiency as fresh agar is continually being presented to the impacted air. This method also allows for the attachment of an isokinetic probe over the slit assembly, so in certain situations the sampling head can be moved up to 8 feet away from the critical sampling location. The latest instruments can be battery/mains operated, or by Power over Ethernet (PoE), or can be built into a customer bespoke software system or a Facility Managed System (FMS), with the controls and vacuum source based remotely.

Design requirements for an AAS for Grade A environments

1. If a sampler has a d_{50} value of 1µm, it has only a 50% chance of impacting an organism of 1 µm (ref). The latest Annex 1 revision gives a target of zero growth. Therefore the design target for a Grade A sampler d_{50} value should be lower than 1µm.

   As a guideline to achieve this, the air velocity between the slit or orifice in the sampling head to the impaction site on the agar surface should not fall below 30 metres/second, but can be considerably higher, providing that the biological efficiency does not drop off.

2. Biological Efficiency should be high. Maintaining an accurate and consistent slit-to-agar surface gap (typically 2.5mm) is important, otherwise impaction rates vary significantly. The type of media, fill volume and moisture content of the agar, all come into play. Fresh media needs to be continually presented to the stream of impacted air to achieve this.

3. The collection efficiency of an AAS should be appropriate to the Grade of the area being tested.

4. An ability to sample for longer periods of time on a single plate before a plate needs to be changed is desirable. A settle plate is typically exposed for 4 hours maximum, so that should be the target for an AAS. This will allow for more meaningful monitoring over an entire batch run, rather than taking a snap-shot interval sample, the latter providing little meaningful information about the air quality through a manufacturing campaign.

5. Minimum human intervention is important. Regular plate changing on an AAS is a sterility risk and should be minimised.

6. Media used can vary widely. This means there is a need for careful validation and regular GMP compliance audits of the manufacturer and their internal methods, controls and SOPs.

   The following considerations apply to media:

   a. Typically, gamma irradiated Trypticase Soy Agar (TSA) is used routinely and, additionally, Sabouraud Dextrose Agar (SDA) is used for moulds if suspected. Both are poured into 9cm petri dishes.

   b. Different agar plate fill volumes are available (typically 18ml, 25ml and 32ml), but exact volumes may vary from one supplier to another.

   c. Moisture content of plates can vary. Room temperature storage packs, triply wrapped and hermetically sealed, retain moisture in the agar better than the original breathable packaged plates. It is important to use fresh plates with the maximum level of retained moisture to optimise performance.

   d. Different manufacturers use different levels of gamma irradiation (anywhere from 12 to > 25 kilo Grays (kGy) are seen) to terminally sterilise their plates. This has significant effects on the fertility, gel strength and moisture retention of the media. Higher gel strength retains more moisture, but reduces the fertility of a plate. The chosen plate from an audited manufacturer needs to show a consistent fertility under challenge testing within each individual batch and also maintain acceptable batch-to-batch variation.

   e. Can a new design of AAS sample for the same length of time on a single plate, as a settle plate? Post impaction, a media plate is incubated for a total of 5 days: either 2 days at 30 to 35°C followed by 3 days at 20 to 25°C; or some incubate at just 30 to 35°C for 5 days, to allow for growth from environmental and human originated (operator) organisms. The PQ validation of an AAS has to prove that a plate has sufficient moisture and fertility remaining to grow organisms impacted over the whole of the selected sample time.

Introducing the ImpactAir ISO-90, a new Slit-to-Agar design

Main design features

The main design features of the new unit are:

a. Slit to agar AAS employing a 9cm agar plate;

b. Factory interchangeable slit assemblies. All slits are 22mm long, but the width can be selected from 0.1mm to 0.8mm;

c. Variable flow rates, in litres per minute: 5, 10, 15, 28.3 (1cfm), 50 and 70;

d. Achieved d_{50} values from 0.46µm to 0.95µm;

e. Can sample 1 cubic metre of air, or can sample continuously for 4 hours on a single plate, sampling typically 3 or 4 cubic metres of air, if set-up selected appropriately;

f. Biological Efficiency is greatly improved, especially important when a set-up with a d_{50} of lower than 1µm is employed. Allows for longer sampling periods;

g. Design options include a stand-alone unit, powered by mains, battery/mains or Power over Ethernet (POE).

Also, a remote unit, powered by an external vacuum source and control, positioned away from the clean zone, which can optionally be integrated into a client's Laboratory Information Management System (LIMS), a bespoke local system or a Facility Managed System (FMS).

Table 1 shows the effect of varying the slit dimensions and altering the air flow rates through the sampling head on the volume of air sampled over prolonged sampling periods of up to 4 hours, on a single plate. This is achieved whilst maintaining high impaction velocities delivering d_{50} performance of well below 1 µm.

Initial validation tests

The initial validation tests were run by a client in a controlled laboratory area and reported on at a recent conference.[5] Four different AAS's were used in the tests, of which one was a client validated reference sampler used in their Grade A areas:

- ImpactAir-140 (14cm TSA plate), slit-to-agar sampler – reference sampler.
- ImpactAir ISO-90 Head (9cm plate) with ISO-CON remote vacuum source and operational touch screen – the new design of slit-to-agar sampler.
- Sieve sampler A (9cm plate) – targeted for Grade A Isolators
- Sieve sampler B (9cm plate) – targeted for Grade A Isolators

The reference sampler had been independently tested against its own

Figure 1: Two alternative ISO-90 Head options: a) mounted on pod with sanitary flange connector for quick release (left); and b) freestanding (right)

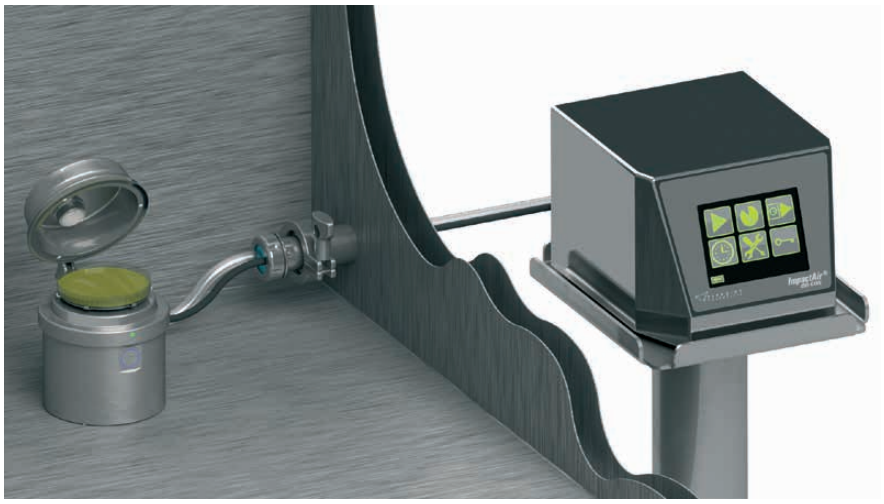

Figure 2: Free standing ISO-90 Sampling Head situated in a Grade A sampling location (left), connecting via a vacuum tube and electrical connection through an easy access gland to an ISO-CON control unit safely situated away from the Grade A area (right). A range of glands and stainless steel stands are available for a variety of installations.

Table 1: The effect of different slit dimensions and different air flow rates on d_{50} values and volume of air sampled.

Slit Width (mm)	Flow Rate (LPM)	d_{50} (µm)	Impact Velocity (m/s)	1m³ Time (Mins)	1 Hour Vol (m³)	2 Hour Vol (m³)	3 Hour Vol (m³)	4 Hour Vol (m³)
0.1	5	0.46	38	200	0.3	0.6	0.9	1.2
0.2	5	0.92	19	200	0.3	0.6	0.9	1.2
0.2	10	0.65	39	100	0.6	1.2	1.8	2.4
0.2	15	0.53	57	66.7	0.9	1.8	2.7	3.6
0.3	15	0.80	38	66.7	0.9	1.8	2.7	3.6
0.4	29	0.76	55	34.5	1.74	3.48	5.22	6.96
0.6	50	0.87	63	20	3	6	9	12
0.8	75	0.95	71	13.3	4.5	9.0	13.5	18

Notes:

1. The set-up shown in the olive green row was used in the initial validation tests.
2. The yellow box is not recommended as a set-up, the information is just for illustration purposes.

Gold Standard test sampler at Public Health England, Porton Down, an ISO 14698 test-house, and shown to be 25% more efficient. It is also used routinely in the client's Grade A critical areas.

The new design sampler comprises an ISO-90 Sampling Head, which works in conjunction with an ISO-CON control unit, the latter comprising a vacuum source, operational touch screen and a HEPA filtered exhaust (essential only if the ISO-CON needs to be positioned in Grade A).

The ISO-CON controls the flow rate, time and other user functions (such as operator details, location and run data) by the touch screen and holds the Run Data Memory. The flow rate ranges from 5 LPM to 100 LPM. Lower rates of 5 LPM or 10 LPM will maintain a d_{50} of about 0.5µm by minimising the drying out of the culture medium, thus allowing longer sampling on a single plate (up to 4 hours). A higher flow rate of 100 LPM would take a 1 m^3 sample in 10 minutes, if a more rapid sample needed to be taken, but the plate would need to be changed after the 1 m^3 sample, due to the media drying out more quickly.

Figures 1 and 2 show illustrations of the new sampler comprising the ImpactAir ISO-90 Sampling Head and the ISO-CON control unit.

The test procedure consisted of the reference sampler and the three samplers under evaluation, being tested simultaneously for 20 minutes at each of four sampling locations, several metres apart.

It can be seen in Table 2 that the average count per location, which is the average from all four samplers, had negligible variation of 5% between the maximum and minimum counts, indicating that the testing environment remained constant throughout the test period. Plates were counted for cfus per m^3 of air sampled, after 5 days incubation at 30 to 35°C. Results were normalised to compare counts per cubic metre of air sampled. A control plate, a 9cm settle plate, was also exposed at each location for 20 minutes, in parallel with the air sampling.

Table 2: Average counts per sample location and normalised counts in cfus per m^3 by air sampler type

Air Sampler	Sampler location and plate (cfu) count				Average plate (cfu) count	Normalised average plate (cfu) count per m^3
	1	2	3	4		
Reference sampler	44	83	71	37	59	105
New sampler	41	34	39	41	39	130
Sieve Sampler A	70	71	66	103	78	78
Sieve Sampler B	71	47	63	47	57	57
Control	5	3	3	0	3	-
Average plate (cfu) count per location	57	59	60	57	-	-

Table 3: Comparison of Relative Recovery Scores and Collection Efficiencies of the four samplers

Air Sampler	Description	Air Flow (lpm)	Air Velocity at slit/ sieve (m/s)	Time for 1 m^3 sample (mins)	d_{50} value (µm)	Biological Efficiency (% v ISO 14698 Test Lab Sampler)	Relative Recovery Score	Calculated Collection Efficiency
Reference sampler	Slit to agar Single slit 0.152 x 44mm 14cm TSA plate	28.3	72	35.3	0.42	125	1.00	1.25
New sampler	Slit to agar Single slit 0.2 x 22mm 9cm plate	15	56.8	66.7	0.53	To be determined by Independent Test House	1.30	1.63
Sieve Sampler A	Sieve sampler 179 holes Radius 0.375mm 9cm plate	50	10.5	20.0	1.6	To be determined by Independent Test House	0.74	0.93
Sieve Sampler B	Sieve sampler 300 holes Radius 0.300m 9cm plate	50	19.65	20.0	1.11	To be determined by Independent Test House	0.54	0.68

The Biological Efficiency, Relative Recovery Score and Collection Efficiency of the 3 samplers on test were compared to the reference sampler. If the counts recovered per m^3 of air by the reference sampler are assumed to be an absolute score of 1, then the Relative Recovery Scores associated with the 3 samplers under test are shown in Table 3. The new Slit-to-Agar sampler had a Relative Recovery Score that was 1.3 times better than the Reference Sampler and 1.8 times and 2.4 times better than Sieve Samplers A and B respectively.

The Biological Collection Efficiency for the reference sampler was determined by an independent test house (PHE, Porton Down), comparing it to their Gold Standard Casella Slit sampler using the method outlined in ISO 14698-1 and was found to be 125%. Using the Relative Recovery Scores, reasonable estimates of the Collection Efficiencies for the 3 other units when operating in a natural environment were determined. The values are shown in Table 3.

Further considerations

The ability of an air sampler to recover airborne contamination can be determined from its Performance Rating (PR). The PR of an air sampler is the concentration of airborne contamination that the sampler is capable of recovering for a defined airborne concentration and can be calculated by the equation:

Performance Rating = n / (t *r * η)

n = Minimum number of microbes needed to show the sampler will measure microbes at the airborne concentration under consideration

t = Sampling time (min)

r = Air sampling rate (m^3/min)

η = Collection efficiency of sampler (as a proportion)

Table 4: Air sampler PRs

Air Sampler	Performance Rating (cfu/m^3)
Reference sampler	0.80
New sampler	0.61
Sieve Sampler A	1.08
Sieve Sampler B	1.47

For an EU Grade A zone, the action limit for airborne microbial contamination is 1 cfu per m^3. Using a value of 1 for n and using the calculated collection efficiencies, the PR for each sampler can be calculated as shown in Table 4. It can be seen that the reference sampler and the new sampler are capable of recovering airborne concentrations below 1 cfu/m^3 but the two commonly used sieve sampler units are not.

Test conclusion

A comparison of the number of airborne microbes simultaneously recovered by the four air samplers within the same environment determined that the new sampler has a recovery that is 1.8 and 2.4 times higher than Sieve Sampler A and Sieve Sampler B respectively and also 1.3 times higher than the recovery of the reference sampler). When the Collection Efficiencies are calculated from this information, the data can be used to determine the Performance Rating for each sampler for use within an environment with an action limit of 1 cfu per m^3 for airborne contamination. The Performance Ratings for both the reference sampler and the new sampler confirm each would be capable of detecting contamination below this limit. However, the Performance Ratings for the Sieve Samplers A and B indicate that both of these units would not be capable of detecting contamination below this limit. Consequently, it is concluded that the reference sampler and the new sampler would be suitable for monitoring in EU Grade A areas but not the Sieve Samplers A and B.

Overall conclusion

The new sampler, the ImpactAir ISO-90 is an innovative Active Air Sampler, which can sample at critical risk assessed locations within an EU Grade A area, whilst exceeding all the Guidelines as outlined in ISO 14698-1, the forthcoming EN 17141 and the latest Revision 12 of the EC GMP Annex 1. The new sampler design has an industry high Biological Efficiency and a d_{50} value in the region of 0.5µm (depending on the slit dimensions selected), enabling accurate sampling down to at least 1 µm particle size in an area where zero growth needs to be proven. Furthermore, the new sampler can run for up to 4 hours on a single 9cm TSA plate reducing human interventions and the potential introduction of microbial contamination into your critical areas.

Monitoring microbiologically throughout an entire production run with minimum human intervention for plate changes is now possible and worth considering for the enhancement of product quality and patient safety.

A final thought is that the settle plate, an inefficient passive air sampler employed for up to four hours, could be replaced by a monitoring AAS over the same time period.

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1. ISO 14698-1: 2018 *Cleanrooms and associated controlled environments—Biocontamination control, Part 1: General principles and methods.* Geneva, Switzerland, International Organization for Standardization, 2003
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5. Eaton T. *Effective Risk Management of Microbial Contamination*. London, UK. SMi ; Pharmaceutical Microbiology Conference. 2020.

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An update on 14644 cleanroom standards: Parts 3 and 4

Stephen Ward

ISO 14644-3:2019 Cleanrooms and associated controlled environments – Part 3 Test methods

This standard has been reviewed and updated by ISO TC 209 Working Group 3 and was published by ISO in August 2019.

The most significant update from the 2005 edition of this standard is the removal of procedures relating to the classification of cleanrooms by airborne particles. When ISO 14644-1 was updated and issued in 2015 it incorporated these procedures.

This current edition still provides supporting tests for cleanrooms and associated controlled environments and the standard is used to enable selection of appropriate tests methods, for verifying the performance of a cleanroom.

Other notable changes include updates to the procedures relating to installed filter system leakage testing, including changes and additions to the designated leak acceptance criteria. There are changes in the specification requirements for test apparatus and a new procedure for a segregation test has been added.

The procedures within the normative section of the standard remain largely unaltered. It is within the informative annexes where the updates are more noticeable, and these are summarised below.

The annex on installed filter system leakage test has been re-written in most sections. The test now has the same maximum allowable designated leak for both the aerosol photometer method and the Light Scattering Air Particle Counter (LSAPC) method. This means that the results achieved by either method are now directly comparable.

Selecting the appropriate testing method now has fewer restrictions, with the aerosol photometer method being suitable for all installations unless situations exist where outgassing of the oil-based test aerosol could be detrimental to the product or processes in the cleanroom or when high concentrations of test aerosol in the system are not desirable.

In addition to aligning the designated leak for both methods, there are now two limits depending on the filter class being tested. The standard maximum allowable penetration is 0.01%. However, for filters with integral efficiency at MPPS of 99.95% to 99.994%, the maximum allowable penetration is 0.1% (10 times more). This means HEPA filters rated H13 (EN1822-1) or ISO35H (ISO29463) could be tested against the 0.1% criteria. This change is in response to perceived issues when testing these lower rated filters, which the previous LSAPC method's "k" factor had compensated for, by effectively making the maximum allowable designated leak value higher.

Filters with efficiency below 99.95% are not commonly tested but they can be, using this method, with appropriate different acceptance criterion.

The most significant update from the 2005 edition of this standard is the removal of procedures relating to the classification of cleanrooms by airborne particles. When ISO 14644-1 was updated and issued in 2015 it incorporated these procedures.

Both photometer and LSAPC procedures recommend probe sizes of either 1cm x 8cm rectangular or 3.6cm diameter circular.

For the aerosol photometer procedure, the required upstream concentration has been updated to reflect improvement in instrument technology and current best practice. So, where instruments have the capability, concentrations between 1-100mg/m^3 are acceptable. The former 10-100mg/m^3 requirement and the previous 20-80mg/m^3 recommendation, have both been removed.

For the LSAPC procedure, there is a formula to determine the upstream concentration required, which is based on probe size, scan rate, instrument flow rate, maximum penetration and acceptance count for the scanning stage. A lower upstream concentration will result in alterations to the scan rate or possibly one of the probe dimensions, to enable the test to be performed.

For the overall leak test of filters mounted in ducts or air handling units, the acceptance criterion is now based on the main unified criteria discussed earlier.

Another notable change is in the recovery test, where there has been the introduction of a 10:1 recovery time in addition to the existing 100:1 recovery time. Using 10:1 is useful when testing in ISO 7, 8 and 9 classified cleanrooms, where very high particle concentrations can be difficult to achieve and measure. This can be demonstrated by comparing the recovery rate at a location in the room with the overall air change rate for the cleanroom.

The new addition to the standard is the segregation test. It provides a method for assessing the effectiveness of segregating two areas by means of airflow. This test is performed across an opening between two areas, for example between an open fronted unidirectional flow workstation (critical area) and the background room (less critical area). The method involves generation of contamination (particles) in one area (the higher classified or less critical area) and determining the level of contamination that reaches the lower classified or more critical area. A particle counter is used to measure the particles in both areas (with a diluter for the contaminated area). A formula is provided to determine a protection index.

The Annex on test apparatus now has three suitability criteria for test instruments to meet. These are the measuring limits, resolution and maximum permissible error. It also highlights the need to ensure calibration points are within the range of use to ensure reliability of the measurement. However, stated calibration frequencies have been removed, therefore moving the responsibility onto the apparatus owner to determine the appropriate frequency.

Other changes within the standard are less significant and relate mostly to improving clarity.

In summary, the standard has seen some significant updates that need to be digested and understood. It is also not without controversy as some elements could have been clearer and better explained. It is important to note that there are currently some editorial errors, which a 2020 version is expected to address.

ISO (CD) 14644-4 Cleanrooms and associated controlled environments — Part 4: Design, construction and start-up

The current 2001 version of this standard is currently under review and revision by ISO TC 209 Working Group 4. Work commenced in 2015 and a draft revision of the document was circulated to ISO TC 209 members for its first round of formal review, as a Committee Draft (CD) in early 2019.

The document is currently being prepared for its second Committee Draft following constructive comments on the first CD. The second CD is expected to be issued shortly.

Now is the best opportunity for the working group to challenge all the technical elements in the document, to develop a clear, concise, and useful document to be published as standard. As document development and review moves on, opportunities to improve become more restricted. The important work in updating this standard happens now, at these CD stages.

The main structure of the proposed revised standard flows through four key normative stages from initial 'requirements', through 'design' and then through 'construction' before finishing with 'start up'. The period once the cleanroom is operating is dealt with by ISO14644-5 – Operations.

These four key normative stages are clearly separated and identified in the CD. The informative annexes have been aligned to match with these four normative sections.

There is the intent to remove some of the outdated information that exists in the current standard, especially around recommended air change rates, which are misleading and should no longer be applied. The proposed revision addresses this with the inclusion of guidance on calculating contamination source strengths within the cleanroom. In a non-unidirectional cleanroom, contamination generated by people, equipment, and processes is diluted by the airflow before removal. This information on source strengths will allow designers a better approach to determining required airflow rates for different classes of non-unidirectional cleanrooms, while also considering ventilation effectiveness in their design and calculations. This aligns well with the recently published new standard ISO 14644-16: 2019, Energy efficiency in cleanrooms and separative devices.

The intention is also to remove information that does not benefit the reader, to make the standard more concise, relevant to the topic and easier to follow.

The section on requirements takes us through the key considerations that become the input into the design section, which is supported by a useful checklist in the related annex. The design section details the potential need for various design stages and the considerations to be made at each stage, from the early concept design through to the end of the detailed design stage.

For the construction section, the revision deals solely with the installing of the cleanroom. All the elements relating to material selection and non-direct construction-based information have been moved to the normative and informative design sections.

Key verification stages are now addressed in each relevant normative section and their associated informative annexes and are linked clearly to the point in the project where these checks and tests will be performed.

Now is the best opportunity for the working group to challenge all the technical elements in the document, to develop a clear, concise, and useful document to be published as standard. As document development and review moves on, opportunities to improve become more restricted.

The original checklists are being updated and moved to annexes that align with the relevant section.

Comments from the second CD will be reviewed by the working group later in 2020 and the output from those reviews will determine the next stage in the process. The current programme target is to see a new updated standard published in 2022.

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A new European standard for Biocontamination Control – EN 17141 will replace EN ISO 14698 Parts 1 and 2:2003

Conor Murray and Roland Durner

Abstract

Cleanrooms and clean controlled environments are classified based on airborne particle concentrations. Depending on the purpose, further characteristics or contaminants can be considered. Biocontamination plays an important role in microbiological control in many applications in a cleanroom or clean controlled environment. The existing standard for *Biocontamination control in cleanrooms and associated controlled environments*, ISO 14698 Parts 1 and 2 from 2003, has had limited application. The European Committee for Standardization (CEN), through an initiative of Technical Committee (TC) CEN/TC 243/WG5 (Working Group 5), has been working on revising and updating the ISO 14698 standard since 2016. The new EN 17141 standard, which is based on this work, will be published in the summer of 2020. Recently countries voted unanimously to withdraw the ISO 14698 Parts 1 and 2 standards as part of the ISO systematic review process. CEN/TC 243 is now putting forward EN 17141 for inclusion in the ISO 14644 family of standards in order to harmonise the approach to contamination control of micro-organisms in air and on surfaces, with that of particles and other contaminants in air and on surfaces.

Biocontamination control in cleanrooms and clean controlled environments

People are the main source of biocontamination on both air and surfaces. While technology has developed significantly since ISO 14698 Parts 1[1] and 2[2] were published in 2003 and has helped to limit the number of people and the intervention of people, the human element is unlikely to be replaced completely.

Cleanrooms are classified according to ISO 14644-1:2015[3] by the maximum concentration of particles of a given size. For certain critical processes, microbiological parameters are also crucial, because biocontamination leads to unacceptable quality losses. Biocontamination control revolves around living micro-organisms, mostly bacteria or fungi that are difficult to detect and identify. In addition, biological contamination can multiply itself through growth. For this reason, biocontamination control is a critical monitoring parameter, especially in the manufacture of pharmaceuticals, medical devices and combinational products. Biocontamination is life threatening in environments that are not classified as cleanrooms, such as operating theatres, intensive care units and isolation wards in hospitals. These are now considered as clean controlled environments in the new EN 17141[4] standard. In food it is pathogens that are of concern and can cause sickness and even lead to death without immediate treatment. Common sources include bacteria such as *Campylobacter* which comes from raw and undercooked poultry and other meat, raw milk and untreated water. One of the most common causes of foodborne illnesses is *Salmonella* which comes from raw and undercooked eggs, undercooked poultry and meat, fresh fruits and vegetables, and unpasteurized dairy products.

What is the need for a new or revised standard for biocontamination control?

Since the publication of ISO 14698 Parts 1 and 2 in 2003, the application of a quality risk-based approach has become well established, especially in pharmaceutical production and food processing. Based on a survey of the application of ISO 14698 in member countries the following points with potential for improvement were identified:

- does not include clear enough guidance on risk and impact assessments with a focus on the different needs and types of applications;
- does not fit into the pattern of the ISO 14644 series, which differentiates between classification and monitoring;
- does not clearly differentiate between aseptic and non-sterile applications;
- does not provide enough help on airborne versus surface biocontamination risks and controls;
- has unclear boundaries between normative and informative sections;
- is, by general consensus, difficult to read and use;
- is presented as two Parts when it only needs to be one;
- does not reflect the current state of rapid and real-time measurement technologies.

Between 2009 and 2014, WG2 of ISO/TC 209 found no consensus on modernising ISO 14698 – yet the need for relevant guidelines on biocontamination control remained. That is why CEN TC/243 set up Working Group 5 with a clear direction and a task list to complete as part of revising ISO 14698. In 2016, a group of European experts in microbiology, engineering, and related scientific disciplines started work under the convenorship of Conor Murray with the secretariat provided by BSI (British Standards Institution).

Table 1: Comparison of the existing ISO 14698 parts 1 and 2 with the new EN 17141

Section	ISO 14698-1:2003	ISO 14698-2:2003	EN 17141 *(2020 expected)*
Title	Cleanrooms and associated controlled environments - biocontamination control Part 1: General principles and methods	Cleanrooms and associated controlled environments - biocontamination control Part 2: Evaluation and interpretation of biocontamination data	Cleanrooms and associated controlled environments - biocontamination control
Total number of pages	32	11	51
Normative pages	11	11	19
Introduction	General information on the importance of biocontamination control in various areas of application	-	Classification into higher-level risk management systems and a PDCA (plan - do - check - act) system of continuous improvement.
Scope	Principles and basic methodology of a formal system of biocontamination control for assessing and controlling biocontamination when cleanroom technology is used for that purpose. This part of ISO 14698 specifies the methods required for monitoring risk zones in a consistent way and for applying control measures appropriate to the degree of risk involved. In zones where risk is low, it can be used as a source of information.	Guidance on methods for the evaluation of microbiological data and the estimation of results obtained from sampling for viable particles in risk zones for biocontamination control. It should be used, where appropriate, in conjunction with ISO 14698-1.	This document establishes the requirements, recommendations and methodology for microbiological contamination control in clean controlled environments. It also sets out the requirements for establishing and demonstrating microbiological control in clean controlled environments. This document is limited to viable microbiological contamination. There is specific guidance given on common applications, including Pharmaceutical and BioPharmaceutical, Medical Devices, Hospitals and Food.
Excluded scope	Application-specific requirements; fire and safety issues	-	Any considerations of endotoxin, prion and viral contamination.
Normative references	ISO 14644-4: 2001: *Cleanrooms and associated controlled environments - Part 4: Design, construction, and start-up* ISO 14698-2: 2003: *Cleanrooms and associated controlled environments - Biocontamination control - Part 2: Evaluation and interpretation of biocontamination data*	ISO 14698-1: 2003: *Cleanrooms and associated controlled environments - Biocontamination control – Part 1: General principles and methods*	ISO 14644-1:2015, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration*
Definitions			Added: Micro-organisms of interest, clean-controlled environment, culturable Removed as unnecessary: bioaerosol, formal system, contact device, audit trail, data stratification, estimate, estimation, estimator, as built, at rest, operational

Section	ISO 14698-1:2003	ISO 14698-2:2003	EN 17141 *(2020 expected)*
Normative section	Principles of biocontamination control Establishing the Formal System Expression, interpretation and reporting of results Verification of the Formal System	Evaluation and interpretation of biocontamination data	Establishment of microbiological control Demonstration of microbiological control Microbiological measurement methods

	ISO 14698-1:2003	EN 17141 *(2020 expected)*
Annex (informative) pages	22	28
Annex A	Guidance on determining airborne biocontamination. (Moved to Normative Section 6 in EN 17141).	Guidance for life science pharmaceutical and biopharmaceutical applications
Annex B	Guidance on validating air samplers. (Moved to EN 17141 Annex E).	Guidance for life science medical device applications
Annex C	Guidance on determining biocontamination of surfaces. (Moved to Normative Section 6 in EN 17141 with additional instructions in EN 17141 Annex E for culture-based methods and Annex F for Rapid Microbiological Methods (RMM) and Alternative Microbiological real-time detection Methods (AMM)).	Guidance for healthcare/hospital applications
Annex D	Removed: Guidance on determining biocontamination of textiles (Not within the scope of EN 17141 as already addressed in EN 14065:2016)	Guidance for food applications
Annex E	Removed: Guidance for validating of laundering processes. (Not within the scope of EN 17141 as already addressed in ISO 14644-5:2004).	Guidance on culture based microbiological measurement methods and sampler verification
Annex F	Removed: Guidance for determining biocontamination of liquids. (Not within the scope of EN 17141).	Rapid microbiological methods (RMM) and alternative microbiological real-time detection methods (AMM)
Annex G	Removed: Guideline for training. (This is already addressed in many other standards and guidelines. The importance of training is highlighted in Normative Section 4.9 in EN 17141).	Not used

Working Group 5 task list from CEN/TC 243

This was the list of tasks approved in the new work item proposal approved by the TC:

1. Retain the relevant parts of the existing ISO 14698 Parts 1 and 2.
2. Review and limit scope to remove viruses, prions, endotoxins and water based biocontamination control. The use of the term micro-organism in this standard applies ONLY to bacteria, yeast and spores/moulds.
3. Include implementation of risk management and control (including ICH QRM[5] and HAACP[6]).
4. Follow the principle of first establishing and then demonstrating microbiological control (environmental monitoring).
5. Provide an overview of various industries, including food, life sciences and healthcare, and deciding whether classification tables are possible and appropriate in each case.
6. Develop application-related checklists of relevant topics in biocontamination control.
7. Improve the structure to make it easier to use the standard and improve readability.
8. Include how to set Alert and Action limits, where appropriate.
9. Carry out an independent review and comparison of alternative real-time microbiological measurement methods (AMMs) and rapid microbiological measurement methods (RMMs) and sampling technology.
10. Consider the role and practical use of scientific/technical progress, especially the possible application of AMM/RMM measurement methods.

The new EN 17141:2020

The aim of the standard is to provide the user with guidelines for first establishing and then demonstrating microbiological control. For this purpose, the normative part adopted the Quality Risk Management (QRM) approach of the EU GMP Annex 1,[7] which is currently in consultation. EN 17141 deals exclusively with monitoring and not classification, since today's methods only allow indirect measurements of biocontamination. These are carried out using growth-based methods, which result in a delay between sampling and results. In addition, the sensitivity of the

measurement is not remarkably high, since not all viable germs can be propagated by incubation.

Large parts of ISO 14698 are still relevant according to the working group. However, it decided to remove unnecessary parts (or those described in other standards). To emphasize continuity, the term 'biocontamination control' remains in the name, although the standard takes into account micro-organisms, but not viruses, endotoxins, prions, or pollen.

Table 1 gives a headline comparison between ISO 14698 Parts 1 and 2 and EN 17141.

The different requirements of different fields of application for biocontamination control are a challenge. For example, microbial steps in the food industry can be part of a production process, whereas the complete absence of micro-organisms in aseptic production is a crucial quality feature. In addition, the new standard should not be in conflict with existing industry-specific regulations.

A lot of consideration was given to microbiological surface and air sampling methods and their validation. For example, the d_{50}[a] number was introduced as a parameter for the physical collection efficiency of active air samplers so the results from different active air samplers with the same d_{50} number are comparable.

Industry-specific checklists facilitate the application

Particular attention was paid to the informative annexes (listed in Table 1). Simple checklists, flowcharts and, in some cases, warning and action limits were compiled based on the current state of technology and science.

Some applications, such as medical device manufacture, are discussed in more detail than those with already well-established regulatory guidance. The guidance for Medical Devices in informative Annex B occupies nearly half of the entire informative section. Three examples are given and Table B1 in the Annex aligns with the corresponding table in EU GMP Annex 1.

With detailed checklists for different areas of application, EN 17141 gives informative guidance on how to establish an effective environmental monitoring program for biocontamination control in clean controlled environments.

A final bibliography enables easy location of further literature on the various issues.

A glimpse into the future: rapid and alternative microbiological methods (RMM/AMMs)

The working group concluded that RMMs and AMMs are not yet mature enough to replace conventional growth-based microbiological detection methods. However, the technology is rapidly evolving and holds the prospect of immediate actionable monitoring results. This view was reflected by including Annex F with general guidance on implementation and validation of these technologies.

as part of a harmonised approach to contamination control in cleanrooms and clean controlled environments. As part of this alignment the term "Biocontamination control" will be changed to "Microbiological control" and align with other parts of ISO 14644 which address total particles, micro-organisms, chemicals, nanoparticles and macroparticles in air and on surfaces. A new work item application to this effect will be submitted to the next plenary meeting of ISO/TC 209 in October 2020.

The ISO 14644 series of standards is designed to support a contamination control plan that first establishes control and then demonstrates control of specified contaminants in cleanrooms and clean controlled environments. This is a central principle of the new EN 17141 and follows on from risk and impact assessments.

Furthermore, it is one of the key objectives of CEN/TC 243 that EU Directives refer to EN 17141 (or a future ISO 14644-??) for guidance on cleanrooms and clean controlled environments. The current revision and update of EU Annex 1 GMP guidance is an example, where it already refers to ISO 14644-1 for total airborne particles. A reference to EN 17141 (or the equivalent ISO 14644-??) for microbiological control would be a welcome scientific addition.

"This document establishes the requirements, recommendations and methodology for microbiological contamination control in clean controlled environments."

What are the next steps?

EN 17141:2020 was adopted by the member states on October 3, 2019 with 20 votes in favour, no rejection and 13 abstentions. The amendments tabled, along with some editorial changes have now been processed by the CEN central Secretariat. The agreed English version of EN 17141 is going through the final translation stage (into German and French) and is expected to come into force in all CEN affiliated countries in the summer of 2020.

As part of the standard ISO systematic review process, countries voted unanimously to withdraw (vs retain or update) the existing ISO 14698 Parts 1 and 2:2003. The next step in the ISO process is a formal vote to withdraw ISO 14698 Parts 1 and 2:2003. This vote is scheduled for some time later in 2020 and is expected to complete the formal withdrawal process of this standard. For Europe, the EN ISO 14698 version will be automatically withdrawn with the publication of EN 17141.

It is the intention of CEN/TC 243 to integrate the new EN 17141 standard into the ISO 14644 family of standards

References

1. ISO 14698-1:2003 *Cleanrooms and associated controlled environments — Biocontamination control — Part 1: General principles and methods*
2. ISO 14698-2:2003 *Cleanrooms and associated controlled environments — Biocontamination control — Part 2: Evaluation and interpretation of biocontamination data*

a. The physical collection efficiency is the cut-off size (d_{50} value) which defines the aerodynamic equivalent particle diameter size at which the sampler collects 50 % of the particles in the air

3. ISO 14644-1:2015, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration*
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Bio-decontamination using vaporised hydrogen peroxide: comments on a recent article

Tim Coles

Abstract

A recent article in *Clean Air and Containment Review* discusses humidity in the vapour phase hydrogen peroxide bio-decontamination process, taking the view that the VPHP cycle may be "wet" or "dry". This is a concept that has been considered invalid for some years. The article introduces the term "relative saturation", apparently defined as the point at which both hydrogen peroxide and water condense together. This present discussion paper acknowledges that RS may be a useful parameter, but seeks to correct the manner in which such data may be interpreted and applied

Discussion

In her article *Understanding critical measurement parameters in vaporized hydrogen peroxide bio-decontamination,*[1] the author, Sanna Lehtinen of Vaisala, makes the following statement: "Some manufacturers of bio-decontamination chambers or isolators prefer subvisible condensation, whereas others prefer dry bio-decontamination processes where humidity is maintained far from condensation". Unfortunately, this statement is incorrect. There are no "wet" or "dry" vapour phase hydrogen peroxide cycles. This was first established by Parks *et al,*[2] and then reinforced by a number of subsequent papers by Coles.[3, 4] In all cases, the rapid sporicidal effect of hydrogen peroxide vapour is caused by micro-condensed hydrogen peroxide (MCHP) at high concentration, and this includes the various aerosol devices.

MCHP forms readily under a wide range of conditions of temperature, and of starting humidity. Bioquell, the well-known manufacturer of hydrogen peroxide bio-decontamination equipment, suggests that a temperature range of 15°C to 25°C is acceptable. It is possible that an even wider range can be used if other parameters are set appropriately. As regards the starting humidity (i.e. the humidity of the air in the chamber prior to the introduction of hydrogen peroxide vapour), personal experience indicates that as long as the humidity is below 50%, then the cycle proceeds normally. If the starting humidity is above 50%, then fully visible, frank condensation is likely to take place. This may not of itself invalidate the cycle because log 6 reduction may have taken place before visible condensation appears, but there may be problems such as lengthy evaporation of runnels and pools, and eventual purging down to 1 ppm.

Where does this leave in-cycle humidity monitoring as envisaged by the article? The concept of "relative saturation" (RS) is presented by the author, this being defined as "the point at which the combined water vapour and hydrogen peroxide vapour will condense". It would therefore seem to make sense to monitor RS during a VPHP cycle, in order to maintain conditions short of what constitutes the full visible frank condensation described above. Indeed, the new instrument offered by the author's company could apparently be used to control the operating parameters of the vapour generator directly, on a servo loop, to give active control. Thus, VPHP cycles could be both monitored and controlled positively, rather than as at present, parametrically. This suggestion has been previously offered to the author's company, with no known response.

In conclusion, the notion of monitoring "relative saturation" in VPHP cycles has some merit, but users must understand how the rapid sporicidal bio-decontamination process operates. The author of the article appears to consider that water vapour and hydrogen peroxide vapour condense together at the same point. In fact, the hydrogen peroxide vapour, with its much lower vapour pressure, condenses way ahead of the water vapour, to form MCHP. There are no "wet" or "dry" cycles, this myth was surely dispelled some years ago.

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3. Coles, T. (2014). *Understanding the sporicidal action of VPHP*. Hospital Pharmacy Europe, Issue 72, pp.28-30.
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Tim Coles, BSc (Hons), M.Phil., Technical Director, Pharminox Isolation Ltd., has worked in the field of isolator technology for over twenty years. He was a founding member of the UK Pharmaceutical Isolator Working Party that produced Pharmaceutical Isolators, Pharmaceutical Press, 2004, and more recently of the PDA committee that produced Technical Report No 51. "Biological Indicators for Gas and Vapour Phase Decontamination Processes" [for the validation of isolator sanitisation]. His book Isolation Technology – a Practical Guide, CRC Press Inc. 2004, is now in its second edition.

Pharminox plays key part in the voluntary supply of scrubs and masks for local hospitals

Pharmaceutical and decontamination specialist, Pharminox Isolation Ltd of Elsworth, Cambridgeshire, UK, is continuing to operate normally as far as possible under lockdown regulations. In addition, the company has worked on a voluntary basis to help the production of much-needed scrubs and masks for a number of local hospitals. The company van has proved ideal for the collection of donated fabric of all types, taking this to an industrial laundry which processes and packs it, at no cost. Clean fabric is then returned to a central hub from where a team of cyclists distributes it to an army of around 500 local sewing machine operators. The voluntary enterprise goes under the name of "Connection Through Crafting Scrubs."

For more information about the services that Pharminox offers, please visit www.pharminox-isolation.com. "Connection Through Crafting Scrubs" has a Facebook page.

ATI equipment for testing respirator masks

Air Techniques International (ATI) has been a global leader in the design and manufacture of specialised testing equipment for HEPA filters, media, filter cartridges, respirators, and protective masks since 1961.

The 100X Automated Filter Tester is ideal for testing N95 respirators that are widely being used to help prevent the spread of the COVID-19 virus. It is designed to test and validate filter media, cartridges and masks used in medical and industrial hygiene applications and can be used to test any grade of media up to and including HEPA and ULPA grade media.

The 100X uses an oil or salt aerosol challenge to measure and report filter efficiency and resistance of the media or filtering piece. It is available with either an oil (PAO, Paraffin, DOP) or salt (NaCl) aerosol generator, depending upon the intended application and offers three flow rates to meet customer needs. ATI has a long history of working with customers to develop custom test fixtures and inserts to satisfy their testing needs.

The 100X meets the requirements of global industry standards including EN143/149/13274-7 and NIOSH 42 CFR Part 84 (the spec for N95 respirators), GB 2626, JICOSH/JMOL, and many others. It is widely used by leading media manufacturers and filter manufacturers around the world within Quality Assurance, R&D, and Production environments.

For more information please visit www.atitest.com/products/100x-automated-filter-tester/

Ecolab offers insights into the latest Annex 1 updates

The latest draft of EudraLex Vol. 4, Annex 1 (v.12), features updates to the guidelines following the public consultation feedback on the 2017 draft. Ecolab have carried out a thorough review to assess the changes relating to cleaning and disinfection and the implications for end users.

Specifically, there is still a focus on the clear distinction between cleaning and disinfection and the importance of disinfectant residue removal. Effective product rotation remains important, and the use of sterile disinfectants in Grade C and D areas is now being highlighted as a consideration where Quality Risk

Management (QRM) demands.

Validation should demonstrate the effectiveness of disinfectants in the specific manner in which they are used and should support the in-use expiry periods of prepared solutions.

Ecolab are able to support with guidance on:

- Appropriate use of a range of product formats which are sterile and ready-to-use
- Validation expertise Including the ValidexTM program
- Interpretation and implementation of the regulations, providing service excellence from their Technical Consultants

More information about Ecolab's products and services in relation to Annex 1 can be found at www.ecolablifesciences.com/annex1 or please contact Emily Buck on emily.buck@ecolab.com

An integrated approach from efficiency specialists EECO2

Global life science efficiency consultants EECO2 have launched a new service offer in order to better support clients to achieve their ongoing sustainability goals.

EECO2's "3 Cs" proposition adopts a holistic view of carbon, cost and compliance, and uses a unique combination of tools, processes and regulatory expertise to tailor solutions to individual clients.

"EECO2 is a well-established business which works with most of the world's top pharmaceutical companies" explained EECO2 director Keith Beattie.

"Our "3 Cs" model is an integrated approach which acknowledges that energy alone is not enough – risk-based analysis and careful evaluation of quality aspects provide opportunities to improve compliance at the same time as reducing cost."

EECO2 cite the example of the implementation of the new GMP Annex 1 as the type of project which would benefit from their integrated approach: "the requirement for a holistic contamination control strategy (CCS) is the perfect opportunity for manufacturers to consider carbon and cost improvements whilst identifying and mitigating risk and improving product quality."

For more information please contact info@eeco2.com.

Contec launches a new hands free mop saturation system

Designed to simplify the cleanroom mopping process, Contec's Hands Free Mop Head Saturation System allows up to 20 mop heads to be presaturated prior to being passed into the cleanroom. The system allows mop heads to be installed and removed "hands free" reducing the risk of cross contamination and speeding up the cleaning and disinfection process.

The use of an easy-fit applicator frame coupled with the mop head frame design, means the mop heads can be fitted hands-free. Once used the mop heads can be removed without being touched using the unique mop removal system, straight into a waste bag if required.

Quiltec I Flat Mop Heads have been specifically designed for use with Contec's Mop Saturation Systems. With high absorbency the mops are suitable for single use saturation, giving a surface coverage up to approximately 20 m^2.

For more information about the mop system, go to www.contecinc.com/eu.

FASTER answers your questions on Covid-19

What are the guidelines for the correct management and handling of pathogenic agents such as coronavirus COVID-19?

The American Centres for Disease Control and Prevention (CDC) and National Institutes of Health are the most recognized institutions in the world for the classification of infectious agents such as Covid19. CDC issued safety guidelines recognized as benchmark all around the world.

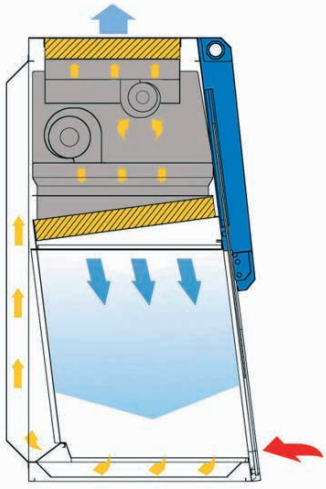
How should my laboratory be classified to perform analysis and handling of pathogenic agents like COVID-19?

According to CDC, virus isolation is only possible in a bio-safety laboratory of at least level 3 (BSL-3) and which uses BSL-3 working practices

What is FASTER's offer and how can I find the most suitable biological safety cabinet for my needs?

Through a network of distributors all over the world, FASTER offers a wide range of safety cabinets. Among these, the SafeFAST range are class II biological safety cabinets.

For more information please visit https://fasterair.co.uk/



Guangzhou Cleanroom Exhibition 2020 to be held on August 16th as planned!

Good news! Guangzhou Cleanroom Exhibition 2020 will be held Aug. 16th-18th at China Import & Export Fair Complex as originally planned, since the COVID-19 outbreak was put under control in China by the end of March.

Exhibitors' enthusiasm is running high for they are eager to grasp the first opportunity for promotion as soon as the pandemic ends. Dozens of exhibitors have signed up for the show, 80% of which are our old friends.

According to exhibitor bookings, the best represented sector is Cleanroom Structures, covering products like aluminum materials, sandwich panels, auto doors, clean lighting, pvc floors, and etc., followed by Purification Technologies, HVAC Systems, Cleanroom Equipment (air showers, clean benches, etc.), Cleanroom Consumables (gloves, clothes, swabs, etc.), and Test & Detection Instrument.

The importance of the cleanroom industry cannot be better illustrated in this global war against COVID-19. We sincerely welcome visitors from worldwide to gather in Guangzhou this Aug. to together push forward the cleanroom industry!

For more info or registration, please visit www.clcte.com

New SAS Super Pinocchio CR compressed air sampling Device from Cherwell

Cherwell Laboratories have introduced the new SAS Super Pinocchio CR to their range of microbial air samplers. This compressed air sampling device offers a more convenient way to monitor for viable particles in compressed air and other gas supplies used in controlled environments.

This updated version of the popular Pinocchio II device can still be fully dismantled for easy cleaning and decontamination. However, it is now manufactured in stainless-steel making this process even more simple and effective. This totally portable system, which is now more compact than the current Pinocchio II, does not require power and, therefore, can be used in high risk areas.

The Pinocchio CR utilises the same method of active air sampling as the rest of the SAS range. Using the multi point impaction method, air is aspirated through a sampling head and any particles present are impacted on to the agar surface of a Contact plate or 90mm Petri dish for subsequent culture. The unit is capable of sampling 100 litres per minute.

For more information about Cherwell Laboratories, please visit www.cherwell-labs.co.uk.

Enzyme Indicators for pharmaceutical validation from PMT (GB) Ltd

Vapourised Hydrogen Peroxide systems, designed to decontaminate an area quantifiably, need to be validated. This has always been a challenge because many parameters influence this such as humidity, temperature, H^2O_2 concentration, injection rate, dwell time and many more. These performance influencers have historically been very difficult to measure, particularly as they can and do vary over the area being decontaminated. The traditional measures of decontamination process efficacy such as chemical indicators and biological indicators have made the process of validation challenging, inefficient and expensive and time restrictive due to the incubation time of BI's.

EI's are an alternative validation tool for performance checks of a decontamination process which are purposefully designed and manufactured for this singular purpose. EI results can be delivered in 60 seconds per test strip and the results are quantifiable rather than binary. EIs are biological but not viable, offering a process challenge that can be used for routine confirmation of cycle efficacy. The EI activity can be compared with the BI inactivation in order to establish a quantitative estimate of "Achieved Log Reduction", rather than the qualitative "Growth"/ "No Growth" of a conventional BI.

Enzyme Indicators (EI's) are an industry-changing advance in measuring decontamination performance. EI's offer a fast, cost effective, accurate and risk-free alternative.

The conventional 7 day wait for Biological Indicator (BI) decontamination results are over by using EI's.

For more information, please contact PMT (GB) Limited on info@pmtgb.com

ONFAB and Envair create new parent company: Envair Technology

Following the acquisition of Envair Limited by ONFAB last year, the two contained air specialists have announced the formation of parent company Envair Technology.

The combined expertise of the companies means the group can now offer a wider range of rigid and flexible containment solutions, with particular specialism in the needs of medical, healthcare, biotech and pharmaceutical sectors. They also expect to continue their strong growth to date, bringing new engineering innovations to market and creating further efficiencies in their service delivery.

ONFAB continues to operate from its facilities in Cheshire, UK and Albacete, Spain, whilst Envair Limited remains close by in Lancashire.

Commenting on the launch, ONFAB Managing Director Mark Arnold said, "I'm excited to be bringing together a team with such strong shared values. We're using the best of our creativity and energy to deliver bespoke solutions to clients, helping them protect the safety of their teams and create process efficiencies."

To find out more, visit www.envairtechnology.com

Particle Measuring Systems releases 20 nm Syringe Sampler for batch sampling applications

February 2020, Boulder, CO – Particle Measuring Systems (PMS) announce the release of the new SLS 20 Syringe Liquid Sampler to be used with the Chem 20™ Particle Counter. The addition of the SLS 20 for batch sampling to the existing on-line capabilities of the Chem 20, provides a complete solution for all chemical monitoring needs. This new combined solution provides an unlimited level of monitoring at 20 nm sensitivity.

The SLS 20 Syringe Liquid Sampler enables Chem 20 particle counters to operate in batch sampling applications. It is ideal for precise, small-volume sampling. The system consists of an SLS 20 which is compatible with either corrosive or non-corrosive liquids, all connections necessary to interface with a compatible Chem 20 or Chem 20-HI particle counter and software.

This is a reliable solution to use anywhere that high sensitivity chemical batch particle monitoring is required including semiconductor, data storage, medical, pharmaceutical, aerospace, or automotive industries for applications such as chemical quality assurance, parts cleanliness testing, water sampling, and more.

"Particle Measuring Systems is the industry leader for sensitivity to 20 nm for chemicals and DI water. Our new Syringe Sampler gives our customers the option to count 20 nm in batch applications", said Jerry Gromala, VP of Electronics Division for Particle Measuring Systems. He continued, "Our engineering team is continually working on innovative new solutions to help our customers meet increasing needs for sensitivity".

Learn more about the SLS Syringe Sampler.
www.pmeasuring.com/products/liquid-particle-counters/syringe-liquid-particle-sampler/
www.pmeasuring.com/products/liquid-particle-counters/chem-20-chemical-particle-counter/

ONFAB launches isolation dome as part of COVID-19 response

Flexible containment specialists ONFAB have launched a new Patient Isolation Dome to help shield healthcare staff from risks of Covid-19 infection.

The company were approached by Dr Neil Sahgal of Aintree University Hospital and took just eight days to develop a prototype, receive approval for clinical use and finish production of the first 30 units.

The pop-up dome is designed to protect healthcare professionals from infectious pathogens when performing AGPs like intubation.

Dr Sahgal said: "The dome provides protection from the spray of droplets which can occur, while staff who have used it also report feeling much safer. To achieve this in just a couple of weeks shows how we can act much more quickly than normal to take a great idea into a product which could reduce the risk of infection to healthcare workers."

Mike Brown, director of ONFAB, commented: "We're honoured to have played our part in supporting the NHS in these most pressing of circumstances and will continue to offer our expertise in the containment of pharmaceutical and medical processes wherever it is needed."

To find out more, call ONFAB on +44 (0)1606 832 080 or email enquiries@onfab.co.uk

Events

2020	Event	Location
August 16-18	Cleanroom Guangzhou,2020,	Guangzhou (Canton), China
September 29-30	Making Pharmaceuticals Ireland,	Dublin, Eire
October 5-8	ESTECH/EDUCON, RESCHEDULED FROM APRIL	Minniapolis St.Paul, Minnesota
October 13-15	25th International Symposium on Contamination Control, ICCCS'20	Antalya, Turkey
October 26-27	Making Pharmaceuticals Exhibition and Conference RESCHEDULED FROM APRIL	Coventry, UK
October 28-29	Cleanroom Technology Conference 2020 RESCHEDULED FROM APRIL	Birmingham, UK
October 28-29	Manufacturing Chemist Live 2020 RESCHEDULED FROM JUNE	Birmingham, UK
November 4-5	Lab Innovations	Birmingham, UK
November 17-19	International Congress A3P	Biarritz, France
November 18-19	Cleanzone	Frankfurt, Germany
November 24-25	Cleanroom Technology Conference 2020	Hyderabad, India
December 1-2	Cleanroom Technology Conference 2020	Singapore
December 16-18	EP and Clean Tech China RESCHEDULED FROM JUNE	Shanghai, China
2021	**Event**	**Location**
May 25-27	Symposium & Exhibition 2021 RESCHEDULED FROM MAY 2020	Naantali Spa, Finland
June 14-18	Achema	Frankfurt, Germany

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2020	**Event**	**Location**
June 8-9	Essential Cleanroom Standards ISO 14644-1 and ISO 14644-2: The Foundations of Contamination Control	VIRTUAL
June 10-11	New ISO 14644-3:2019 - Basic Information and How to Implement	VIRTUAL
June 16	Understanding the Cornerstone Cleanroom Standards: ISO 14644-1 and 14644-2	Schaumberg, Illinois
June 16-17	Universal Cleanroom Operations Guidelines with ISO 14644-5	VIRTUAL
July 14	Contamination Busters: Get the Dirt Out of the Cleanroom	Schaumberg, Illinois
July 15	The Unseen Contaminant: Taking Charge of Electrostatic Contamination	Schaumberg, Illinois
July 16	Stop Contamination in Your Operations with Reusable and Disposable Garments	Schaumberg, Illinois
October 5	Basics of Cleanroom Design, HVAC System Design, and Engineering Fundamentals	ESTECH/EDUCON 2020, St. Paul, Minnesota
October 6	Cleanroom Basics: What is a Cleanroom and How Does it Work?	ESTECH/EDUCON 2020, St. Paul, Minnesota
October 7	Beyond Cleanroom Basics: Fundamental Information for Cleanroom Operations	STECH/EDUCON 2020, St. Paul, Minnesota
October 8	Cleanroom Classification Testing and Monitoring	ESTECH/EDUCON 2020, St. Paul, Minnesota

CCN (Contamination Control Network) www.theccnetwork.org		
2020	**Event**	**Location**
November 10-12	CTCB-I Testing and certification course	Liphook, England

ICS (Irish Cleanroom Society) www.cleanrooms-ireland.ie		
2020	**Event**	**Location**
TBA	CTCB-I Advanced Cleanroom Technology course, 1 day	Dublin. Ireland
TBA	CTCB-I Cleanroom Testing & Certification, 2/3 days	Dublin. Ireland

R3Nordic www.r3nordic.org Safety Ventilation www.safetyventilation.com		
2020	**Event**	**Location**
October 6-7	CTCB-I Testing & Certification, Associate Level	Gothenburg, Sweden
October 6-8	CTCB-I Testing & Certification, Professional Level	Gothenburg, Sweden
For courses run by R3Nordic see https://r3nordic.org/		

VCCN (Association of Contamination Control Netherlands)		
2019	**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		
2020		
For courses run by TTD see https://www.temizoda.org.tr/en/trainings		

Note:
CTCB-I Certification: Cleanroom Testing and Certification Board International Certification, see CTCB-1 website: www.ctcb-i.net/index.php

Life-lines

Quotations of Jonas Salk

Our greatest responsibility is to be good ancestors.

Who owns the patent on this vaccine? 'Well, the people' I would say. There is no patent. Could you patent the sun?

Reply when questioned on the safety of the polio vaccine he developed: There is hope in dreams, imagination, and in the courage of those who wish to make those dreams a reality.

Intuition will tell the thinking mind where to look next.

When things get bad enough, then something happens to correct the course. And it's for that reason that I speak about evolution as an error-making and an error-correcting process. And if we can be ever so much better – ever so much slightly better – at error correcting than at error making, then we'll make it.

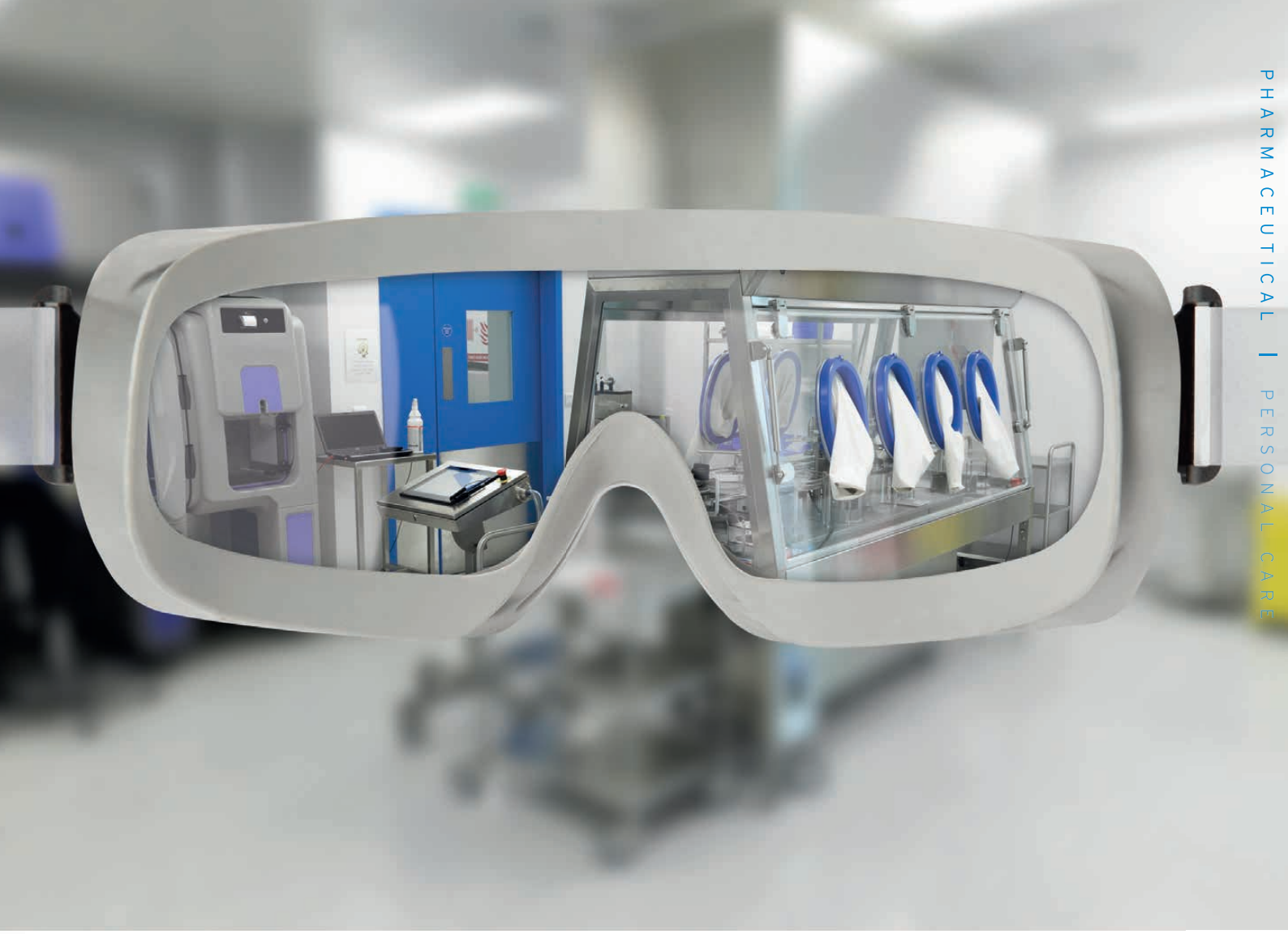
'It is safe, and you can't get safer than safe.'

There is no such thing as failure, there's just giving up too soon.

Some people are constructive, if you like. Others are destructive. It's this diversity in humankind that results in some making positive contributions and some negative contributions. It's necessary to have enough to make positive contributions to overcome the problems of each age.

I feel that the greatest reward for doing is the opportunity to do more.

I have had dreams, and I've had nightmares. I overcame the nightmares because of my dreams.



PHARMACEUTICAL | PERSONAL CARE

A CLEARER VIEW OF **ANNEX 1**

Ecolab remains at the forefront of industry regulations, providing insight into the Annex 1 updates.

With the latest draft* making more exacting demands around cleaning and disinfection for pharmaceutical manufacturers, Ecolab can help your compliance with:

- A range of **product formats** which are sterile and ready-to-use as well as **Hydrogen Peroxide Vapor (H_2O_2) technology** that provides an aseptic processing environment
- **Validation** expertise through our Validex program
- **Service excellence** from our Technical Consultants to provide guidance around interpretation and implementation of the regulations

To help guide you through Annex 1, speak to your Ecolab account manager today, or visit our dedicated web page at

ecolablifesciences.com/annex1

ECOLAB LIFE SCIENCES
FOR LIFE SCIENCES. FOR LIFE

**Annex 1 of EudraLex Volume 4 - Good Manufacturing Practice (GMP) guidelines, draft 12 - February 2020*

ECOLAB®
Everywhere It Matters.™