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Enhance your knowledge of contamination control

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TEMİZODA TEKNOLOJİLERİ DERNEĞİ

"Eğitim, İletişim, Paylaşım"

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.

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Editorial

Welcome to CACR39!

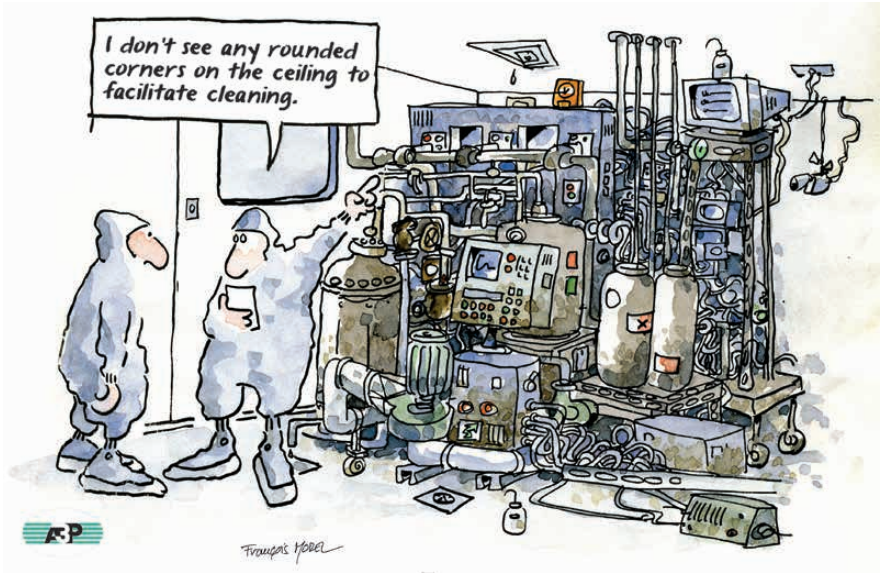
I would like to take the opportunity in this editorial to publicise two books which should be of great interest to readers of CACR. Both these books are published by Euromed Communications who also publish CACR, *Industrial Pharmacy* and other journals.

The first of these is Advances in Cleanroom Technology, a large selection of published articles by Dr William Whyte, a renowned international expert in the field of cleanroom contamination control. The book was reviewed in CACR35 by Gordon Farquharson who wrote "The book will be of great value across the cleanroom community from academia, to specifiers and designers, testers and certifiers, and of course users." The book covers a lot of ground right up to "the latest thinking on energy and sustainability" and "particle deposition, a cleanliness attribute which some consider is more valuable than the traditional consideration of airborne sub-micron particles."

The other book is *Cleanroom Management in Pharmaceuticals and Healthcare, 2nd Edition*, edited by Tim Sandle and Madhu Raju Saghee. Victor Grayson of Pharmig writes "The book remains an indispensable text for those involved with cleanroom management, whether microbiologists, cleanroom operators, engineers or facilities managers. The book is particularly useful in balancing practical approaches with robust engineering practice and scientific theory. … The new edition highlights several changes to the approach and methods for certifying cleanrooms. Most importantly, there is a comprehensive update in relation to the revised ISO 14644 cleanroom standard, parts 1 and 2."

Both these valuable books are available to readers of CACR at highly discounted prices for a limited time – please see the advertisement on page 35.

John Neiger



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Clean build protocols – concepts and considerations

Andrew D. Watson

Abstract

A clean build protocol (CBP) is an essential component of a cleanroom construction project. This paper provides guidance on how to develop and implement a CBP in order to deliver a cleanroom that can successfully achieve its designated ISO classification.

Introduction

A Clean Build Protocol (CBP) is a fundamental part of the construction quality documentation of any cleanroom build. It should be proportional in response to the specific cleanroom project and encompass all aspects that will influence the handover quality of the internal cleanroom surfaces. Stricter controls are often necessary if work is occurring in close proximity to an operational facility or if the finished cleanroom will be a sterile environment.

Construction is fundamentally a messy business. Contamination is inevitable and ultimately necessary if we want to deliver a cost-effective project. Ultimately, we want a series of protections and controls that will deliver a sufficiently clean facility that can be commissioned and classified in a predictable and timely manner.

The purpose of this document is not to envisage every scenario, but provide a broad approach that should help to facilitate an individual response to any cleanroom project.

Clean-at-the-end -vs- clean as you go

There are three main sources of contamination during construction:

- Construction related activities
- Material that enters the site from the outside environment
- Material that proliferates due to inadequate cleaning practices and waste removal

It is feasible that the main cleaning activity occurs at the end of the project just before commissioning, but what risks does this add to the project? It is well acknowledged that the implementation of a CBP will add cost and time to a project – Whyte, 2010,[1] however the overall cost and time for a facility that fails the first round of testing due to residual contamination could end up being more expensive. For sterile facilities, colonies of micro-organisms can become established that make an aseptic space very difficult to achieve. Also, irreparable damage to flooring, seals and even sensitive production equipment can occur.

Control of contamination during construction in accordance with specific procedures will reduce the risk to budget and program, particularly in the final stages of project completion.

References in ISO standards

There is limited reference to clean build (construction) protocols in the ISO 14644 suite of cleanroom standards:

- ISO 14644-4:2001 Design, construction and start up[2] – There is a reference in the normative section (6.4) "A clean construction protocol and cleaning procedures shall be developed as part of the quality plan… " Further, in Annex E, Construction and Materials Section E.3.3 a CBP is outlined in four short paragraphs. ISO 14644-4 is currently being revised. More details on CBPs have been proposed.
- ISO 14644-5:2004 Operations[3] – In Annex F, Cleanroom Cleaning, there is a section on a Construction-related cleaning program (F.9). In this section a cleaning program, based on 10 separate project stages, is provided. It should be noted that this is quite a strict protocol, possibly best suited for construction that is occurring in close proximity to an operational area.

Setting things up

Anyone involved in the delivery of a cleanroom project should have thought through their part in contamination control during their involvement. At the earliest stages of the project, consideration should be given to:

- Movement of staff, materials and waste through the site during each stage of the construction process – ensures that waste flows and personnel and material flows do not overlap and there is sufficient separation from any operational (non-construction) staff movements.
- Location of a setdown area – it should be adequately sized and well protected from the outside elements. There should be sufficient space for de-crating and decontamination, as well as locations for materials requiring inspection and rejected items.
- Construction staff amenity location – it should not present its own contamination hazard to the site, nor should it be too far removed to encourage construction staff to make "short cuts" or ignore other aspects of the CBP.
- Waste storage – should be removed from staff movements and not compromise site containment or provide a contamination issue during removal.
- Methods and paths for installation of equipment – errors in equipment size versus doorway widths are common experiences in any industrial build. Any demolition activity that has to occur in the late stage of a cleanroom build can introduce a huge amount of contamination that may have been, up to this stage, successfully kept out.
- Any segregation requirements of adjacent operational areas – operational staff flow paths should not cross with construction staff flow paths.

A holistic approach

With the design concept in place, and the above considered, a CBP should be developed and integrated into the overall Project Quality Plan.

Architectural and engineering firms, construction companies, material suppliers, cleaning contractors and

clients that regularly operate in the cleanroom space should at least have a list of common practices and at best a template to be offered to the project team for the preparation of the CBP.

The site induction and programs should integrate the CBP concepts and detail the personal responsibilities required of each project individual.

Suppliers should have contamination control activities in place before dispatch and strategies to ensure equipment / materials get to site in the best state possible.

A proportional response

It is important, in the interests of delivering a cost-effective build, that the level of the CBP and the methods employed be proportional to the type of cleanroom to be built and its classification. Similarly, the contamination control activities should also be proportional to the stage of build. Even though the CBP should be applied across the entire project, a pressurised site, with full gowning and regular wiping of every surface is probably not appropriate for all cleanrooms and throughout the project.

A key step in the development of a CBP is to identify the key stages of the project where a change in contamination control is warranted. An example of a set of stages could be as follows:

1. Shell enclosure – internal is no longer affected by the external weather conditions
2. Cleanroom shell complete – internal cleanroom space is separate from external building area
3. Services installation complete – all penetrations have been made
4. "Air on" – air flow inside the facility commences operation, finishes and sealants are installed
5. Final interior sealing – controls in place to ensure a clean application of sealant
6. Commissioning and certification – completed facility commissioning commences
7. Handover – facility is handed over to client. Cleaning and monitoring commences.

At the commencement of each stage a new set of controls can be implemented.

Format

A CBP is often seen in two formats – a long form, Standard Operating Procedure (SOP)-like document, or a matrix type document.

The long form SOP can be embedded permanently into a company's quality system and provide sufficient information. However, it can be difficult to integrate into a specific project.

A matrix type document that summarises each specific stage and the requirements, procedures, gowning and cleaning techniques for each stage can also be used. It needs to be project specific, but is particularly useful for clearly communicating the requirements to all staff. It should be included in the induction program. An example is provided in Figure 1.

Of course, a bespoke matrix document that is backed by a detailed SOP should provide the best outcomes for each project.

Fundamentals

The CBP should be part of the Project Quality Plan and integrated into training documents and the induction program.

Clean Build Construction Protocol Matrix

PROTOCOL LEVEL	LEVEL I	LEVEL II	LEVEL III	LEVEL IV	LEVEL V
NAME	SHELL ENCLOSURE	PERIMETER ENCLOSURE	"AIR ON"	"AS BUILT" CERTIFICATION	HOOK UP / HAND OVER
OBJECTIVE	Create a weather proof building shell/enclosure	Provide a controlled entry and exit of people/materials	Complete cleanroom envelope and **HVAC** services to provide continuous room pressurisation to exclude ingress of debris	Achieve "As Built" Certification.	Installation of Equipment/Process tools Achieve "At Rest" / " Operational" Certification.
CLOTHING	* Site PPE (Personal Protective Equipment	* Site PPE.	* Site PPE * Badge/Permitry * Disposable Mop Caps, Suit & Shoes	* Site PPE * Badging/Permitry * Disposable Mop Caps, Beard Covers, Suits, Gloves & Shoe Covers	* Badging/Permitry * Client supplied disposable cleanroom clothing
PROTOCOL TRAINING	NONE	NONE	YES	YES	YES
CLEANING	**OUTDOOR** None	**BUILDERS CLEAN** * Broom Sweep	**PRE-CLEANROOM** * Broom Sweep * Standard Vacuum * Local Extract	**CLEANROOM CONSTRUCTION CLEAN** * HEPA Vacuum * Wet Mop Wipe Down * IPA Wipe Down	**CLEANROOM OPERATIONAL** * HEPA Vacuum * IPA Wipe Down
MONITORING AND MEASUREMENT	**None**	**Visual Inspection**	**Visual Inspection & Airborne Particle Count (5 Micron)**	**Particle Counts & " White Glove " Visual Inspection**	**Particle Counts & " White Glove Visual Inspection**
CONSTRUCTION ACTIVITIES	* General Civil Works * Erect Steelworks * Pour Floor * Perimeter Cladding * Fit Ext. Doors/Louvres	* All Dry Lining Walls * 1st Fix A, M&E, process * Base Build Services * Sealnig of all fibrous materials	* Fit out cleanroom * 2nd Fix A, M&E, process * Pre-Commissioning * Electrical Commissioning * Plant Commissioning (Final Steps of Level III Protocol Stage) * Wipe down * Silicone Sealing	* Clean down / Blow down * Superclean * GEL pour * Fit Final Filters * Final Balance * Filter Scans * Room Integrity Tests * Environmental Tests * "As Built" Certification	* Hook Up Equipment. * Hook Up Process Services & Tools. * "At Rest" Certification * Characterisation Tests
CLEAN BUILD PROTOCOL - DO'S	* Remove all waste & debris daily	* Use defined access and transport routes * Remove waste material daily * Carry out continuous rough cleaning/sweeping * Offload materials in designated areas * Remove/clean off surface dirt prior to entry to construction area	* Clean shoes at entrance. Staff or material must enter via designated access routes * Unpack material in designated areas only * Store WIP materials inside designated areas only * Remove packaging & left over material daily * Remove debris at place of work * Carry out all works in a controlled manner as per manufacturer's instructions * Use standard vacuum * Entry permit & badge for designated areas required	* Follow gowning procedure before entry * Remove packaging in staging area before entry * Wipe down tools before entry * Follow prior written work plan * Use HEPA vacuum * Use bubbles for penetration * Entry permit and badge required	* Follow prior written work plan * Use bubbles for tool hook up * Use HEPA vacuum * Entry permits and badge required
CLEAN BUILD PROTOCOL - DONT'S	* No smoking	* No eating and drinking in construction area * No smoking	* As per Protocol Level II * No cutting,grinding and welding. * No unpacking of materials inside area. * No unscheduled work or work without work plan and protocol requirements.	* As per Protocol Level !II	* As per Prptocol Level !V * As client requirements.
PROTOCOL CHANGE CONTROL	NONE	None	* Client acceptance and sign off * "Out of protocol" form * Isolation action plan	* Client acceptance and sign off * "Out of protocol" form * Isolation action plan * Special measurements	* Client acceptance and sign off * "Out of protocol" form * Isolation action plan * Special measurements

Figure 1 – Example of a CBP Matrix, courtesy of Conor Murray of 3dimension

It is recommended that all CBPs include references to the following:

- Key quality system documents.
- Key safety system documents.
- Overall responsibility of the CBP across all contractors, both those under the main construction contract and those under control of other parties; for example, where the client is in control of equipment procurement and installation.
- Site layout – see Setting things up.
- Stages of the project – see section headed 'A proportional response.'
- Training and induction requirements for construction staff – expected staff conduct is key, restricted and no-go areas should be clearly defined.
- Setdown area layout – Location, zones and controls applied to this area.
- Cleaning responsibilities – clear demarcation of cleaning responsibilities should be made in the CBP. While everyone should be making a contribution to the cleaning effort, the responsibility of the overall condition of the facility during construction should reside with one party. At some point this responsibility will shift to the client, however it should not interfere with the cleanroom contractor's obligation to meet set as-built and at-rest cleanroom certification requirements. However, for any conducted "in operation" tests, it makes sense for the client to take on the cleaning process, as this will help to qualify their cleaning processes, and the fact that their conduct in the cleanroom will impact "in operation" cleanroom compliance.
- Cleaning processes to be applied at each stage – usually comprises of variations on sweeping, vacuuming and wiping. Cleaning equipment and chemicals may be specified. It is important to consider the residual contamination that each cleaning method may create, such as smaller dust particle generation through sweeping, and potential residual chemical contamination from cleaning chemicals.
- Protection of surfaces – damage to installed flooring, such as vinyl or epoxy, during construction can be difficult and costly to fix. Floor scratches become a cleaning issue in the long term. Floor protection using thin sheets of fibre board, either across the entire surface or common pathways should be used. Even with floor protection, the use of booties/ overshoes will help to reduce the amount of outside contamination that is brought in which could damage surfaces.
- Sealing of duct and pipework – Ductwork and critical process or utility pipework should have the same status of contamination control as your internal cleanroom surfaces. As such they should be cleaned in an appropriate area (preferably off-site) and be capped and sealed for storage on site. The seal should only be broken at the time of connection. This should be extended to fans, filter boxes and air handling unit componentry.
- Storage of filters – The storage of HEPA filters and other fragile sensitive equipment needs to be considered. All instructions on the outer packaging should be strictly adhered to.
- Sealant application – Sealant should be applied in a clean environment with no other activity in the room, in order to get the best finish possible. Contamination that infiltrates silicone is there for the life of the facility. Activity in room where sealant has been applied should be restricted at least until a skin has formed on the sealant.
- Vermin control – Will vary according to season, climate and geographical location.

Other contamination control considerations

There is a range of other contamination control techniques that may be useful for specific facilities, particularly those that will operate aseptically, or to a very low ISO classification number:

- Specific cleanliness attributes – not all cleanrooms are focused solely on particle contamination. Chemical contamination, viable contamination, macro particle and nanoparticle contamination and these types of contamination on surfaces or in air, will all require specific considerations for cleaning materials, equipment and techniques.
- Pressurisation of the construction space – this is an expensive, but highly effective option for contamination control from an early stage. Pressurisation can be achieved with the proposed HVAC system, using sacrificial filters (changed over just before commissioning), or with portable units specifically for the build process. Note that this method is effective in keeping contamination out, but may not be as effective in containing contamination that is generated within. These systems can also be expensive to run, however, the better sealed the perimeter, the less air that is required.
- Airlocks – an airlock can be used in conjunction with a pressurised space, or simply as a transition point between the outer and inner construction zones. They can be used as a gowning location and a decontamination location for equipment, materials and tools prior to entering the facility. Note that if the construction zone is operated at an extremely clean level, a separate airlock for gowning should be considered.
- Gaseous decontamination – there are a range of different products and methods available to provide a final decontamination step, using materials in a gaseous or volatilized form. They should be considered for new sterile facilities, or non sterile healthcare facilities where contamination has perhaps got out of control. It should be considered for any healthcare facility built in a tropical or sub-tropical environment. It is critical that surface compatibility of any interior materials be tested prior to performing such a decontamination.

Common issues

There are a range of issues that can occur during a project that CBPs may not necessarily cover, including:

- Gowning non-compliance – gowned staff who briefly leave the cleanroom site without changing can provide a significant contamination risk to the facility. If gowns and other protective clothing such as hairnets and

overshoes can be put on and removed easily and replacements are always available, then non-compliance will be reduced.

- Connection to sewers – connections into live sewers, even on the perimeter of the proposed facility must be immediately sealed or trapped with water, particularly for sterile facilities. They will be a constant source of microbial contamination otherwise.
- Shipping conditions – often machinery must be shipped in from far flung corners of the world. During shipping, the interiors of containers can experience extremes of humidity, heat and cold. Condensation that forms inside the containers can occur early in what might be a six to eight-week journey – longer if it gets held up at a border. As a result, bacteria and mould can proliferate and cause quite a dilemma if discovered just prior to installation, or worse, post installation.
- Animals on site – in some countries it is common for workers to bring their pets onto site. This can cause serious contamination issues. What can be worse, is if the animals are left behind at the conclusion of the project.
- Stagnant water – Stagnant water is a major contamination risk. The cleanroom construction zone should be made weather-tight as soon as possible. Any pooling of water due to leaks or spills needs to be cleaned up quickly.
- Broken glass – Broken glass on vinyl flooring can provide a long-term hazard if it becomes embedded in the material. Often this hazard comes in the form of fluorescent lighting tubes. Although they are becoming rarer with the advent of LED, these tubes are still used and provide the added hazard of traces of mercury.
- Welding and grinding – Welding and grinding need to be performed in specific locations where the contamination can be contained. If it has to occur in the presence of final internal cleanroom surfaces, complete protection of the surfaces must be provided. Frequently metal particles become embedded in vinyl flooring, stainless steel benches and silicone sealants. These then react with cleaning chemicals and provide further contamination through oxidation.
- Separation of stainless steel and other steel materials – For the same reason as above, stainless steel can become contaminated with iron particles. Client complaints about stainless steel rusting or orange staining is usually due to this.
- Rogue contractors – occasionally, some contractors who might be under the control of the client rather than the head contractor can make their way onto site. The CBP must ensure that all on-site personnel adhere to the CBP.

Operational sites

Where construction is occurring on an operational site, whether it is for an extension or renovation, extra controls will be required for both sides of the containment barrier.

For the construction side there needs to be a clear demarcation of the no-go zones for construction staff. Entry and exit paths should not mix with operational staff. In addition, service interruptions require careful planning and notification. An interruption to a cleanroom service can have serious ramifications to the product or the recipient of the product.

The construction barrier, the key transition between the operational and construction zones, requires careful design. It should be designed in conjunction with the client and their operational staff. The barrier should be regularly monitored for damage or deterioration.

There should be a direct line of communication between the construction team and the operational team. Project progress, changes and future schedule should be regularly communicated by the construction team. In addition, production schedules, maintenance downtime and shift changes should also be communicated by the operational team.

The operational team should perform risk assessments on their facility and process to ascertain where problems from the construction zone could impact their product/patient. Extra monitoring should be performed throughout the entire project, particularly around the construction barrier.

Commissioning and certification

The final stages of the cleanroom construction phase prior to handover, the commissioning and certification phase, is usually time critical. The success of this phase relies in part in the quality of the design and the skill of the construction team, but also to the controls applied during the build. As such, from a client perspective, it makes sense to ensure that the commissioning process is thorough and robust enough to ensure that the facility is indeed fit for purpose, therefore ensuring that successful certification is assured.

For the commissioning process the following should be considered:

- Gowning – gowning should be specified for the initial "air on" processes of blow through and airflow balancing. Once filters are installed the gowning should be equivalent to the intended gowning regime of the operational facility.
- Use of an "as-built" particle count – ISO 14644-1:2015[4] specifies the "as-built" operational state as "condition where the cleanroom or clean zone is complete with all services connected and functioning but with no equipment, furniture, materials or personnel present" (3.3.1). A suitable ISO classification should be able to be achieved before commencing the next steps of commissioning. It indicates the ability of the facility to achieve a certain level of cleanliness, but also that the room has been cleaned to an adequate level. Analysis of the ≥5.0 micron particle count will provide valuable information regarding the success of the cleaning effort.
- Cleaning responsibility transition – a time needs to be determined when the cleanroom cleaning becomes the responsibility of the client. This time should balance confirmation of when the facility is fit for purpose with when development of a facility cleaning program should commence.

Conclusion

A clean build protocol is an essential element in the delivery of successful cleanroom projects. It controls the necessary details to ensure a trouble-free cleanroom certification process.

There are a number of elements to the document and each must be addressed according to the stage of the project, the ultimate use of the cleanroom and eventual cleanroom classification.

It requires consideration from the earliest parts of the project and must be embraced by the entire project team to ensure its usefulness.

Acknowledgements

The author thanks Conor Murray of 3dimension for the use of his example Clean Build Protocol Matrix.

References

1. Whyte, W., Cleanroom technology: fundamentals of design, testing and operation, 2nd ed. Wiley, 2010.
2. International Organization for Standardization. ISO 14644-4:2001, Cleanrooms and associated controlled environments – Part 4: Design, construction and start-up.
3. International Organization for Standardization. ISO 14644-5:2004, Cleanrooms and associated controlled environments – Part 5: Operations.
4. International Organization for Standardization. ISO 14644-1:2015, Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration.

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

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Monitoring and controlling of vaporized hydrogen peroxide bio-decontamination cycles

Sanna Lehtinen

Abstract

This article starts by describing the advantages of using vaporized hydrogen peroxide for bio-decontamination where highly resistant pathogens including bacterial spores might be present. The advantages are its efficacy at room temperature, material compatibility, lack of toxic residue and the relative ease of validation. Several commercially available measurement technologies are described and compared and inline measurement sensors are compared with chemical indicators (CIs, biological indicators (BIs) and enzyme indicators (EIs). The article reports on the results of asking attendees at a Vaisala webinar: "How do you use H_2O_2 ppm measurement today?" and "What are the most important sensor features. Following on from this, the article examines the benefits of using sensors for monitoring and controlling bio-decontamination processes.

Vaporized H_2O_2 applications

Vaporized hydrogen peroxide (H_2O_2) is widely used in room and enclosure bio-decontamination. Typical applications include isolators, transfer hatches (air locks), and cleanrooms. These enclosures are common in life science industries, such as research and the production of medicines, vaccines and cell-based products. Another common use of vaporized hydrogen peroxide for bio-decontamination is hospitals, especially procedures or operating rooms, and patient rooms occupied by patients with communicable diseases. Vaporized hydrogen peroxide is also used in military applications, food and beverage manufacturing, transportation, and construction.

Why vaporized hydrogen peroxide?

Among other benefits, vaporized hydrogen peroxide is easy to use. It destroys numerous micro-organisms, including resistant pathogens such as viruses and bacterial spores. Bacterial spores are highly resistant, dormant structures (i.e. no metabolic activity) formed in response to difficult environmental conditions. The spores remain dormant until favorable environmental conditions occur, at which point they become metabolically active. Vaporized H_2O_2 has been found to be effective against these "sleeping bugs".

Another advantage of hydrogen peroxide is its efficacy at room temperature. Typical bio-decontamination cycle conditions are between 18 to 40°C. Additionally, validating vaporized H_2O_2 bio-decontamination is relatively easy. Further, H_2O_2 is compatible with many different kinds of materials, such as stainless steel. Finally, but increasingly important as industries focus more on operator health and environmental impacts, vaporized hydrogen peroxide leaves no toxic residue, decomposing naturally into water and oxygen. This is a huge advantage, especially in cleanrooms, isolators and transfer hatches used to manufacture medicines for human use. Any residues remaining after bio-decontamination should be washed away with highly purified water, such as WFI (water for injection).

Current measurement technologies

Because the effectiveness of vaporized H_2O_2 is well documented, there are several commercially available measurement technologies for vaporized hydrogen peroxide concentration, each with their own advantages and disadvantages. Table 1 shows a simple comparison of commonly used sensor technologies. Some are used to detect very small concentrations (ppb) and others measure higher concentrations (ppm). The benefits derived from an initial investment in equipment varies tremendously because equipment ranges from measurement sensors to complex analyzing devices.

It is worth mentioning that equipment based on NIR technologies, as well as gas analyzers, is not fit for

Table 1: Common technologies for measuring vaporized hydrogen peroxide.

Technology	Benefits	Challenges	Measurement parameters
Electrochemical cells	Sensor cell easy to change	Short lifespan, repeatability	ppm (H_2O_2)
NIR (near infrared technologies)	Stable, for R&D	Expensive, big size, not for low measurements	ppm (H_2O_2/H_2O), a (H_2O_2, µg/l), a (H_2O, g/m^3)
Gas analyzers (laser technology)	High selectivity, detection limit, low measurements	Expensive, big size, heavy, non-continuous measurement	ppb, only low level measurements
Capacitive thin-film polymer sensors	Several measurement parameters, stable, repeatable, small size	Not for safety applications (≤1 ppm)	RH%, RS%, °C, ppm (H_2O_2), absolute H_2O_2 and H_2O, H_2O ppm by volume, water vapor saturation pressure (H_2O and H_2O_2+H_2O), dew point temperature, vapor pressure (H_2O and H_2O_2)

monitoring and controlling bio-decontamination due mainly to price, size and/or H_2O_2 vapor concentration measurement range.

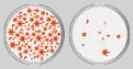
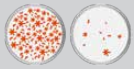
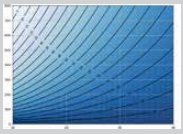
Proving bio-decontamination efficacy

The effectiveness of bio-decontamination cycles is evaluated based on the results of indicators (biological, chemical or enzyme indicators). Biological indicators (BIs), which may take various forms, contain *Geobacillus Stearothermophilus* spores. These rod-shaped, Gram-positive, spore-forming, and thermophilic (heat loving) bacteria are the accepted, worst-case organisms that must be used in bio-decontamination validation runs. It is accepted that if your process can destroy these organisms, it can basically handle all others. A 6-log reduction of BIs is proof that the cycle was effective.

While this is the industry norm, it is expensive and time-consuming to ensure an adequate number of indicators, then test, locate, collect, incubate and analyze the results. In addition, there are known issues with BIs, foremost are "rogue indicators" that will show spore clumps that will not be deactivated even after long exposure times. Because of the non-uniform quality of commercially available BIs, the industry norm in usage is to add triplicate BIs at worst-case scenario positions in bio-decontamination validation – see Coles.[1]

Companies that rely on bio-decontamination processes often also measure vaporized hydrogen peroxide concentration, indirectly or directly, in their target area. Indirect measurements are performed by evaluating the amount of hydrogen peroxide liquid on the heated plate (ml/minute, g/minute or g/m^3 created) during the vaporization processes. Direct measurements provide a value for the actual air ppm concentration of vaporized H_2O_2 in the target area. These direct measurements are obtained with an inline measurement sensor. Table 2 is a comparison of indicators to inline measurement sensors. Inline measurement sensors collect continuous measurement of H_2O_2 ppm concentration data, often with other parameters such as temperature and humidity. However, an inline sensor doesn't indicate log reduction. Biological and enzyme indicators are used to obtain this information, providing the data to calculate the log reduction of micro-organisms during decontamination cycles.

Table 2: Vaporized hydrogen peroxide indicators versus inline measurement sensors. RH = Relative Humidity, RS = Relative Saturation, SAL = Sterility Assurance Level.

	Chemical indicators (CI)	Biological indicators (BI)	Enzymatic indicators (EI)	Measurement sensor; Vaisala HPP272
PROS	Inexpensive Easy to use	Quantitative results	Quantitative results Instantaneous reaction	Continuous, inline measurement gives knowledge of the process throughout, allows for corrective action if process parameters aren't met
CONS	Gives "±" value only Non-quantitative	7-day wait for results, requires qualified lab and personnel	Manual process, no continuous measurement data	No value for log reduction, used in combination with BIs/EIs
Measurement results	Change in color; H_2O_2 concentration +/-	Reduction of micro-organisms (SAL min. 10^{-6}) 	Reduction of micro-organisms (SAL min. 10^{-6}) 	H_2O_2 ppm, Relative Humidity, Relative Saturation and Temperature 

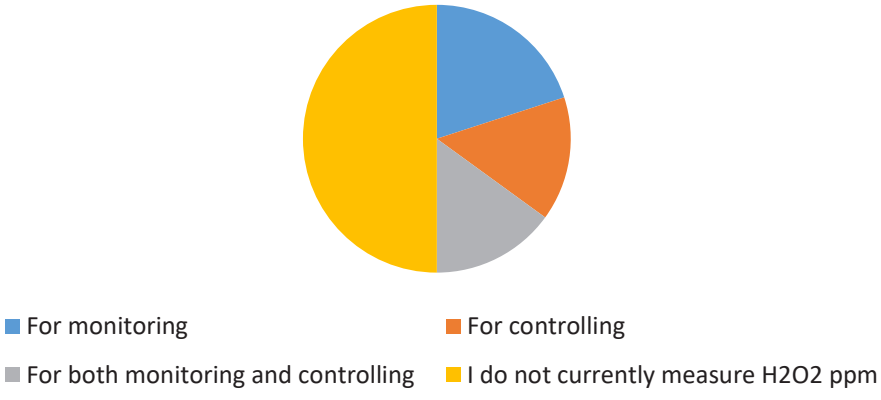


Figure 1: How do people use vaporized hydrogen peroxide ppm measurements today (n=20)?

Listening to Industry

In a webinar presented in June 2019 by Vaisala: "*From Monitoring to Controlling with vaporized H_2O_2 Sensors: Why, How & a Case Study*", attendees were asked: "**How do you use H_2O_2 ppm measurement today**"? Figure 1 shows attendee answers. Half of the respondents do not measure H_2O_2 ppm concentration at all. For those who do measure ppm during bio-decontamination, 20% use it for monitoring, 15% for controlling and 15% for both monitoring and controlling purposes. If these results demonstrate the current state of industries using vaporized hydrogen peroxide for bio-decontamination, this indicates an enormous opportunity for improvement that can become a competitive advantage for firms using vaporized hydrogen peroxide in bio-decontamination. With inline monitoring and control of vaporized hydrogen peroxide in real time, continuous concentrations can provide better process control, improved documentation for change control, validation and compliance, as well as time and cost savings in validation.

Monitoring and controlling of bio-decontamination cycles

When we say monitoring we usually mean that process parameters are followed continuously during a process using an inline measurement device. Inline measurement involves a sensor located inside the real test environment throughout the process. In bio-decontamination, inline measurement can provide values for related process

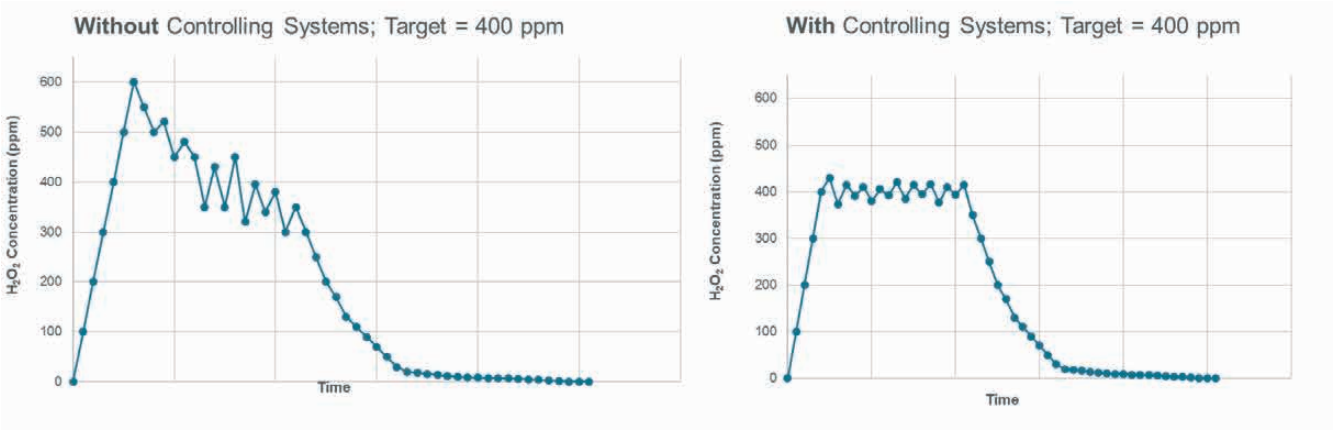


Figure 2: Example of two bio-decontamination processes with and without inline measurement for process control, both with a target level of 400 ppm of vaporized H_2O_2

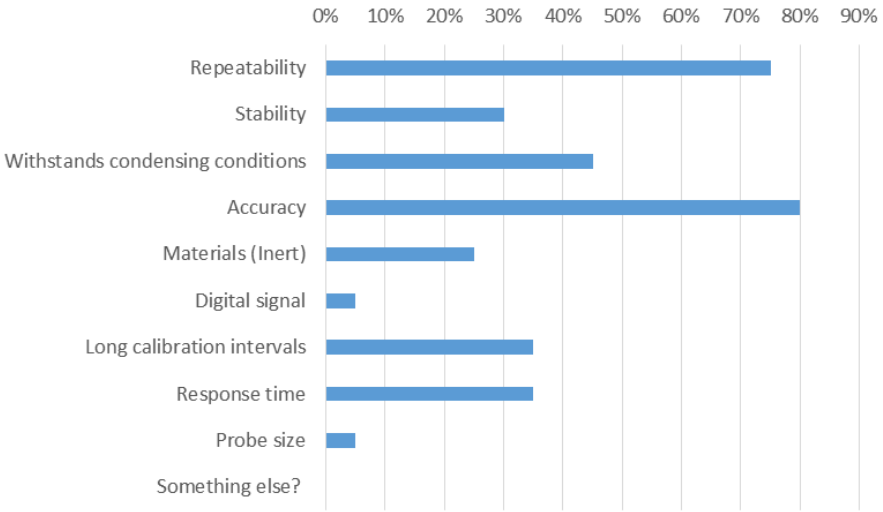


Figure 3: What are the most important features for a measurement sensor used for controlling purposes? (n=20, multiple selections enabled)

parameters such as H_2O_2 vapor concentration (ppm), humidity and temperature.

With inline measurements providing continuous measurement data, operators see real-time data throughout the cycle. An understanding of KPIs (key performance indicators) like temperature, humidity and H_2O_2 ppm values throughout a cycle gives assurance that the process is going according to plan. Often this can decrease the number of biological, chemical or enzyme indicators required in recurring validation runs because the inline measurement data is available. Further, inline monitoring data enables good documentation practices, recording and reporting during batch manufacturing and validation runs.

In addition, monitoring processes also between validation runs enables you to see changes in the environment (°C, %RH) that might have a tremendous effect on process control. This idea was demonstrated by Nieskes.[2] More information about how environmental conditions can affect the achievable ppm concentrations can be found in a Vaisala white paper.[3]

A sensor with good repeatability not only provides monitoring data, but can be used to control the decontamination process. It is increasingly common for companies using inline bio-decontamination measurement sensors to use sensor data to control a vapor generator in a room or isolator. With the sensors integrated to control systems, the H_2O_2 vapor generators can be controlled, not based on predetermined injection profile of H_2O_2 liquid, but based on actual inline measurement values. This method provides flexibility and enables a fast response to any changes in environmental variables during decontamination cycles. Inline measurement used to control processes also automatically decreases the variability of conditions from batch to batch and leads to more stable ppm levels in processes. Validation efforts can be reduced by having reliable data throughout a process.

This method of monitoring and controlling critical process parameters follows the PAT (Process Analytical Technology) ideology. Equipped with real-time data on processes, operators can immediately respond to changes or unexpected events. Figure 2 offers an example of two bio-decontamination processes; one with and one without inline measurement used for control. As shown, processes controlled based on real-time measurements facilitate more stable ppm concentrations for bio-decontamination cycles. When the process is controlled by the actual conditions, rather than pre-determined calculations and assumptions, the system is made more efficient at achieving process requirements.

Industry speaks: What is needed in a sensor?

When attendees in Vaisala's webinar mentioned earlier were asked: "**When measuring for control, the most important sensor features are…**" the answer was a clear preference for accuracy and repeatability, as shown in Figure 3.

Based on this feedback, the three most important features of a sensor used for control are: accuracy, repeatability, and withstanding condensing conditions. Other characteristics like long calibration intervals, response time, stability, and inert sensor materials were selected by responders. Digital signal and probe size might also be important in some circumstances.

* See https://www.vaisala.com/sites/default/files/documents/PEROXCAP-TechNote-B211653EN-A-LOW.pdf

There are a number of companies that manufacture instruments for measuring the concentration of hydrogen peroxide vapor. For obvious reasons, the author is most familiar with those manufactured by Vaisala. The Vaisala HPP270 series probes, with PEROXCAP® sensor using thin-film polymer technology, were designed to fulfill all of the requirements listed.* This technology represents a unique measurement principle and is created based on Vaisala's proven HUMICAP® humidity measurement technology. Three-in-one HPP272 sensors measure hydrogen peroxide concentration (ppm), and temperature and humidity, referring to both relative humidity and relative saturation. This gives exact hydrogen peroxide readings in ppm throughout the whole bio-decontamination cycle. Dew point and vapor pressure measurements are also possible.

"Based on the survey experience of sterilization and bio-decontamination professionals,there is still room for improvement in the use of monitoring and control for bio-decontamination processes."

A Finnish vapor generator manufacturer Cleamix uses Vaisala's HPP272 sensor in controlling H_2O_2 vapor generator cycles. While selecting a sensor for their vapor generators, their control sensor requirements were:

1. Sensors need to be rugged enough to maintain accuracy through multiple processes.
2. Multiple measurement parameters are required to provide better understanding of process conditions (ppm, temperature, %RS, %RH, dew point, vapor pressure).
3. Sensors must provide a digital output signal. Analog signals are subject to deterioration from noise during transmission and write or read cycles. Communication should be achieved via Modbus RTU. HPP272 and a portable vaporizer that can use RS-485 allowing communication in a local area network, nearly resistant to electromagnetic interference.
4. Superior sensor stability, with calibration only once a year.
5. Ability to control condensation. The sensor described measures %RS (relative saturation) that gives the ability to maintain dry conditions with minimum condensation in enclosures or rooms during bio-decontamination processes.

Future trends for monitoring and controlling bio-decontamination processes

Bio-decontamination cycles are still often monitored and controlled by indirect measurements of added H_2O_2 liquid (mass or volume per time or air volume) on the heated plate. However, monitoring and control of bio-decontamination cycles based on inline, real-time measurement increases our knowledge of bio-decontamination processes, allowing users to witness and respond to changes in the environmental conditions. It is well understood that temperature and humidity have a huge effect on validated bio-decontamination cycles. Controlling bio-decontamination cycles based on real-time measurement can decrease batch-to-batch variability and simplify validation. For these reason both OEMs (Original Equipment Manufacturers) and end users are increasingly using inline monitoring with control in their vaporized H_2O_2 bio-decontamination processes for vapor generators, isolators and transfer hatches.

Based on the survey experience of sterilization and bio-decontamination professionals, there is still room for improvement in the use of monitoring and control for bio-decontamination processes. Several measurement devices are available on the market such as Vaisala's HPP272, so lack of technology is not the problem. The PAT ideology is proven and accepted in drug manufacturing. We believe that bio-decontamination, as a critical process, is moving toward adopting PAT mechanisms to ensure quality, control costs and reduce waste.

References

1. Coles, T. (2017). Enzyme indicators (EIs) – an advanced replacement for biological indicators (BIs) in the qualification of vapour phase hydrogen peroxide bio-decontamination. Clean Air and Containment Review, Issue 31, pp 4-5.
2. Nieskes. R. Field Comparison of Hydrogen Peroxide Measurement Systems for Isolators. https://www.vaisala.com/sites/default/files/documents/VIM-G-Comparison-H_2O_2-Measurement-for-Isolators-Success-Story-B211802EN-A.pdf
3. Vaisala White Paper. (2019). Understanding Critical Process Parameters in Vaporized Hydrogen Peroxide Bio-decontamination. https://www.vaisala.com/sites/default/files/documents/Understanding-Critical-Measurement-Parameters-Vaporized-Hydrogen-Peroxide-Bio-decontamination-B211784EN-A.pdf

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Risk and science-based validation of cleanroom garments

Milenko Pavicic and Thierry Wagner

Abstract

Important quality attributes of cleanroom garments that to worn during the manufacture of sterile medicines include: cleanliness; sterility; particle and microbial filtration efficiency; durability; usability; and comfort. Important risk factors related to cleanroom garment systems include gowning processes and related activities, such as laundering, packing, sterilization, repairs, storage, handling and logistics, as well as change management. Because many factors contribute to the overall quality, adequacy and suitability of cleanroom garment systems, a thorough and focused validation of cleanroom garments is critically important.

After providing a review of current and emerging regulations and standards, this article proposes a risk- and science-based quality-by-design approach for the development, implementation and validation of sterile cleanroom garment systems. With this approach, more effort is spent at the front-end during the design phase as well as during design qualification. This will lead to designed-in risk reductions; enhanced scientific knowledge on selected technical solutions; and better awareness of limitations and residual risks. As a result, there should be fewer issues during cleanroom qualifications and process validations, leading to more effective routine operations as well as improved patient safety. The proposed approach, if implemented correctly, is not only the correct strategy to effectively control contamination risks related to people, but also an adequate response to the latest regulatory requirements.

Introduction

Parenteral medicines are administered through injection, infusion or implantation, and must be sterile and pure to assure product safety. Therefore, the manufacture of parenteral medicines requires a controlled and validated clean production environment. Sterile medicines can be manufactured by terminal sterilization. In this case, the product is sterilized in its final packaging, resulting in a sterility assurance level (SAL) of at least 10^{-6}. If terminal sterilization of the final product is not possible, aseptic manufacturing is the only alternative. In aseptic production, exposure of the sterile product to the environment may take place during different stages of the manufacturing process (i.e., from preparation of the product using sterile ingredients to filling the product in its final container). In Europe, exposure of sterile products to the environment is only allowed in EU GMP grade A zones placed in a grade B cleanroom or in an isolator.[1]

Aseptic manufacturing of sterile products requires a high level of contamination control. Figure 1 shows the important elements that must be addressed in a contamination control strategy to assure purity of the products, sterility of sterile products and good microbiological quality of non-sterile products.

According to current Good Manufacturing Practices (GMP) guidelines, (EU,[2] US,[3] Japan,[4] WHO[5,6]), processes, equipment, facilities and manufacturing activities should be managed in accordance with Quality Risk Management (QRM) principles[7] that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. A quality-by-design approach,[8] combined with effective risk management, should be applied to ensure the safety, quality and efficacy of sterile products. This comes from the belief that quality cannot be tested into the product, it can only be built into the design of products and the processes used to produce them. Risk assessments must be performed to identify, assess, eliminate and control

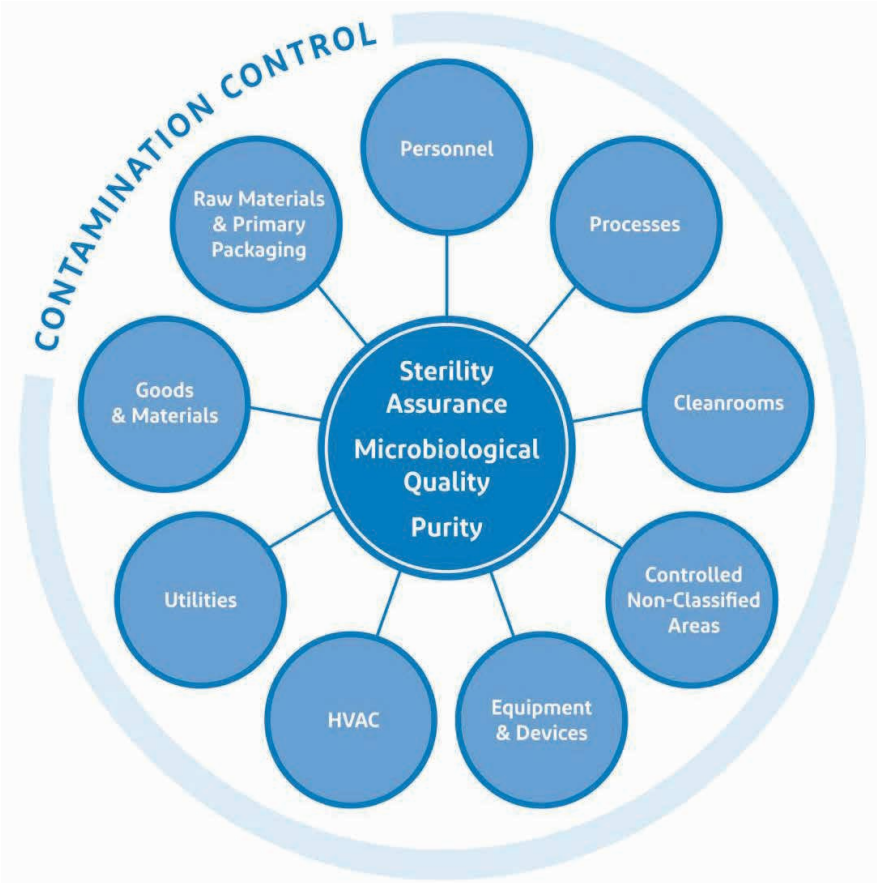

Figure 1: Important elements of a contamination control strategy for sterile manufacturing

contamination risks from the design phase of an aseptic process; to monitor and detect contamination; and to establish process requirements and acceptance criteria for all elements of a sterile manufacturing process. Risk assessments should be documented as well as maintained and should include the rationale for decisions taken in relation to mitigating risks, discounting of potential risks and residual risk.

An important risk factor in sterile manufacturing is personnel. People can cause contamination of the production environment and products in many ways.[9] Contamination from people mainly consists of hair, skin cells, skin flakes, saliva, sebaceous matter, sweat, particles from clothing and many different exogenous particles and substances picked up in the environment. These contamination sources mostly contain different endogenous (i.e., commensal) and exogenous microorganisms present in numbers which vary from a few (e.g., skin cell) to thousands (e.g., sweat) or even millions e.g., saliva). Therefore, it is important that people working in an environment, where sterile products are manufactured, wear adequate cleanroom garments.

Contamination control related to people starts with good personal hygiene based on adequate hygienic procedures, such as hand washing and hand disinfection; aseptic behavior; aseptic skills; and a good working discipline. Adequate cleanroom garments, as well as undergarments are critically important to minimize the risk of contaminating the environment or products with contamination generated by people. Cleanroom undergarments[10] serve as a first barrier against contamination from people. The cleanroom garments must form a very robust barrier between the person and the environment.

Additional protective measures, such as adequate cleanroom footwear, cleanroom socks, head coverings, face masks, eye coverings and (sterile) gloves, may be necessary or required from a regulatory point of view, to minimize the contamination risk.

Important quality attributes of cleanroom garments are cleanliness (free from chemicals, particles, pyrogens, fibers); sterility; particulate and microbial filtration efficiency; durability (tear, puncture, seam strength, abrasion); and comfort. Personal protection against chemical or biological agents may also be a relevant quality attribute. A quality-by-design approach[8] combined with effective risk management,[7] should also be applied to the design, selection and implementation of adequate cleanroom garments.

With the quality-by-design approach, more effort is spent at the front-end, in the design phase as well as in the design qualification, leading to designed-in risk reductions; better understanding of key aspects, limitations and residual risks; and fewer issues during final simulation runs and routine operations. This approach also creates the basis for proper root cause analysis (in case of issues) and adequate change management.

Other important risk factors related to cleanroom garments include gowning procedures and processes and activities related to cleanroom garments, such as laundering, packing, sterilization, repairs, storage, handling and logistics. Because many factors contribute to the overall quality, adequacy and suitability of cleanroom garment systems, a risk- and science-based validation of cleanroom garment systems is very important.

This article provides an overview of the various qualification, validation and monitoring aspects of cleanroom garments.

Current regulatory guidance for validation of cleanroom garments

Depending on the jurisdiction, aseptic production of sterile medicines must meet various regulatory requirements such as those set out in Annex 1 of the EU Guidelines to Good Manufacturing Practice[1] or in the U. S. Food and Drug Administration (FDA) Guidance for Industry on sterile drug production[3].

The FDA guidance outlines various recommendations for gowns, such as proper gown control; no unreasonable contamination risk to the gown; providing a barrier between the body and exposed sterilized materials; and preventing contamination from particles generated by, and microorganisms shed from the body. Gowns should be sterilized and non-shedding. Methods used to don each gown component in an aseptic manner should be detailed. Manufacturers should implement an aseptic gowning qualification program to assess the ability of a cleanroom operator to maintain the quality of the gown after performance of gowning procedures, including periodic requalification and microbiological monitoring of strategically selected locations on the gown.

The current EU GMP guidelines require sterile (sterilized or adequately sanitized) garments to be provided for grade A/B areas and changing and washing to follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas. It further requires that clothing and its quality be "appropriate" without defining what would be considered appropriate. It also requires clothing to "be worn in such a way as to protect the product from contamination". In terms of attributes, "protective clothing should shed virtually no fibers or particulate matter and retain particles shed by the body". Reusable garments are required to be cleaned and handled in such a way that the garment does not gather additional contaminants that can be shed later.

The current EU GMP Annex 1 for the Manufacture of Sterile Medicinal Products[11] includes little guidance on cleanroom garment qualification except that it needs to be "appropriate".

The new draft EU GMP Annex 1[12] published for consultation in December 2017 explicitly introduces the application of QRM principles and provides more details on gowning, including the requirement that gowning is part of a holistic contamination control strategy. It further requires that:

- Personnel are trained on gowning practices, which must be assessed
- Personnel are qualified through a successful aseptic process simulation test
- Microbial monitoring of personnel is performed

In addition, this new draft EU GMP Annex 1[12] requires that garments are visually checked for cleanliness and integrity. It also provides several new requirements regarding clothing of grade A/B; body parts that should be covered; the prevention of droplets, particles and fibers; and the folding of packaged garments to make sure that "contact to the outer surfaces of the garment is reduced to a minimum".

A key addition is the requirement that "reusable garments should be

replaced at a set frequency determined by qualification or if damage is identified". This requires manufacturers to produce data regarding the effect of reprocessing on the fabric and the overall garments.

However, there is little guidance on how to qualify those garments other than stating in subclause 4.11 that "clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination".

The Japanese Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing,[4] developed by a task force of Japanese experts, is an extensive document covering all areas of aseptic processing. It includes recommendations on gowning, operations, monitoring and controls that are comparable to other standards. It provides some interesting design recommendations on gowning and de-gowning areas and highlights the need to establish appropriate control procedures, including visual inspection. It also defines maximum allowable frequency of steam sterilization for reusable materials, such as aseptic gowns, to "ensure maintenance of specifications, safety, and intended functions after repeated exposure to steam at its maximum intensity".

ISO 14644-5[13] includes an informative annex B on cleanroom clothing requirements that provides some useful guidance on aspects to consider during qualification of such clothing. It provides guidance on barrier properties; evaluation of electrostatic properties; some guidance on fit and function; and helpful guidance on construction, finishing of seams and general design criteria that can be used to establish URS. It proposes use of the dispersal chamber or body box[14] as a simulation procedure to evaluate performance; recommends that shelf life of sterile packaging be determined; and includes considerations on thermal comfort and some guidance on cleaning, referring to IEST-RP-CC003.4.[14]

ISO 13408-1[15] on general requirements of aseptic processing includes some general requirements on cleanroom garments but does not provide much guidance on cleanroom garment system qualifications.

IEST-RP-CC003.4 "Garment Systems Considerations for Cleanrooms and Other Controlled Environments"[14] provides guidance on design, selection, specification, maintenance and testing of garment systems. It includes useful guidance on material qualification attributes, considerations on processing (cleaning, re-sterilization, etc.), gowning system specifications and quality management. Appendix B proposes various tests for assessments of particle penetration and garment cleanliness, which includes the well-known and very useful body box test,[16,17] that allows simulation of the actual use of the garment, as well as the Helmke drum test.[18] Overall, IEST-RP-CC003.4[14] is the most useful document to support qualifications of cleanroom garment systems.

The EU general guidance on validation (GMP Annex 15[19]) provides the general framework that we will apply to the qualification of cleanroom garment systems.

Validation approach for cleanroom garments

The main stages of validation of equipment, facilities, utilities or systems are:

- Definition of User Requirements Specification (URS)
- Design Qualification (DQ)

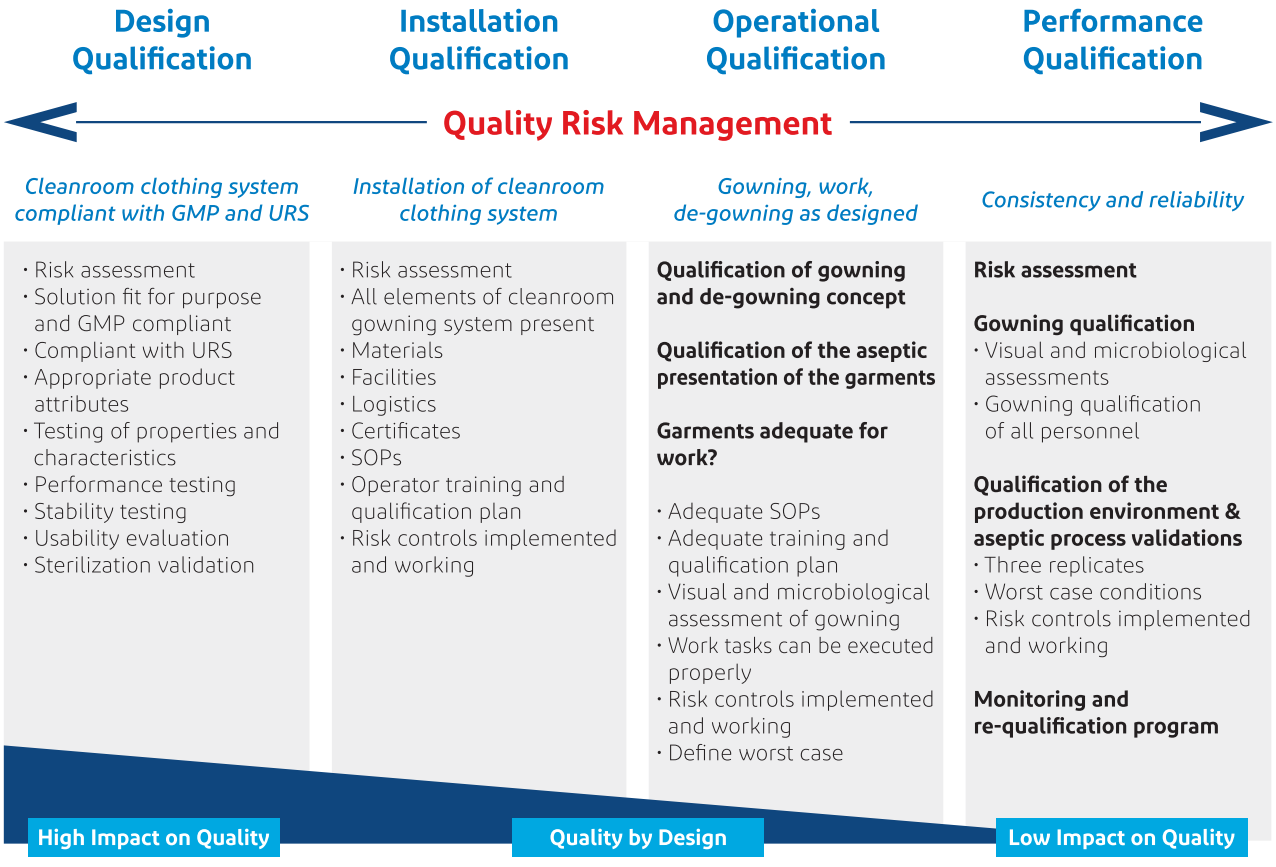

Figure 2: Overview of the different validation stages for cleanroom garments used in EU GMP grade A/B cleanrooms

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

This approach is also appropriate for cleanroom garments. Some stages of the validation can focus mainly on the quality of the cleanroom garment itself, but in other stages, the other items of the cleanroom clothing system (i.e., cleanroom undergarments, footwear, socks, head coverings, face masks, eye coverings, gloves and other accessories) must be included. The packaging (sterile and non-sterile barriers) of the cleanroom garments should be part of the validation. An overview of the different validation stages and validation items for cleanroom garments is given in Figure 2. Each validation stage must be formally finalized before progressing to the next stage.

The GMP (EU, US, Japan) guidelines state that QRM7 should be used for qualification and validation activities. If changes occur during the project phase or during commercial production (e.g., change of garment design, fabric, zipper type, packaging, laundering process or sterilization process), the risk assessments must be repeated to determine if additional validation must be performed. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

For critical goods and materials, such as cleanroom garments, it is also important to qualify the supplier. This qualification should provide an appropriate level of confidence that the supplier is able to supply cleanroom garments with consistent quality and acts in compliance with regulatory requirements. A supplier qualification should also include qualification of subcontractors, suppliers of base materials (e.g., fabric and garment accessories) and outsourced service providers (e.g., laundries and sterilization facilities).

User Requirements Specification (URS)

The specification for cleanroom garments should be defined in a User Requirements Specification (URS). The URS is a document that specifies requirements necessary and sufficient to create a feasible design, meeting the intended purpose of the material, equipment, utility or system. The URS may also include additional requirements, such as protection of people against chemical and/or biological agents.

An example of a URS for cleanroom garments is given in Table 1.

Cleanroom garments for use in EU GMP grade A/B cleanrooms should

Table 1: Example of a URS for cleanroom garments used in EU GMP grade A/B cleanrooms

General
1. The clothing must consist of a suit or coverall; a hood that can be firmly and reliably tucked into the neck of the suit; and boots. The hood may also be attached to the suit. It must be possible to tuck the trouser legs firmly and reliably into the boots. Boots shall have an anti-slip sole.
2. The garments may be reusable or single-use.
3. Unpacking and gowning must be conducted in an aseptic manner.
4. The garments must fit well and be available in different sizes (e.g. XS to XXL).
5. The clothing must be comfortable to wear (e.g., ease of movement, thermal, tactility).
6. Garments must be traceable, including number of laundering and sterilization cycles.
Cleanliness and sterility
1. The garments should be clean (low levels of ions and organic extractables).
2. The garments shall not shed fibers, including filaments of the fabric and thread.
3. The garments shall not shed too many particles (≥ 0.5µm and ≥ 5µm). Maximum number of particles (≥0.5µm and ≥ 5µm) must be specified.
4. The garments shall be sterile (sterility assurance level ≤ 10^{-6}).
5. The garments shall have a low pyrogenicity.
Barrier properties
1. The garments shall have a good particulate and bacterial filtration efficiency.
Packaging
1. The garments shall be double or triple sterile packed.
2. The sterile packaging must be robust and should endure common manipulations without jeopardizing the integrity of the packaging.
3. The sterile packaging shall be clean.
4. The sterile packaging shall not shed too many particles (≥ 0.5µm and ≥ 5µm) and shall not shed fibers. Maximum number of particles (≥ 0.5µm and ≥ 5µm) must be specified.
5. The space between the sterile packaging shall not contain too many particles (≥ 0.5µm and ≥ 5µm) and should not contain fibers. Maximum number of particles (≥ 0.5µm and ≥ 5µm) must be specified.
6. The sterile packed garments must be packed into a clean, low bioburden bag that is present in a firmly closed clean box.
7. The box and the last sterile packaging of the garments must be labeled with a clear description of the manufacturer, content, size, batch number, production date, expiry date, storage conditions and indicator that the sterilization was done.
Identification
1. Each garment must have an unique identification number.
2. Labels must be firmly attached to the packaging or exist as an integral part of the packaging.
3. Labels must be clean and should not shed too many particles (≥ 0.5µm and ≥ 5µm) and should shed no fibers. Maximum number of particles (≥ 0.5µm and ≥ 5µm) must be specified.
4. Labels and printed text must be resistant to disinfectants that are commonly used (e.g., 70% alcohol, 6% hydrogen peroxide solution or a 600-ppm hydrogen peroxide vapor, 1000 ppm active chlorine).

adequately protect the environment and products against contamination from people. A trained and qualified operator, wearing a nonwoven polypropylene head cover, clean polyester two-piece undergarment, clean dedicated socks, double sterile gloves, a sterile face mask and sterile goggles, must be able to work at least three hours in the same set of cleanroom garments without causing unacceptable (cGMP) levels of contamination of the garments and the aseptic working environment.

Design Qualification (DQ)

During DQ, compliance of the cleanroom garment design with cGMP must be demonstrated and documented, and the requirements of the URS must be verified. The purpose of the DQ is to confirm that the selected cleanroom garment is qualified for the intended use. Therefore, it should also include tests to simulate the intended use. The DQ must be executed and authorized by suitably qualified persons who are knowledgeable enough to challenge the proposed design and its performance.

Following the model of design validations of sterile barrier systems described in ISO 11607-1,[20] it is recommended to split the DQ into four key areas: material qualification, performance testing, stability testing and usability evaluation. For reusable garments, reprocessing should be the subject of a separate DQ by the manufacturer and IQ-OQ-PQ by the supplier.

The material qualification includes the qualification of key characteristics and key properties of the materials and fabrics used, the cleanroom garments and the packaging.

Performance testing includes testing of the cleanroom garments and the packaging under simulated and standardized conditions using standardized test methods.

Stability testing must be performed to assure that key material characteristics and properties remain sufficiently stable during the life cycle. Characteristics and properties that change over time (e.g., deterioration of filtration efficiency of garments due to repeated laundering and sterilization; wear of the garments due to multiple use; and changes to the integrity of the sterile packaging during storage due to long-term effects of gamma irradiation) should be validated under worst-case conditions. Information for material qualification, performance testing and stability testing normally should be provided by the supplier. It is important to verify that the data has been generated using validated and sound scientific methods.

The purpose of the usability evaluation is to assure that the cleanroom garments can be used with acceptable remaining contamination and safety risks due to the design of the garments and the established gowning, working and de-gowning procedures. The usability evaluation is typically done by the end-user. However suppliers can also evaluate their garments for the intended use and supply that data to users for verification and further mitigation of identified risks during gowning and operations. The concept of usability engineering and testing has developed into a well-accepted way to successfully reduce use-related risks by reviewing these risks during the design phase and systematically reviewing the design and use of the product against those identified risks (see also IEC 62366-1 on usability engineering of medical devices[21]).

Relevant items to be covered for each of the four areas are presented in Table 2. A summary is given in Figure 2.

Reusable versus single-use cleanroom garments.

The validation of reusable cleanroom garments is more complex and more extensive compared to single-use cleanroom garments. Repeated laundering, repeated sterilization, multiple use and repairs influence the quality of reusable cleanroom garments. This also means that the influence of these factors must be validated throughout the entire

Table 2: The four key areas of the Design Qualification (DQ) for cleanroom garments used in EU GMP grade A/B cleanrooms

Material qualification	Performance testing	Stability testing	Usability evaluation
Cleanroom garments • Fiber and particle shedding • Sterilization compatibility • Sterility assurance level • Pyrogenicity • Particle filtration efficiency • Bacterial filtration efficiency • Porosity • Surface resistivity • Perforation resistance • Mechanical strength • Chemical resistance • Protection against biological agents	**Cleanroom garments** • Body box testing • Helmke drum test	**Single-Use garments** • Properties and characteristics at the end of shelf life **Reusable garments** • Properties and characteristics after maximum number of laundering and sterilization cycles	**Use scenarios** • Transfer to classified storage area • Readability of label • Easy opening of packaging • Aseptic unfolding of garments • Gowning • Donning additional accessories (e.g., sterile gloves, face mask, goggles) • Work situations • Safety, biosafety • De-gowning
Packaging • Fiber and particle shedding • Bioburden • Penetration of commonly used disinfectants **Sterile packaging** • ISO 11607-1	**Sterile packaging** • Influence of transport on integrity/sterility (ISO 11607-1)	**Sterile packaging** • Packaging integrity/sterility at the end of shelf life (ISO 11607-1)	**Packaging** • Aseptic presentation of garments (multiple layers)

life cycle in the frame of the stability testing and the performance testing at the end of the life cycle. In addition, not only the supplier of the garments but also the cleanroom laundry, sterilization facilities and repair service must be qualified. Reprocessing should be the subject of a separate DQ by the manufacturer and IQ-OQ-PQ by the supplier.

Installation Qualification (IQ)

The IQ for cleanroom garments is a formal check to verify if all required elements of the cleanroom gowning system are present. These include the gowning and de-gowning facilities; certificates of conformance and/or analysis; implementation of instructions from the supplier; standard operating procedures for gowning and de-gowning; logistical processes for the cleanroom garments and related accessories; and the operator training and qualification plan. Risk assessments that were executed as part of the DQ of the cleanroom garments should be finalized and risk controls should be implemented.

In addition, it is important to verify that the correct materials have been received for performing the OQ and PQ (i.e., the correct cleanroom garments, correctly folded, in the correct packaging and correctly labeled). A summary of items to be included in the IQ is given in Figure 2.

Operational Qualification (OQ)

During the OQ, the objective is to qualify the gowning and de-gowning concept. For this purpose, all relevant steps of the gowning and de-gowning process, including logistics, should be qualified. In addition, the aseptic presentation of the garments should be qualified. To validate the aseptic gowning procedure, at least three independent, consecutive, successful visual and microbiological assessments for at least one person who is trained for aseptic gowning should be performed. The OQ should also include a formal assessment to verify that different work tasks can be executed properly from a practical point of view (e.g., moving, bending, stretching and lifting). It is recommended to perform this assessment with all available sizes of the cleanroom garments and with people of different body shapes. A summary of items to be included in the OQ is given in Figure 2.

Performance Qualification (PQ)

During PQ, the objective is to validate the performance of the cleanroom garment system when it is actually in use. The requirements specified in the URS must be complied with fully.

The PQ of cleanroom garments consists of two stages. In the first stage of the PQ, compliance with aseptic gowning procedures should be assessed and confirmed. This gowning qualification must involve both a visual and microbiological assessment. The visual assessment is to qualify that people don the cleanroom garments in a correct and aseptic manner, which shall be described in detail in a gowning procedure. After gowning, the microbiological quality shall be assessed by taking surface samples from several locations on the cleanroom garments, gloves, goggles and face mask. Locations must be determined based on a risk assessment.

Each person accessing an EU GMP grade A/B environment must perform a gowning qualification. For the PQ, it is important to determine how many gowning qualifications are required to demonstrate compliance with the requirements. Typically, initial gowning qualification is performed three times for each person. It is important that adequately trained, qualified and experienced persons execute the PQ to exclude failures due to causes other than quality issues with the cleanroom garments.

The second stage of the PQ focuses on the validation of the microbiological quality of the gowned personnel with the garments and other accessories (e.g., gloves, face mask, goggles) during the actual work (e.g., aseptic compounding, aseptic filling, cleaning and disinfection, and other activities).

The second stage of the PQ also includes validation of the microbiological and particulate quality of the environment people are working in and the execution of aseptic process validations (i.e., media simulations or media fills). The number of runs for these validations must be determined based on a risk assessment. Typically, these validations are performed three times. To exclude failures due to causes other than quality issues with the cleanroom garments, it is important that adequately trained, qualified and experienced personnel execute the PQ in areas with an excellent quality history.

The PQ is typically done under worst-case conditions. These worst-case conditions must be determined based on a risk assessment. Also, the actions that should be taken if established criteria are not met during the PQ, must be defined before executing the PQ. Only after a successful PQ can the cleanroom clothing system be formally implemented. A summary of items to be included in the PQ is given in Figure 2.

Revalidation and change management

The cleanroom clothing system should be evaluated at an appropriate frequency (e.g., annually or biennially) to confirm that it remains in a state of control. Gowning qualifications shall be repeated at least annually and even more frequently in cases where there is doubt about the quality of the aseptic gowning process or aseptic gowning skills of specific persons. The cleanroom clothing system is included in validations which must be performed periodically (i.e., cleanroom qualifications under dynamic conditions and aseptic process validations).

Changes must be reviewed critically and may lead to revalidations that are more or less extensive, depending on the type of change. Properly and well documented DQs, as well as IQ-OQ-PQ, are the basis for successful change management.

Monitoring

Personnel monitoring must be part of the environmental monitoring program[1, 3, 22]. The microbiological quality of cleanroom garments for persons working in a grade A/B environment must comply with the EU GMP1 grade B limit for surface samples (i.e., the action limit is 5 CFU/contact plate). Alert limits are usually lower (e.g., 2 or 3 CFU/contact plate). Cleanroom garments, face masks, goggles and gloves are typically sampled at the conclusion of activities in a grade A/B area, but just before leaving the area. For this "exit monitoring," contact samples are taken from different locations. Sample locations must be determined based on a risk assessment. After sampling, the person must leave the area to prevent spreading contamination due to medium residues present on the cleanroom garments.

Gloves should be sampled after performing activities in a grade A environment to verify the quality of the aseptic conditions and aseptic handling. Gloves of operators working in a grade B environment should also be monitored during each work shift. Gloves are typically sampled with a frequency ranging from once to multiple times per work shift.

In addition to personnel monitoring, samples from several locations in the cleanroom should be taken to determine if the production environment and processes are in control. Sampling is typically performed during (passive and active microbiological air sampling and particle counting) or at the conclusion (surface sampling) of operations but may also be performed under static conditions (i.e., in the at-rest state of an area), to verify cleanliness.

In the case of non-conformities, assessments must be done to determine root causes. The cleanroom clothing system as a potential root cause should be included in these assessments.

It is also recommended to assess if gowning procedures, cleanroom behavior guidelines and aseptic procedures are followed correctly. These visual assessments should be done on a regular basis.

Conclusion

A science- and risk-based quality-by-design approach for the development, implementation and validation of sterile garment systems for EU GMP grade A/B aseptic processing areas is not only the correct approach to effectively control contamination risks related to people, but also an adequate response to the latest regulatory requirements. The new EU GMP Annex 1 draft is based on QRM principles and introduces the concept of a holistic contamination control strategy that considers all aspects of contamination control over the entire life cycle based on thorough technical knowledge and sound process know-how. Considerable efforts will be required by manufacturers to update their technical files, with cleanroom garments being just one of the many aspects.

With a risk-based quality-by-design approach applied to cleanroom garment systems, more effort is spent at the front-end, in the design phase, as well as in the design qualification. This will lead to designed-in risk reductions; better scientific knowledge of key aspects, attributes, limitations and residual risks of the selected technical solutions; and fewer issues during cleanroom qualifications, process validations and routine operations. In case of failures, it can be difficult to determine the root cause or the elements that have failed. That's why a quality-by-design approach, with focused and extensive design qualifications for each element, is the only way to successfully and systematically reduce the risk of failure. This approach also creates the foundation for adequate and risk-based change management.

References

1. European Commission. Eudralex - Volume 4 - EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use - Annex 1: Manufacture of Sterile Medicinal Products (corrected version 1. March 2010). In: Commission E, ed. Brussels2008:16.
2. European Commission. EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines - Chapter 1 Pharmaceutical Quality System. In. Vol SANCO/AM/sl/ddg1.d.6(2012)8603622013.
3. U.S. Food & Drug Administration (FDA). Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. In: FDA, CDER, CBER, ORA, eds. Rockville: FDA; 2004.
4. Task Force on Sterile Pharmaceutical Products by Aseptic Processing. Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing (1st revision of original version). In. Japan2006.
5. World Health Organization (WHO). WHO Technical Report No. 986 - Annex 2 -WHO good manufacturing practices for pharmaceutical products: main principles. In:2014:60.
6. World Health Organization (WHO). WHO Technical Report No. 996 - Annex 6 -WHO Good trade and distribution practices for pharmaceutical starting materials. In:2016:16.
7. International Council for Harmonisation (ICH). ICH Q9 - Quality risk management. In:2005.
8. International Council for Harmonisation (ICH). Pharmaceutical Development Q8(R2). In: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ed2009.
9. Reinmüller B, Ljungqvist B. Modern Cleanroom Clothing Systems: People as a Contamination Source. PDA Journal of Pharmaceutical Science and Technology. 2003;57(2):114-125.
10. Moschner C. Cleanroom Undergarments. Cleanroom Technology,. 2002.
11. Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme. Guide To Good Manufacturing Practice For Medicinal Products - Annexes. In. Guide To Good Manufacturing Practice For Medicinal Products. Geneva: PIC/S Secretariat; 2017.
12. European Medicine Agency (EMA). Annex 1 - Manufacture of Sterile Medicinal Products. In: European Medicine Agency (EMA), ed2017.
13. International Organization for Standardization. ISO 14644-5: 2004 - Cleanrooms and associated controlled environments - Part 5: Operations. In. Geneva2004.
14. Institute of Environmental Sciences and Technology (IEST). IEST-RP-CC003.4:2011 - Garment system considerations in cleanrooms and other controlled environments. In. Rolling Meadows, Illinois: IEST; 2011.
15. International Organization for Standardization. ISO 13408-1:2008 - Aseptic processing of health care products — Part 1: General requirements. In. Geneva2008.
16. Institute of Environmental Sciences and Technology (IEST). IEST-RP-CC003.4:2011 - Garment system considerations in cleanrooms and other controlled environments - B2.4 Particle Dispersion Test (Body Box) Test Method. In. Rolling Meadows, Illinois: IEST; 2011.

17. Hu SC, Shiue A. Validation and application of the personnel factor for the garment used in cleanrooms. Data Brief. 2016;6:750-757.

18. Institute of Environmental Sciences and Technology (IEST). IEST-RP-CC003.4:2011 - Garment system considerations in cleanrooms and other controlled environments - B2.5 Helmke Drum Test Method. In. Rolling Meadows, Illinois: IEST; 2011.

19. European Commission. EudraLex - Volume 4 - EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Annex 15: Qualification and Validation. In: DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY, ed. Brussels2015.

20. International Organization for Standardization. ISO 11607-1:2019 Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems. In. Geneva: ISO; 2019.

21. International Electrotechnical Commission (IEC). IEC 62366-1:2015 Medical devices -- Part 1: Application of usability engineering to medical devices. In: International Organization for Standardization.

22. United States Pharmacopoeia (USP/NF). USP 41 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments. In: USP, ed.

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Milenko Pavicic, PhD, started his career as a microbiologist in the pharmaceutical industry in 1994. He occupied several functions in R&D, QC and production. His specializations are in the field of contamination control related to aseptic and sterile production, microbiological quality control and (practical) training. In 2003 he founded Pavicic Pharmaceutical Microbiology (PPM). PPM supports pharmaceutical companies and hospital pharmacies in an advisory role, or by participating in or managing projects. PPM is also specialized in practical training, courses and development of tailor made e-learning modules in the field of aseptic and sterile pharmaceutical production.

Thierry Wagner has spent over 30 years working for DuPont in its polyester films and nonwovens businesses and from the 1st of October 2019 as Global Director, Regulatory & Standards – Healthcare, DuPont – Safety & Construction. He is convenor of ISO TC198/WG7 "Sterilization of Health Care Products—Packaging", chairman of the Sterile Barrier Association (SBA), member of the Parenteral Drug Association (PDA) and actively involved in various ISO and CEN technical committees on medical and pharmaceutical packaging like CEN TC102 "Sterilizers for Medical Purposes—Packaging" and ISO TC76 "Transfusion, infusion and injection equipment for medical and pharmaceutical use". Thierry is also a member of ISO/TC 210 in charge of ISO 13485 and medical device symbols, ASTM Committee F02 and of the CEN Advisory Board for Healthcare Standards-Europe (CEN ABHS). Thierry Wagner earned a master's degree in mechanical and process engineering from ETH Zürich in Switzerland. He is a featured speaker at international conferences and seminars on medical and pharmaceutical packaging regulatory aspects.

Life-lines

Quotations of Sir James Dyson

I could buy companies, tart up their products and put my name on them, but I don't want to do that. That's what our competitors do.

Everyone gets knocked back, no one rises smoothly to the top without hindrance. The ones who succeed are those who say, right, let's give it another go.

In business you will be wrong, by and large, 50 percent of the time. The trick is to recognise when you have gone wrong and correct the damage—not to worry, at the moment of making the decision, whether it is the right one.

The key to success is failure… Success is made of 99 percent failure.

In order to fix [something], you need a passionate anger about something that doesn't work well.

Risk aversion is a hapless approach for a company that's hoping to develop new technology. It's tempting in a downturn. But long-term research and development, expensive and often filled with failure as it is, is the only route to discovering it. By taking the cautious path, companies risk a drought of ideas.

I learned that the moment you want to slow down is the moment you should accelerate.

We always want to create something new out of nothing, and without research, and without long hard hours of effort. But there is no such thing as a quantum leap. There is only dogged persistence—and in the end you make it look like a quantum leap.

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Ansell

Review: Cleanroom Technology Conference 2019

Murielle Gonzalez

This year's event fulfilled its promise to deliver a high-calibre programme to an international audience.

The spring in full swing played its part in welcoming attendees to the *Cleanroom Technology Conference 2019*. Professionals from 31 countries across Europe, Asia, North America and further afield descended on the National Conference Centre in Birmingham, UK. Having just under 600 people under one roof on 22-23 May proved it a busy event in its third year running. Calling it a conference does not do justice to the event. The 67 exhibitors pushed the boundaries, not to mention the ambition, towards becoming a trade show. The exhibition space is a sought-after feature and a valuable bonus to the networking platform, as Mike Gould, HVAC Manager at JD Cooling, recognises: "We had by far the greatest interest, prospects and networking opportunities from other exhibitors," he tells me.

Whatever the reason to attend—networking, business leads or education – the *Cleanroom Technology Conference 2019* fulfilled its promise to deliver a high-calibre event. Let's review the take-home messages of some of the topics on the agenda.

GMP best practice

The first presentation by industry consultant Gordon Farquharson put good manufacturing practice (GMP) in the spotlight. The Principal and MD of Critical Systems commented on the existing standard and the Annex 1 revision on the horizon—he expected publication by the end of 2019. Farquharson urged the audience to understand that GMP will always be about five years behind today's best practice, and probably a decade behind 'state-of-the-art' manufacturing. Farquharson also presented three concepts that could help manufacturers to adhere to the GMP principles. He talked about 'the direction of travel' of technology innovation, and that such tools should be incorporated within a contamination control strategy (CCS). For Farquharson, the CCS should comprise the mechanisms and define the priorities for contamination risk mitigation. In pharmaceutical manufacturing, the CCS calls for the implementation of advanced aseptic processing with equipment ranging from blow-fill seals, isolators, RABS, to the automated robotic unit.

The presentation by Simon Tebb, Senior Regional Sales Manager at TSI, about air monitoring with fluorescence-based viable detection technology emphasised the real-time benefits of the tool. Based on TSI's Biotrak unit, Tebb dissected the operation of the equipment and explained how Pfizer reaped cost-efficient gains.

With the question "should particle counters be used to test HEPA filters for leaks?" Andy Worsick set the tone of his presentation that explored the feasibility and practicality of using a particle counter for installed filter leak testing.

He recognised that ISO 14644-3 describes methods for testing HEPA filters using both photometers and particle counters, but admitted that in some parts of the world the particle counter method is more common. He pointed out that some particle counter manufacturers hope to increase sales by promoting particle counters to test HEPA and ULPA filters for leaks. Based on the analysis of claims versus reality, Worsick demonstrated that whether particle counters can do the job, depends entirely on the application.

Microbiology focus

The analysis of recurrent microbial contamination in grade A (ISO 5) filling restricted access barrier systems (RABS) was the topic of Walid El Azab, Technical Services Manager at STERIS. His presentation was based on a case study of a sterile biotechnology manufacturer that implemented VHP disinfection on the RABS every month. He demonstrated that the interaction of measurement, materials, and methods played a part in the cross-functional team investigation that led to short- and long-term corrective and preventive actions (CAPAs). El Azab recommended complying with the validated wet contact time by re-applying where needed. He also suggested increasing the frequency of use for VHP in critical areas such as grade A and B (ISO 5), and the creation of a task force to review microbial contamination control strategy and programme.

Talking about aseptic processing, David Keen, Senior Global Microbiology Consultant at Ecolab, explained why

The exhibition space is a sought-after feature and a valuable bonus to the networking platform

humans working in these critical areas are a gaping flaw in the operation. The take-home message was simple: a mindset shift is paramount. Companies invest time and efforts into reducing the direct factors that cause or contribute to human errors, but Keen suggested to nudge humans out of mistakes might be even more cost-efficient. He demonstrated the nudge theory: the notion in behavioural science that proposes positive reinforcement and indirect suggestions to influence the behaviour and decision-making of groups or individuals. With various ordinary life examples such as the musical staircase in Brussels part of an active life campaign, and the Icelandic road paintings pushing drivers to slow down ahead of a crossing, he illustrated the theory.

How to nudge people out of errors in the cleanroom? Keen pointed to subtle ways of influencing behaviours and that microbiologists are good with understanding invisible risks, but also good at understanding the practices that cause them. "Nudge allows small changes to deliver big savings," he said.

Energy efficiency expert Keith Beattie of EECO2 discussed energy-reduction in cleanroom operations without impact on performance. For Beattie, the focus on the air change rate is secondary and pointed out that reduction strategies should be considered on a case by case basis. He concluded that demand-based control of cleanroom HVAC systems has tremendous potential for energy reduction globally.

Also focusing on HVAC, Nigel Lenegan of Energy & Carbon Reduction Solutions, dissected the GMP principles of pharmaceutical manufacturing from both the regulatory and operational front and pointed out that when it comes to air changes, the scientific approach ensures an optimised and transparent solution. For Lenegan, essential considerations include effective ventilation, the number of people in the cleanroom, the type of garment and grade of dress, and any reasonable gap between calculated and class limits.

Speaking about controlling contamination sources, DuPont's Steve Marnach and Helen Tebay of Connect 2 Cleanrooms, outlined the new selection criteria of protective garments for cleanrooms and controlled environments inspired by the imminent release of Annex 1. As well as describing the different test methods, they pointed out that companies should assess, validate and audit the entire value chain and life-cycle of the garments, not only to adhere to the GMP guidance but also as part of a risk management culture. Both insisted that suppliers should provide information, tools and help for these types of risk assessments.

Looking to 2020

What's new for the 2020 programme? The fourth edition of our conference will see the debut of ***Manufacturing Chemist Live***, a two-day conference running alongside our cleanroom agenda, and focus on the latest technology and best practice for optimising pharmaceutical processing.

Organised by the sister magazine of Cleanroom Technology, Manufacturing Chemist, the conference is set to uncover key HPAPI strategies and how to maximise and develop current processing strategies. Commenting on the 2020 event, Kevin Robinson, Editor of Manufacturing Chemist, said: "We're delighted to introduce the inaugural and complementary event that will address the pressing issues in the drug manufacturing industry. In 2020, the spotlight will be on producing, processing and packaging highly potent dosage forms and tackling topics such as containment, process optimisation and safety. We're looking forward to some insightful discussions and helping you to enhance your business activities."

Feedback from all parties involved this year have been taken on board, and work is underway to repeat and improve the world-class event that Cleanroom Technology Conference has become to be known—this time around with a co-located event with a pharma focus.

Our May conference drew to a close on a high note with the support of our sponsors Ansell Nitritex, Guardtech, JD Cooling, Contec and Microncleanclean. The *Cleanroom Technology Conference 2020* takes place on 2-3 June at the National Conference Centre in Birmingham.

What they say in 2019

Feedback on the Cleanroom Technology Conference 2019 keeps coming in, and all the input, positive and less so, is being taken on board in preparation for the event next year. The messages agree, however, that our event has become a unique opportunity to build industry contacts and knowledge, as the following testimonials point out:

"There are lots of people here to meet that you can't see every day, so to have an annual event is brilliant because you get to talk to people you haven't seen in a while, and learn of new contracts, possibly new business and new technology" Nigel Slater, CM Supply

"This event is well put together and well attended by the industry, both by exhibitors and speakers, and it is one that we always attend. We find that the quality between exhibitors and delegates is very good; if you are in the cleanroom business, this is a must-attend event." Steve Gibson, Sales Director, NGS Cleanroom Solution.

"The take-home message from this conference is new technologies and anything innovative that's going to change the industry's practice, and also about regulatory updates." Qamar Nawaz, Director, Sterling Pharmaceuticals

"The facility arrangements, the agenda and the general buzz made for a great event in 2019. The highlight for me is the venue and size of the event. It is a big effort with a lot of commitment to setup and organise on such a scale." Tim Triggs, Chairman of CCN, the new Contamination Control Network.

"I like the Cleanroom Technology Conference, I think this is the third time we have been here, and it seems to get busier and busier." Simon Tebb, Senior Regional Sales Manager, TSI

This report featured in the August 2019 issue of Cleanroom Technology and is published by kind permission of Cleanroom Technology. The author, Murielle Gonzalez, is editor of Cleanroom Technology.

Wrap for Cleanroom Guangzhou Exhibition 2019!

From August 16 to 18, nearly 8000 global cleanroom professionals gathered at 2019 Asia-Pacific Cleanroom Technology & Equipment Exhibition (Cleanroom Guangzhou Exhibition 2019) in China Import and Export Fair Complex, to celebrate the 5th banner year!

Co-organized by Guangdong Association of Cleanroom Technology, the show was very honored to have invited presidents of 8 trade associations from Taiwan, Hong Kong, Macao, Suzhou, Henan, Jiangsu, Jiangxi, and Hubei to cut the ribbon for its opening ceremony.

This year's overseas brands made up 10% exhibitor attendance (Dynaco, TSI, Gerfloor, Purafil Filtration, Watreat, Hollingsworth & Vose, CHYI LEE, Osbert, Ahlstrom-Munksjö, and etc), together with China's leading brands (Zhong Ke Sheng Jie, Clima, Zhongjing, Jiu Sheng, E-Zone, Lairun, HUAAO, Juxing, and etc.), treating our buyers with the latest products and solutions.

The two best represented sectors were Cleanroom Equipment (41%) and Cleanroom Framework (30%), followed by Testing Instruments & Organizations (7.5%), Cleanroom Consumables (8%), HVAC System (6%), Other Products & Services (4%) and Associations & Media (3.5%).

The organizer is now moving on to the global promotion campaign for 2020! August 16-18, See you again in Guangzhou. For more information, please contact Mrs. Mae Law at grand2@grahw.com

Lab Innovations 2019 hosts 160+ scientific suppliers under one roof

Lab Innovations returns to the NEC, Birmingham, for its 8th successive year on 30 and 31 October 2019. With hundreds of laboratory and cleanroom products on show, informative CPD-certified seminars and all the right people to talk to, it's no wonder that this award-winning trade show is growing.

Free-to-attend, Lab Innovations hosts over 160 leading science and healthcare suppliers presenting cutting-edge equipment and services for a range of industries. Exhibitors focusing on controlled environments include: SLS, Bigneat, Felcon, Kimberley-Clark Professional, Helapet, Monmouth Scientific, Guardtech Cleanrooms, Contained Air Solutions, Esco, Mayteck, Shield Scientific and Containment Technology Services.

The "Cleanroom Hub", in association with Cleanroom Technology, will again provide a zone dedicated to cleanroom solutions, with specialist experts available. Here you can discover new products, best practice and regulations to ensure your cleanroom is up-to-standard. Education includes the latest trends for cleanroom technologies, the impact of EU Biocidal Product Regulations, microbial aspects of water quality in controlled environments, cleaning and disinfection, and Cleanroom 4.0.

Building on its reputation as the leading meeting place for laboratory professionals, procurement managers and suppliers, Lab Innovations this year introduces the Lab Connect free online meeting planner to ensure productive B2B matchmaking. This free-to-use service will provide visitors and exhibitors with the opportunity to pre-arrange meaningful one-to-one meetings with exactly the right companies or attendees for their needs, ensuring an even more productive visit.

Register for free now to attend Lab Innovations, 30 and 31 October 2019, or for more information, visit: www.lab-innovations.com

Cherwell appoints new Engineering Manager

Jonathan Roger, Engineering Manager, Cherwell Laboratories

Cherwell Laboratories has announced the appointment of Jonathan Roger as Engineering Manager and part of Cherwell's management team.

Jonathan will head up Cherwell's experienced team of engineers, responsible for the routine servicing and calibration of customers' SAS microbial air samplers within the Company workshop and at customer sites. Jonathan will continue to maintain focus on providing excellent customer service, ensuring fast turnaround times for service and calibration, minimising SAS air sampler downtime.

Jonathan studied Mechanical and Manufacturing Engineering at Portsmouth University before completing 15 years in the newspaper printing industry. He then worked for 8 years in various roles in the fast-moving consumable goods industry. His previous roles have focused on engineering, quality and production management. His skills in these areas will help identifying key opportunities to further enhance manufacturing processes and engineering systems at Cherwell.

For more information about Cherwell Laboratories, please visit www.cherwell-labs.co.uk, follow @CherwellLabs on Twitter or follow us on LinkedIn.

Foresight invests £4.0m into ONFAB to support acquisition of Envair Holdings Limited

Foresight Group LLP ("Foresight") is delighted to announce a further £4 million growth capital investment into portfolio company ONFAB to fund the acquisition of Lancashire based designer and manufacturer of clean air containment products, Envair Holdings Limited ("Envair").

ONFAB produces flexible clean-air enclosures and consumables, designed and manufactured in-house from sites in Cheshire and Spain. Founded in 2005 by Oliver Nulty, ONFAB received investment from the £60 million Foresight Regional Investment LP fund in September 2017 to facilitate a majority buyout of the business. Since then, with an enlarged team and renewed focus on sales, margins and new products, it has grown by over 30% per year and continues to benefit from ever stricter safety standards protecting workers across the globe.

Envair is an established and well-recognised brand in the UK specialising in rigid clean-air products, with customers primarily in the healthcare space. Its products and services include a range of rigid isolators, laboratory fume cupboards, consumables and ongoing maintenance.

In combination, the enlarged group will benefit from a highly complementary product and customer portfolio providing both rigid and flexible containment products and servicing customers in the healthcare, pharmaceutical and manufacturing markets.

Gary Bagshaw, Managing Director, Envair, commented: "I have led Envair for over 10 years and watched the company grow every year. The combination of this business with ONFAB will allow us to expand our reach to a number of large markets while benefitting from ONFAB's back office and sales infrastructure.

For more information see:

www.foresightgroup.eu www.onfab.co.uk www.envair.co.uk

Particle Measuring Systems expands support to ensure environmental monitoring system operations

February 26, 2019 Boulder, CO USA – In response to customer requests for increased levels of professional support, Particle Measuring Systems announced today that they now offer Software Support contracts for Facility Monitoring customers that have FacilityPro® systems. Effective immediately, customers have access to a variety of support packages to meet their support needs at various price points.

"Service contracts allow us to provide our environmental monitoring customers with the support they need to minimize manufacturing downtime while meeting regulatory contamination monitoring requirements", said Paul Hartigan, Product Line Manager, Software. He continued, "In an increasingly interconnected world, problems can arise from a variety of areas and affect facility monitoring – our industry experts can provide our customers with the fast and effective support they need either by phone, email, remote connection or enhanced on-site services".

PMS is offering three different levels of contracts to meet the varying needs of customers, large and small: Standard, Plus, Premium. All provide fast response times with a variety of methods to quickly address environmental monitoring issues.

For more information visit www.pmeasuring.com.

Cleanzone 2019 offers more in the field of plant engineering

Numerous companies from the field of plant engineering will be at the trade fair in Frankfurt on 19-20 November 2019 to exhibit their concepts and solutions for increasing both product quality and production efficiency in cleanrooms within modern production facilities. Kerstin Horaczek, Group Show Director for Technology at Messe Frankfurt, explains: "We are delighted that we have been able to expand the range of products and services on offer in this area. This means that all visitors who are planning new production facilities or looking to overhaul their existing systems will find even more professional partners, contacts and expertise at the trade fair."

The plant engineering offering includes not only planning and construction services, but also ceiling and lighting systems, building management systems, ventilation and air-conditioning technology, airlock systems, laminar flow modules, mini-environments, cleanroom workstations and cleanroom flooring. Exhibitors include Asys, Cleanroom Competence, Colandis, Dittel Engineering, Drees + Sommer, Klima Systeme 2000, Metisafe Cleanroom and Biosafety, nora systems, Ortner Reinraumtechnik, Viessmann Technologies, Weiss Klimatechnik, ROM Technik, and Siemens.

For more information, please visit www.cleanzone.messefrankfurt.com

Events

Dates	Event	Organiser
2019		
October 2-4	22nd GERPAC Conference, Hyères, France	GERPAC
October 9-10	Pharmaceutical Cleanroom Technology Europe, London, UK	SMi
October 15-17	International Congress A3P, Biarritz, France	A3P
October 30-31	Lab Innovations, Birmingham, UK	Easyfairs
November 12-15	Fall Conference, Rosemont, Illinois	IEST
November 19-20	Cleanzone, Frankfurt, Germany	Messe Frankfurt Exhibition GmbH
November 28-19	Pharmig 26th Annual Microbiology Conference, Nottingham, UK	Pharmig
2020		
April 27-30	ESTECH, Minniapolis/St.Paul, Minnesota	IEST
June 2-3	Cleanroom Technology Conference 2020, Birmingham, UK	HPCi Media
June 2-3	Manufacturing Chemist Live 2020, Birmingham, UK	HPCi Media
June 22-24	EP and Clean Tech China, Shanghai, China	Informa Markets Sinoexpo
August 16-18	Cleanroom Guangzhou, 2020, Guangzhou (Canton), China	Cleanroom Guangzhou, 2020, Guangzhou (Canton), China

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2019	**Event**	**Location**
October 8	Cleanroom Basics: What is a Cleanroom and How Does it Work?	Schaumburg, Illinois
October 9	Beyond Cleanroom Basics: Fundamental Information for Cleanroom Operations	Schaumburg, Illinois
October 10	Cleanroom Classification Testing and Monitoring	Schaumburg, Illinois
November 11	Cleanrooms Won't Fix a Contaminated Product	IEST Fall Conference, Rosemont, Illinois
November 12	Contamination Busters: Get the Dirt Out of the Cleanroom	IEST Fall Conference, Rosemont, Illinois
November 13	Stop Contamination in Your Operations with Reusable and Disposable Garments	IEST Fall Conference, Rosemont, Illinois
November 14	Develop Standard Operating Procedures Using IEST Recommended Practices	IEST Fall Conference, Rosemont, Illinois
December 9-13	Requirements Needed for Compounding Pharmacies Using USP 797	Irving, Texas
2020		
February 25	Understanding the Cornerstone Cleanroom Standards: ISO 14644-1 and 14644-2	Phoenix, Arizona
February 26	Application of ISO 14644-3	Phoenix, Arizona
February 27	Universal Cleanroom Operations Guidelines with ISO 14644-5	Phoenix, Arizona

CCN (Contamination Control Network) www.theccnetwork.org		
2019	**Event**	**Location**
November 12-14	CTCB-I Testing and certification course	Liphook, England

ICS (Irish Cleanroom Society) www.cleanrooms-ireland.ie		
2019	**Event**	**Location**
November 26	CTCB-I Cleanroom Testing & Certification	Dublin
For other courses run by ICS see https://www.cleanrooms-ireland.ie/2017_training_programme/		

R3Nordic (Scottish Society for Contamination Control) www.r3nordic.org		
2019	**Event**	**Location**
For courses run by R3Nordic see https://r3nordic.org/		

VCCN (Association of Contamination Control Netherlands)		
2019	**Event**	**Location**
For a complete list of courses including CTCB-I courses, please see 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

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