CACR

Clean Air and Containment Review

Enhance your knowledge of contamination control

Issue 46
2021 Number Two

ISSN 2042-3268

Picture: Bag handling in the latest Rapid Gassing Isolator from Envair Technology.

EUROMED communications

Contents

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.**

CACR is indexed by Scopus and Embase.

www.cleanairandcontainment.com
A comprehensive source of information for clean air and containment practitioners on relevant Standards, Publications, Guidelines, Events and Training courses with links for details, ordering/booking and free downloads.

EUROMED communications
County House, Easton Lane, Winnall,
Winchester, Hampshire SO23 7RU
T: +44 (0)1428 752222
F: +44 (0)1428 752223
e: publisher@euromedcommunications.com
www.euromedcommunications.com

Editorial

Welcome to CACR, the second and last issue of 2021. The intention is to publish four issues in 2022 as normal. This issue has the usual mix of articles that should be of interest to everybody involved in our technology and starts with the introductory chapter from an important new book by Bill Whyte, *Cleanroom Testing and Monitoring*. Further sample extracts from the book, which has a total of 14 chapters and 10 annexes, will be published in future issues, the idea being to give readers a flavour of its scope and content. The book, which I have reviewed on page 22 of this issue, is available from Euromed Communications, click here.

COP26 and the much anticipated imminent publication of EU GMP Annex 1 are both hot topics so this issue includes a feature on COP26 and some related UK initiatives in the pharma and lab sectors, and an article on Annex 1 with emphasis on continuous environmental monitoring (EM). On the same theme, an article by Mark Hallworth of Particle Measuring Systems discusses the placement of environmental monitoring probes.

Andrew Watson's 'known unknown' series continues with some interesting observations on the solutions currently on offer for making spaces safe for people. In some cases, 'known knowns' that should allow us to make better choices have been disregarded.

Sophie Bullimore, editor of *Cleanroom Technology*, has very kindly allowed us to reproduce her report on the very successful Cleanroom Technology Conference 2021. How nice it is that these events are taking place again and people are able to meet and mix. Let's hope that the new omicron variant doesn't set things back again.

CACR46 concludes, as always, with News items, Events, Training courses and, of course, Life-lines which I hope will make you laugh!

John Neiger

Assistant editor required for CACR to help with and gradually take over the commissioning and editing of articles. Would suit a retired contamination control expert or someone active in the field with time and energy for a small 'job on the side'. Good understanding of the subject required and an ability to write clear English. Contact jneiger@johnwrite.co.uk

Pearls of wisdom

The newly announced Energize programme will enable 10 big pharmaceutical organisations to access renewable energy and collaborate with sustainable suppliers to counter their carbon footprint.
Jamie Young, page 4

The location of the monitoring points must be based upon a formal risk assessment using tools such as Failure Mode and Effects Analysis (FMEA), Failure Mode, Effects & Criticality Analysis (FMECA) etc.,
Mark Hallworth, page 10

The original work on liquid droplet behaviour dates from 1934 through work by the US sanitary engineer William F. Wells. The Wells curve and the subsequent work with Richard L. Riley to create the Wells-Riley Model, was used to demonstrate airborne transmission of Tuberculosis. Over time the Wells curve has been improved upon and used in other research, such as that on the transmission of measles. In the light of this work, it is puzzling why it was not the go-to-model at the outbreak of COVID.
Andrew Watson page 14

The new Annex 1 revision emphasises the importance of the concept of continuous EM to quality and safety to ensure risk reduction – a key aim of the QRM based approach.
Andy Whittard, page 16

All in all, 600 people attended in person, whilst 200 participated from their home offices. A 70-30 split that reflects a world in recovery.
Sophie Bullimore, page 20

Clean Air and Containment Review

Issue 46 | 2021 Number Two
ISSN 2042-3268

EDITOR
John Neiger
T: +44 (0)1494 882094
M: +44 (0)7967 572958
e: jneiger@johnwrite.co.uk

EDITORIAL PANEL
Koos Agricola (Holland)
Tim Eaton (UK)
Gordon Farquharson (UK)
Didier Meyer (France)
Berit Reinmuller (Sweden)
Madhu Raju Saghee (India)
Tim Sandle (UK)

PRODUCTION
Clare Beard

SUBSCRIPTIONS
Jill Monk

Published by:
E C Pharma
County House,
Easton Lane,
Winnall,
Winchester,
Hampshire SO23 7RU
T: +44 (0)1428 752222
F: +44 (0)1428 752223
e: publisher@euromedcommunications.com
www.euromedcommunications.com

Clean Air and Containment Review
is published quarterly in
Winter, Spring, Summer
and Autumn

Annual subscription rate £90.00

COP26

Jamie Young

Abstract

As the world reviews the actions necessary to curtail the global rising of temperatures at COP26,[1] the pharmaceutical and cleanroom industries must also consider their role in the effort to collectively create a more sustainable future for our planet. This article overviews the key outputs of COP26 whilst highlighting various points of progress in the life science sector.

COP26 – What does it mean for Pharma?

With the closing of COP26 on 13 November, the opportunity to analyse its greater impact on the environment and the life science sector has arrived.

Across the two-week conference, delegates from almost 200 countries attended to discuss and agree targets with regards to climate change mitigation, adaptation, mobilisation of finance and collaboration between parties. This resulted in a number of key points being agreed upon, with great significance to the wider environment:

- 100+ countries agreed to end deforestation by 2030
- An agreement was made to cut methane emissions by 30% before 2030
- Financial backing of clean and renewable tech supported by organisations responsible for $130tn
- Plans were agreed between all nations to reduce the reliance on coal for energy

What Can Pharma Do?

At COP26, the overall examination of the way our planet is used has called into question the role private industry plays in climate change. With the latest study from **My Green Lab**[2] concluding that just 4% of organisations within the pharmaceutical industry are aligned to commitments that will deliver a 1.5°C future (aligned with COP21), there is substantial room for improvement.

With the latest study from My Green Lab concluding that just 4% of organisations within the pharmaceutical industry are aligned to commitments that will deliver a 1.5°C future (aligned with COP21), there is substantial room for improvement.

However, there are some signs of growth towards a more sustainable life science sector. The newly announced **Energize**[3] programme will enable 10 big pharmaceutical organisations to access renewable energy and collaborate with sustainable suppliers to counter their carbon footprint. Such an initiative aims to tackle the operational impact of **Scope 2** and **Scope 3**[4] emissions whilst considering the entire value chain and progress all facets of the industry towards 100 percent renewable energy. Further support for private industry has come from the development of the **Science Based Targets initiative (SBTi)**,[5] which aims to guide companies in the creation of 'science-based' targets that match the 1.5°C ambition that was established within the Paris Agreement. AstraZeneca have been one of the first companies to be recognised by the SBTi, committing to targets of 100% reduction within scope 1 and 2 by 2025 and paving the way for further progress whilst moving another stage towards decarbonisation!

Every long journey begins with the first step, so how will you achieve greater sustainability?

1. COP26: 26th UN Climate Change Conference of the Parties
2. My Green Lab® is a pioneer in laboratory sustainability. The organisation developed the first nationally recognised standard for laboratory operations, established the first ENERGY STAR category for laboratory equipment, and released the first eco-label for laboratory products, see https://www.mygreenlab.org/
3. Energize is a program to increase access to renewable energy for pharmaceutical supply chains, see https://neonetworkexchange.com/Energize
4. Greenhouse gas emissions are categorised into three groups or 'Scopes' by the most widely-used international accounting tool, the Greenhouse Gas (GHG) Protocol. Scope 1 covers direct emissions from owned or controlled sources. Scope 2 covers indirect emissions from the generation of purchased electricity, steam, heating and cooling consumed by the reporting company. Scope 3 includes all other indirect emissions that occur in a company's value chain, see https://www.carbontrust.com/resources/briefing-what-are-scope-3-emissions
5. The Science Based Targets initiative (SBTi) is the lead partner of the Business Ambition for 1.5°C campaign - an urgent call to action from a global coalition of UN agencies, business and industry leaders, mobilising companies to set net-zero science-based targets in line with a 1.5°C future.

Jamie Young joined EECO2 in July 2021 and has since been working in the marketing department to promote energy efficiency solutions in the life science and cleanroom industries.

Cleanroom Testing and Monitoring – Chapter 1: Introduction

W Whyte

This article is the first of a short series of extracts from Bill Whyte's new book *Cleanroom Testing and Monitoring* and is reproduced here with the kind permission of the author, Bill Whyte, the publisher, Euromed Communications, and the owner of the copyright, the Cleanroom Testing and Certification Board – International (CTCB-I)*. The objective in publishing these extracts is to give readers a flavour of the content and depth of the book which is recommended as a comprehensive textbook and an essential reference for cleanroom managers, cleanroom test engineers, cleanroom service engineers, cleanroom designers and specifiers and anybody who is concerned with cleanrooms. All too often testing and monitoring are insufficiently considered until an installation is physically complete. If you design and build an installation to achieve a certain performance, it is essential that you understand and plan at an early stage for how that performance will be verified and monitored throughout the life of the installation.
Editor

Chapter 1 Introduction

When a cleanroom is first installed, or when significant modifications are made to its structure, ventilation system, or equipment and machinery, it should be tested to ensure that it is functioning correctly and providing the correct level of cleanliness for the task for which the cleanroom is designed. The cleanroom should also be tested throughout its life to ensure that it continues to function correctly. Therefore, tests for the quantity and quality of air supplied, air movement within and between cleanrooms, particle (and where necessary microbial) concentrations, and a variety of other tests, are carried out. These tests are discussed in this book.

1.1 Types of Cleanroom

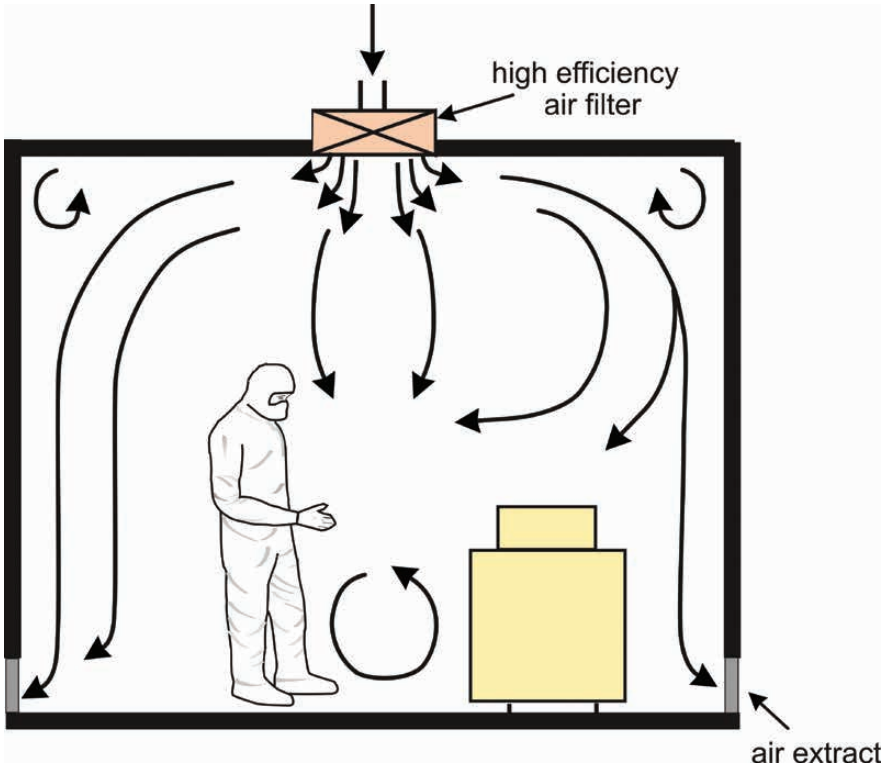


Figure 1.1 Non-UDAF type of cleanroom

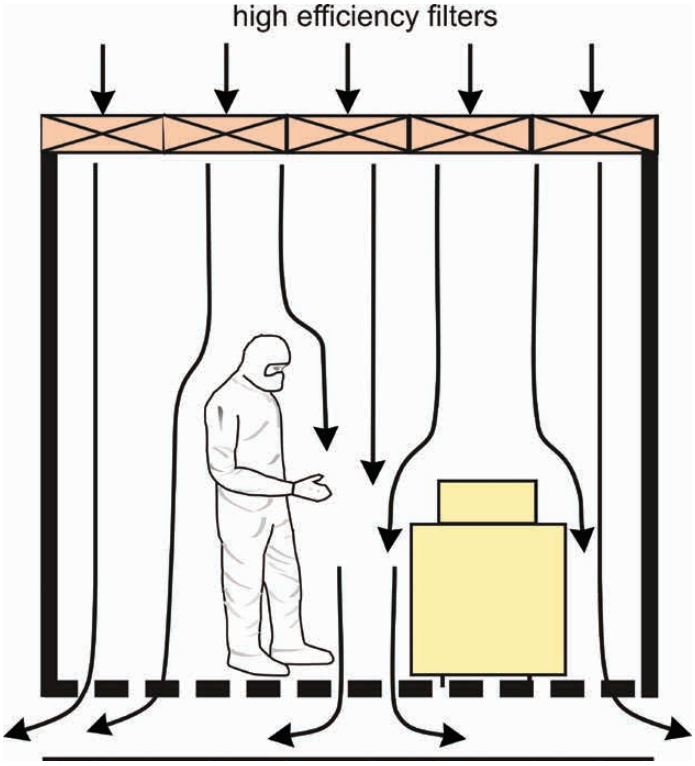


Figure 1.2 Unidirectional airflow type of cleanroom

There are two major types of cleanroom that are differentiated by their method of ventilation i.e. non-unidirectional (non-UDAF) and unidirectional airflow cleanrooms (UDAF). UDAF cleanrooms were originally and incorrectly known as 'laminar flow' cleanrooms but as the airflow is not 'laminar' in the scientific sense they should not be called 'laminar flow'. Non-UDAF cleanrooms are variously known as 'turbulent', 'mixed airflow', or 'conventionally ventilated'.

The distinguishing characteristics of the two major types of cleanroom are shown in Figures 1.1 and 1.2. Figure 1.1 shows an example of a non-UDAF cleanroom. This cleanroom is supplied with clean air that passes through a high efficiency filter in an air supply terminal in the ceiling. Contamination generated by people and machinery is mixed and diluted with the supply air, and removed through the air extracts at low level. The air supply rate, when expressed as air changes per hour, is likely to be at least 20, and is normally much greater than in ordinary mechanically ventilated rooms such as offices or hotels.

Figure 1.2 shows an example of a UDAF cleanroom. In this example, high efficiency air filters are installed across a whole ceiling. The supply air sweeps through the room in a unidirectional manner at a velocity that is usually between 0.3m/s and 0.6m/s and exits through the floor, thus removing the airborne contamination from the room. This system uses much more air than a non-unidirectional airflow cleanroom but, because of its directed unidirectional airflow movement, it minimises the spread of contamination about the room and sweeps it out through the floor.

Clean air devices, such as UDAF workstations, restricted access barrier systems (RABS), minienvironments, and isolators, can be installed in both non-unidirectional and unidirectional ventilated cleanrooms. These clean air devices provide clean zones where enhanced airborne cleanliness conditions are required, such as critical locations where the product is open to contamination. They normally have a localised supply of filtered air and a physical barrier that protects the critical location against the transfer of contamination from the room in which they are located.

Throughout this book, the word 'cleanroom' will often be used when either a cleanroom, or a clean zone are discussed.

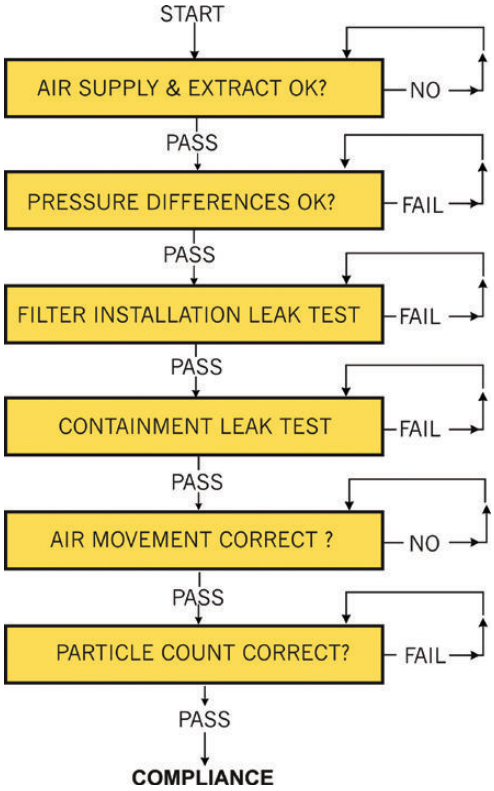


Figure 1.3 Cleanroom test sequence

1.2 Principles of Cleanroom Testing

To show that a cleanroom is working satisfactorily, it is necessary to demonstrate that the following main principles have been satisfied:

- The air supplied to the cleanroom is of sufficient quantity to dilute or remove the contamination generated in the room to produce the required airborne cleanliness.
- The air supplied to the cleanroom is of a quality that will not significantly add to the contamination within the room.
- The air movement within the cleanroom should ensure that there are no critical locations where product or process is subject to high concentrations of airborne contamination.
- The air within the cleanroom suite moves between the different cleanrooms in a manner that minimises the undesirable movement of contaminated air.
- The concentration of particles and, where necessary, micro-organisms, does not exceed the maximum concentration that is specified.

These, and other tests that are carried out in a cleanroom, are described in this book.

1.3 Cleanroom Tests

Shown in Figure 1.3 are the main tests that are carried out to demonstrate that a cleanroom fulfils its design requirements. If the cleanroom is being tested just after being built, the tests will normally be carried out in the order shown in Figure 1.3. However, if the cleanroom is being monitored during its lifetime, the tests need not be carried out in the order shown. Other tests that measure segregation, surface contamination, and particle deposition rate, may be carried out and these are discussed in the second part of the book. In some cleanrooms, it is necessary to additionally count the microbial concentrations; these test methods are also discussed in this book. A brief description of these tests is now given.

Air supply and extract quantities

In the case of non-UDAF clean areas, the correct air supply volume rate should be measured as it is this that determines the concentration of airborne contaminants. In the case of

UDAF systems it is the air velocity that determines the concentration of airborne contaminants.

Pressure differential between areas
It is necessary to demonstrate that air flows in the correct direction between areas in a cleanroom suite, i.e. from the clean to the less-clean, to prevent the entry of contaminated air into the cleaner areas. This is ascertained by measuring the differential pressure between areas to ensure that the cleanest area is at a higher pressure than the less-clean areas and the magnitude of the pressure differences are correct.

Filter installation leak test
The high efficiency air filter, and its frame, housing, and gasket, at the entry of the air supply to the cleanroom, should be tested to ensure that no airborne contamination enters the cleanroom as a result of contaminated air leaking through the filter installation.

Containment leak testing
Testing should be carried out to show that airborne contamination does not enter a cleanroom through leaks in its construction materials from areas adjacent to the cleanroom.

Air movement and recovery within the room
The use of air movement and recovery tests is dependent on whether the cleanroom is non-UDAF or UDAF. If the cleanroom is non-UDAF, it is necessary to demonstrate that there are no areas, especially at critical locations, where poor airflow is likely to cause high concentrations of airborne contamination, and that the cleanroom is capable of quickly recovering from the generation of high concentrations of airborne contamination.

If a cleanroom or clean air device has unidirectional airflow, it is necessary to demonstrate that the filtered supply air sweeps away contamination from critical locations, and maintains low levels of airborne contamination. It is also desirable to demonstrate that the airflow does not move contamination to critical locations.

Airborne particle and microbial concentrations
If the above tests are satisfactory, then measurements are carried out to ascertain that the concentration of particles and, where appropriate, the air and surface concentrations of microbes comply with the cleanroom design specification.

Other types of contamination control tests
Other tests, such as segregation tests, surface particle counts, and measurement of the particle deposition rate (PDR), may be carried out to ensure that the cleanroom and clean zones are working satisfactorily. These tests are described in the second part of this book.

1.4 Additional non-contamination control tests

As well as the contamination control tests described above, it may be necessary to measure some of the following parameters:

- temperature;
- relative humidity;
- heating and cooling capabilities of the cleanroom;
- sound levels;
- lighting levels;
- vibration levels.

The additional tests in the list are not considered in this book, as they are tests that are carried out in all types of mechanically ventilated rooms and not just in cleanrooms. If required, information about these types of tests is available in various building services textbooks and in guides provided by associations, such as the American Society of Heating Refrigeration and Airconditioning Engineers (ASHRAE) in the USA, and the Chartered Institute of Building Services Engineers (CIBSE) in the UK.

Before discussing the methods required for testing a cleanroom, it is necessary to familiarise the reader with the design and function of an air conditioning plant and its components, especially high efficiency air filters. These topics are discussed in the next two chapters (Chapters 2 and 3). It is also necessary to familiarise the reader with the standards required to be met when cleanroom testing, and this topic is discussed in Chapter 4. In addition, Chapter 13 discusses how people who test cleanrooms should conduct themselves in a cleanroom. Some of the information given in Chapters 2, 3, 4 and 13 is included in the book 'Cleanroom Technology – Fundamentals of Design, Testing and Operation' written by the author of this book. However, it is necessary that this information is repeated to avoid the need to consult another book.

Chapter 5 to Chapter 10 explains the methods used to carry out the more common tests used in cleanrooms. The second part of the book contains Annexes A to J that describe test methods that are not so commonly used in cleanrooms as the first part, and how a cleanroom is monitored to ensure that it continues to function correctly.

*CTCB-I (Cleanroom Testing and Certification Board – International) is an association which promotes, prepares and accredits internationally recognised educational courses for people who design, construct, test, monitor, operate and work in cleanrooms. Only societies set up for the education and promotion of contamination control techniques in cleanrooms can apply for membership of the CTCB-I. They must run or wish to run CTCB-I courses. Current members of the CTCB-I are Belgian Cleanroom Workgroup (BCW), Contamination Control Network (CCN), Cleanroom Technologies Society of Turkey (TTD), Irish Cleanroom Society (ICS), Cleanrooms and Contamination Control Association for Denmark, Finland, Norway and Sweden (R3 Nordic), Scottish Society for Contamination Control (S2C2) and Netherlands CC Society (VCCN). The CTCB-I is run by a Board of Delegates comprising delegates nominated by each member society. The Board of Delegates monitors the written and practical content of the cleanroom courses and the standard of examinations to ensure the maintenance of a common and high standard across the courses, and evaluates the course structure and teaching material from each new submission from a cleanroom society. The aim of the CTCB-I is to help foster the development of cleanroom practitioners in its member societies so that they practice to a very high standard. For further information please visit http://www.ctcb-i.net

Choosing the most suitable particle sample point locations in the cleanroom

Mark Hallworth

Abstract

As environmental system designers, we are often asked where to place sample points for particle monitoring, whether it be performed in a pharmaceutical cleanroom or clean device (RABS, isolator, etc.).

The answer is not always straightforward. There are several guidance documents that offer advice on what processes need to be monitored, along with advice on suitable distances from the process being monitored. The goal of this article is to identify the considerations, establish the most suitable locations for monitoring a process, and build a scientific rationale for that decision.

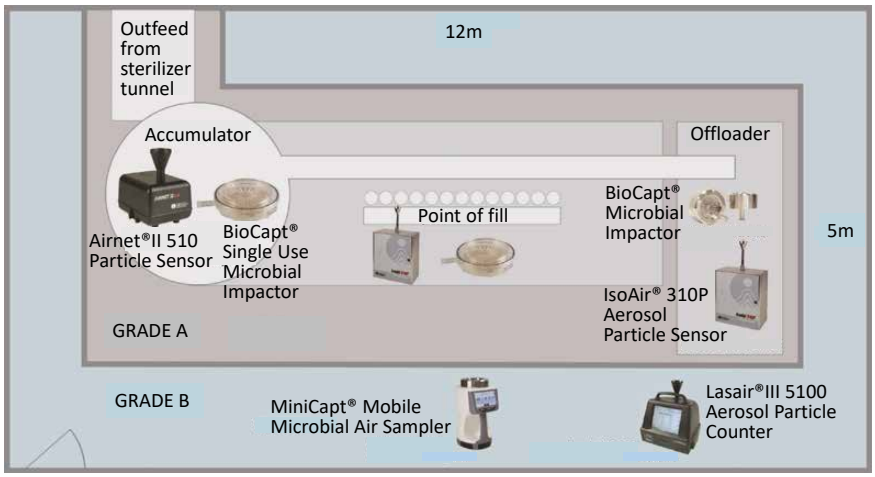


Figure 1: Diagrammatic representation of a classic filling machine in a Grade A/ISO 5 area in a Grade B/ISO 7 background area with testing and monitoring instruments by Particle Measuring Systems.

Introduction

Particle counting in pharmaceutical applications can be clearly segregated into one of three categories: certification, qualification and monitoring. Each category requires a different approach.

Certification

Measuring a cleanroom to a standard. The only standard recognized worldwide is ISO14644-1:2015, *Classification of air cleanliness by particle concentration,*[1] which defines how a cleanroom performs and its ability to show uniformity across the entire space. This is done irrespective of the activities performed in it.

Qualification

The process of analyzing risk assessment for the activities in the room. Qualification follows grid methodology testing methods. Particle counts are measured in both operational and at-rest states; however, the operational data is the most valid.

Monitoring

The ongoing sampling of the cleanroom at a frequency relative to the degree of control required to prove to management risk to the finished product. The number of sample points and their location is determined by risk assessment, and the qualification and certification processes.

"The international standard means that a cleanroom tested to meet compliance with ISO class 5 air cleanliness will meet that standard independent of geography and regulatory aspects (i.e., FDA or EU GMP). This provides a universal standard to show that a cleanroom classification class has been established."

Classification

As mentioned above, cleanroom certification is based on ISO14644-1:2015. The specifics of the assessment may vary slightly for the FDA (Aseptic Processing Guideline[2]) or the EU GMP (Annex 1[3]) regulations, but the underlying methodology is standard.

Certification demonstrates that the entire area meets a specific ISO classification by particle concentration. That is, irrespective of the final use of the room. The international standard means that a cleanroom tested to meet compliance with ISO class 5 air cleanliness will meet that standard independent of geography and regulatory aspects (i.e., FDA or EU GMP). This provides a universal standard to show that a cleanroom classification class has been established.

Most manufacturer's test instruments now comply with new ISO standard set in 2015. Some include interactive software to walk the user through the certification process.

There are many different resources to prove ISO compliance and this paper will not cover these in depth. However, using the example of a classic filling machine (Grade A/ISO 5) within a Grade B (ISO 7) background area, shown diagrammatically in Figure 1, the basic rules of testing can be demonstrated.

1. The number of sample points is based on a statistical function of the area.
   - Calculate the area of Grade A/ISO 5.
   - Calculate the area of Grade B/ISO 7.

2. Sample point placement for the Grade A (ISO 5) area:
    - The sample points must all be equidistant and at work height, irrespective of the activity at the location of their placement.
    - Samples are taken in a grid pattern at the identified locations. Derive the minimum number of sampling locations, NL, from ISO 14644-1 Table A.1. This table provides the number of sampling locations related to the area of each cleanroom or clean zone to be classified and provides at least 95 % confidence that at least 90 % of the cleanroom or clean zone area does not exceed the class limits.
    - PASS/FAIL criteria are calculated for ISO and EU GMP Annex 1. It is recommended to have both sets of data, as the FDA requires ISO14644-1, and the EU requires Annex 1 data points (although the EU data would suffice for the FDA).
3. Sample point placement for the Grade B (ISO 7) area:
    - Repeat the steps used for the Grade A (ISO 5) area.
    - It may be more difficult to determine the locations of the sample points due to the unusual shape of the room. Derive the minimum number of sampling locations, NL, from ISO 14644-1 Table A.1. This table provides the number of sampling locations related to the area of each cleanroom or clean zone to be classified and provides at least 95 % confidence that at least 90 % of the cleanroom or clean zone area does not exceed the class limits.
4. A final report is created and marks the end of the certification phase.

Qualification

The qualification phase considers the risks to the quality of the finished product. Each activity must be considered and assessed. Continuing with the example of the filling line, let us consider the accumulator table at the exit of the sterilizer tunnel. The risk is that glassware (vials/bottles) are exposed to the open environment and the operator. Therefore, contamination can fall into clean vials/bottles prior to filling. Operator intervention and the shifting of glassware causes turbulent air movement on the table, impacting contamination risk to the exposed vials/bottles. Therefore, it is an area of contamination risk and the following actions should be taken:

1. Divide the area of risk into a 3 x 3 or a 4 x 4 grid. If the activity can occur at several levels, then each level (i.e. working height, +150 mm from work height and +300 mm from work height) must be considered. Figure 2 is an example of this.
2. Take a particle sample at the center of each of the grid squares and on each level.
    - Samples are taken during 'At Rest' and 'Operational' states. It may be required to work around an activity or operator to gain suitable data.
    - Slight movement of sample points within the grid square is acceptable. A location is invalid if found to impede normal activities.
3. When all samples are taken this will provide a particle map of the pharmaceutical activity.

Each of the key functions within the cleanroom (filling point, stoppering, general background activities, etc.) should be analyzed accordingly.

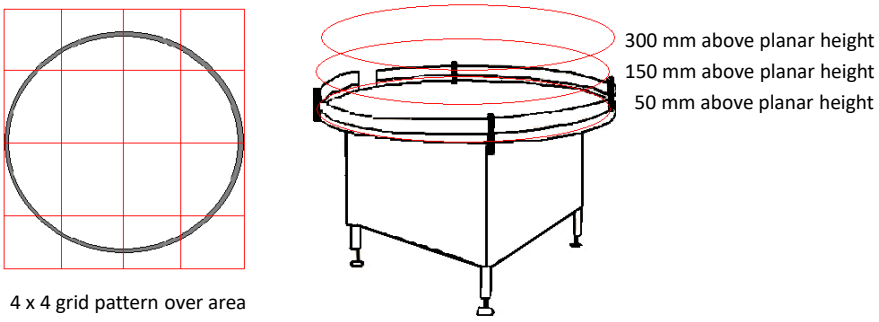


Figure 2: Accumulator table sampling plan

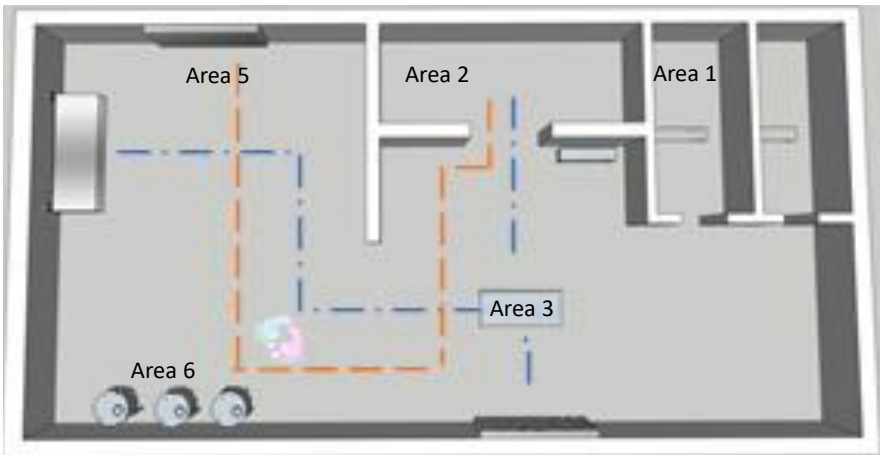


Figure 3: Example Gemba walk of a new process rooms.

"In the current regulatory environment, a risk assessment is absolutely required. Without one, poor or incorrect sampling methodology can lead to data unreliably associated to the process and potential impact to finished product quality."

* The Gemba walk is similar to MBWA (management by walking around) and denotes the action of going to see the actual process, understanding the work, asking questions, and learning. It is also known as a fundamental part of Lean management philosophy

Monitoring

The location of the monitoring points must be based upon a formal risk assessment using tools such as Failure Mode and Effects Analysis (FMEA) , Failure Mode, Effects & Criticality Analysis (FMECA) etc., with data from the certification and qualification testing. Other factors, such as equipment interference, mounting points, operator impedance and operator intervention contribute to selecting the final location for each sample probe. In the current regulatory environment, a risk assessment is absolutely required. Without one, poor or incorrect sampling methodology can lead to data unreliably associated to the process and potential impact to finished product quality. Without the option of correlating events, the lack of connection between location and sample frequency can lead to long investigations for out of tolerance events.

There are several steps to defining a risk-based environmental monitoring plan:

1. **Process understanding**: You must study personnel and material flows within the assessed area in addition to the production operations. This will give an understanding how the system is used and what evidence there is to support its state of control, such as:
   - Current monitoring practices
   - Historical data
   - Smoke studies

   A Gemba* walk of the process and rooms is necessary to define the scope of monitoring required and to aid in applying a process that fits with an organization's internal practices. Figure 3 is an example.
2. **Definition of critical areas**: Identification using Hazard Analysis Critical Control Point (HACCP)[6] helps identify which critical areas require environmental monitoring, and which areas meet the needs of a critical sample location.
3. **Evaluation of sampling methods**: You need to make a determination between traditional methods such as volumetric air samplers, newer technologies such as Rapid Microbiological Methods, or manual collection techniques such as swabbing and contact plates. Also, determine if the chosen method needs to be portable, continuous, remote, etc.
4. **Definition of potential sample locations**: Determine a single sample location within a critical area, following these criteria as shown in Figure 4.
   - Check the available space around the critical area.
   - Measure the size of probes and plate holders.
   - Determine the accessibility to the location for operator maintenance.
   - Assess the interaction between the process operation with personnel and material flows.
   - Calculate the probability of potential contamination events.
5. **Definition of critical control points (CCP)**: Each individually considered location is evaluated according to the FEMA method to rank and identify critical sample locations.
6. **Define sampling parameters**: The sample frequency is found based on the criticality of operations, along with any additional criteria such as incubation parameters, and mitigating measures that might be put into place prior to establishing a monitoring plan.
   Sampling practicalities include elements such as:
   - The isokinetic sample probe should face into the air stream.
   - The minimum length of tubing should be used. Although different manufacturers claim specific lengths of tubing can be used with their particle counter, this is typically a function of vacuum pump dynamics, and not of particle transportation. Particles of 0.5 µm move freely in long lengths of tubing. However, 5.0 µm particles do not have this same mobility. As 5.0 µm particles are a greater concern, the tubing should be maintained at its shortest recommended lengths. The author's company, for example, quotes maximum tubing lengths based upon the same conditions of airflow, and has a recommended maximum length of 3 m. However, for pharmaceutical particle systems a reduced length of 2 m is recommended to ensure

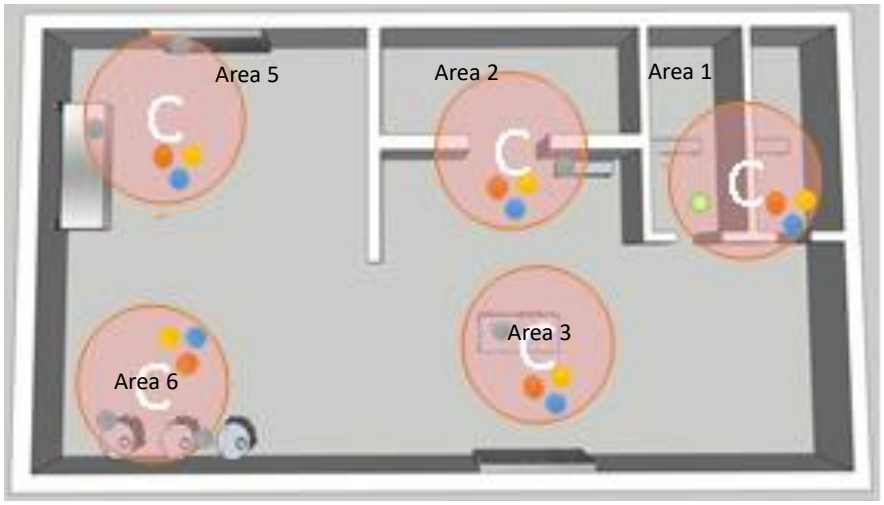


Figure 4: Determination of potential sample point locations.

"You need to make a determination between traditional methods such as volumetric air samplers, newer technologies such as Rapid Microbiological Methods, or manual collection techniques such as swabbing and contact plates. Also, determine if the chosen method needs to be portable, continuous, remote, etc."

transportation of the larger particles. The FDA's Aseptic Processing cGMP Guideline states:

"Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations would be of appropriate particle quality when it has a per-cubic-meter particle count of no more than 3520 in a size range of 0.5 µm and larger when counted at representative locations normally not more than 1 foot away from the work site, within the airflow, and during filling/closing operations. This level of air cleanliness is also known as Class 100 (ISO 5)"

The frequency of sampling should reflect the risks and follow from the FDA guidelines on sterile manufacturing and the EU GMP Annex 1. Particle monitoring should be automated and maintained in a continuous state when glassware and products are exposed.

References

1. 14644-1:2015. *Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration*
2. *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*. FDA. 2004
3. EU GMP Annex 1: *Manufacture of Sterile Medicinal Products*. 2008
4. *Failure Modes and Effects Analysis (FMEA) Tool*. Institute for Healthcare Improvement; 2017
5. FMECA. U.S. military published MIL-STD-1629; 1974
6. *HACCP Principles & Application Guidelines*. US Food & Drug Administration (FDA). 1997

Mark Hallworth is the Life Sciences Strategic Senior GMP Scientist at Particle Measuring Systems. Mark has managed the design, installation and validation of over 200 environmental monitoring system projects worldwide. He has designed several products specific for pharmaceutical environmental monitoring, including particle counters for explosive and corrosive areas and 21 CFR part 11 compliant software for batch test and release. He currently lectures for the PDA, ISPE and other international pharmaceutical societies on environmental monitoring and GMP compliance design and validation. Mark has written over 100 technical papers on environmental monitoring and contributed to several books specific to this field. Additionally, he was awarded the IEST James Mildon award for "significant contributions to the advancement and increase of knowledge in the field of contamination control".

Known Unknowns: Known Knowns and COVID mitigation

Andrew Watson

Abstract

This article will review the evolution of our response to the COVID crisis. In particular the tools and strategies that are being put forward to assist in making spaces safe for habitation. In many cases there are shortcomings that are well documented, however we overlook these 'Known Knowns' in order to make ourselves feel better about doing 'something'. In some of these cases a simple tweak might make a major improvement, in other cases we are just throwing good money after bad. In extreme cases we are being outright fraudulent and hoping some money can be made before somebody calls it out. In all cases, the work has been done and the knowledge is there that can allow us to make better choices that will make a difference.

Introduction

It's always interesting to see terminology that you use in your (somewhat esoteric) day job start popping up in your social media feed. The recent discussion on the role that aerosols contribute to COVID-19 infection compared to droplets intersects with many concepts we employ in the design of cleanrooms.

Put simply, droplets are generally particles larger than 5 micron that when generated tend to settle onto surfaces and can only be removed by cleaning. Aerosols are generally less than 5 microns, tend to be easily entrained in the airflow and are removed by well-designed air conditioning systems.

Usually in cleanrooms we think of particles as solid objects. Liquid droplets and aerosols are a bit different because they change size over time due to evaporation. Therefore, a largish droplet falling to the floor can become an aerosol (dried residue) before it gets there, becoming a droplet nuclei (we will call them this to differentiate them from regular aerosols). However, if still liquid, once it lands it is unlikely to be re-entrained by local air movement. The proportion of droplets that hit the floor or remain in the air as droplet nuclei is determined largely by the humidity. The higher the humidity, the fewer the droplets that evaporate down to droplet nuclei and the higher the proportion of droplets that hit the floor. The lower the humidity, the more and the larger are the droplets that become droplet nuclei which can re-entrain in the airflow.

The original work on liquid droplet behaviour dates from 1934 through work by the US sanitary engineer William F. Wells.[1] The Wells curve and the subsequent work with Richard L. Riley to create the Wells-Riley Model, was used to demonstrate airborne transmission of Tuberculosis. Over time the Wells curve has been improved upon and used in other research, such as that on the transmission of measles.

In the light of this work, it is puzzling why it was not the go-to-model at the outbreak of COVID. Indeed, it was not into late 2020 after some intense lobbying of the WHO by 239 experts, led by Lidia Morawska and Donald Milton through the paper *It Is Time to Address Airborne Transmission of Coronavirus Disease*[2] before airborne transmission was properly considered and ultimately accepted.

This is a true case of a 'known known', where previous work is forgotten or dismissed, however such 'known knowns' are to be ignored at their peril. The myriad of equipment that are turning up in our schools, workplaces and social spaces to keep us safe are there to do an important job. Mostly they have a sound scientific basis, but some seem to have missed a fundamental 'known known' which makes them much less effective than we would like them to be.

What are we trying to solve?

Mitigating airborne transmission of COVID-19 is an important and immediate need as Europe and the US potentially enters its "fourth wave". The challenge is to find the mitigation that is truly effective, as many mitigations really only nibble around the edges. A mitigation that addresses a minor risk can end up distracting from the real problem. Similarly, we need to look at all aspects of the physics and engineering to assess if the mitigation is truly effective. The principles of cleanroom design are uniquely positioned to contribute to this body of knowledge.

Specific risks for specialist areas, such as COVID hospital wards aside, the key challenge for infection mitigation is against close contact in spaces where numerous people can be found in an enclosed environment. This includes offices, schools, public transport and restaurants.

Taking the lead from cleanroom design, any contamination generated ideally needs to be removed from the critical zone quickly and effectively. While unidirectional airflow is unlikely to be viable in a public setting, the concept of net downward flow is attractive; liquid droplets and aerosols that are forced to a surface are unlikely to re-suspend.

This is just one concept. There are a range of other potential mitigations that can be employed; let's look at those we know to see how effective they really can be.

Air dilution

Air dilution is the mainstay of non-unidirectional cleanrooms, however there are certain caveats. One is that the dilution needs to be in proportion to the contamination present. Dictating a specific air change rate may be effective in certain settings, but definitely not all. Air replacement through open windows and single pass air provide an additional level of dilution, but it is not possible to do this throughout the year or maintain a level of climate control without equipment modification.

The amount of viable SARS-CoV-2 virus that can make it through an air conditioning system would be difficult to determine accurately, however even with a rudimentary filter system, low air change rates and high level return air points, you would expect that dilution would be pretty significant. Whether that

dilution is a sufficient mitigation will depend on many things; for example, with a highly vaccinated population a small concentration of virus is not significant whereas with a largely un-vaccinated population, a small concentration of virus is potentially significant.

Air movement

Air movement is an essential requirement to do the work that gravity cannot, however non-targeted movement can just take contamination from one critical area to another. For example, a pedestal fan blowing past one person and onto another just provides an effective contamination conduit.

A local school guideline[3] I have reviewed mentions the use of ceiling fans.

If used, ceiling fans can be operated on the winter setting (where air is drawn upwards) and at the lowest speed.

While ceiling fans are not used in cleanrooms, we go back to the principal that we would want a downdraft to push particles down to where they will hopefully adhere to a surface. Drawing air upwards is a convenient way to redistribute particles. Of course there will be updraft at some point regardless of the rotation of the fan, so potentially there may be the same problem at the transition zone between downdraft and updraft.

What a ceiling fan will do however is better distribute the air around the room, which will disperse high concentrations around a room. Again, potentially of benefit for highly vaccinated populations only.

Air purifiers

The use of air purifiers has been promoted from the early days of the pandemic. Their effectiveness in cleaning the air is well documented and typically involve the use of HEPA filters. However, their effectiveness will only be as good as their air distribution. They may clean air within their immediate proximity, but not necessarily across an entire room.

When used in conjunction with targeted air movement and interaction with an existing HVAC system, they could be highly effective. However, often the volume of the room is compared with the output of the unit and the statement is made that the room is cleaned in X number of minutes! In reality the clean-up rate depends entirely on the airflow pattern in the room, and a single point discharge of clean air is unlikely to reach and clean all corners of the space.

UV lights

The issues with UV lights are well documented. UV lights are highly effective as long as the contaminant in question gets a direct dose at a high incidence angle. Obviously it is not practical to thoroughly irradiate an occupied room. Some systems radiate UV at a high level but, in reality, what is the number of contaminants that would actually make it up to that section of the room, particularly a mechanically ventilated one? (Note the epilogue – perhaps more than we think.)

The use of UV in ductwork, if through a sufficient length and of a high enough intensity, may be effective, but so is a HEPA filter. In addition, what level of decontamination are we expecting or looking for in an air supply to a public space?

Cleaning

There is no doubt that in public spaces or cleanrooms, physical cleaning is the most effective means of permanently removing contamination from an area. It is not a terribly attractive method – no smooth lines, fancy lights or high technology, just a procedure, some equipment and chemicals and people.

To be truly effective we need a way to get the contamination out of people's breathing zones and then, as frequently as possible, to have it removed by cleaning.

Epilogue

It is interesting to learn how the sanitary engineer William Wells applied the above technology. He was able to prevent measles being transmitted in a classroom by directing air past a UV light. Note that this was in the day before the commercialisation of HEPA filters and of course air conditioning for classrooms, however it is interesting to read how airflow was described:[4]

"There is no system of ventilation other than windows, and the lower portion of the room thus ventilates to the upper irradiated only by natural convection currents."

Simply put, in an unventilated room natural convection draws contaminated air upwards which is irradiated by the UV light.

References:

1. Wells, W. F. (1934-11-01). "On Air-Borne Infection". American Journal of Epidemiology. 20 (3): 611–618. doi:10.1093/oxfordjournals.aje.a118097. ISSN 0002-9262
2. *It Is Time to Address Airborne Transmission of Coronavirus Disease*. 2019 (COVID-19) Lidia Morawska, Donald K Milton. Clinical Infectious Diseases, Volume 71, Issue 9, 1 November 2020, Pages 2311–2313, https://doi.org/10.1093/cid/ciaa939
3. Operations Guide. Victorian government schools. From Saturday 2 October 2021.Victorian State Government Department Education and Training
4. Wells WF, Wells MW, Wilder TS. The environmental control of epidemic contagion I: an epidemiologic study of radiant disinfection of air in day schools. Am J Hyg 1942;35:97-121.

Andrew Watson is a Director of CBE, Centre for Biopharmaceutical Excellence, Australia. He is a Bachelor of Engineering (Chemical and has 25 years' experience in the design, construction, commissioning/validation and operation of a wide range high tech facilities, including pharmaceutical manufacturing, high containment, industrial cleanroom, hospital pharmacy and specialist research facilities. This experience extends to facility layout, building fabric design, construction, and HVAC, utility and purified water specification. His project management experience encompasses all aspects of FDA, EU, TGA, PIC/S and associated regulations, local and international standards and general quality practices. He has performed gap analyses on many pharmaceutical manufacturing facilities and sterile/cytotoxic dispensing suites to assess aspects of compliance, safety, design and rectification. Andrew is a past president of ISPE (Australasia) and is active in establishing ISO standards. He is Independent Chair of ME-060 (Cleanroom Standards) for Standards Australia and a committee member for ISO TC-209 – (ISO 14644 and 14698 suite of standards).
andrew.watson@cbe-ap.com.au

Continuous environmental monitoring (EM) and Annex 1

Andy Whittard

Abstract

The regulatory landscape for pharmaceutical manufacturing has been in a state of flux for a couple of years now as the much-discussed revision to GMP Annex 1 has undergone numerous consultations. Its publication is anticipated for early 2022 and will herald a notable shift in the requirements for environmental monitoring within the industry. The most obvious changes being a focus on continuous monitoring and a change to the limits for grade A spaces.

Continuous EM in Annex 1

Environmental monitoring (EM) is an established method of reducing the risk of contamination of sterile products and is used by manufacturers in the pharmaceutical and associated healthcare industries, in the manufacture of advanced medicinal products, as well as in the specialist food industry.

Highlighting the importance of EM to maintaining the sterility of medicinal products, the latest EU GMP Annex 1 draft revision[1] calls for continuous EM in sectors with stringent environmental control and which carry a risk to public health should contamination occur at manufacturing facilities.

But why do the latest regulations place such as strong emphasis on continuous EM? The short answer is that it is the most effective way to reduce contamination risk.

The benefits of continuous EM

The level of environmental monitoring conducted during sterile product manufacture is currently left to the discretion of the manufacturer. However, the guidance for which action level is required is based on the type of product manufactured and the intended use of the facility, which covers a broad spectrum of actions.

The new Annex 1 revision emphasises the importance of the concept of continuous EM to quality and safety to ensure risk reduction – a key aim of the QRM based approach. This new guideline gives far more insight into best EM practice and outlines a range of specific techniques that are important for the implementation of an effective continuous EM program. These techniques include monitoring of viable and non-viable particulates, as well as aseptic process simulations. The guidelines also now strongly advise that airflow patterns and complex gas flow paths be considered, and that risk assessments be re-evaluated when maintenance activities are carried out.

There are several benefits to manufacturers of making the transition to continuous EM in line with the latest revision of Annex 1, the core benefit being the reduced risk of contamination in grade A environments, such as filling lines, to guarantee production of safe medicinal products. Continuous EM ensures this by enabling the more effective measurement of potential microbiological contaminants.

Reducing contamination risk long-term

Implementing a robust continuous EM program can provide both immediate and long-term benefits for businesses. In the short-term, the regular and accurate contaminant readings from facilities not only provide detailed information about potential risk sources in the manufacturing process, but also enable these risks to be dealt with more rapidly.

In the longer-term, effective continuous monitoring of both viable and non-viable microbiological entities prevents disruption to manufacturing processes – supporting company growth and strengthening industry reputation.

For continuous EM programs to be as effective as possible in the long-term, manufacturers should be able to demonstrate that the techniques they implement can maintain a sterile environment indefinitely. Processes should be substantiated with detailed rationales and validation reports, and the information gathered used to make improvements to the program as this will be an integral part of the site wide contamination control strategy (CCS).

Moving to continuous EM

The first step that manufacturers should take when planning a new continuous EM program is to conduct a thorough audit of every area of their manufacturing facility. This should include details of all the equipment and processes at every stage of the manufacturing process, as well as current protocols for cleanroom staff in all areas of production.

Other aspects that must be evaluated at this stage include the effectiveness of detection systems in alerting operators to ongoing contamination, training and behaviour of staff at facilities and the suitability of current SOPs. The species of microorganism that have been previously recovered from the facility should also be assessed.

Before making the transition to continuous EM, manufacturers must evaluate the comprehensiveness of their current EM program. This means making detailed reports of the methods and frequency of monitoring carried out, and recording when any changes to procedures or equipment are made. These reports should contain information on viable and non-viable particulates, pressure differentials, temperature and humidity, direction of air flow and surface microbial contamination.

Once the potential weak points in the current program have been identified, the next stage is to identify the equipment and protocols which will enable a transition to and implementation of continuous EM to the standard required by the latest Annex 1 revision.

Important considerations for a holistic EM program

Continuous EM programs should be tailored to suit individual facilities, taking into consideration the size of the business and the sector in which they operate. The most effective programs encompass a combination of monitoring techniques and equipment to minimise contamination risk.

For example, monitoring of surfaces for microbial contamination is important for adherence to the revised Annex 1

guidelines, and can be achieved using a combination of contact plates and swabs. Gases used during manufacturing should be sampled for contamination, and their associated containers should also be assessed for sterility.

To reduce contamination from external sources and minimise cross contamination, comprehensive personal protective equipment should also be provided for staff, including gloves, face masks, hair coverings and garments.

In addition, the new Annex 1 draft contains a 'utilities' chapter, outlining required equipment and highlighting the need for the regular monitoring of equipment that may directly or indirectly come into contact with a sterile product. This includes water systems, steam used for sterilisation, compressed gas, as well as vacuum and cooling systems.

All of these factors need to form a part of the contamination control strategy mentioned earlier to form a series of linked events and measures to deliver collective effectiveness. Equally importantly, this strategy needs regular review as processes or equipment change, or new sampling techniques and technology come to market which warrant consideration.

Continuous air monitoring is crucial for Annex 1 compliance

Measuring microbial air contamination is an important aspect of any EM program, and there are several methods available to manufacturers which are based on passive or active monitoring. Passive methods include using gamma-irradiated settle plates – petri dishes that contain culture media that are exposed to air, incubated and checked for the microbial growth over time (Figure 1).

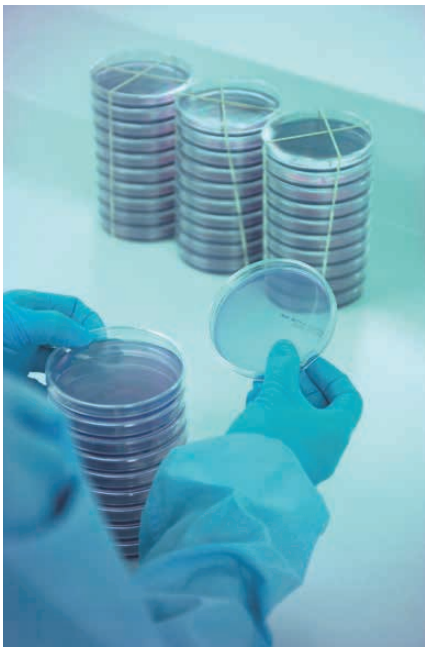


Figure 1: Settle plate checking

Active air monitoring can be conducted in two ways – through air sampling or via continuous air monitoring. Air sampling devices include sieve-based surface air samplers (SAS), These take rapid cubic metre samples and are simple, portable devices useful for background room monitoring (Figure 2).

While sieve samplers remain an important part of any EM program, they can only provide a snapshot of microbial contamination in a given area, meaning that manufacturers cannot meet the requirements of the new Annex 1 revision using these devices alone.

For complete compliance with the latest Annex 1 revision, manufacturers must upgrade to continuous air monitoring, a slower form of sampling at a fixed point. This can be achieved with high efficiency, continuous monitoring devices that use slit-to-agar air sampling which enable continuous, quantitative measurement of microbial air contamination over an extended time period (Figure 3).

Slit-to-agar microbial air monitors rotate the petri dishes to prevent dehydration and increase biological efficiency because the sampled air is constantly impacting a new section of the agar. With innovative modular

Figure 2: A portable surface air sampler

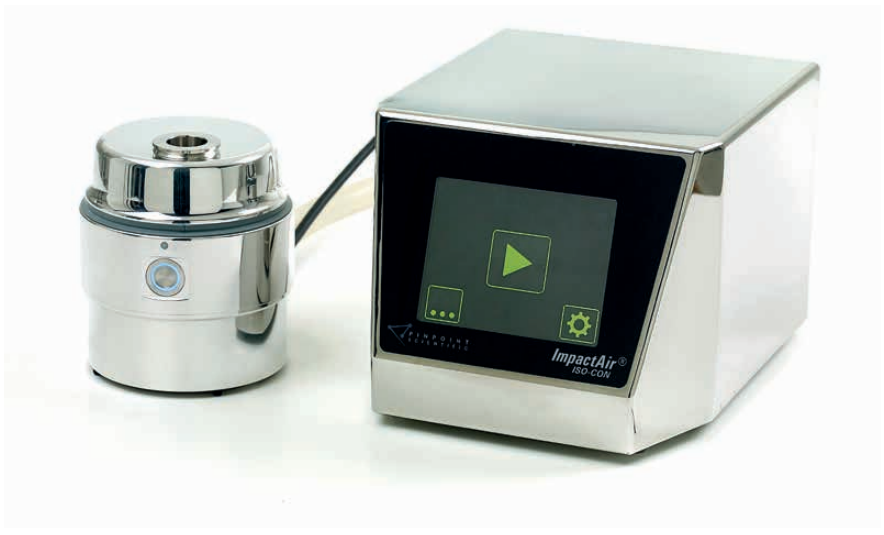


Figure 3. An example of a slit-to-agar continuous monitoring system, the ImpactAir® range of microbial air monitors

designs now available (e.g. ImpactAir® ISO-90 monitoring head), such monitoring devices can be easily adapted into a range of formats to suit specific deployment needs depending on the application.

Aiming for zero CFU!

Unlike previous iterations of Annex 1 which set the limit for microbial contamination in grade A environments at an average of less than one colony forming unit (CFU), the new revision sets manufacturers a target of zero. Therefore, new monitoring devices must be capable of detecting as few as one CFU as this level of sensitivity is crucial for compliance.

Advances in active air monitoring technology now mean that the latest devices are capable of detecting as few as one colony forming unit (CFU). However, it should be noted that the collection efficiency of any active biological sampler or monitor is a combination of the physical collection efficiency of the device and the biological efficiency of the agar.

By combining validated protocols designed to prevent contamination with continuous microbial air samplers suited for the unique needs of individual businesses, continuous EM can be implemented rapidly and effectively, ensuring facilities meet the requirements of the new Annex 1 revision.

Annex 1 compliance and global standards

The new EU GMP Annex 1 revision represents an important step towards a truly global standard in cleanroom environments and will be used by the Pharmaceutical Inspection Co-operation Scheme (PIC/S), the World Health Organisation (WHO), and EU GMP.

With this new draft expected to be published shortly, if they haven't done so already, it is crucial that manufacturers of sterile medicinal products start the process of evaluating the needs of their business and planning how to transition to continuous EM as soon as possible.

With regulations on EM only expected to get tighter, moving to continuous EM and learning how to accurately monitor, report and counter identified risks is now more essential than ever.

References

1. EU Commission (2020). EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft). Annex 1 Consultation Document December 2020

Andy Whittard is the Managing Director at Cherwell Laboratories. Since being appointed MD in 2005 he has overseen significant growth in the business as Cherwell has focused its offer on cleanroom microbiology solutions for the pharmaceutical and related sectors. Andy is a Cranfield School of Management Business Growth Programme alumnus, has a background in service and sales and is second generation in the family business.

Cleanroom Technology Conference 2021

Sophie Bullimore

Introduction

The 2021 hybrid event has wrapped up in Birmingham and many are now mulling over the interesting debates and business discussions from the two days of presentations, networking, and collaboration. Gathering prominent cleanroom experts in one building has once again been an interesting exercise.

Aside from the exhibition hall having seen microbiologists together, it always makes for a productive conversation, and when talking about the standards and how to meet them, this is never more true.

If you ever feel overwhelmed by the minefield that is ISO, CEN, or EN standards, Gordon Farquharson, MD for Critical Systems and ISPE member, gave a great presentation to clear up a lot of the confusion. Later talks gave a lot of ways to achieve these standards from design, to operation, to containment, cleaning, and monitoring.

There was a lot of interesting discussion on the future direction of the cleanroom industry over the two-day event. David Keen from Ecolab spoke about a conversation with an isolator manufacturer, who said: "The pharmaceutical industry is too conservative and won't buy equipment if there is no glove box even though [it] has been fully automated, even for spilt vials."

Another potential future trend that was discussed multiple times at the 2021 event was dynamic cleanroom HVAC control. With the amazing potential to reduce energy consumption and extend filter life, there was justifiably a lot of interest from delegates.

After 18 months of pixelated faces on glowing screens, it was nice to see these pixels become actual humans, but was also great to be able to include those abroad and quarantining through the hybrid approach that allowed those to watch from their home offices. The brilliance of a live Q&A with a floating voice from America answering the queries of the room is something that delegates will probably remember for a long time.

A hybrid approach

As exhibitors arrived at their stands and the morning coffees began to be served, the conference in Birmingham was just starting. But it was not just those in Birmingham that were gearing up for the conference.

Whilst delegates picked up their badges and showed their vaccine passports, almost a testament to the very industry many were there to support, many from the US and across Europe were instead booting up their computers to attend virtually. The beauty of a hybrid event is that no matter the travel restrictions of the moment, everybody could attend in some fashion.

For the attendees from home, all talks and Q&As were live-streamed, and an app allowed business meetings to be scheduled with exhibitors. Speaking to those in attendance at the event, this seemed to be a highly regarded approach and one that should be implemented far more in the future.

Hearing back from those on the floor, many were unsure what to expect after how much the pandemic disrupted the events industry. So, people were very pleased when they were able to meet new potential customers and to be able to catch up with existing clients and suppliers. Exhibitors were also happy to have the virtual side of the show alongside the physical because it meant that they could continue to follow up with people they weren't able to see over the two days, as well as tune in to any presentations that they couldn't watch due to being on their stand.

All in all, 600 people attended in person, whilst 200 participated from their home offices. A 70-30 split that reflects a world in recovery.

Day 1

The first day of talks took an in-depth look at the regulatory state of the sector. Though this side of the industry is very diligent and, as such, not necessarily fast-moving, there seems to be a lot in the pipeline.

With 18 cleanroom standards in the ISO, and the living document sections under constant review, cleanroom veteran, Gordon Farquharson, spoke about the ISO 14644-4:2001 that is currently being reviewed and drafted. "You need to keep your finger on the pulse," said Farquharson when advising the audience to look out for the finalised version to be published.

The first mention of COVID-19 also came on day one, during Camfil's Alan Sweeney's talk about HEPA filter technology. "No building is completely airtight and contaminants WILL enter," he said. Amid an airborne disease pandemic, this was a well-attended talk and delved into the Total Cost of Ownership and best practices for this essential product.

An interesting discussion that came up multiple times over the two days, but was first brought up by Connor Murray from 3dimension Cleanroom, was the idea of over-performance of cleanrooms and their product for purely performative reasons. "We generally murder cleanrooms with air," Murray joked. David Keen from Ecolab talked about a similar issue when it came to isolators, telling a story of a completely automated machine that had glove ports only due to the mindset of customers. "The pharmaceutical is too conservative and won't buy equipment if there are no glove ports even though the thing is fully automated," Keen retells.

The rest of the day moved from regulatory matters onto the topic of monitoring and the risk assessments for microbiological contamination. "GMP Implementation of alternative airborne microbiological detection methods: Biofluorescent particle counting" was a particularly forward-thinking talk given by Patrick Hutchins from TSI. Hutchins also explained that the origin of the technology came from bioweapon defence research, which was a surprise to many in the audience.

The day ended with networking drinks sponsored by ASAP Innovations. This was a very well attended part of the session and really seemed to accentuate the benefits of a live event for those who have been unable to get together for almost two years.

Day 2

The second day of the conference featured some very futuristic talks among the practical guidance ones. Among these forward-looking talks was the issue of the environment. Sustainability was an overarching theme of the two days, and on day two EECO2 gave an excellent talk about dynamic HVAC control for energy savings, which sparked a lot of discussion over where this lies within the regulatory framework and its practicalities for everyday cleanroom managers. However, sustainability is not limited to energy usage, and EECO2 made a good point that this would also extend the life of filters within the system, and therefore reduce the waste output of a facility.

Another talk that seemed to focus on increasing the lifetime of a product was given by Micronclean, breaking down testing they did on some of their materials. Questions from the audience delved into data collection points on a gown, emphasising the need for testing on the body and at the seams. Micronclean's Jenny Steinlet explained that part of improving the garment is to improve the typical garment contract length, which currently stands about three years.

A talk about UVC disinfection given by Paul Bradley from B.Braun presented some startling information about the technology. A comment in the Q&A section of the virtual app said: "The data on 13,697 bugs is astounding."

An out of the box talk came from a Doctors without Borders representative who discussed the need for HVAC at humanitarian efforts like the Gaza strip, Lebanon, Sierra Leone, and Afghanistan. It seemed there is a huge amount of need for these systems, under hugely difficult project environments. This talk was a real reminder that the end goal of the industry is the product, and to keep the end-user safe.

Breaking camp

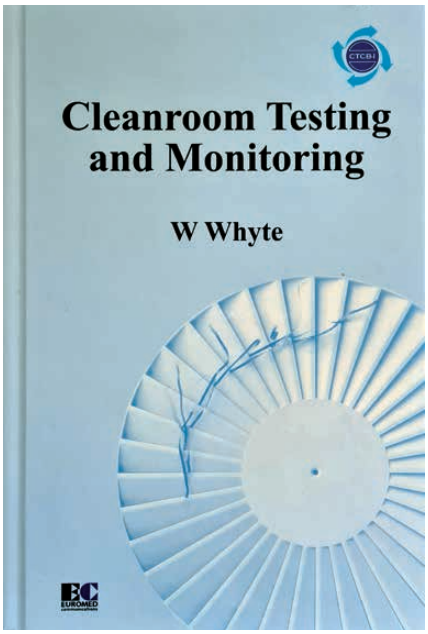
Takeaways from the event seemed very positive and despite the few growing pains of this new type of event, it feels like they are the future. Hybrid events allow accessibility and options that are going to be a must-have going forward.

So with the 2021 outing finished up, let's start getting ready for 2022!

This report was first published in the October 2021 issue of Cleanroom Technology and is reproduced here with their kind permission. The author, Sophie Bullimore, is Editor of Cleanroom Technology.

Cleanroom Testing and Monitoring by William Whyte

Reviewed by John Neiger



I have to declare an interest in this review. Before Bill sent this book to the publishers, he asked me to give it a final check and polish, and having worked with him like this on the second edition of his earlier book, *Cleanroom Technology – Design, Testing and Operation*, I was excited and honoured to accept. I knew that I would receive a comprehensive, well-structured and clearly explained manuscript, and so it turned out.

Bill has been around the cleanroom world since the late 1960s and is internationally respected, not least for his broad, soundly based and well-reasoned contributions to standards work. He has also made a massive contribution to the fountain of knowledge of cleanroom technology by way of lectures, training courses, learned papers (over 140) and books such as this. His research is carried out with other experts who often provide the test equipment and the facilities where the work can be carried out. Quite often he is behind work reported by others. He is clearly an avid reader of all publications concerned with cleanrooms, be they standards, guidelines, articles or books and has an encyclopaedic knowledge of these. He has been involved in testing since the year dot!

Cleanroom Testing and Monitoring is written in two parts. The first part consists of 14 chapters starting with an introductory chapter, followed by three chapters that cover the basics that must be understood before the tests themselves can be described. These basics are the design and ventilation of cleanrooms, high efficiency (HEPA) filters and their housings and standards used for contamination control and testing of cleanrooms. There follow nine chapters covering the various standard tests that are used routinely to verify that a cleanroom is performing to the specified air cleanliness classification and microbial levels and that all other attributes that contribute to this are functioning correctly. The final chapter in this part gives advice on the conduct of cleanroom testers in a cleanroom with information on cleanroom clothing, changing into and out of cleanroom clothing and disciplines within the cleanroom.

The second part of the book consists of ten annexes that describe cleanroom monitoring, tests that are not routinely used in cleanrooms and aspects of standard tests such as sequential sampling of airborne particles to cut the time for cleanroom classification. One annex describes the measurement of particle deposition rates, a relatively recent concept which makes a lot of sense as it is the particles that deposit on a surface that do the damage, not those in the air.

The whole book is well illustrated with full-colour diagrams and photographs. There is a comprehensive reference section comprising mainly international (ISO) standards, international guidelines from IEST (Recommended Practices), Eudralex (EU GMP), ASTM etc. and various papers by the author and others. And of course, there is an index.

The book is aimed directly at cleanroom testers and is indeed derived from and now forms the basis for CTCB-I testing courses, but it is really also an essential reference for cleanroom managers, cleanroom service engineers, cleanroom designers and specifiers and anybody who is concerned with cleanrooms. If you know how your cleanroom must be tested, you will design a better cleanroom!

It is my intention to publish a small number of sample chapters in CACR and in this issue we have Chapter 1 Introduction – see page 6. The object is to give readers a flavour of the content and depth of the book, to show the clarity of the text and illustrations and to encourage readers to buy the book itself.

Cleanroom Testing and Monitoring is published by Euromed Communications and is available via this link: https://euromedcommunications.com/collections/cleanroom-publications/products/cleanroom-testing-and-monitoring

Comments on a recent article on bio-decontamination with vapourised hydrogen peroxide

Sir,

The recent paper by Farquharson and Kawasaki on the application of ultrasonic agitation to hydrogen peroxide aerosol bio-decontamination published in CACR45 is very relevant to the industry, and at the same time eminently readable. I would however like to make a comment about the mechanism of the aerosol bio-decontamination process, as such. The writers express the view that the aerosolised hydrogen peroxide simply wets the internal surfaces of the enclosure, this wetting layer apparently having the same peroxide concentration as the bulk solution. I do not believe this to be the case.

Hydrogen peroxide has almost twice the molecular weight of water, MW 34 and MW 18 respectively. It therefore has a much lower vapour pressure than water vapour. The finely-divided aerosol has a large surface area, and hydrogen peroxide molecules readily leave this surface to condense out on the solid surfaces of the enclosure. This condensate has the same high concentration of peroxide, perhaps 70%, as that produced by the flash evaporation (FE) method. It is this layer of concentrated hydrogen peroxide solution that produces the rapid sporicidal effect seen in both the aerosol and the vapour methods of peroxide delivery. This layer has been termed micro-condensed hydrogen peroxide (MCHP).

I have absolutely no experimental data to support this assertion. I do, however, have over 30 years of experience in the design, development, construction, validation and operation of both vapour and aerosol hydrogen peroxide bio-decontamination systems. Indeed, I am named as inventor on a number of relevant patents, including GB 2 223 678, dated 1990, describing a system which included an ultrasonic nebuliser, technology which is still in use to this day. Such experience leads me to believe that it is MCHP which delivers the rapid deactivation of resistant test organisms seen in both vapour and aerosol devices. There is no "wet" or "dry" cycle, there is only micro-condensed hydrogen peroxide, even in so-called dry processes. The distinction between "wet" and "dry" is perhaps rather more commercial than technically correct. ("Understanding the hydrogen peroxide vapour sanitisation process and introducing the MCHP concept, a personal account" Tim Coles, CACR, January 2016)

One final point, I have yet to see a hydrogen peroxide aerosol system in which the delivery nozzle did not produce a problematic dribble of solution at the end of the cycle.

Yours sincerely,

Tim Coles. BSc. MPhil.
Technical Director,
Pharminox Isolation Ltd.

Cherwell appoints ANT Medikal as Redipor® prepared media distributor in Turkey

Cherwell Laboratories announces that it has added ANT Medikal, in Turkey, to its international distribution network for the Redipor range, as part of the company's continued strategic focus on building its overseas markets.

ANT Medikal is a specialist distributor of laboratory equipment throughout Turkey, supplying medical and pharmaceutical testing equipment. Mirroring Cherwell's customer and quality focused approach, ANT Medikal strive to ensure that the service and products that they supply to laboratories are of the highest quality.

Emma Millburn, Director of Sales, Cherwell Laboratories commented, "We are very proud to have ANT Medikal joining our distributor partnership and working with them to become one of the most effective and largest diagnostic companies in Turkey. ANT Medikal has a proven track record within the environmental monitoring space in the Turkish market, making our Redipor® prepared media range an ideal addition to its offerings. It is a great collaborative opportunity for both Cherwell and ANT Medikal, with some exciting new products to bring to the Turkish market."

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

Pharminox installs fluid transfer ports for Valneva

The Directors of Pharminox Isolation Ltd are delighted to announce the successful completion of a major contract for speciality vaccine company, Valneva, at their new facility, currently under construction in Livingston, Scotland.

The project involved the installation of a series of fluid transfer ports which allow the sterile transfer of bulk liquids from one location to another. The ports use a system originally developed by the nuclear industry for the translocation of extremely hazardous radio-active materials, and more recently adopted by the pharmaceutical industry for the transfer of sterile, pathogenic and cytotoxic substances. The ports were fitted into special stainless-steel windows, designed, and fabricated by Pharminox. Working in co-operation with the building contractors, Bouygues SA, the complete assemblies were installed into the walls of the cleanroom complex, at a number of locations.

Once fitted, the ports were all tested using special single-use transfer containers, the work being witnessed by the Valneva validation department, with appropriate documentation being completed for quality assurance purposes.

A fluid transfer port being prepared for assembly into its special window in the cleanroom wall panel on the right of the picture

Pharminox Isolation Ltd has been associated with Valneva since 2008. The directors of Pharminox are proud to have contributed to this new facility, which was designed to manufacture Valneva's COVID-19 vaccine - the only inactivated, adjuvanted, whole virus COVID-19 vaccine in clinical development in Europe.

For further information please contact Dr Helen Hale on +44 (0) 1954 267359 or e-mail helen@pharminox-isolation.com

Envair Technology opens new facility in Heywood UK

Clean air and containment specialist Envair Technology has opened its new 63,000 ft2 (6,000 m2) facility in Heywood, Lancashire. The move brings the manufacturing teams for group brands Envair and Total Containment Solutions (TCS) together under one roof. This will enable cross-skilling of the teams and more of the production process to be managed in-house to guarantee faster turnaround times and help smooth out peaks in demand.

The investment also brings increased capacity to the group – a 150% increase in fume cupboard production capacity and a 25% increase in rigid isolators, as well as a home for the 42 strong team of production and assembly technicians. New equipment at the site includes a CNC router for Trespa and plastics, laser cutter machines (shown), press brakes, ovens and powder coating spray booths.

After sales service will also benefit, with more parts now available for 24-hour despatch and improved inventory management.

For more information, please visit our new website www.envairtechnology.com

EECO2 identifies energy and cost saving opportunities overlooked in heating systems

There are many ways to decrease the energy expenditure of cleanrooms, from HVAC air change rate reduction to implementing innovative technologies such as dynamic cleanroom control. However, perhaps the least mentioned area for long-term cost and carbon reduction lies with heat generation. Potential projects in this area have often been overlooked due to the hitherto comparatively low cost of natural gas, but such thinking may be short-sighted, with world governments at COP26 and beyond placing a heightened emphasis on ditching fossil fuels in favour of cleaner alternatives. The electrification of heat provision, including the use of heat pumps, is one such opportunity for carbon reduction. Utilising renewable energy to deliver this poses questions of local infrastructure and clean energy availability, but as greener energy becomes increasingly incentivised, the future outlook for renewably generated heat improves.

For more information e-mail info@eeco2.com or visit www.eeco2.com

Particle Measuring Systems (PMS) announces the new PRO Series of Contamination Control Instruments for viable and non-viable, remote and portable monitoring

PMS is pleased to announce the new PRO Series, a portfolio of complete contamination monitoring instruments. These are fully compliant with the most recent global regulations and are positioned for anticipated regulatory requirements. Use together for a total and industry leading solution from a single manufacturer.

The new PRO Series of complete contamination control particle counters includes portable and remote, viable and non-viable instruments with environmental monitoring and data management software; all designed to provide the highest level of environmental control. Added to this is our expert Advisory Services for a total contamination control solution.

"The PRO Series is a collection of benchmark environmental monitoring technology, principles and applications in one product portfolio. Five decades of hard work and dedication by industry-leading engineers at PMS has resulted in multiple flagship product lines and services. It has earned us the ability to directly offer the pharmaceutical manufacturing industry the best contamination control solutions available.", said Frank Panofen, GM Pharmaceutical Division, Particle Measuring Systems. He continued, "We are immensely proud to be a part of the formula that provides the highest quality lifesaving products to the public."

For more information see https://www.pmeasuring.com/industries/new-pro-series-for-complete-contamination-control/

Validair supplies Airborne Particle Counter for study of soil from Mars

Was there life on Mars? Amongst the excitement of space missions to the Red Planet, successful landings and the deployment of the Mars Rover, it's easy to forget that the vital analysis of samples retrieved from the surface will take place here, on our Blue Planet.

In preparation for the return of soil samples, the University of Leicester has designed a new double-walled isolator to provide a super-sterile research and analysis environment, protecting the invaluable Martian material from earthly contaminants. That protection will be constantly monitored by a TSI AeroTrak 9110-01 Airborne Particle Counter supplied by Validair Monitoring Solutions Ltd.

The entire Mars project looks to the future, in more ways than one. With these extra-terrestrial exploration projects spanning many years, planning is crucial. Even though soil samples from the surface of Mars are not expected back on Earth for 10 years, the new isolator, its instruments including the Validair APC, and the research facilities will be ready and validated. Some of the students at the University's Space Park working on project preparations today will be fully qualified research scientists by the time the analysis process begins. At that point, we can expect to be closer to answering the question: was there life on Mars?

Tel: +44 (0)1684 576452
Email: stephen-wake@validair.com
Web: www.validair.com

Mars Rover simulation

Events

2022	Event	Location
January 25-26	S2C2 covers cleanrooms	Coatbridge, Scotland
April 4-8	Achema	Frankfurt, Germany
April 26-27	Making Pharmaceuticals. Exhibition, Conference and Awards	Coventry, UK
May 2-5	IEST ESTECH 2022	Portland, Oregon
May 9-11	r3nordic Symposium & Exhibition 2022	Naantali, Finland
October 11-13	25th International Symposium on Contamination Control, ICCCS'20	Antalya, Turkey
November 14-17	IEST EDUCON	Schaumburg, Illinois

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2022	**Event**	**Location**
January 19	Air Flow Visualization (AKA Smoke Studies) Techniques and Technology	Virtual
January 25-27	ISO 14644 Fundamentals Certificate	Virtual
February 9	Introduction to Cleanroom Operations	Virtual
February 15	Practical Considerations for Implementing a GMP Annex 1 CCS – Cleaning And Disinfection	Virtual
February 22	Basics of Cleanroom Design	Virtual
February 24	Ask the Experts: Mold/Fungal Contamination in Cleanrooms	Virtual
For a complete list of courses, please see https://www.iest.org/Training-Certs/IEST-Contamination-Control-Learning-Path		

CCN (Contamination Control Network) www.theccnetwork.org		
2022	**Event**	**Location**
March 1-4	CTCB-I Cleanroom Testing Course	TBA
April 12-14	CTCB-I Cleanroom Testing Course	TBA

Other training courses including CTCB/I* training courses are provided by:		
BCW	Belgium	www.bcw.be/
ICS	Ireland	www.cleanrooms-ireland.ie/training/
R3Nordic	Nordic Countries	https://r3nordic.org/symposium-exhibition-2022/
VCCN	Netherlands	www.vccn.nl/cursusaanbod
TTD	Turkey	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

Woody Allen quotes

You can live to be a hundred if you give up all the things that make you want to live to be a hundred.

It's not that I'm afraid to die. I just don't want to be there when it happens.

The food here is terrible, and the portions are too small.

It seemed the world was divided into good and bad people. The good ones slept better while the bad ones seemed to enjoy the waking hours much more.

I believe there is something out there watching us. Unfortunately, it's the government.

Money is better than poverty, if only for financial reasons.

My one regret in life is that I am not someone else.

What if everything is an illusion and nothing exists? In that case, I definitely overpaid for my carpet.

BUILDING YOUR CONTAMINATION CONTROL STRATEGY?

WE'RE WITH YOU EVERY STEP OF THE WAY

CC STRATEGY

Take the first step to a compliant CCS

ecolablifesciences.com/CCS

Whether you're in the process of defining, developing or maintaining your CCS, we can work with you to help build a compliant Contamination Control Strategy for cleaning, disinfection and decontamination.

Our team of expert technical consultants can deliver a range of bespoke contamination control solutions including **Klercide**, **Bioquell** and **Validex**, and give you access to the tools and resources you need to implement an effective strategy.

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

ECOLAB®

107901_EU