Clean Air and Containment Review

The journal to enhance your knowledge of cleanroom, contamination control and containment technology

Issue 36 | Autumn 2018 ISSN 2042-3268

Statistical treatment of sampling in ISO 14644-1:2015

H_2O_2 surface sterilization: a robust process

Cleanroom monitoring and data integrity

Risk Assessment

E-learning module: Annex 1 disinfection requirements

ISCC'18 and Cleanzone reports

EUROMED communications

Picture: ENVAIR Rapid Gassing Isolators for the aseptic preparation of medicines

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.

Contents

Main features 4

The statistical treatment of sampling in ISO 14644-1:2015: comments on a recent article 4
Niels Væver Hartvig

H_2O_2 surface sterilization: a definitely robust process for routine use in isolators 6
Didier Meyer

Cleanroom routine environmental monitoring – FDA Guidance on 21CFR part 11 Data Integrity 10
Tony Harrison

Creating, implementing and maintaining a monitoring plan based on Risk Assessment 14
Hasim Solmaz

Standards 18

Assessment of cleanroom suitability of equipment and materials by chemical concentration – ISO standard now available for designers, suppliers, and users 18
Berthold Düthorn

Learning 20

E-learning module from Pharmig supports Annex 1 disinfection requirements 20
Tim Sandle

Conference report 24

International Symposium on Contamination Control 2018 – ISCC'18 "The world behind contamination control" 24
Koos Agricola

Exhibition report 26

Mission accomplished: Cleanzone 2018 draws more international visitors to Frankfurt 26
Based on a press release from Cleanzone

News 28

Cherwell publishes guide on EM programs for revised EU GMP Annex 1 28
EECO2 Launches in-house research into cleanroom performance 28
CRC has designs on Wales 28
Biopharma Group launches a new era for Faster air safety cabinets in the UK 29
Envair Limited sells Envair Lab to Biopharma Group 29
Pharma Clean Tech 2019, SNIEC Shanghai, June 18–20, 2019 29

Life-lines 29

Events and Training courses 30

EUROMED communications
Passfield Business Centre, Passfield
Liphook Hampshire, GU30 7SB
T: +44 (0)1428 752222
F: +44 (0)1428 752223
e: publisher@euromedcommunications.com
www.euromedcommunications.com

Editorial

Welcome to CACR 36. This issue includes responses to two articles in CACR 35. On page 4, Niels Væver Hartvig explains the statistical treatment in ISO 14644-1:2015 in response to the article by Alexander Fedotov in CACR 35. On page 6, Didier Meyer asserts that H_2O_2 surface sterilization is a robust process. This is in response to the well-publicised blog of Andrew Hopkins, also reproduced in CACR 35, which warns that it is fragile. I am very happy that CACR is able to represent different points of view. Standards and regulations need to be applied with common sense and understanding; the greatest dangers arise if they are applied blindly. More than once, I have heard regulators say that they will listen to a reasoned justification for deviations from recommended practices as much as they will look for evidence of 100% compliance.

The next main feature on page 10 is a white paper of Beckman Coulter Inc. written by Tony Harrison, about the application of 21CFR part 11 and improvements in data integrity when carrying out environmental monitoring using particle counters. The final main feature, starting on page 14 is a paper from Hasim Solmaz on risk assessment based on his presentation at ISCC'18.

Supporting the ISO standardisation programme, we have an article by Berthold Düthorn on page 18. This is the first of what is intended to be a series of ISO 'outreach' documents, to explain the various parts of ISO 14644, in this case ISO 14644-15:2017, the part that specifies the assessment of the suitability of equipment and materials with respect to airborne chemical concentration.

One of the key requirements of the draft EU GMP Annex 1 is training of technicians and operators. In his article on page 20 Tim Sandle describes the e-learning module on cleaning and disinfection developed by Pharmig, the non-profit-making professional organisation that represents the interests of individuals who work with, have responsibility for, or work alongside microbiology within Pharmaceutical, Healthcare, Cosmetics and NHS Industries.

Finally, there are reports on ISCC'18, the biennial symposium of the ICCCS and on Cleanzone, the major European cleanroom event.

This issue completes my ninth year as editor of CACR. When I started, I saw it as an opportunity to publicise some of my own hobby-horses and to use the knowledge of experts to educate people generally in the technology. Now, it is truly international and the material for it seems to grow and grow. I hope that it continues to satisfy the needs that I identified all those years ago for a long time to come. That, of course depends in part on you, the reader, continuing to feed me with interesting ideas and topics, and continuing to challenge some of the thinking in our technology.

I hope you enjoy CACR 36.

John Neiger

Words of wisdom

"The soul and spirit of education is that habit of mind which remains when a student has completely forgotten everything he has ever been told."

Professor Charles Inglis, Head of Engineering at Cambridge University 1919-1943

Quoted from *Cambridge Engineering, The First 150 Years* by Haroon Ahmed, Third Millennium Publishing, 2018

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Clean Air and Containment Review

Issue 36 | Autumn 2018
ISSN 2042-3268

Published by:
E C Pharma
Passfield Business Centre,
Lynchborough Road,
Passfield, Liphook, Hampshire
GU30 7SB, UK
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

The statistical treatment of sampling in ISO 14644-1:2015: comments on a recent article

Niels Væver Hartvig

Abstract

This article presents a response to the critique of the statistical principles in ISO14644-1:2015 raised in a recent paper by Dr Alexander Fedotov in the July/August issue of Clean Air and Containment Review. A distinction between the sampling uncertainty and the concentration variation is made and the assumptions in the ISO-standard of these two sources of uncertainty is discussed.

Comments

In the paper *Getting rid of 95% UCL calculations in ISO 14644-1:2015 standard: new weaknesses and possible solutions*,[1] Alexander Fedotov discusses the statistical principles of the sampling plan and acceptance criteria in ISO14644-1:2015.[2] As a statistician and one of the authors of *Sampling Plan for Cleanroom Classification with Respect to Airborne Particles*,[3] I would like to respond to the critique raised.

The sampling plan and the acceptance criteria in ISO 14644-1:2015 are the result of the *statistical method* applied and of the desired *quality level*. Though both will affect the final test procedure, from a conceptual level the two are different questions and need to be distinguished. I will only discuss the critique of the statistical principles that Dr Fedotov raises, and not the choice of the quality level; the latter includes for instance a change in the concentration limits and is for the ISO working group to reach consensus on.

Dr Fedotov states that the selection of a distributional model is critical and must have a scientific rationale. I of course completely agree with that. The important distinction here is the two sources of randomness that may be described by probabilistic methods:

1. the *sampling variation*, i.e. the uncertainty induced by selecting a finite number of sample locations in the room;
2. the *concentration variation*, i.e. the uncertainty induced by variation in the particle concentration across positions the room or over time at the same position.

> *"a more pragmatic wording of representative sampling is given in the standard, leaving some room for interpretation on how to conduct this."*

The sampling variation primarily depends on the structure of the room and on the selection of sample locations. The important new principle in ISO 14644-1:2015 is that sample locations must be drawn *representatively*, which allows for an evaluation of the sampling uncertainty by statistical techniques. This was not possible with the old version of the standard, where the sampling uncertainty was not explicitly accounted for.

The hypergeometric distribution arises automatically when samples are drawn randomly, and when the room is conceptually modelled as a collection of unit areas. The justification of the hypergeometric distribution in this context is a fundamental result of sampling theory, and it is explained in detail in *Sampling Plan for Cleanroom Classification with Respect to Airborne Particles*.[3] While the hypergeometric distribution arises naturally as a result of the sampling, a relevant discussion is whether it is reasonable to consider a cleanroom as a collection of independent unit areas. Firstly, the unit area is 2 m^2 for rooms below 12 m^2 and 4 m^2 for rooms above, and not 10.5 m^2 as Dr Fedotov claims. Following his example, when a room of 232 m^2 is qualified based on 22 samples, it is because 22 x 4 = 88 m^2 have been measured, and by the random sampling of the room this provides 95% confidence that at least 90% of the room complies. The claim that the method assumes a region of 10.5 m^2 to be homogeneous is simply incorrect.

One could choose the unit areas to be smaller. This would make the assumption of homogeneity more reasonable, and would result in more sample locations for small rooms. However, it would make it *less* reasonable to assume that areas are independent of each other. If areas are not independent, a simple random sampling methodology cannot be applied, and one would have to move to for instance stratified sampling, which requires more specific knowledge of the room. The current choice of unit areas of 2-4 m^2 was an attempt to strike a reasonable balance between the homogeneity and independence assumption in general, and with a view to the sample sizes in the 1999-version of the standard.

Inarguably specific knowledge of the room would be useful in the qualification, and smoke studies of air flow in the room would be one way to obtain a more informed selection of sampling positions. The question for the ISO working group to consider is the role that such studies should have in an international standard that must be applied world-wide and in different industries. The power of statistical sampling, however, is that it ensures valid inference can be made, even when one does not have this detailed knowledge of the room under study.

From the sample size calculation point of view, sample positions should ideally be chosen completely randomly. In order to adapt this to the reality of cleanroom classification, a more pragmatic wording of *representative* sampling is given in the standard, leaving some room for interpretation on how to conduct this.

Regarding the second source of uncertainty – particle concentration variation – it is important to remember that the current standard *does not* prescribe a model for this, it merely

considers a classification of whether the concentration is above or below the limit.

The old version of the standard implicitly assumed a stationary normal distribution across the entire room for rooms with less than 9 samples (by the UCL criterion) – which somewhat unexpectedly could cause a failure when the concentration was unusually low in some parts of the room, but acceptable in all others. The assumption of a common distribution across the room is avoided in the current version of the standard, exactly for the reasons that Dr Fedotov describes. Based on experience with the old standard, the assumption of a common distribution across the room did not seem reasonable, and it was considered more scientific to avoid any assumptions on this.

The statistical method underlying ISO 14644-1:2015 is without doubt a pragmatic simplification of the complexity of cleanroom dynamics, but it does provide a risk based interpretation of the classification, which the 1999-standard did not. As discussed in detail in *Sampling Plan for Cleanroom Classification with Respect to Airborne Particles*[3] the principles and assumptions are quite different in the two versions, which is the reason why the sample size tables do not match in a simple way.

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Niels Væver Hartvig is Principal Specialist in Statistics, Novo Nordisk A/S, Denmark. Niels has 17 years of experience as a non-clinical statistician in the pharmaceutical industry. He holds a PhD in mathematical statistics from the Univerisity of Aarhus in Denmark. He contributed to the update of the ISO14644-1:2015 as a statistician representing Novo Nordisk A/S. Contact: nvha@novonordisk.com

H_2O_2 surface sterilization: a definitely robust process for routine use in isolators

Didier Meyer

"Life is really simple, but men insist on making it complicated" (Confucius)

Abstract

Hydrogen peroxide vapor has been in use as a surface sterilizing agent for isolators since the beginning of the nineties. The robustness and validation of its use has been reported in numerous scientific and practical physical, chemical and microbiological studies. This article shares the reports of scientists, end-users, regulators and suppliers in its successful use.

Introduction

A sterile dosage form is *"A product introduced in a manner that circumvents the body's most protective barriers, the skin and mucous membranes, and, therefore, must be 'essentially free' of biological contamination."*[1]

I also refer to the current Good Manufacturing Practice cGMP[2]

"There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization."

"In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together. Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment. Aseptic processing involves more variables than terminal sterilization. Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. For example, glass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration. Each of these manufacturing processes requires validation and control. Each process could introduce an error that ultimately could lead to the distribution of a contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the possibility of error."

To avoid the risk of contamination by the 'possibility of error', the surroundings of the aseptic process are 'controlled areas' and 'cleanrooms' to separate the process from the potentially contaminated people and environment.

PDA Technical Report N° 34[3] comes up with an 'isolation continuum' which shows that the highest sterility assurance regarding the surroundings is reached with the use of isolators. It gives this definition of isolators: *"An isolator is sealed or is supplied with air through a microbiologically retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed, it uses only decontaminated (where necessary) interfaces or Rapid Transfer Ports (RTPs) for materials transfer. When open, it allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination. It can be used for aseptic activities, for containment of potent compounds or simultaneously for both asepsis and containment".*

How to achieve 'reproducibly decontaminated' in an aseptic process isolator

Isaacson's presentation[4] mentioned hydrogen peroxide vapor among the gasses and fumigants within the other sterilization process to be used with the following cautions:

- Must demonstrate that process does not adversely affect product;
- Ensure product load is adequately heated and humidified prior to sterilization (called "conditioning")
- Need to take into account validation performed in summer or winter.

The hydrogen peroxide vapor mechanism as a sterilizing agent is described by Block who gives figures of its performances as a germicidal and sporicidal agent.[5]

Another peroxygen compound, peracetic acid, with the same mode of action i.e. liberation of nascent oxygen, has been used since the late 40s for the sterilization of isolators for the breeding of germ free rodents.[6] The germ free rodents need sterile food, water and bedding and have to stay in sterile isolators sometimes for more than one year. The improvements in animal isolators and associated equipment[7] have brought to the pharmaceutical industry a relevant and easy to use isolator technology.[8]

Although inexpensive, peracetic acid has two disadvantages for routine use on bio-pharmaceutical isolators: corrosion and unreliable measurement of its concentration. Since the beginning of the 90s, hydrogen peroxide which is reliably measurable and has a much reduced risk of corrosion has been widely used. Vapor Phase Hydrogen Peroxide (VPHP), Micro-Condensed Hydrogen Peroxide (MCHP), dry fog process and other H_2O_2 sterilization methods have been used for sterilizing isolators, usually now described as 'biodecontamination'. This sterilization process must be at room temperature and able to sterilize both surface and atmosphere, be reproducible, measurable and without any risk of corrosion.

The protocol of hydrogen peroxide sterilization must take into account the WHO recommendations:[4]

- Temperature distribution must be within defined limits;

- Concentration of sterilant gas must be sufficient;
- Use of Biological Indicators (BIs) is important;
- Half cycle tests should be carried out (if cycle of half normal time destroys biological indicators (10^6 organisms), double time will achieve SAL of 10^{-6});
- Aeration should include consideration of ventilated conditions, defined limits of residuals, processes to be included in validation;
- Safety and toxicity issues should be considered.

Each installation has its own equilibrium between surface micro-condensation and airborne effect considering the surroundings and the aseptic process equipment. As the bioburden to be killed (including vegetative spores) of a defined isolator (surfaces + atmosphere) is not constant, spores are used to validate the sterilization process. Resistant spores constitute a worst case scenario at a concentration of 10^6.

Can hydrogen peroxide vapor be considered as a sterilizing process as it's only a surface sterilization method and not a core sterilizing method like a moist heat process?

The pharmaceutical industry needs traceability and reproducibility. If we consider the of an isolator for an aseptic process, the surroundings are the first important criteria to take in account. Isolators have to be located in at least an EU GMP class D environment with control of temperature, relative humidity (RH) and a limited number of gowned operators. Temperature and RH are important factors for keeping the reproducibility of the equilibrated hydrogen peroxide vapor process,[9] especially due to the fact that generally there are important cold stainless steel surfaces to sterilize; too cold and the micro-condensation could become full condensation with small puddles attracting the incoming hydrogen peroxide vapor, breaking the equilibrium and so decreasing the sterilizing effect.

The micro condensation process on a surface has been described in detail by Coles[10] as "Micro-Condensed Hydrogen Peroxide" (MCHP) which is more widely named in the industry as Vapor Phase Hydrogen Peroxide (VPHP) or VHP.[8]

"Given the length of time that the process has been in use… we can consider that the routinely found results of the H_2O_2 surface sterilization of filling lines in isolators for aseptic processing demonstrate a robust and reproducible process"

The H_2O_2 resistant spores used are *Geobacillus Stearothermophillus* (American Tissue Culture Collection – ATCC 7953 or 12980) which incubate at 55°C avoiding false positives from other species. The concentration used is 106 and the time for the Spore Log Reduction (SLR) is either doubled to reach a Sterility Assurance Level (SAL) of 10^6 [4] or is completed with the addition of 2 logs of D value.

These spores are laid on a carrier and then the carrier is wrapped in a leak-tight Tyvek® packaging to become a Biological Indicator (BI). For a surface sterilization process, the spores on their support must be monolayer. Details for manufacturing these BIs are in PDA TR 51.[12] Improperly manufactured BIs are called 'rogue' BIs. False positives from using rogue BIs necessitate a repeat validation so extending the time spent validating the sterilization of the isolator. The BIs must be placed at the key locations of the key steps of the process.

Prior to its sterilization, the isolator must be cleaned and dried. This operation must also follow a strict protocol with operators gowned for EU GMP Grade B and with ISO 5 conditions in the open isolator.

Factors for consideration for control of sterility assurance

In addition to the surrounding conditions the protocol must take into account:

- the concentration of the chosen ultra-pure liquid H_2O_2 (35 or 50 %),
- the time cycles of the process, the reached H_2O_2 airborne concentration,
- the total consumption of H_2O_2
- the measurement of the traces of H_2O_2 outside of the isolator regarding the safety of the operators.

All these physical and chemical values have to be the same as those found during the validation. Where BIs are used, the results are only available after an incubation time of 5 to 14 days. With the recent introduction of the Enzyme Indicators (EIs)[13] it will only take a few minutes for the analysis at the end of the sterilization process to validate it. The expected result will reinforce the assurance of quality before production starts.

The H_2O_2 surface micro-condensation process is controlled through a secondary effect of airborne vapor concentration.[9] The excess of vapor concentration during the plateau phase is maintained or slowly decreased before the aeration phase.[9] All the surfaces have been reached by H_2O_2 either by means of micro-condensation or by H_2O_2 vapor. During the aeration phase, the peak H_2O_2 concentration results from evaporation from the micro-condensation on surfaces.[9]

"With the recent introduction of the Enzyme Indicators (EIs) it will only take few minutes for the analysis at the end of the sterilization process to validate it."

Can we consider the above mentioned H_2O_2 process as safe and robust regarding stopper hopper sterilization bearing in mind the recent exchanges between Hopkins' blog[14] and the European Journal of Parenteral & Pharmaceutical Sciences editorial?[15]

Given the length of time that the process has been in use, even in complex conditions (some stopper distribution systems look like rail yards!!!) and considering the improvements and simplifications made on fillers, isolators and H_2O_2 sterilizers during the last 20 years[16, 17] we can consider that the routinely found results of the H_2O_2 surface sterilization of filling lines in isolators for aseptic processing demonstrate a robust and reproducible process.

The present and future use of robotic

arms in gloveless isolators requires EU GMP Grade B gowned operators to replenish the stopper hopper among other items without any packaging (risk of particles) and to clean it before closing the ISO 5 ventilated isolator prior to its successful H_2O_2 surface sterilization.

To conclude this article, I would like to emphasise the simplicity and efficiency of the H_2O_2 surface sterilization process, which brings a unique quality to drugs that are aseptically processed in isolators compared with those produced in A/B cleanrooms or RABS environments.

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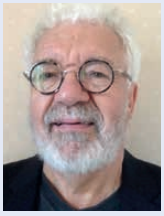

Didier Meyer worked with Millipore in separation technology and started and developed the use of isolators in pharmaceutical production and control within La Calhène, now Getinge. He is currently consultant at DMCompliance specialising in aseptic production and operator protection in the bio-pharmaceutical fields. Didier was educated in Biochemistry and has contributed to scientific and technical work for the development of isolation technology within the bio-pharmaceutical industry including for ISO and PDA. He is also an active member of A3P, ISPE and PHSS.

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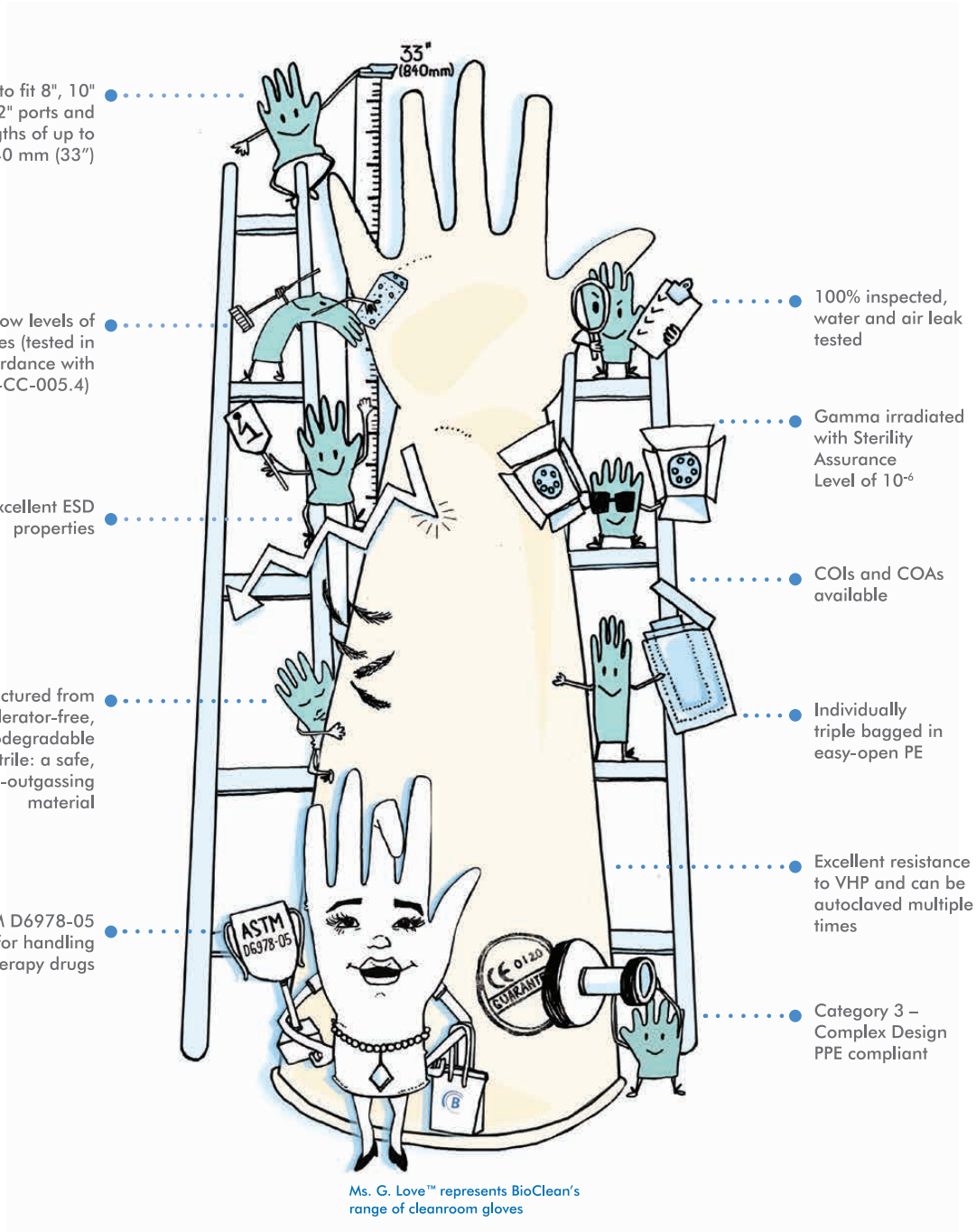

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Cleanroom routine environmental monitoring – FDA Guidance on 21CFR part 11 Data Integrity

Tony Harrison

Abstract

A recent report suggests that circa 79% of 483 warning letters issued by the FDA to the biopharmaceutical industry sited deficiencies in their data integrity.[1] Despite guidance from the FDA, cleanroom environmental monitoring remains an intensely manual process, with many opportunities for human error to create gaps and errors in the data. In their 21CFR part 11 guidance, the FDA have given recommendations on what good data integrity looks like and this article explains their advice in the context of current cleanroom environmental practices and shows how the FDA guidance can be applied to improve data integrity.

"In larger biopharmaceutical manufacturing plants, there can be teams of 10 technicians or more whose job it is every month to take thousands of routine environmental monitoring samples."

Cleanroom Routine Environmental Monitoring

Of course the FDA mandates the air quality conditions for bio/pharmaceutical production in cleanrooms. In fact the real danger is the microbes on the human body. Humans shed around 30,000 skin cells per hour,[2] all of which are potential carriers of microbes. Unfortunately we do not currently have technology to detect and identify the species of airborne microbes real-time. So air particle counters are used as a surrogate.

Discussions between the author and Environmental Monitoring Managers at facilities across the world highlights an increasing trend where the burden of carrying out environmental monitoring is moving away from the QC microbiology team over to the production staff, for two reasons:

"the correct way forward is to reduce manual steps in the SOP in order to reduce the human errors and make the whole process more robust."

1. microbiology staff are relatively expensive to employ to carry out such routine tasks;
2. to reduce the number of people inside the cleanrooms, thus reducing the potential for product contamination.

However, the production team do not have the same level of knowledge about routine environmental monitoring and this is creating challenges itself.

- 30 to 50 trillion microbes on and inside the human body
- Humans shed 30,000 skin cells per hour, approximately 3.6 kilos/year

Figure 1: Human skin and microbes

- Increasing regulator burden
- Responsibility passing from QC to production team
- 1,000s of data points/month

Figure 2: Risks to environmental monitoring data integrity

In larger biopharmaceutical manufacturing plants, there can be teams of 10 technicians or more whose job it is every month to take thousands of routine environmental monitoring samples. At each location, they have to manually type the location name into the counter before they start sampling. Counters have to be manually configured following written SOPs. At the end of each day, the paper print-outs from each sample location have to be photocopied because the printers in the particle counters are thermal and the print-outs fade over time. Then the results from every location have to be manually transferred into electronic format one by one.

Following environmental data errors, a typical response is to mandate re-training for the team. However, the industry and the FDA are gradually coming to the conclusion that this does not solve the problem, it merely treats the symptoms for a short while until human error starts to creep in again. The correct way forward is to reduce manual steps in the SOP in order to reduce the human errors and make the whole process more robust.

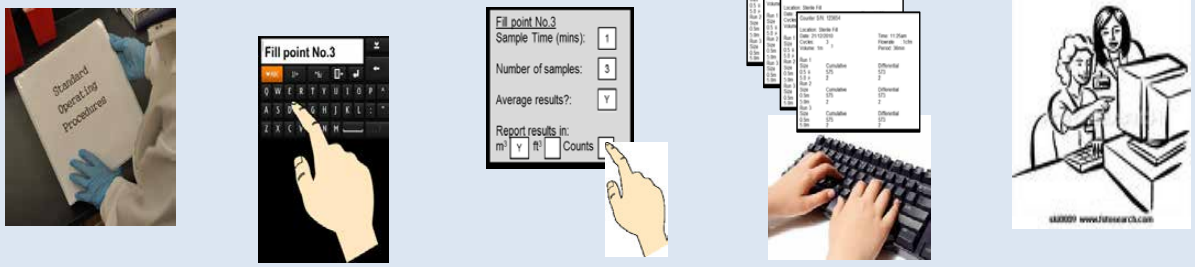
FDA Guidance on Data Integrity

In their guidance on the implementation of their 21CFR part 11 data integrity rule,[3] the FDA use the acronym ALCOA, where they define good data integrity practice as creating records that are Attributable to the technician carrying out the testing, Legible, created Contemporaneously, Original and Accurate.

In this case Attributable means that the records should somehow be traceable to the technician who did the test. They should also include a label stating where the sample was taken and the date and time it was taken.

The record of course is required to be legible, which implies that hand-written records are not acceptable. The FDA goes on to suggest that electronic records should be stored in a format that is open and can be read on many computing formats so that it will be accessible and readable for years to come. The FDA recommends typical formats such as PDF, XML or SGML.[3]

In this instance the word contemporaneously implies that the electronic records should be created immediately the sample is measured,



Touch-Point 1:
- Ensure correct SOP
- Read and understand SOP

Touch-Point 2: Manually type each and every sample location name

Touch-Point 3: Manually configure counter:
- Sample time
- Number of samples
- Results averaging
- Correct multiplier for m^3

Touch-Point 4:
- Collate and organise print-outs
- Manually transcribe results into electronic form

Touch-Point 5: Review and approve results

Figure 3: Manual Routine Environmental Monitoring SOPs

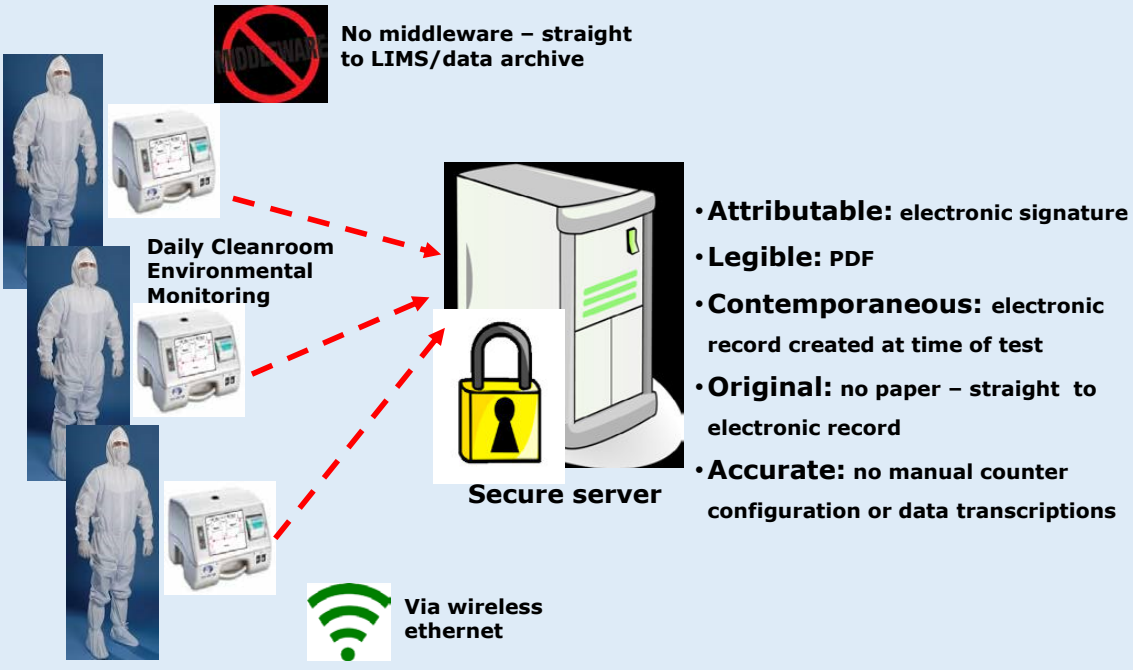


Figure 4: Particle counters with automated routine environmental monitoring SOPs, such as the Beckman Coulter Met One, help with data integrity – diagram courtesy of Beckman Coulter

implying that manual transcription of paper records is not good practice and that collating paper records and then manually transcribing them into electronic format at a later time/date is not good practice.

Naturally the electronic records should be accurate. This implies that the process for capturing those electronic records should be robust, implying manual calculations and manual data entry where opportunities for human error exist should be avoided.

Now let's take a look at current environmental practices in the light of the FDA ALCOA guidance. There are

many manual steps in the typical environmental process and usually the paper record does not contain an electronic signature, so it is not attributable to the technician. Sample locations are manually typed in for each location, inviting human error and miss-typing, preventing the sample being easily attributed to the sample location. Usually the final electronic record is legible, but it certainly is not created in a contemporaneous manner, instead the original paper record is created by a thermal printer and fades over time, so the final record is not the original and, as it is manually created, the final record cannot be guaranteed to be accurate.

Fortunately more up to date solutions exist that are more compliant. Such air particle counters have the sampling SOP and locations pre-programmed and automated to remove the manual sample location entry and counter configuration steps. Instead of producing paper records that have to be manually transcribed at a later stage, the counter instantly generates an electronic record that contains the user's electronic signature and the sample location name. This electronic record is in one of the recommended formats from the FDA, PDF, and can be transmitted via wired or wireless Ethernet to a secure server where the user keeps the final records. This removes all manual configuration steps, manual location typing and manual data transcription, thus reducing the opportunities for human error and improving data integrity.

Conclusion

In many cases, cleanroom routine environmental monitoring programs still carry a high risk of human error with SOPs being implemented manually and thousands of data records being manually transcribed into electronic format. No matter how often staff are trained, the opportunity for error is such programs remains very real, with the associated implications for data integrity. The technology exists and is commercially available to mitigate this problem and make these programs more robust, reducing the impact on data integrity and also supporting the industry's move towards environmental monitoring by production staff in the cleanroom.

"Instead of producing paper records that have to be manually transcribed at a later stage, the counter instantly generates an electronic record that contains the user's electronic signature and the sample location name."

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Tony Harrison held the Convenorship of the ISO Working Group revising ISO 14698-1 & -2 for microbial control in cleanrooms and was the UK subject matter expert to the ISO Working Group who issued the 2015 revised versions of the ISO 14644-1 and -2 documents for cleanroom classification at the heart of the aseptic manufacturing chapters of both the European GMP and the USA cGMP documents. Tony holds a Bachelor's Degree in Electrical and Electronic Engineering and is employed by Beckman Coulter Life Sciences as a Senior Marketing Manager.

Experienced in water system TOC, conductivity and ozone analysis and cleanroom environmental monitoring as well as particle characterisation, Tony has spent the last fifteen years in applied metrology for the pharmaceutical and healthcare manufacturing industries. Prior to that, he worked for companies providing process control automation solutions for manufacturing industries. Tony was joint-editor on the ISPE Guide to Ozone Sanitization of Pharmaceutical Water Systems and was also chief editor of the PHSS Best Practice Guide for Cleanroom Monitoring.

Tony is a well-known international speaker and has provided educational seminars on TOC, liquid particle counting, ozone sanitization for water systems and cleanroom monitoring in UK, France, Italy, India, Malaysia, China, USA, Scandinavia, Ireland, Hungary, Switzerland, Indonesia, Belgium, Greece, Switzerland, Turkey, Egypt, Denmark, Poland, Italy and most recently South Africa and Columbia.

Creating, implementing and maintaining a monitoring plan based on Risk Assessment

Hasim Solmaz

Abstract

Clean areas used for aseptic manufacturing of sterile medicinal products are subject to standards and guidelines to ensure quality of production and to minimize risks of particulate and microbiological contamination. In recent years, a proper monitoring plan with a risk-based approach has become a part of many standards and regulations such as ISO 14644-2:2015 and ICH Harmonized Guideline ICHQ9 Quality Risk Management. However it is also obvious that there is a lack of good application practices for proper monitoring plans that are based on risk assessment. This study provides information with an example of how to prepare a risk based monitoring plan incorporating risk assessment tools, current standards, regulations and guidelines.

Cleanroom monitoring

Cleanroom non-viable airborne particle monitoring is essential. Particles are significant because they can enter a product as an extraneous contaminant, and can also contaminate it biologically by acting as a vehicle for microorganisms. There are different particle monitoring systems with remote locations such as manifold systems and online monitoring systems. For manifold systems, the particle counter should be connected to the manifold unit which changes sampling locations at defined intervals such as per minute. Between each sample, there is a buffer time which allows the sampling pathway in the manifold and the particle counter to clean.

Thus sequential sampling manifold systems are not suitable for sterile pharmaceutical monitoring since monitoring should cover every sample location continuously without delay or interruption. However, unlike manifold systems, online particle monitoring systems have independent particle counters with isokinetic sampling probes in every critical location and particle monitoring can be undertaken for the full duration of critical processing, including equipment assembly, in every selected monitoring location without delay or interruption.

How to select locations for monitoring

For cleanroom classification, the minimum number of single sample locations is defined based on the table in the standard (ISO 14644-1:2015). The cleanroom should be divided into similar sized zones and the sampling locations should be selected to represent the characteristics of each zone.

By contrast, for cleanroom monitoring, sample locations should be selected based on a formal risk assessment. Each representative location should be defined and verified based on historical data, trends and production routines. These representative locations are normally not more than 30cms away from the work area and within the airflow. The FDA Aseptic processing guideline recommends that measurements to confirm air cleanliness in critical areas be taken at sites where there is most potential risk to the exposed sterilized product, the containers, and the closures. The particle counting probe should be placed in an orientation that has been demonstrated to provide a meaningful sample. Regular monitoring should be performed during each production shift. Non-viable particle monitoring should be conducted with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters.

For the selection of locations to be sampled, the main considerations are:

- Location(s) should be based on the risk in the activity,
- Microbial contamination affects risks in product quality,
- Potential microbiological growth areas during production,
- Product flow considerations,
- Personnel flow considerations,
- Locations based on nature of process (wet areas, transfers, personnel intervention points etc.),
- All locations where there is a possibility of operator intervention, for example access points to the Grade A environment,
- Original room classification studies, qualification studies and the rationales for previously used sampling/monitoring arrangements,
- Areas where there are normally no interventions, but sterile components/products are still potentially exposed to airborne particulate contamination due to abnormal interventions or for other reasons,
- The length of time that sterile components and/or products are exposed during processing: An example might be stoppers in a feed hopper. In this instance, there is little risk of intervention. However, the stoppers may well be sitting exposed in the hopper for some time, so that there is a potential for build-up of particulate contamination over time. It would therefore be good practice to sample air at this location to demonstrate continued compliance of the air quality being delivered to the components during the processing time.

Critical areas to be considered are:

- The point of fill
- Component hoppers
- Inspection hatches
- Descrambler tables
- Stopper and capping stations
- Loading of Freeze Driers
- Unloading of sterile components which are not protected by autoclave bags
- Interfaces between equipment and the Grade A area
- Isolator transfer devices
- Aseptic manipulations
- Operator interventions

Table 1: Classification and monitoring

	Classification	Monitoring
Standard or regulation	**ISO 14644-1:2015**	EU GMP Annex 1/PIC's, WHO, ISO14644-2:2015
Period	Periodic classification testing shall be undertaken **annually** in accordance with ISO 14644-1. This frequency can be extended based on risk assessment.	**Online/continuous** *Should be undertaken for the **full duration of critical processing**, including equipment assembly*
Number of sampling points and their locations	**Based on ISO 14644-1:2015 Table A.1** Derive the minimum number of sampling points, N_L, from Table A.1. Select within each section a sampling location considered to be representative of the characteristics of that section.	Based on **formal risk assesment** (ICH-Q9) There is no magical calculation. Focus on locations where the product is open such as turn table, filling location, stoppering, lyophilizer loading etc. Use risk tools listed in ISO 14644-2:2015 to define risk level.
Sample duration	**Sample duration(min)= V_s/Particle Counter Flow Rate** If result is less than 1 minute then the minimum should be 1 minute at each location, *The volume sampled at each location shall be at least 2 litres, with a minimum sampling time of 1 min for each sample at each location.*	**Online/continuous** *Should be undertaken for the **full duration of critical processing**, including equipment assembly*
Sample volume	**ISO 14544-1:2015** $V_s = \left\{\frac{20}{C_{n,m}}\right\} \times 1000$ Where: V_s is the minimum single sample volume per location expressed in litres $C_{n,m}$ is the class limit (number of particles per cubic metre) for the largest considered particle size specified for the relevant class ***20*** is the number of particles that could be counted if the particle concentration were at the class limit	**Best option to get fast action** *The sample sizes taken for monitoring purposes using automated systems will usually be a **function of the sampling rate of the system used**. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.*
Risk assessment method	**Cleanroom classification report**	**Alarm interface** *all interventions, transient events and any system deterioration are captured, and alarms triggered if alert limits are exceeded.*

Difference between classification and monitoring

Even though both classification and monitoring target airborne particle counts, there are different parameters such as regulations, sampling intervals, location selection etc. Table 1 can help users to identify these differences.

Risk assessment method

Probability (likelihood)

An estimation of the probability of the risk occurring classified as:

- **Low:** The risk occurs once per year.
- **Medium:** The risk occurs once per month.
- **High:** The risk occurs once per week.

Severity (impact)

An estimation of how serious the consequence is if the risk occurs:

- **Low:** Minor consequence and the effect declines fast.
- **Medium:** Moderate consequence, the effect is short to medium.
- **High:** Serious consequences with long term effect and potential catastrophic effect in the short term.

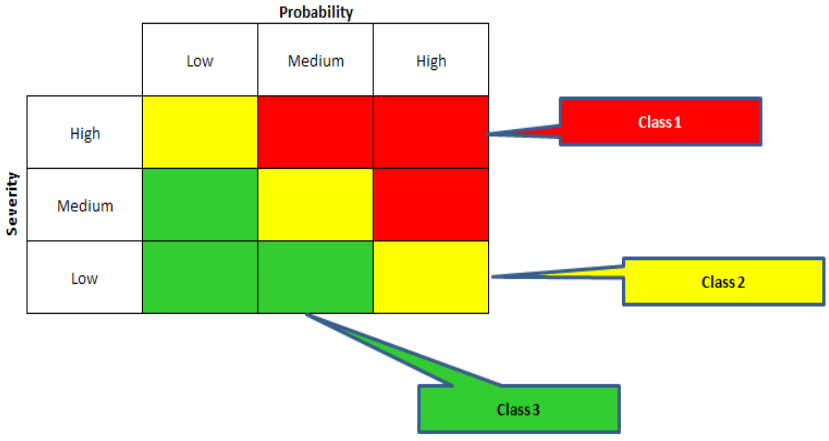


Figure 1: Risk class

Risk class
A combined estimation of the severity (impact) and probability (likelihood) enables the risk to be classified (see Figure 1):

Detectibility
An estimation of the probability for a risk scenario to be discovered:

- **Low:** Low or less than one in three occurrences.
- **Medium:** Medium or about one in two occurrences.
- **High:** Likely to be discovered at every occurrence.

Priority
Prioritizing the risk scenarios allows better judgement of what measures are needed (see Figure 2):

- **Priority 1:** High priority means that the risk is high and that extended testing or possible system change should be carried out to minimize the risk.
- **Priority 2:** Medium priority means that testing at installation is recommended as well as the need for routine testing.
- **Priority 3:** Low priority means that some installation testing is recommended but routine testing is normally not necessary.

Risk assessment example:

In the RABS sterile filling line for lyophilized products shown in Figure 3, there are over 100 potential locations for a non-viable sampling isoprobe. However, considering product work flow, invasion points, operator interventions, the highest risk locations are considered to be:

1. **Tunnel exit:** All vials are open to ambient air under unidirectional airflow,
2. **Point of fill:** Area where the moving vials are filled with medicine by moving needles. Please note, probe locations are selected so as not to interfere with operator activities (e.g. gloved operations) and within 30 cm of needle movement area.
3. **Stopper insertion:** Where vials stoppers are inserted to vials. In the example, stoppers are not fully closed due to the lyophilization process
4. **Point of exit:** Exit point from filling where the semi-closed vials are transferred to the lyophilizer

In this example, location 1, the tunnel exit, is considered.

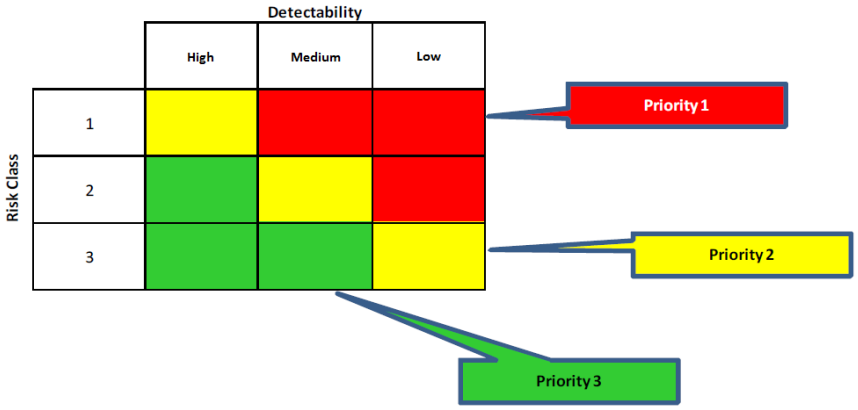


Figure 2: Priority

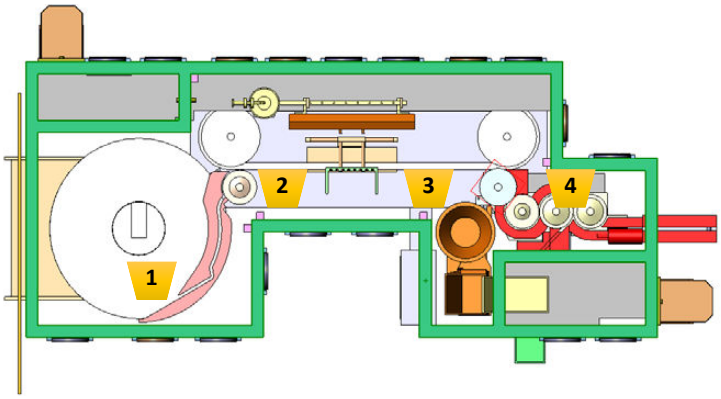
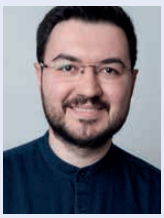


Figure 3: Sterile filling line for for lyophised products

Before installing a non-viable particle montioring system to this RABS, a pre-risk study showed that the risk of particle contamination at location 1 was judged to be 'high probability' and 'high severity' and therefore a 'Class 1' risk (see Figure 1). The 'detectability' at that point was judged to be 'low' and the risk was therefore Priority 1(see Figure 2).

After installation of the non-viable particle monitoring system, the post-risk assessment showed that the risk of particle contamination at location 1 remained 'high probability' and 'high severity' and therefore a 'Class 1' risk (see Figure 1). In other words it was not possible to reduce the likelyhood of particles at that point. However, because the detectability increased to 'high' with the installation of the online non-viable particle monitoring system, the risk could be reduced to Priority 2 (medium).

The same methodology was applied to the other locations. Suitable forms are of course always used to document the pre-risk and post-risk studies in each location



Hasim Solmaz is General Manager of Lighthouse Worldwide Solutions EMEA Operations located in Istanbul, Turkey. Hasim's focus is on cleanroom design and management concepts, environmental monitoring systems, pharmaceutical manufacturing and regulatory concerns. Hasim is a founding chair of Cleanroom Technologies Society of Turkey (TTD), head of delegation to ISO TC209 – Cleanrooms and associated controlled environments – and technical expert to ISO TC209 WG3 – Test methods. He was recently appointed as honorary chair of the International Confederation of Contamination Control Societies, ICCCS.

Hasim is an active member of ISPE, IEST and PDA and holds a Bachelor of Science degree with high honors in Atmospheric Science and Meteorological Engineering from Istanbul Technical University.

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Assessment of cleanroom suitability of equipment and materials by chemical concentration – ISO standard now available for designers, suppliers, and users

Berthold Düthorn

Abstract

Within the International Organization for Standardization (ISO), Technical Committee (TC) 209 is chartered with standardization of cleanrooms and associated controlled environments. A series of 15 international standards (thirteen parts under ISO 14644 and ISO 14698 Part 1 – 2) has been established for controlling contamination by means of cleanroom technology. The documents address design, classification and support operation of cleanrooms.

The recently published standard ISO 14644-15:2017 specifies assessment of the suitability of equipment and materials with respect to airborne chemical concentration. Three sampling procedures are described as well as calculation procedures for emission rate and specific emission rate in g/s for equipment(s) or g/(m²s) for material(s). The emission rate and specific emission rate and proscribed inspection result are used for the cleanroom suitability assessment.

The specific emission rate can be used by designers, suppliers and users for acceptance or impact evaluation of equipment and materials considered for use in existing or future applications of cleanroom technology.

1. Introduction

International standards facilitate global trade by providing a common basis of communicating specifications in purchase transactions. The responsibility for cleanroom standardization within the International Organization for Standardization (ISO) is held by Technical Committee (TC) 209, Cleanrooms and associated controlled environments. In 1992, United States ISO Member ANSI proposed the formation of the technical committee to ISO at the recommendation of IEST, and has delegated the responsibility for the administration of ISO/TC 209 to IEST. ISO/TC 209 currently publishes standards as parts of the ISO 14644 and 14698 series. The objective of this paper is to announce the availability of a new ISO 14644 standard to facilitate assessing the suitability of equipment intended for operation in cleanrooms. The cleanroom standards are available from ISO and national standards organizations.

2. ISO 14644 — Part 15: Assessment of cleanroom suitability of equipment and materials by airborne chemical concentration

2.1. Position of ISO 14644-15 within the ISO 14644 series of standards

In 2017, ISO published standard ISO 14644-15, which is intended to cover a critical aspect of ISO/TC 209's scope. ISO 14644-15 addresses the need for testing of equipment and materials for use within controlled zones[1] or cleanrooms classified as described in ISO 14644-1, Classification of air cleanliness by particle concentration, when chemicals in the air are of special interest. This standard complements ISO 14644-14, Assessment of suitability for use of equipment by airborne particle concentration, which focuses on airborne particle emission by equipment.

2.2. Target audience

ISO 14644-15 is targeted for suppliers of equipment and materials as well as designers and users of cleanrooms and controlled associated environments. It enables contractual partners, or suppliers and users of equipment or materials to assess the chemical impact on a cleanroom environment prior to installation or during troubleshooting.

2.3. Content

ISO 14644-15 references the classification system of ISO 14644-8, Classification of air cleanliness by chemical concentration (ACC). Priority is given to volatile, total organic compounds (VOC), but other groups of contaminants as stated in ISO 14644-8 can be used for testing as well.

ISO 14644-15 considers equipment as well as materials that are exposed to the environment. Equipment is identified without dimension (unit number 1), while materials' emission depends on surface area (unit m²). ISO 14644-8 provides information on contaminants, generic analysis methods, levels and a logarithmic scale (10–x/g*m³ = ISO ACC –x (X)) as the basis for airborne chemical cleanliness. Therefore, ISO 14644-15 focuses on the test method, sampling and assessment of results.

The specific emission rate for equipment (g/s; without dimension) and material (g/m²*s) is introduced to allow comparisons between different equipment and different materials. As reference, chemical volatile organic compounds are chosen, if nothing else is stated. Other airborne chemical contaminations can be assessed as they are mentioned in ISO 14644-9, Classification of surface cleanliness by particle concentration.

ISO 14644-15 provides three different normative test set ups for sampling:

a. Closed Design: This test set up is chosen for equipment that is of moderate size and movable. The approach is simplified and can be considered a chamber test using a purge gas for transporting chemicals to trapping systems.
b. Closed Design special application: This test set up is intended for the testing of material samples with even surfaces.
c. Open Design: This set up is written for larger equipment which cannot be easily tested with the Closed Design (see a) or for equipment, which has already been installed in a cleanroom or controlled environment.

All the test set ups have the following consideration in common: The intended use of the material or equipment must be defined as a precondition for testing. This is covered by the expression "representative mode" for equipment and "representative form" for material.

A detailed step-by-step test description guides the user of the standard from set up of the equipment or material for sampling to final test result (mass values), which

consecutively are used to calculate the specific emission rate for the equipment or material.

In addition to chemical sampling and analyses results, a visual inspection is an important part of the cleanroom suitability assessment.

2.4. Application

After establishing the cleanroom suitability of the equipment or material, the specific emission rate can be used to evaluate the impact on a controlled zone or cleanroom in two major ways:

a. **Prospectively, for a future installation**
   This approach considers the specific emission rate with proposed cleanroom/clean zone operational parameters such as internal volume, change rates for makeup and recirculated air, and efficiency of chemical filtration to predict a chemical mass concentration (g/m^3).
b. **Assessment for an existing cleanroom/clean zone**
   This approach considers the specific emission rate(s) with existing cleanroom/clean zone operational parameters such as internal volume, change rates for makeup and recirculated air, mass concentration of the makeup air, and efficiency of chemical filtration to predict a chemical mass concentration (g/m^3).

Both options show the versatility of ISO 14644-15, since it gives guidance for designers, suppliers of equipment and materials and their users.

3. Standardization work of ISO/TC 209 and CEN/TC 243

3.1. Overview on ISO/TC 209 standardization work

Since 1993, ISO/TC 209 has been responsible for International standards on cleanrooms and associated controlled environments.

The use of cleanrooms and associated controlled environments is becoming more and more common and a key enabling technology for production. In response, ISO/TC 209 working groups (WGs) have contributed standards for design, testing and use of cleanrooms and associated controlled environments to aid in the acceptance of this beneficial technology by different user groups and regions.

There are currently 23 participating member (P members) countries, which are eligible to nominate experts for WGs and vote on standards in development or systematic review. There are currently 22 countries (O members) that can observe the work of ISO/TC 209.

Up to the present, a series of 15 standards has been published under the responsibility of ISO/TC 209 in the 14644 and 14698 series. Three standards are under development or revision at present.

ISO/TC 209 standards are written generically in that they can be applied for testing and monitoring, or in a broader sense to control cleanliness in various industries such as

- automotive,
- aerospace,
- electronics,
- semiconductors,
- food,
- life sciences (e.g. pharmaceuticals, health care, hospitals),
- scientific research.

In addition, industry or national standards and guidelines are sometimes used to provide deviating or more specific requirements and aspects.

ISO/TC 209 has established formal liaisons with five other ISO TCs and the International Confederation of Contamination Control Societies (ICCCS) to ensure transparency and consistency in its standardization efforts.

In 2017, ISO/TC 209 revised its business plan and scope to capture and address current and future standardization needs of consumers, regulators and industry regarding cleanrooms. The revised scope reflects technical progress and the recognition that cleanroom technology has become more widely applied in various industries and the applications have become more diverse. Additional information can be retrieved from the websites of ISO,[2] CEN[3] and ISO/TC 209.[4]

4. Summary

ISO/TC 209 advances applicability and use of cleanrooms and associated controlled environments by providing standards for specification, design, testing/monitoring and operation. In 2017, ISO 14644-15 was published as one of a series of 15 standards. This new standard addresses the cleanroom suitability for use of equipment and materials by quantifying airborne chemical concentration. ISO 14644-15 can be used by designers of facilities, suppliers of equipment and materials and users in various phases during the lifetime of an installation to support decisions on acceptance or to assess the impact of equipment or material(s) in the design of a future installation when chemical contamination is of interest.

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Dr. Berthold Düthorn, pharmacist by education received a PhD from the faculty of natural sciences of University Erlangen-Nürnberg. He is vice-president of Robert Bosch Technology GmbH and Managing Director of Valicare GmbH. His responsibilities are the product areas qualification and validation services, plant design and industry 4.0.

For more than 20 years he has been engaged in national and international standardization of cleanrooms and associated controlled environments as a nominated expert, convenor of ISO/TC 209 WG 11 and the German mirror group, and head of the German delegation in ISO/TC 209 and CEN/TC 243. He can be reached under berthold.duethorn@bosch.com.

This paper is the first of a series of outreach articles that are being produced by ISO/TC 209 Working Group Convenors to spread the word about the work of ISO/TC 209, the Technical Committee on Cleanrooms and associated controlled environments. It is reproduced with the kind permission and encouragement of the ISO/TC 209 Secretariat Team.

E-learning module from Pharmig supports Annex 1 disinfection requirements

Tim Sandle

Introduction

In December 2017, the European Medicines Agency issued a new draft of EU GMP Annex 1 for sterile medicinal products manufacture.[1] While the draft has yet to be converted into a finalised document, much of what is contained within the document is being used by European inspectors to assess facilities (this is unsurprising given that the revisions are intended to codify current best practices). Central to the update is the requirement for each facility to develop a contamination control strategy, and central to such a strategy is the cleaning and disinfection of cleanrooms. The application of detergents and disinfectants to well-designed and operated cleanrooms is essential for contamination control.[2]

The regulatory revisions to cleaning and disinfection present two challenges. The first being implementing the changes and the second being how to ensure all operators within a pharmaceutical or healthcare facility are trained. This latter point is doubly important given that concerns both with cleaning and disinfection practices and with the quality of training feature high among observations from both the US Food and Drug Administration (FDA) and European inspectors.[3] Research undertaken by this author found that, within Europe in 2017:

- Contamination control accounted for 9% of all inspection observations made.
- Potential for microbial contamination accounted for 4.5% of observations.
- Environmental monitoring accounted for 3% of observations.
- Environmental control accounted for 1.5% of observations.

Similarly, with the FDA, for the period 2013-2018:

- 16% of all audit observations related to cleaning and disinfection.
- Cleaning/sanitisation/maintenance was the 8th most common deficiency.
- Other prominent issues:
  - Cleaning and maintenance records not kept.
  - Deficiencies in cleaning and sanitisation procedures.
  - Building not clean/ free of infestation.
  - Cleaning and sanitisation procedure not followed.
  - Deficient process for room disinfection.

Pharmig, the not-for-profit professional organisation representing pharmaceutical microbiologists, has recognised these trends and the associated need to address cleaning and disinfection training and competency standards. Part of Pharmig's remit is to develop training and education in relation to microbiology. Weighing up different options for delivering training, Pharmig selected an e-learning route and subsequently developed an interactive training package.

This article considers the benefits of e-learning, the new on-line module from Pharmig, as well as the key requirements from the revised Annex 1 in relation to disinfection contamination control.

Annex 1: Contamination control and disinfection of cleanrooms

A substantial part of the revised Annex 1 is given over to each facility having a detailed, facility-specific, risk-based contamination control strategy. To be effective such a strategy needs to be an approach that can assess seemingly isolated contamination events holistically and which is capable of putting appropriate corrective and preventive actions (CAPAs) in place. This is intended to signal a new paradigm in terms of contamination control, shifting the risk review process to one that assesses the impact of a contamination event in a far wider context – that is, a holistic approach to reviewing contamination incidents.[4]

Central to contamination control within the cleanroom environment is the need for effective cleaning (with a detergent) followed by disinfection. While this principle is not new, the revised Annex 1 contains some additions relating to cleaning and disinfection. These are:[5]

- The need to rotate between two different disinfectants. While this features in the current Annex, the text has been expanded to state that one of the disinfectants should be a sporicidal agent. The revised Annex reads: "More than one type of disinfecting agent should be employed, and should include the periodic use of a sporicidal agent."
- Reference is made to disinfectant qualification. Not only is disinfectant efficacy testing described as important, the Annex infers that this is a type of testing that needs to be carried out within each facility. For this, surface (coupon) testing is recommended, i.e. where portions (coupons) of different surface materials are challenged with microorganisms against the disinfectants to be used.
- With the discussions about disinfectants, references are made to the need to assess the bioburden of non-sterile disinfectants and to assign expiry dates.
- With cleaning, the draft Annex appears to infer that cleaning needs to be undertaken prior to each use of disinfectant.

With disinfection, the confusing reference to 'resistant strains' remains. The phrase ''development of resistant strains "is often misinterpreted as development of acquired resistance (a theory which, in this author's view, has largely been discredited). However, this does imply that regular reviews of cleanroom microbiota are required.

The combination of inspectorate findings and the Annex 1 revisions accentuates the importance of cleanroom cleaning and disinfection. In terms of why there are so many regulatory findings and why the text within the draft Annex has been expanded, suggests

pharmaceutical and healthcare organisations are not consistently delivering what is required. Part of the solution is a renewed focus on training. With many organisations deploying conventional forms of training this raises the question as to whether new forms of training are required, such as e-learning.

"E-learning has advantages in that the material can be structured so the learning is consistent (in terms of control of the content and delivering of the core message)."

E-learning

E-learning ('electronic' learning) concerns the application of multimedia content using electronic educational technology and represents an alternative to a) classroom-based learning, b) the use of text books or c) other forms of 'learning' such as shadowing another person in the workplace. E-learning has advantages in that the material can be structured so the learning is consistent (in terms of control of the content and delivering of the core message). In addition, it offers a flexible and convenient solution for most workplaces where the entire team cannot easily be taken off-line at the same time as study can take place anytime and anywhere. Furthermore, the pace of learning can be varied to suit individual needs.

This mode of learning can also be more engaging, in terms of the use of graphical and video content, compared with other types of training. As with any other form of learning, success is dependent upon the motivation of the student. The use of interactive content is one method for helping the trainee to engage with the subject matter.[6]

E-learning is increasingly used by educational institutions, it is also being adopted by pharmaceutical firms and healthcare organizations.[7] Video, for example, is useful for demonstrating how a medical device or piece of laboratory instrumentation can be used; 360° interactive video adds another level of engagement to standard video; and 3D animation and simulations can help to visualise and explain the mechanisms of action of a process.

E-learning also encompasses automated tests and ongoing assessments, providing demonstrable progress to satisfy regulators, and the use of individual log-ins with passwords addresses data integrity concerns.

Pharmig's e-learning module on cleaning and disinfection

Taking on-board the advantages of e-learning, Pharmig have developed an e-learning platform.[8] The platform has been designed to host multiple modules relating to microbiology and contamination control. In light of the perennial concerns surrounding cleaning and disinfection, this is the topic selected for the first module. The material is based on Pharmig's Guide to Cleaning and Disinfection,[9] which reflects current regulatory guidance including the revisions to Annex 1.

The Pharmig module addresses best practices for cleaning and disinfection. These practices include:

- The selection of detergents and disinfectants.
- The difference between a standard disinfectant and a sporicide.
- Regulatory guidance.
- Qualification of new vendors and agents.
- In-use expiration dating.
- How disinfectants are qualified.
- Sterility of solutions.
- Cleaning and disinfection techniques, including bucket methods and wiping.
- Frequency for cleaning and disinfection.
- The reasons for disinfectant rotation.
- Hold times for cleaning areas.

The topics are presented in three chapters. Chapter one is an introduction to contamination in cleanrooms, considering the importance of controlling contamination in the cleanroom and classification limits for microorganisms and particulates. Chapter two looks at disinfectant selection, storage and usage. This includes the types of disinfectant and cleaning agent, plus the preparation and storage of solutions. Chapter three focuses on cleaning techniques covering: the control of cleaning equipment, the importance of cleaning prior to disinfection, the correct sequence of cleaning and disinfection tasks, good mopping and wiping techniques, and how to dispose of waste solutions safely. The target audience is production operators and their managers, although the module will also be of interest to cleanroom engineers, QA and microbiology personnel.

The Pharmig platform is accessed via an online training portal. Each module uses a combination of live footage and animation to bring training topics to life. Comprehension is then assessed by multiple choice questions, with each trainee being issued a certificate. The pass mark and number of attempts can be tailored to each organisation.

Summary

The effective use of detergents and disinfectants are important for keeping cleanrooms used in pharmaceutical and healthcare facilities clean and with a microbial bioburden appropriate to the cleanroom grade. This is necessary for the manufacture of safe medicines and for the protection of patients. Recent regulatory findings, and the revisions to EU GMP Annex 1, suggest that these principles are not always consistently adhered to, presenting potential microbial risks.

The primary reason for cleaning and disinfection inconsistencies, together with poor procedures, is training. To teach operators about effective cleaning and disinfection needs a new approach and e-learning offers an engaging and interactive means to deliver this. To address the gap in this space, Pharmig have produced an e-learning module on cleaning and disinfection with the aim of improving standards throughout pharmaceutical and healthcare cleanroom environments.

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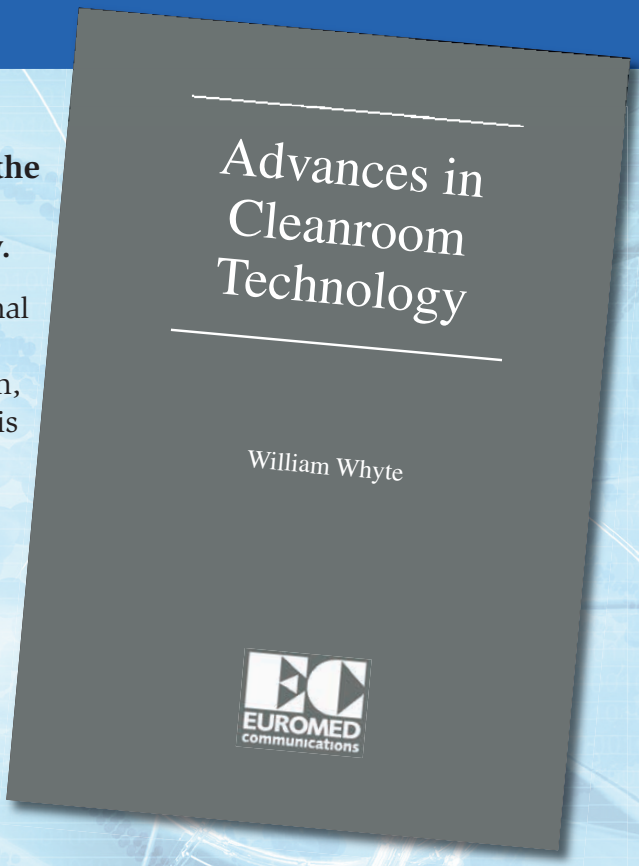
Tim Sandle, PhD, CBiol, MSBiol is Head of Microbiology at the UK Bio Products Laboratory and a visiting tutor at the University of Manchester. In addition, Tim sits on LBI/30, the BSI Cleanrooms Committee, and the Pharmig committee. He also runs a blog: Pharmaceutical Microbiology – http://www.pharmamicroresources.com

Advances in Cleanroom Technology



This book is based on the author's work that has been published over the last sixteen years to advance knowledge of cleanroom technology.

The author, Bill Whyte, is an international authority on cleanrooms, having been involved for over 50 years in the design, testing and running of cleanrooms. This book is over 500 pages in length and divided into seven sections that group Dr Whyte's scientific writings into topics that include the history of cleanrooms and operating theatres, risk management and risk assessment methods, contamination of products, ventilation design of non-unidirectional airflow cleanrooms, and standard of cleanrooms required for a specified product contamination.

In addition, the book provides further new information on measuring air supply volumes and air velocities, ventilation effectiveness, Computational Fluid Dynamics (CFD), high efficiency air filters, decay of airborne contamination, collection efficiencies of sampling methods, airborne dispersion of particles and MCPs from people, dispersion from floors, transfer of surface contamination, and surface deposition of contamination.

Each of the seven sections is provided with a useful introduction explaining the background to the research and summarising the key points. Overall, this is a book that will prove very useful to anyone involved in any aspects of design, testing and operation of cleanrooms.

For further information and to order see the Euromed Communications website at:
http://www.euromedcommunications.com/

EUROMED communications

Passfield Business Centre, Lynchborough Road, Passfield, Liphook,
Hampshire GU30 7SB, UK
Tel: +44 (0)1428 752222
Fax: +44 (0)1428 752223
email: info@euromedcommunications.com
www.euromedcommunications.com

International Symposium on Contamination Control 2018 – ISCC'18 "The world behind contamination control"

Koos Agricola

From 23 to 26 September 2018, in the World Forum in The Hague, VCCN (the Netherlands Society of Contamination Control) hosted ISCC'18, the 24th biennial ICCCS Symposium, on behalf of the ICCCS (International Confederation of Contamination Control Societies). During the five days after the symposium VCCN also hosted various ICCCS and ISO TC 209 meetings in the Marriott Hotel. As a member of the ISCC'18 steering committee I look back on a number of exciting days that were the culmination of an extensive period of preparation.

In the 2013 ICCCS Council of Delegates meeting in Reno, VCCN offered to organise the 2018 ICCCS symposium in The Netherlands. On 11 February 2014, VCCN set up an ISCC'18 steering group. In the autumn we participated in the 2014 ICCCS symposium organised by KACA in Seoul. This was a typical three day scientific conference with a technical tour that combined technology and culture. The exhibition was separate from the conference.

In 2014 it became clear to the steering committee that an ICCCS symposium should be a get together for people that are both new to cleanroom technology and contamination control and people that are experienced. Therefore the conference program should be a good mix of scientific contributions and practical applications. An educational program should be included.

In 2016 SBCC organised ISCC 2016 in São Paulo and combined the conference program with an educational program. The exhibition was mixed with the conference and education location. There were many guides around to show the visitors where to go. It was a very lively ICCCS symposium.

After Brazil the VCCN steering committee started to put all the details of a diverse program together. Various subcommittees were formed to address the different aspects of the symposium. The goal was to make an international meeting and learning place within and in the world behind contamination control. The conference program was condensed from three to two days. This led to there being many parallel activities. For participants it was sometimes difficult to select which activity to attend, and also to find where to go. There were three parallel conference sessions, a complete tutorial program, and workshops where people could exchange their experiences on various topics. Schools and universities hosted various demonstrations.

Both conference days were opened and closed with keynote speakers on the subjects of nano-technology, medical challenges, nano-lithographic equipment and the future of products of advancing digitalisation. There was a banquet at Louwman Museum on the first evening of the conference.

For the conference program a matrix was made with on one side showing the different aspects of contamination control:

- Risk assessment
- Set-up requirements
- Contamination control concepts/ solutions
- Design and construction (establishing control)
- Energy management
- Start up
- Verification
- Operations and Monitoring

and on the other side the applications:

- Microelectronics
- MEMS devices
- Electro-mechanical products
- Optics and aero-space
- Life sciences and pharmacy
- Health care
- Food
- General.

77 papers and 10 posters were submitted. However, about a quarter of the speakers did not send in their material before the conference, which meant that the proceedings and presentations on the USB stick issued at the conference were incomplete. The participants later received a file with the additional presentations. The proceedings became an impressive 626 page book with interesting research, studies, applications and ideas.

The content of the conference and poster program covered many areas within the program matrix and people were encouraged to read the proceedings. Some of the papers may be published in due course with permission of the authors. It is difficult to pick out subjects of particular interest, but the increased attention to surface cleanliness, chemical contamination, particle deposition, cleaning and hospitals was of note.

ISCC'18 offered a diverse program. The layout was a mix of 55 exhibitions, four conference rooms, a poster area and two demonstration areas. The tutorials and workshops were given on a floor above the exhibition area. For some participants the layout was too complex to find the place they wanted to go to. Also it was observed that many participants were not aware of the various parts of the program. All information was available in the program book, but it became clear that more visual guidance on the seminar floor was necessary. That was also the case in São Paulo. When there is too much information people do not read it.

The symposium was a success, but unfortunately did not reach the organiser's expectations. The program was planned for 500 participants but only 80% of this target was achieved. Participants came from 22 different countries but the majority were from the Netherlands and neighbouring countries – see Figure 1.

The conference was closed with a ceremony where an ICCCS sculpture was presented to the organization of the 25th ICCCS symposium, the Cleanroom Technology Society of Turkey.

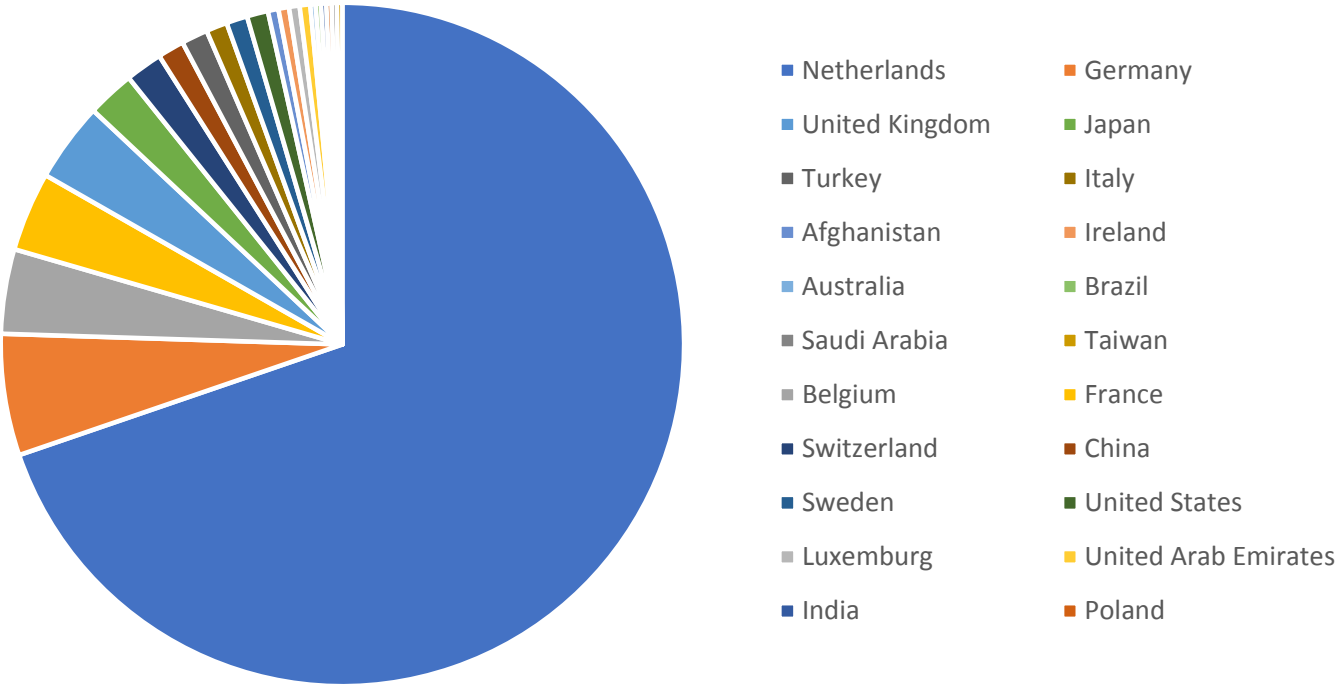


Figure 1: Analysis of participants

"It is difficult to pick out subjects of particular interest, but the increased attention to surface cleanliness, chemical contamination, particle deposition, cleaning and hospitals was of note."

After the conference there were three interesting technical visits to ESTEC Noordwijk, ASML and Philips in Eindhoven, and HAL Allergy GMP-facility and Biotech Training Facility in Leiden.

After more the four years of preparation and contributions by many people the ISCC 2018 was a big success, but could have been better with more participants.

Figure 2: Closing ceremony

Koos Agricola is an Applied Physicist and has worked in R & D at Océ Technologies, a Canon Company, since 1986 and part time at Technology of Sense since 2017. His responsibilities include contamination control in cleanrooms for the manufacture of critical parts. Koos is a member of ISO/TC 209, convenor of WG 14, secretary of WG 4 and technical expert in ISO/TC 209 WGs 3, 11, 12 and 13 as well as CEN/TC 243 WG 5. He is chairman of the ICCCS Education and Technical Committees and the CTCB-I and secretary of the VCCN and the ISCC 2018 steering committee.

Mission accomplished: Cleanzone 2018 draws more international visitors to Frankfurt

Based on a press release from Cleanzone

Cleanzone, which was held at Messe Frankfurt on October 23 and 24, increased the international share of visitors this year to more than 38% (2017: 35%). The overall number of participants also increased compared to the previous event, with nearly 1,300 cleanroom technology experts from 39 countries discussing the latest innovations and trends over two days in Frankfurt. For the first time, potential customers who travelled to the trade fair included visitors from countries such as Korea, Japan and Indonesia. The number of visitors from Great Britain and Turkey increased markedly. A total of 78 companies from ten countries presented their innovations and trends in an exhibition space in Hall 5.1 that was over 30% greater than in 2017. Iris Jeglitza-Moshage, Senior Vice President of Messe Frankfurt reported "With its large international component, Cleanzone 2018 is the most important trade fair for cleanroom technology in Europe. We are delighted by the positive feedback from our exhibitors regarding our efforts to advertise this event internationally."

Visitors included representatives from Infineon, Continental Automotive, Bosch, Bayer, Carl Zeiss, Fresenius Kabi, BASF, Sanofi Aventis, the German Cancer Research Center (DKFZ), Mainz University Hospital and the Max Planck Institute. The trade fair's expanded range was a hit, with 84% of all visitors (2017: 83%) and 88% of German trade visitors (2017: 82%) expressing satisfaction with what was on offer. Furthermore, 71% of all visitors (2017: 67%) and 81% of German participants (2017: 80%) agreed that the mood in the industry is positive.

Cleanzone is the industry's forum for innovation, and the trade fair was once again focused on new products and services that offer digital and flexible solutions for the cleanrooms of tomorrow. There was a particular focus on process simulations conducted in advance, training using virtual reality, methods for automatic and robot-controlled disinfection, various aspects of data and counterfeit protection, and flexible cleanroom modules that can be set up quickly.

The Cleanroom Award, which was presented for the seventh time this year, went to KEK, stainless steel specialists in Saxony, for their convenient and easy-to-fold table for temporary use.

Frank Duvernell, Managing Director of ReinraumAkademie (Leipzig) and partner of Cleanzone said "Be it digitalisation, virtual reality or new business models, Cleanzone 2018 succeeded in illuminating the themes that are important to the industry's future. New ideas were also supplied by the high-quality supporting programme and the speakers' visions for the future."

Cleanroom solutions for state-of-the-art biopharmaceuticals, utilisation of the building information modelling (BIM) method for planning industry production facilities, new disinfection processes and the requirements for hospital pharmacies were some of the highlights at the Cleanzone Conference. At the Cleanzone Plaza event stage, experts discussed cleanroom technology 5.0, the Russian pharmaceutical market, and data and counterfeit protection, while the German Cleanroom Institute (DRRI), Austrian Cleanroom Society (ÖRRG) and a group of companies associated with mycleanroom.de (https://www.mycleanroom.de) presented their products and services at a large joint stand.

Besides Germany, the most important visitor countries included the Netherlands, Switzerland, Ireland, Austria, Great Britain, the Russian Federation, China, France and Denmark. Cleanzone's trade visitors came from every industry where production is carried out under cleanroom conditions, including the automotive, semiconductor, aerospace, laser, optics, surface technology, food and pharmaceuticals industries, hospitals and pharmacies.

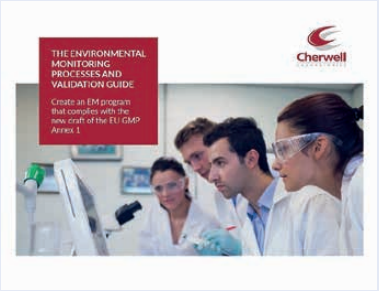
Cherwell publishes guide on EM programs for revised EU GMP Annex 1

Cherwell Laboratories has drawn on its in-depth pharmaceutical and related industry knowledge to publish an eBook titled, "The Environmental Monitoring Processes and Validation Guide" which is available to download from Cherwell's website.

The guide is intended to assist sterile product manufacturers with reviewing and improving their environmental monitoring (EM) programs in preparation for the proposed changes to EU GMP Annex 1 – Manufacture of Sterile Medicinal Products.

The eBook highlights the most business-efficient EM measures organisations can take to comply with the latest iteration of the EU GMP Annex 1, and practical steps they can take to create the ideal EM process. It covers: Why the EU GMP Annex 1 draft has been proposed; how it helps all industries move closer towards a global standard; how to prepare for compliance; examples of best practice for EM programs and the right tools needed for an effective and compliant program.

The environmental monitoring processes and validation guide can be downloaded at: https://resources.cherwell-labs.co.uk/guide-to-em-processes-and-validation-lp



The Environmental Monitoring Processes and Validation Guide from Cherwell Laboratories

EECO2 Launches in-house research into cleanroom performance

EECO2, a leading provider of researched, tested and proven engineered efficiency solutions for the life science industry, has recently designed and built a high-grade cleanroom at the head office in Macclesfield, Cheshire. The aim of building the cleanroom was primarily to test innovative control strategies to substantially reduce energy and maintain classification.

Keith Beattie, EECO2's Life Science Lead, reveals that the in-house cleanroom has been extremely beneficial to the company, he states "It allows us to change many variables and measure effects, helping us understand complex system performance. The changes can be made easily, without disturbing a manufacturing process. It is also a great asset for hands-on training and independent product testing".

Look out for EECO2's researched whitepaper on cleanroom control, which will be published in the next few months. For more information on EECO2, visit www.eeco2.com, contact EECO2 at info@eeco2.com or on 01625 660717.

CRC has designs on Wales

Cleanroom design and build specialist Clean Room Construction Ltd (CRC) has designs on Wales after securing three contracts in Bridgend, Neath and Carmarthenshire.

CRC has been awarded contracts to build a new manufacturing facility for MicroPharm, which produces antivenoms, and to design a new ISO 8 cleanroom facility for Ortho Clinical Diagnostics (OCD) at Bridgend for their immunoassay and immuno haematology products. CRC will also design, supply and install two separate airlocks for the blending/decanting area and main warehouse at Ecolab in Neath as well as a goods inward inspection booth. Ecolab is a global leader in water hygiene and energy technologies and services that protect people and vital resources. All three projects are scheduled for completion by spring 2019.

CRC's Managing Director Steve Lawton said: "Clean Room Construction is proud to be working with the best of British science and technology companies that are specialists in their respective fields, leading the way in identifying groundbreaking solutions for the manufacture of antivenoms, early screening of diseases and water hygiene solutions around the globe."

www.crc-ltd.co.uk

Biopharma Group launches a new era for Faster air safety cabinets in the UK

Biopharma Groupis very pleased to announce that it has become the exclusive distributor of Faster S.r.l. laminar airflow cabinets, biological safety cabinets, isolators and fume cupboards in mainland UK. Andrew Cowen, CEO of Biopharma Group, said "We're delighted to bring the Faster product range into our product portfolio as the cabinets are a great synergetic addition to the ranges we already represent in the UK." We are also able to offer a brand new product to the UK market, namely the ChemFast Premium fume cupboard, which has key benefits:

- Hybrid cabinet utilizing a recirculation principle which offers lower air consumption resulting in lower power consumption
- Built-in charcoal filter (total of 72kg for 1.5m cabinet)
- Built-in DC blower
- LED lights
- Touch screen controls
- 160mm ductwork occupying less space than standard ductwork of ducted fume hoods

To discover more about our new Faster products, please contact Matthew Stubbs at faster@biopharma.co.uk or visit www.faster-air.com

Envair Limited sells Envair Lab to Biopharma Group

On 1st November 2018 the assets of the Envair Lab Limited business were sold to Biopharma Process Systems Limited.

All existing warranty and guarantees will be honoured and no other part of Envair Limited manufacturing or service and maintenance business has been sold or transferred.

Envair Limited wishes to reiterate its long-term strategy, which is to continue to develop and enhance its manufactured product portfolio for opportunities to unlock further value while also focusing on its core Pharmacy Isolator ranges by developing and introducing new innovative features including integrated rapid gassing systems.

For further information regarding this announcement, please contact Michelle Bamber on 01706 228416, or alternatively by email on sales@envair.co.uk

For regular news and updates Follow Envair on LinkedIn.

Life-lines

Quotations of William Shakespeare

All the world's a stage, and all the men and women merely players. They have their exits and their entrances; And one man in his time plays many parts.
(As You Like it Act 2, Scene 7)

Brevity is the soul of wit.
(Hamlet Act 2, Scene 2)

We have seen better days.
(Timon of Athens Act 4, Scene 2)

Uneasy lies the head that wears the crown.
(Henry IV, Part 2 Act 3, Scene 1)

We know what we are, but know not what we may be.
(Hamlet Act 4, Scene 5)

All that glisters is not gold.
(The Merchant of Venice Act 2, Scene 7)

Pharma Clean Tech 2019, SNIEC Shanghai, June 18–20, 2019

Concurrently with P-MEC China and CPhI China, Pharma Clean Tech 2019 will launch its 14th edition during June 18-20, 2019 in SNIEC Shanghai, China.

Pharma Clean Tech 2019 is an international and high-quality annual exhibition, attracting over 70,000 professionals in the pharma and clean tech industry from China and abroad.

Over 100 Chinese and overseas pharma clean tech exhibitors such as Dynaco, Gusu, MAX, Sinoarch, Linsen, and Sujing, etc. will showcase their upgraded purification products and equipment, latest cleanroom technology and policy, pharma cleanroom project cases and solutions.

Concurrently with P-MEC China and CPhI China, the total exhibition will occupy 17 halls with a total area of 200,000m2 and over 3,200 exhibitors and is expecting to welcome over 70,000 pharma professional visitors from China and overseas.

In addition, Pharma Cleanroom Technology Forum 2019 and Pharma Clean Tech Matchmaking Event will be organized at the same time and are expected to gather over 100 audience & VIP buyers from pharmaceutical enterprises and biotechnology industry.

Pharma Clean Tech 2019, concurrently with P-MEC China and CPhI China, are your gateway to successfully grow your business at the 2nd largest pharma market in the world. Whether you are looking for sourcing new business or getting the latest market insight, this is your one-stop shop pharmaceutical platform in Asia.

For more information visit http://en.pmecchina.com or e-mail jennifer.yang@ubmsinoexpo.com

Events

Dates	Event	Organiser
2018		
November 12-15	IEST Fall Conference, Schaumberg, Illinois	IEST
November 13-15	International Congress A3P	A3P
November 28-29	Pharmig 26th Annual Microbiology Conference – INDUSTRY – Nottingham, UK	Pharmig
November 28-29	Pharmig 26th Annual Microbiology Conference – NHS – Nottingham, UK	Pharmig
2019		
April 29 – May 2	ESTECH 2019, Las Vegas,Nevada	IEST
May 21-22	Cleanroom Technology Conference 2019, Birmingham, UK	HPCi Media
June 18-20	Pharma Clean Tech 2019, SNIEC Shanghai, China	(concurrently with CPhI & P-MEC China)
August 16-18	Cleanroom Guangzhou 2019, Guangzhou (Canton), China Guangzhou Grandeur International Exhibition Group	TBA
November 12-15	Fall Confenence, Rosemont, Illinois	IEST

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2018	**Event**	**Location**
November 12	Cleanroom Basics: What Is a Cleanroom and How Does It Work?	IEST Fall Conference Schaumburg, Illinois
November 13	Beyond Cleanroom Basics: Fundamental Information for Cleanroom Operations	IEST Fall Conference Schaumburg, Illinois
November 14	Cleanroom Classification Testing and Monitoring	IEST Fall Conference Schaumburg, Illinois
November 15	Understanding the Cornerstone Cleanroom Standards: ISO 14644-1 and 14644-2	IEST Fall Conference Schaumburg, Illinois
February 19	Contamination Busters: Get the Dirt Out of the Cleanroom	Phoenix, Arizona
February 20	The Unseen Contaminant: Taking Charge of Electrostatic Contamination	Phoenix, Arizona
February 21	Stop Contamination in Your Operations with Reusable and Disposable Garments	Phoenix, Arizona

ICS (Irish Cleanroom Society) www.cleanrooms-ireland.ie		
2018	**Event**	**Location**
November 6	CTCB-I Testing and Certification (2/3 days) Dublin, Ireland	Dublin, Ireland

S2C2 (Scottish Society for Contamination Control) www.s2c2.co.uk		
2018	**Event**	**Location**
November 6-8	Cleanroom Testing and Certification (CTCB-I)	Coatbridge, Scotland
November 21	Cleanroom Technology (CTCB-I)	Letchworth, England

R3Nordic www.r3nordic.org		
2018	**Event**	**Location**
For courses run by R3Nordic see https://r3nordic.org		

VCCN (Association of Contamination Control Netherlands)		
2018	**Event**	**Location**
October 2-4	For a complete list of courses including CTCB-I courses, please see www.vccn.nl/agenda	

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

A DIFFERENT PERSPECTIVE ON **ANNEX 1.**

So, you've reviewed the proposed changes to Annex 1 in relation to your manufacturing processes, but...

...have you assessed the impact of likely changes relating to cleaning and disinfection procedures in your facility?

This is where Ecolab Life Sciences will help you ensure compliance, whilst optimising your processes.

Our highly experienced team can support you with solutions to the requirements that Annex 1 raises relating to your cleaning and disinfection.

The work you do impacts millions of lives, you need a reliable partner in life sciences to ensure compliance and patient safety.

We can be that partner.

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