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Enhance your knowledge of contamination control

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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 CACR38. Writing editorials can sometimes be a challenge for me and I greatly admire those who can write something meaningful month after month, or even week after week! I only have to do it every three months and so should not complain too much. Before I started this time, I decided to read through all my previous editorials for inspiration. The first thing I noticed was that they were not too bad at all. They were all readable and interesting, although I say it myself. They comprised of observations on the contents of the particular issue, anecdotes from my own personal experience, my thoughts on some of the innovations reported on and, in some issues, a cartoon that had taken my fancy. But it was many of the innovations mentioned and described that stood out so I thought I would catch up with some of them to see where they are now.

The carbon neutral Class II microbiological safety cabinet reported on in 2010 (CACR04) is still available from Contained Air Solutions Limited and is being sold in good quantities. I am sure there are many more such products now. The zoned ultra clean air operating theatres described in 2011 (CACR06) are in use in several hospitals in Norway and Sweden. The patent expired a while ago, the inventor retired and sold his business on and to my knowledge the system, which makes ingenious use of temperature differentials to bring the most appropriate air conditions to the operation zone, the surgeons' zone etc. is no longer being actively sold. The Klercide UV Validation Torch, which also featured in 2011 (CACR07), is still very much on the market. The torch highlights contamination by a variety of particles on all surfaces and can play a useful part in operator training and confirmation of training effectiveness. In 2012 (CACR09) we wrote about a replaceable sensor element for optical particle counters. I understand that this has been widely adopted in measurement instruments for environmental air quality (e.g. roadside), but not, alas, in cleanroom particle counters where there were significant cleanroom operating cost savings to be made. We also had an article about robotics for aseptic manufacture (CACR10). The author was Christopher Procyshyn, pronounced 'procession'. Christopher has a number of patents on the go and his company, Vanrx Pharmasystems Inc., is still very active in the field. Then in CACR11, Gordon Farquharson wrote about ViESR®, a new laser light sheet method for visualising particles in real time developed by Shin Nippon Air Technologies in Japan. I haven't heard much more about that over here but the company's website shows a number of interesting applications.

In my editorial in CACR12, I drew a comparison in my mind between military radar systems that detect incoming enemy aircraft and something that would give a similar warning for incoming airborne particles and microbes in isolators or other critical areas. The ViESR® laser light sheet method came near to that vision, which is why I named it 'CACR Innovation of the Year'.

So there is a summary of some of the innovations that had a mention in the editorials in the first three years of CACR, and this editorial is done. Phew!

I hope you enjoy CACR38.

John Neiger

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A global study of the performance of cleanroom garments over their life cycle

Matheus Barbosa, Jean-François Teneul

Abstract

Sterile garments for cleanroom use often present a variable performance over their entire life cycle as they are vulnerable to damage from laundering and sterilization methods. A study was conducted to understand how reusable garments perform when subjected to multiple laundering and irradiation cycles – tear strength, particle shedding, permeability, etc.. The study enables a cost comparison with single use garments.

Introduction and key concepts

In the context of a global business with ever-increasing quality standards and effectiveness requirements as well as the latest draft review of the Good Manufacturing Practice (GMP) Annex 1 of December 2017, one of the main technical areas explored is related to studying and mitigating potential process/product contamination risks against biological bodies, particulates and pyrogen agents. One key strategy for cleanroom supervisors should be to carry out complete Risk Assessments in order to map, classify, and then reduce contamination risks.

Humans are the main source of potential contamination inside cleanrooms (more than 70%), as shown by several past global studies (Akers, J. *et al.*, 2004; Ramstorp M, 2000 and Whyte and Hejab, 2007). Hence, cleanroom garments serve as the last protection barrier against controlled environment contamination by the thousands of human particles (potentially carrying microorganisms) that are shed every minute. In terms of contamination risk management, it is critical to evaluate the variables related to human contamination and cleanroom garment barrier performance besides HEPA filtering, process air flow velocity and other factors. This study aims to explore several important technical aspects of cleanroom garments that should be considered when evaluating contamination risks.

The process of wearing, laundering and sterilizing reusable cleanroom garments can impact their physical properties and change their functionality. Laundering and wearing abrades garment fibers. Simultaneously, changes to the polymers that make up the garments can occur at the molecular level. Although routine visual inspection is often part of garment quality evaluation programmes, non-visible properties also change with time.

When selecting reusable garments for use in cleanroom environments, it is important to understand how they will perform over their intended life cycle. Consideration of all the degradation aspects should be part of the decision process for when to take reusable garments out of service, or alternatively to change to a single-use garment system. Several factors should also be considered when evaluating intrinsic risks generated by cleanroom garments, such as: particle shedding, biological/particle barrier, worker comfort and protection, durability, packaging, sterilization continuous validation – besides process and supply factors: logistics chain reliability, damages and repairs, shrinking and ergonomic fit, among others.

Physical property data are often available for new cleanroom garments; however, there are less physical property data for the remainder of the garment life cycle. To aid in garment choice, DuPont conducted a study, led by Jennifer Galvin PhD, DuPont Principal Investigator, of the physical properties of reusable cleanroom garments after a set number of laundering and gamma radiation exposure (sterilization) cycles.

Methodology

Two sets of commercially branded, reusable coveralls were purchased for testing and designated as Garment A and Garment B. Garments were made of woven polyester with integral carbon fiber for electrostatic decay properties. Garments were laundered under standard industrial settings and subsequently exposed to gamma radiation; this was considered one cycle. Garments were removed for testing after pre-determined numbers of cycles until a total of 30 cycles had been completed.

Not all properties were tested at the same frequency. Initial properties of the garments were either measured on "as-received" garments or garments that had been laundered one time, but not exposed to gamma radiation. Parameters for garment laundering and gamma exposure were consistent throughout the study.

Garments were not worn or exposed to simulated work scenarios between cycles and the effect of routine garment "wear and tear" was not part of this study.

A summary of the garment testing methods is shown in Table I, according to IEST (Institute of Environmental Sciences and Technology), ASTM (American Society for Testing and Materials) and AATCC (American Association of Textile Colorists and Chemists) standards. Most of testing was done at third-party laboratories. Results for property testing are shown with the average and the Bonferroni confidence interval on the mean. Changes in both absolute performance and variability within the garment population may factor into formulation of end-of-life criteria.

Table 1: Test Method Summary

Test	Test Method
Particle shedding via Helmke Drum	IEST RP-CC003.4
Particle dispersion (Body Box)	IEST RP-CC003.4
Hydrostatic head	AATCC TM127
Trapezoidal tear strength	ASTM D5587

Results and discussion

3.1 Studied parameters

Based on all experimental parameters listed above, a number of results were obtained. The object was to analyze critical limits of cleanroom garment performance in order to help end users

a. evaluate which garment system solution to choose (single-use or reusable),

or

b. after how many cycles reusable garments become non-performing and have to be replaced.

The properties studied reflected key features including process protection, people protection (when needed), comfort and durability.

3.2 Polyester reaction mechanism after gamma exposure

The impact of gamma radiation exposure on a variety of polymers is well studied (Skiens, W. E, 1980). Although multiple reaction mechanisms can occur simultaneously, there is typically a predominating reaction type. The extent and type of each reaction depend on many factors and combinations of factors, including:

- Polymer composition (different polymers behave differently)
- Presence or absence of air during irradiation
- Crystallinity of the polymer and changes in crystallinity
- Physical configuration (e.g., fibre, film or tubing)
- Additional processing (e.g., laundering, calendaring or surface treatment)
- Presence of antioxidants or other additives in the polymers
- Cumulative radiation dose

The two primary reaction mechanisms that occur in polyester (PET) after exposure to gamma radiation are chain scission and cross linking (Potnis, S. P., Shetty, S. M., Rao, K. N, Prakash, J, 1969; Nair, P. D., Sreenivasan, K., and Jayabalan, M, 1988). Changes in the polymer makeup can result in changes to a garment's physical properties. To better understand which mechanism predominated under the conditions of this study, PET molecular weight was measured by size exclusion chromatography (SEC) using hexa-fluoro-isopropanol (HFIP) as the solvent.

Results for Garments A and B overlapped, so the data was grouped (Figure 1). Because the molecular weight of the PET decreased with laundering and exposure to gamma radiation, chain scission was the predominant mechanism. As garments were both laundered and exposed to gamma radiation (but not used by operators), this data includes the combined simultaneous impact of both factors.

This initial result indicates that reusable textile garments suffer degradation throughout their life cycle. As mentioned before, the polymer molecular weight decrease effect is a result of laundering and irradiation processes, but in actual use there are other additional effects. Repeatedly wearing and submitting garments to physical stress (standard operation moves), as well as transportation/manipulation, donning/doffing or the exposure of chemical/biological compounds could also impact and intensify degradation effects.

In order to analyze garment performance that result from the PET degradation process, other important physical properties were tested. These are categorized under: Process Protection, People Protection and Durability.

3.3 Process protection

The primary function of cleanroom garments is to protect a product or a process against contamination from humans (particle shedding and biological exposure) or from the garment itself (particle or linen shedding). To represent process protection, particle shedding was measured via the Helmke Drum method (Figure 2), and particle dispersion via the Body Box method (Figure 3).

3.3.1 Helmke Drum test

The best known measurable parameter for cleanroom garment cleanliness is particle shedding. This is tested in accordance with the Helmke Drum testing standard. Garments or fabric swatches are tumbled for determined cycles inside a rotating drum equipped with a standardized particle counter. The final measurement defines the shedding rate (particles/minute). Seeking to normalize test results, fabric swatches were tested, and swatch data can be evaluated for performance trends. The results show that particle shedding increased after 25 cycles or exposure to a cumulative mid-dose of 754kGy units of ionising radiation, but was fairly consistent until that point (Figure 4).

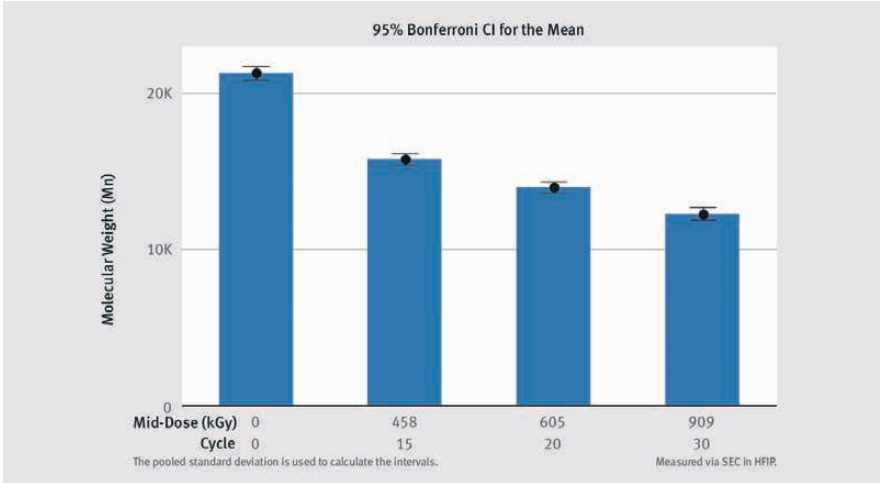


Figure 1: Number average polymer molecular weight (Daltons) for garments A and B

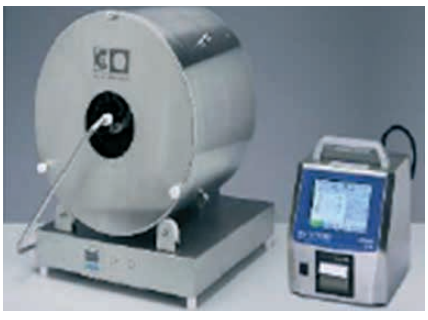


Figure 2: Helmke drum

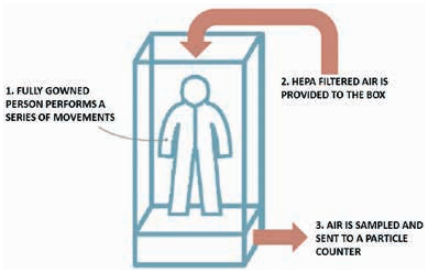


Figure 3: Body box

The key preliminary conclusion for these results indicates that cleanrooms that are sensitive to particle shedding should establish a monitoring program to better understand when their garments are no longer performing as required for cleanroom compliance. As observed above, after a determined number of laundering and sterilization cycles, reusable polyester materials will not only increase their magnitude of particle shedding, but also the variability of the same property. This effect can also generate an extra layer of unpredictability when determining contamination control standards and procedures – especially because the garment's "performance breaking point" may vary based on specific application, physical stress and size fit for the operators.

A final point to consider is that the Helmke Drum test is a well-known and effective method to evaluate garment cleanliness and particle shedding from its material (polyester), but it does not indicate garment particle/bacterial barrier performance against human shedding – which is the main source of contamination for cleanrooms. In that matter, complementary tests were conducted according to the Body Box method.

3.3.2 Body Box test

Body Box testing measures not only particle generation from the garment, but can also indicate its function as a particle barrier. The method is described in the same standard as the Helmke Drum (IEST-RP-CC003.4). In this test, a fully garbed trial subject conducts a series of movements inside a box supplied with HEPA-filtered air. Air in the box is sampled by a particle counter and shedding rate is reported as a function of activity as well as a total rate for all activities conducted during the test. This data also showed a shift in performance and variability after increased cycles of laundering and gamma radiation exposure (Figure 5).

Both the Helmke and Body Box data show an increase in both amount and variability of shedding. Cleanroom operators who are particularly prone to particle shedding should consider establishing a monitoring programme to determine when garment performance no longer meets requirements. Particle sizes typically monitored in a cleanroom are too small to be visible to the naked eye, so visual inspection alone cannot indicate an increase in garment shedding. Other potential contamination factors related to the garments should also be studied and considered, such as the intrinsic abrasion effects of wear and tear and sterile packaging.

3.4 People protection

It is not uncommon to identify chemical and biological hazards in controlled environments or cleanrooms. In these instances, the garments not only need to perform as a process contamination barrier, but also serve as a PPE (Personal Protective Equipment) to guarantee the health and safety of the operators. Several applications and common activities may present a potential risk to workers in cleanrooms, among them:

- Oncology drugs compounding and manipulation (cytotoxic handling)
- HPAPI (High Potent Active Pharmaceutical Ingredient) manufacturing
- Hormones handling and production
- Activities with different Biosafety levels (bacteria or virus manipulation)
- Chemical products manipulation (solutions preparation, cleanroom sanitizing)
- Infectious residues (animal, human)

Several standards exist to certify chemical and biological protective garments, such as the ISO 16602 (for chemical risks) and ISO 16603/EN 14126 (for biological hazards).

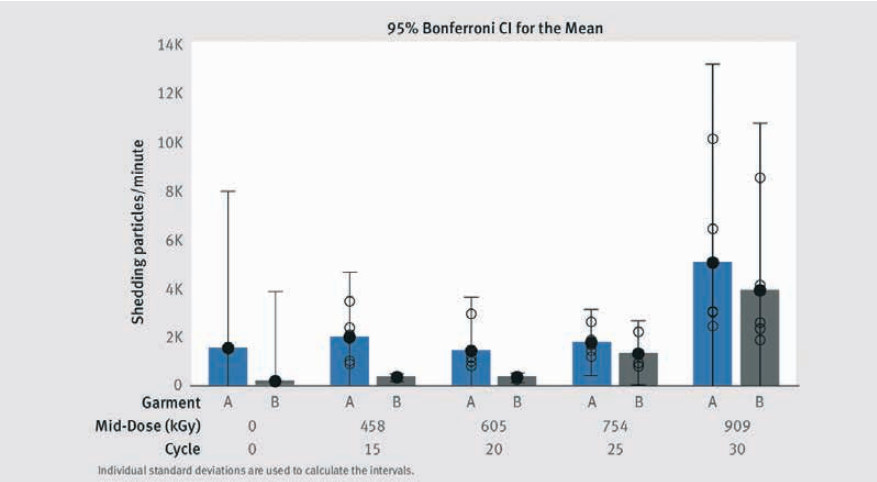


Figure 4: Helmke Drum particle (greater than 0.5 microns) shedding of swatches

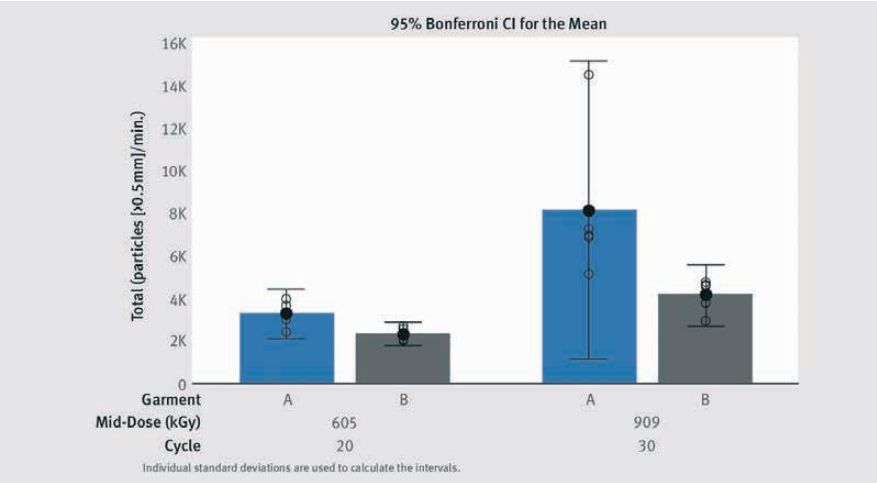


Figure 5: Body Box valuation by the sum of shedding for all activities

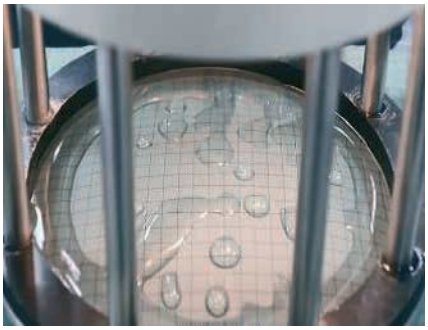


Figure 6: Hydrostatic head test

Properties such as permeation and repellency should also be considered for significant chemical/biological risks.

The hydrostatic head test (Figure 6) was used to evaluate fabric performance against an aqueous challenge. Fabric was subjected to a water column of increasing pressure until three drops penetrated the fabric. The data show a significant drop in performance as a function of exposure to laundering and gamma radiation (Figure 7). If garments are considered for incidental, light aqueous splash protection, understanding the degradation per cycle is important.

Many potential hazards are found in liquid form, so partial impermeability of the garment fabric should be considered and/or studied when selecting cleanroom equipment for applications with an exposure risk level. Part of the health and safety procedure could include establishing the garment's worker protection performance over its life cycle. As mentioned before, other international standards and certifications may assist companies to verify the chemical/biological barrier effectiveness for cleanroom garments, such as the CE Category III PPE certification and specific permeation data.

3.5 Durability

The length of a garment life cycle is also affected by the last performance parameter studied: durability. Garments should withstand normal wear and tear. Without adequate durability, garment breach is possible. Besides significant process contamination, extra costs could be generated as the repair of polyester garments is often a complicated and costly activity, sometimes not included within a company's budget or laundering contract service.

To understand the impact of laundering and exposure to gamma radiation on garment durability, trapezoidal tear strength was measured (Figure 8). Cross direction (CD) tear strength is shown in Figure 9 while machine direction (MD) tear strength is shown in Figure 10. Often in woven garments, there are different constructions in the two directions, so differences in tear values between MD and CD are expected.

Testing showed that garment durability decreases with increasing cycles of laundering and exposure to gamma radiation. Reducing potential impact from garment tearing is important, especially in cleanrooms and controlled environments where workers may have physical activities such as climbing stairs or bending to monitor or adjust equipment. In terms of contamination control procedures, the decay of mechanical resistance for cleanroom garments adds an extra layer of

Figure 8: Tear strength test

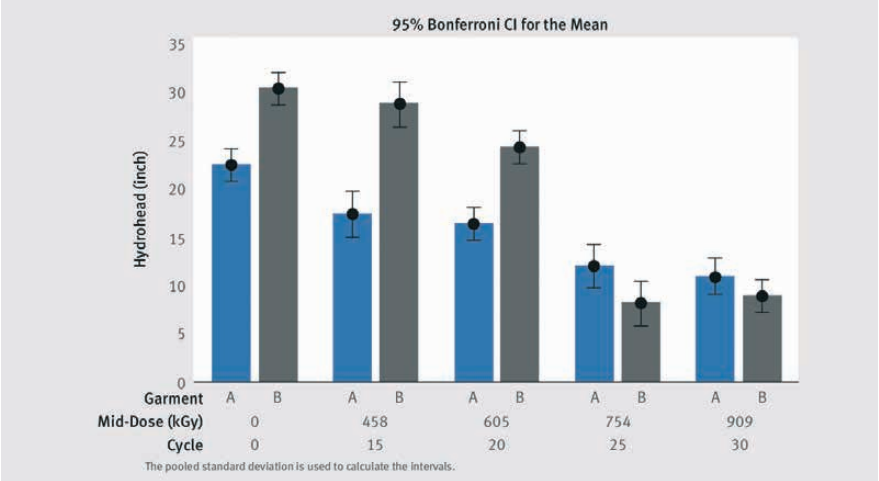


Figure 7: Interval plot of Hydrohead (inches)

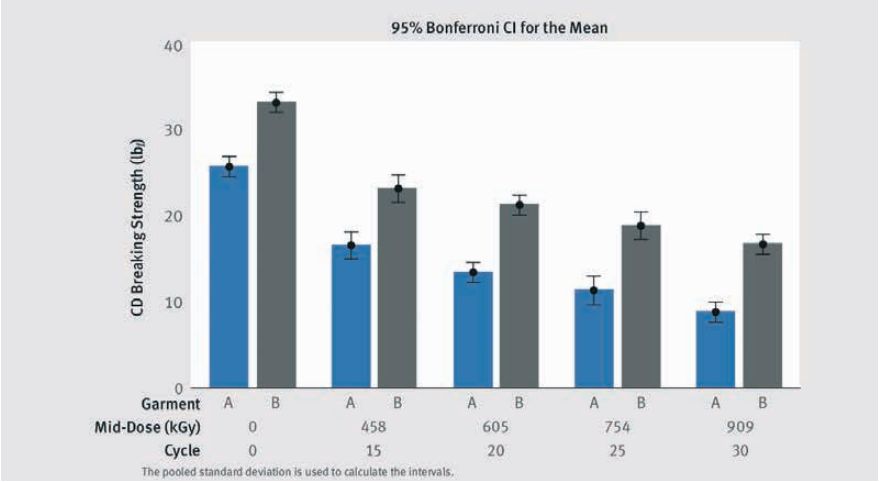


Figure 9: CD Trapezoidal tear strength (lbf – Pound-force)

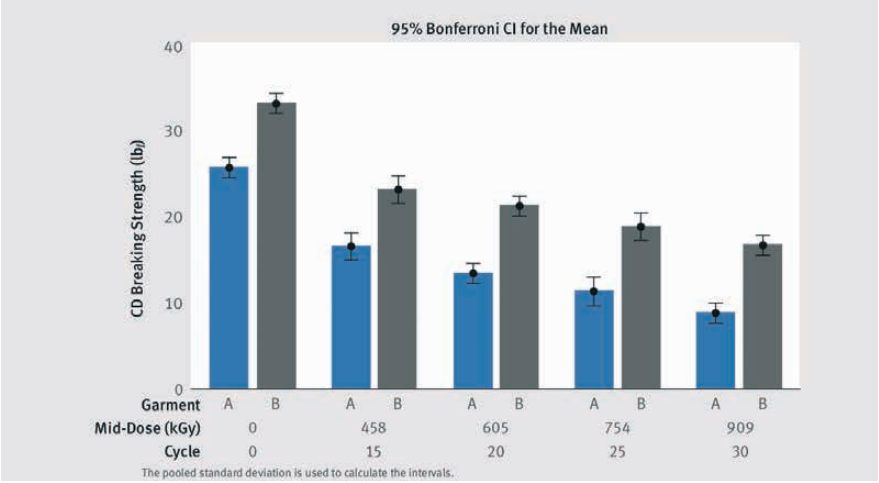


Figure 10: MD Trapezoidal tear strength (lbf)

complexity on establishing a monitoring standard to determine each garment's life cycle end point; variables such as workers' activities and potential external abrasion factors also need to be considered.

Conclusions

People are the main source of contamination in controlled environments, and cleanroom garments are the main and last barrier to protect critical processes and products. The data outlined here demonstrate that garment properties do change after several laundering and gamma exposure cycles. These changes are not always visible to the naked eye, so visual garment inspection alone may not be sufficient to understand garment performance. Based on these findings, the following guidelines are recommended:

- Even though tests were conducted with sterilization via gamma irradiation, several studies show that other sterilization methods also present abrasion and degradation effects over the garment's life cycle. Autoclaving, for example, uses a physical process that may degrade polyester composition after several utilization cycles (Nair, P. D., Sreenivasan, K, 1984). It is important to consider that continuous laundering (shrinking & expanding), and wearing of cleanroom garments also play a considerable part in the structure degradation of fabrics.
- Consider performance data over the entire garment life cycle. If not available, question your cleanroom garment provider or assess the risk of not having control of your garments' system in place;
- When cleanroom garments also need to perform as Personal Protective Equipment, companies should consider looking for specific technical data and certifications that would enhance worker safety and protection. Asking garment providers for permeation data for specific risks or barrier technical claims might be an effective strategy;
- Enact testing protocols to monitor the performance of garments as they age, based on the risk assessments and needs of each individual cleanroom. Parameters should not only consider particle shedding and cleanliness of the garment itself, but also its barrier effectiveness against human contamination (particle shedding and biological filtering) and sterility validation assurance. Then, establish criteria for taking garments out of service when they no longer meet functionality requirements;
- It is also important to continuously map, evaluate and control the risk of the entire garments system value-chain: from the fabric weaving and sourcing, garment assembly, packaging and sterilization and, if applicable, the laundry process as well.

It ought to be noted that since garment requirements vary by cleanroom operation, establishing initial and ongoing fitness for use is the responsibility of the end user. Garment assessment may require evaluation of additional information beyond what is presented here. For example, seams and closures may have lower barrier properties than fabric. Properties of garments and fabrics subjected to other conditions, including different sterilization methods, may also vary.

In conclusion, when assessing risks related to potential contamination in controlled environments, cleanroom companies should question and require their suppliers to support their quality claims with continuous technical data, risk mitigation and process control.

References

Akers, J. *et al.*, Development of a Highly Automated PAT- Compatible Aseptic Processing System, paper presented at the A3P congress, Biarritz, France, 2004.

Galvin, J (DuPont de Nemours). A Life Cycle Assessment of Reusable Garment Properties, Cleanroom Technology, June 2017

Skiens, W. E. Radiat. Sterilizing radiation effects on selected polymers. Phys. Chem., 1980, 15, p. 47-57

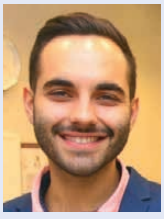
Potnis, S. P., Shetty, S. M., Rao, K. N. and Prakash, J. Die Angew. Effect of γ-radiation on synthetic fibres – II irradiation in the presence of chemicals. Markromol. Chemie, 1969, 6, p. 127-135

Nair, P. D., Morphological changes of poly(ethylene terephthalate) on multiple steam sterilization. Clinical Materials, 1990, 5, p. 43

Nair, P. D., Sreenivasan, K. Effect of steam sterilization on polyethylene terephthalate. Biomaterials, 1984, 5, p. 305

Nair, P. D., Sreenivasan, K., and Jayabalan, M. Multiple gamma radiation sterilization of polyester fibres. Biomaterials, 1988, 9, p. 335-338

Whyte, W. and Hejab, M., Particle and microbial airborne dispersion from people, European Journal of Parenteral and Pharmaceutical Sciences, 12 (2). pp. 39-46. ISSN 0964-4679, 2007



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Monitoring of nanoscale particles in cleanrooms: ISO 14644-12, outreach article

Anne Marie Dixon-Heathman, Dr David Ensor

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

Abstract

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

One of the committee's most recently published standard, ISO 14644-12, *Cleanrooms and associated controlled environments—Part 12: Specifications for monitoring air cleanliness by nanoscale particle concentration*, provides specifications for the cleanroom monitoring of nanoscale particles (nanoparticles) smaller than 100 nm with a condensation particle counter or equivalent. The standard provides guidance for air monitoring for the purpose of identifying the contributions of sources to the cleanroom burden of particles.

Sources of nanoscale particles are primarily from the processes in the cleanroom. The standard includes example specifications for instrumentation performance and information on how to apply the data. Intended users include process engineers and cleanroom specialists. It is anticipated that as the nanotechnology field advances, this standard may find extensive use.

Keywords

ISO, TC 209, 14644, cleanrooms, standards, nanoscale particles, ultrafine particles, nanoparticles, processes, monitoring

Introduction

International standards facilitate global trade by providing a common basis of communicating specifications in purchase transactions. The responsibility for cleanroom standardization within the International Organization for Standardization (ISO) is held by Technical Committee (TC) 209, Cleanrooms and associated controlled environments. In 1992, United States ISO Member ANSI proposed the formation of the technical committee to ISO at the recommendation of IEST and delegated the responsibility for the administration to IEST. ISO/TC 209 currently publishes standards as parts of the ISO 14644 and 14698 series. These standards are available from IEST in the United States and from ISO member bodies globally.

The objective of this article is to foster understanding regarding a newly available ISO 14644 standard developed by ISO/TC 209 Working Group (WG) 10 Nanotechnology. ISO 14644-12[1], *Cleanrooms and associated controlled environments—Part 12: Specifications for monitoring air cleanliness by nanoscale particle concentrations* provides specifications for the monitoring of airborne particles smaller than 100 nm with a condensation particle counter (CPC) or equivalent. Although nanotechnology standardization in ISO has generally fallen under ISO/TC 229, Nanotechnologies, much of the production involved in nanotechnology requires the use of cleanrooms.

The first international consensus cleanroom standard was developed in 1999 as ISO 14644-1:1999,[2] *Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness*. For classification purposes, the smallest particle size was 0.1 µm, but the standard also included sections on "ultrafine" particles of less than 0.1 µm. During the development of the second edition of 14644-1[3] in 2015, the sections on ultrafine particles were removed and earmarked for transfer into a pending document (ISO 14644-12) on nanotechnology. (The terms "ultrafine" from the early standards have evolved into the generally accepted "nanoparticle and "nanoscale particles." Nanoparticle is defined by size and a spherical shape. Nanoscale particle is a more general term and may refer to an equivalent diameter determined by a particle counting instrument.)

The initial drafts of the nanotechnology standard extended the cleanroom classification tables from ISO 14644-1:1999 below the 0.1 µm threshold. However, it was felt that this had the potential to create unrealistic technical conditions and confusion in the industry. The draft classification tables were removed when it became clear that current understanding of nanoparticles in cleanrooms limited the scope of ISO 14644-12 to providing guidance on monitoring—rather than classification—of cleanrooms. For example, nanoscale airborne particles appear to be generated mainly by intermittent emissions from process tools in semiconductor cleanrooms. At the present time, open literature is not available from other industries. Monitoring includes obtaining time-dependent concentration trends of nanoscale particles and developing monitoring goals for troubleshooting of the processes in the cleanroom.

Background of nanoscale particle measurement

The measurement of nanoscale airborne particles dates back to 1875. A French investigator, Coulier, performed experiments with water supersaturation of air to simulate the formation of clouds and found that particles in the atmosphere promoted the formation of cloud droplets. Over the years, a number of different concepts were employed to detect particles by creating supersaturated atmospheres including adiabatic expansion or continuous flow

vapor condensation. The early investigators termed the particles "nuclei" because the particles had the chemical properties to serve as nuclei or sites for water condensation. Modern instruments have the capability to detect particles regardless of the chemical composition. Currently, condensation particle counting is an established measurement method for nanoscale particles.[4] One of the first applications of CPCs to cleanrooms is described in Ensor and Donovan.[5]

Particle size distribution data encompassing nanoscale particles is very limited in current cleanroom literature. The absence is due to the very low concentrations and that measurements are normally conducted to establish compliance with the classification levels in ISO 14644-1:2015. Ensor *et al.*[6] reported the measurement of particle size distributions in a variety of cleanrooms in various operational states.

Sem[7] analyzed cleanroom nanoscale airborne particle behavior based on established aerosol dynamics found in Hinds[8] and data shared by Texas Instruments, Inc. Based on the well-established tri-modal size distribution found in the ambient atmosphere, Sem suggested similar airborne particle size distributions' behavior would be mirrored in cleanrooms. To summarize, the behavior of aerosols in the nanoscale mode is formed from reactions or condensation (less than 0.1 µm); the accumulation mode is formed by coagulation of particles from the nanoscale mode or direct industrial emissions and is shaped by larger particle deposition between 0.1–1 µm; and coarse mode greater than 1 µm is formed from suspended dust. The main difference between the ambient atmosphere and cleanrooms is that the particle concentration in the 0.1–1 µm decade would be shaped by penetration of ambient particles at the most penetrating particle size through the filters. The industrial semiconductor cleanroom nanoscale particle concentration was observed to occur in "bursts." This phenomenon was interpreted to indicate small point sources of particles or that particle precursors were being emitted from processing tools and were detected when the plume passed the sampling inlet of the instrument.

Ensor *et al.*[9] reported measurements in an ISO Class 5 cleanroom from 0.05–5 µm using a parallel array of two CPCs with inlet diffusion batteries and two optical particle counters. The reason for using a parallel array of instruments was to average the bursts of nanoscale particles. The characteristic "at rest" state (during the night) curve followed that predicted earlier by Ensor *et al.*[6] where very few nanoscale particles were observed. However, when the cleanroom was in an "operational" state (during the day when the processes were operating) the shape and slope of the curve approached ISO 14644-1:1999 classes from nanoscale emissions from the process and operating personnel.

Ahonen el al.[10] reported the measurement of nanoscale particles in a contemporary semiconductor cleanroom using advanced condensation particle detection equipment with a size cutoff of near 1 nm. The study found sub 2 nm particles formed from the condensation of vapor from processing tools (atomic layer deposition [ALD], Indium Tin Oxide [ITO]-sputtering, lithography) tend to rapidly coagulate into larger particles. The emissions from processing tools appeared in bursts similar to the phenomena (probably coagulated nanoparticles) reported by Sem many years earlier. Some of these bursts from the ALD exceeded $>10^5$ cm^{-3} (10^{11} m^{-3}). However, between the bursts, the particles of 1.4 nm were very low—less than 10 cm^{-3}. In the 1.1–1.4 nm particle size range, a constant concentration between 200–700 cm^{-3} was measured. The study found the concentration did not appear to be related to the process in the cleanroom or have time-dependent properties but may have been due to particle or cluster formation from radiation such as cosmic rays or from the earth.[10]

One additional explanation for the high concentration of 1.1–1.4 nm particles might be thermal rebound from fibers within the high efficiency ventilation filters. It was hypothesized by Wang and Kasper[11] that particles below a very small particle size (thought to be in the 1 nm diameter range) have sufficient velocity from Brownian motion to bounce and not stick to fiber surfaces.

Givehchi and Tan[12] reviewed the thermal rebound literature (over 20 investigators had failed to detect the phenomena) and advanced a new theory identifying relative humidity as an unrecognized factor in explaining some cases with positive experimental results. In a recent paper, Givehchi *et al.*[13] found evidence of thermal rebound of particles smaller than 1.17 nm at low relative humidity from thin electrospun polymer fiber filters. Therefore, it is possible that thermal rebound may exist in the filtration systems under the environmentally controlled conditions found in cleanrooms.

As the nanotechnology field advances, additional research may be undertaken to more fully understand nanoscale airborne particle behavior in the cleanroom environment. Standardized monitoring data gathered through broader use of ISO 14644-12 may also lead to additional observations that merit further investigation.

How ISO 14644-12 fits into the ISO 14644 family of standards

Using the concept presented earlier that airborne particle size regions have distinctly different physical behavior from sources of particles and removal mechanisms, a comparison table (Table 1) can be generalized.

Targeted users of ISO 14644-12

Process Engineering

ISO 14644-12 is intended to support nanotechnology research, development, and manufacturing. One example of a growth area of nanotechnology may be the semiconductor industry, due to shrinking feature sizes over the past decades. Monitoring requirements may be in the nanoscale region. A recent presentation[18] suggested that applications of nanoscale particle monitoring might include:

- Monitoring nanoscale particles from processing tools.
- Monitoring cleanrooms to identify problem areas.
- Monitoring ultrapure inert gases with a pressure reduction device on the inlet.
- Detecting nanoscale particles below the critical flying height in hard disk drives.

One potential reason for monitoring process tools is to provide an independent indication of the process such as the integrity of the process vessel. In addition,

there is a possibility of cross-contamination by nanoscale particles between processes within the cleanroom. Remiarz[19] described a CPC designed with low background for cleanrooms and with a lower particle cut-off of 10 nm using the water-based laminar flow concept invented by Hering *et al*.[20] As reported by Ahonen *et al*., semiconductor processing tools including chemical and thermal process may be greater sources of nanoscale particles than previously suspected.

Monitoring and surveys for industrial hygiene purposes

Airborne nanoparticles are receiving increased attention as a health concern in nanotechnology manufacturing environments including cleanrooms. Particle counting instruments are being used because traditional filter sampling methods have insufficient sensitivity and time resolution. Shepard and Brenner[21] described the use of a CPC and other instruments in semiconductor wafer polishing areas within a cleanroom. Ahonen *et al*. considered whether process emissions from processing tools were potential hazards but was inconclusive.

Another application for ISO 14644-12 could be monitoring of nanoparticles released from drug compounds in cleanrooms and isolators (separative devices).

As reported by Dutton:[22]

According to Dr. Steven Oldenburg, "Nanoparticles are enablers". "It is not the size that sets them apart but how their properties change at the nanoscale that makes them useful".

Nanoparticles are being used as active ingredients and carriers in a wide range of newly formulated therapeutics

Table 1. Comparison of the application of ISO 14644 standards relating to particle size range

ISO/TC 209 Standard (under the title "Cleanrooms and associated controlled environments")	Size Range	Particle Mechanisms	Application
ISO 14644-8:2013[14] Part 8: Classification of air cleanliness by chemical concentration (ACC) (Note: In the future "classification" will be reserved for ISO 14644-1.)	Molecular Smaller than 0.001 µm (1 nm)	Sources: Off-gassing from materials and deposited organic test aerosols; atmospheric contaminants entering through filters. Mechanisms: Condensable and reactive precursors for nanoparticles and deposition on surfaces.	Attributes used in design of facilities and monitoring
ISO 14644-12:2018 Part 12: Specifications for monitoring air cleanliness by nanoscale particle concentration	Nano scale 0.001 µm to 0.1 µm (1 nm to 100 nm)	Sources: Emissions from equipment, corona discharge or radiation induced clusters, filter leaks or possibly thermal rebound from filter fibers. Mechanisms: Brownian motion drives movement and coagulation.	Monitoring
ISO 14644-1:2015 Part 1: Classification of air cleanliness by particle concentration	Micro scale 0.1 µm to 5 µm	Sources: Emissions from processes and personnel, and resuspension from surfaces. Leaks and penetration of filters. Mechanism: Movement by air convection.	Classification
ISO 14644-2:2015[15] Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration	Micro scale 0.1 µm to 5 µm	Companion document to ISO 14644-1.	Monitoring Contains specifications for a risk-based program
ISO 14644-17[16] Part 17: Specification of requirements for particle deposition monitoring [Currently under development.]	Macro scale > 5 µm	Sources: Resuspension from surfaces and emissions from personnel. Mechanisms: Movement dominated by gravity; air convection.	Monitoring
ISO 14644-14:2016[17] Part 14: Assessment of suitability for use of equipment by airborne particle concentration	Uses ISO 14644-1 to determine suitability of equipment for specified ISO classes	In the future, principles in ISO 14644-14 might be extended to other particle size ranges, if required by application, e.g. ISO 14644-12.	Suitability

in various stages of introduction to the market place. The use of high-potency active pharmaceutical ingredients (HPAPI) is increasing as companies develop more effective and better targeted medicines.[23] Monitoring for HPAPI nanoparticles may become a critical parameter in many areas of the operations, including the cleaning of an isolator after operations. Some of these therapeutics might be emitted as nanoscale particles during manufacturing. Data could be generated during validation to determine the recovery of the isolator and the safety margin for opening these units after operations. ISO 14644-12 could benefit this industry in the monitoring effort.

Content of ISO 14644-12

For the purposes of monitoring, airborne nanoscale particle counting can be carried out most effectively by CPC. The reference test method for CPC monitoring is given in Annex A of ISO 14644-12. Table A.1 in the Standard contains an example instrumentation specification. The justification for including only example specifications is that instrumental requirements such as the nanoscale particle size and detection limits may evolve as process monitoring needs change. The method for performing the monitoring of air cleanliness by nanoscale particle concentration should provide a systematic plan, well-defined procedure, and identify how the assessment should be performed. In general, the establishment of alert and action limits is based on a risk assessment. (ISO 14644-2 is suggested for an example of monitoring plan guidelines.) If there is a requirement by buyer-seller agreement, the limits may be established per agreement.

Criteria for determining the counting method will include:

- nanoscale particle size to be measured;
- time dependence of sampling and analysis;
- sample volume;
- location of sampling;
- number of samples;
- criticality of process/product;
- design/layout of clean zone.

Alternative methods and/or instrumentation, with documented evidence of having at least comparable performance to CPC measurement may be specified. If no alternative is specified or agreed upon, the reference method shall be used.

The nanoscale particle size to be measured is critical to the specification. The CPC measures the cumulative concentrations above the 50% cutoff particle size (sometimes called the size resolution). The 50% cutoff particle diameter and the shape of the cutoff curve will determine the size dependent response of the instrument. Typically, the cutoff curve is "S" shaped. Annex B of ISO 14644-12 contains information on the minimum sharpness of the cutoff curve.

Tests performed to demonstrate compliance to the standard shall be conducted using calibrated instruments. Reporting requires complete documentation of the characteristic of the instrument such as cutoff and zero counts, description of the sampling plan, sampling results and any other information required by the buyer of the information.

Summary

ISO 14644-12 includes requirements for nanoscale airborne particles in a standalone document. Nanoscale particles within cleanrooms have limited references in open literature because the traditional focus in cleanrooms has been on microscale particles. Major sources of nanoscale particles in an operating semiconductor cleanroom are emissions from process tools, often in short-term bursts. ISO 14644-12 supports process monitoring and provides instrumentation guidance for industrial hygiene studies for airborne nanoparticle measurement in cleanrooms.

Specifically, ISO 14644-12 provides:

- Consensus of application of CPCs and other instruments in the airborne nanoscale particle range.
- Potential for wide-spread use as instrumentation technology improves.
- An example of instrument specification intended as the impetus to start further dialogue on the requirements for instruments for cleanroom use.
- Support of the historical trend for the dimensions of features of manufacturing to be reduced. Nanotechnology is the most recent expression of that trend. Nanotechnology-enabled products will likely be manufactured in cleanrooms, possibly in reactors or processes.

About ISO/TC 209

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

There are currently 24 participating member (P members) countries, which are eligible to nominate experts for WGs and vote on standards in development or systematic review. There are currently 21 countries (O members) that can observe the work of ISO/TC 209.

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

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

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

ISO/TC 209 has established formal liaisons with five other ISO TCs and the International Confederation of Contamination Control Societies (ICCCS) to ensure transparency and consistency in its standardization efforts. In 2017, ISO/TC 209 revised its business plan and scope to capture and address current and future standardization needs of consumers, regulators, and industry regarding cleanrooms. The revised scope reflects technical progress and the recognition that cleanroom technology has become more widely applied in various industries and the applications have become more diverse.

Bibliography

1. ISO 14644-12:2018, Cleanrooms and associated controlled environments — Part 12: Specifications for monitoring air cleanliness by nanoscale particle concentration.
2. ISO 14644-1:1999, Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration.
3. ISO 14644-1:2015, Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration.
4. Mohnen, V. A. and G. M. Hidy. Ensor D. S., ed. 2011. Atmospheric Nanoparticles: Early Metrology and Observations (1875–1980). *Aerosol Science and Technology: History and Reviews* 411. RTI Press Book series, RTI International, 3040 Cornwallis Road, Research Triangle Park, NC.
5. Ensor, D.S. and R.P. Donovan. 1985. The Application of Condensation Nuclei Monitors to Clean Rooms, *Journal of the IEST* 28: 34–36.
6. Ensor D.S., R.P. Donovan, and B.R. Locke. 1987. Particle Size Distributions in Clean Rooms. *Journal of the IEST* 30 (6): 44–49.
7. Sem, G.J. Donovan, R.P., ed. 1990. Ultrafine (<0.1 µm Diameter) Particles. In: *Particle control for Semiconductor Manufacturing* 79–103. Marcel Dekker, Inc., New York. SBN 9780824782429 - CAT# DK4199
8. Hinds, W.C. 1982. *Aerosol Technology*. John Wiley and Sons, New York.
9. Ensor D.S., A.S. Viner, E.W. Johnson, R.P. Donovan, P.B. Keady, and K.J. Weyrauch. 1989. Measurement of Ultrafine Aerosol Particle Size Distributions at Low Concentrations by Parallel Arrays of a Diffusion Battery and a Condensation Nucleus Counter in Series. *Journal of Aerosol Science* 20: 471–475.
10. Ahonen, L.R., J. Kangasluoma, J. Lammi, K. Lehtipalo, K. Hämeri, T. Petäjä, and M. Kulmala. 2017. First Measurements of the Number Size Distribution of 1-2 nm Aerosol Particles Released from Manufacturing Processes in a Cleanroom Environment. *Aerosol Science and Technology* 51: 685693. DOI: 10.1080/02786826.2017.1292347.
11. Wang, H.C. and G. Kasper. 1991. Filtration Efficiency of Nanometer-Size Aerosol Particles. *Journal of Aerosol Science* 22(1): 31–41.
12. Givehchi, R. and Tan, Z. 2015. The effect of capillary force on airborne nanoparticle filtration, *Journal of Aerosol Science*, 83, May 2015, Pages 12- 24. https://doi.org/10.1016/j.jaerosci.2015.02.001.
13. Givehchi, R., Li, Q., and Tan, Z. 2018. Filtration of sub-3.3 nm tungsten oxide particles using nanofibrous filters, *Materials*, 11(8), 1277; doi:10.3390/ma11081277.
14. ISO 14644-8:2013, Cleanrooms and associated controlled environments—Part 8: Classification of air cleanliness by chemical concentration (ACC).
15. ISO 14644-2:2015, Cleanrooms and associated controlled environments—Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration.
16. ISO/PWI 14644-17, Specification of requirements for particle deposition monitoring. (Under development.)
17. ISO 14644-14:2016, Cleanrooms and associated controlled environments—Part 14: Assessment of suitability for use of equipment by airborne particle concentration.
18. Anonymous. 2014. Nanoparticle counter applications in advances processes. *Symposium on Technical Standards for the Measurement of Nano-particulate matter*. Particle Measuring Systems, Inc. http://www.semi.org/zh/sites/semi.org/files/docs/Nanoparticle Counter.
19. Remiarz, R. 2017. Measurement of Airborne Nanoscale Particles Using Condensation Particle Counters. Semicon Europa November 14-17, 2017, Munich, Germany. http://www.semi.org/eu/sites/semi.org/files/events/presentations/03_Richard%20Remiarz_TSI_0.pdf.
20. Hering, S. V., M.R. Stolzenburg, F.R. Quant, D.R. Oberreit, and P.B. Keady. 2005. A Laminar-Flow, Water-Based Condensation Particle Counter (WCPC). *Aerosol Science and Technology* 39 (7): 659-672. DOI: 10.1080/ 02786820500182123.
21. Shepard, M. N. and S. Brenner. 2014. An Occupational Exposure Assessment for Engineered Nanoparticles Used in Semiconductor Fabrication. *Annals of Occupational Hygiene* 58 (2): 251–265. DOI:10.1093/annhyg/met064.
22. Dutton, G. 2018. Nanoparticles for Multiple Applications, *GEN* October 15, 2018.
23. Avraam, M. HPAPI Technology Trends, *Contract Pharma* October 2018.

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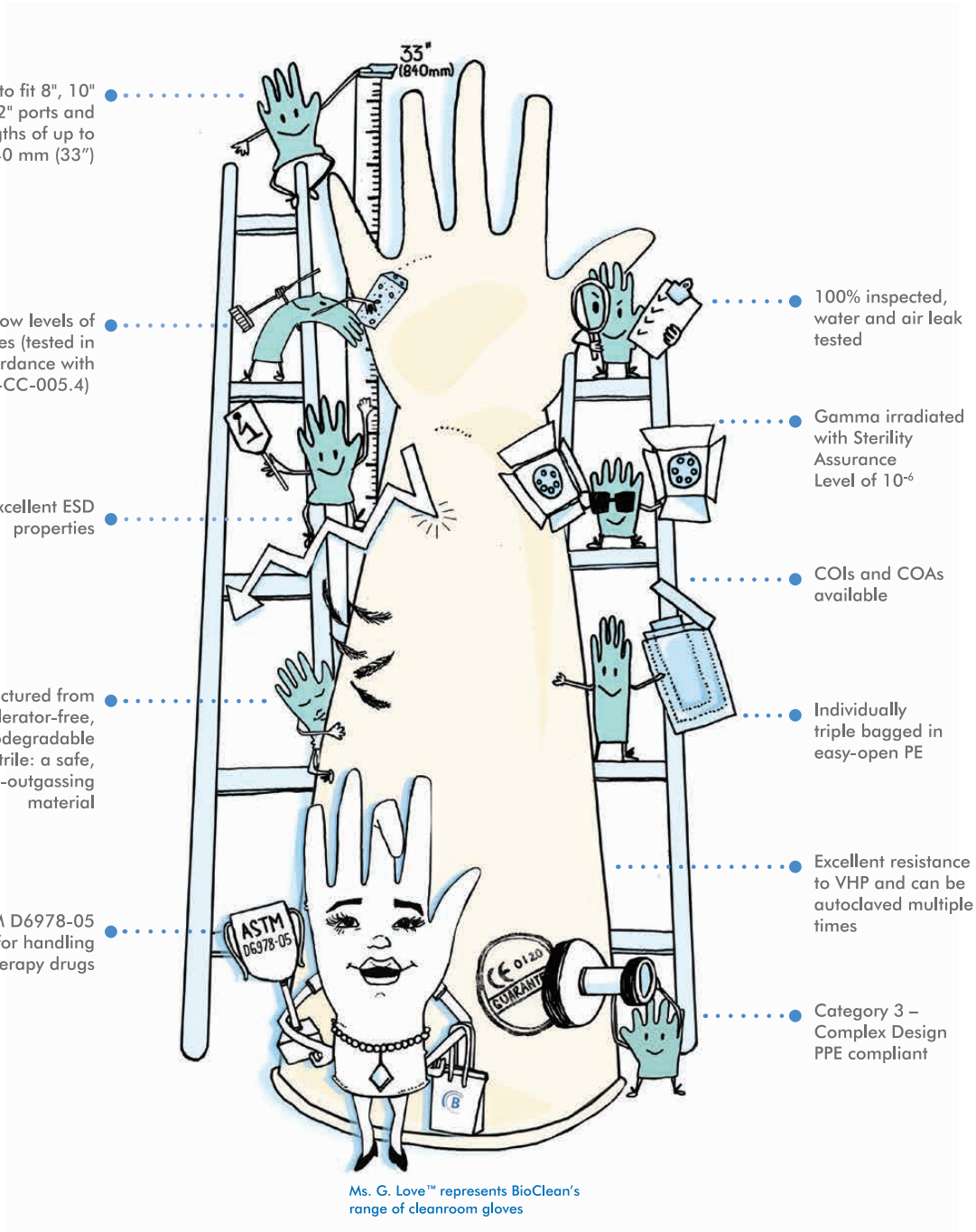

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EN ISO 374, Protective gloves against dangerous chemicals and micro-organisms, summary of changes and FAQs

Peter Clarke

Abstract

Purchasers of disposable gloves for protection against dangerous chemicals and micro-organisms should ensure that they comply with the most recent EN ISO 374 standard. This article highlights changes made to the EN 374 standard at the last update. The latest EN ISO 374 standard defines the required capabilities for gloves that protect workers whose hands are subject to chemical and/or micro-organism exposure. The article includes a number of FAQs to help readers understand the changes, new performance ratings, test methods and rating symbols.

Introduction

EN ISO 374 ensures consistency in testing and helps users and safety professionals as they determine their chemical protection needs. The revised requirements are reflected in pictograms that appear on gloves and on glove packaging certified for chemical and micro-organism exposure. The glove markings associated with the new standard are summarized in this guide.

Questions:

What parts does the latest EN standard – 'Protective gloves against dangerous chemicals and microorganisms' consist of?

The new standard consists of four parts set out in Table 1.

EN 374-3: 2003, which defined the test method for the determination of chemical permeation performance specifically for gloves, has been withdrawn. It has been replaced by EN 16523-1:2015, Determination of material resistance to permeation by chemicals. Permeation by liquid chemical under conditions of continuous contact, which has a broader scope of application.

Why was the standard changed?

- To ensure consistency between test results
- To better assist users in their glove choice by more accurately reflecting the chemicals being used throughout industry
- The standard stipulates the requirements of manufacturers to test for Permeation, Penetration and the new tests for Degradation

What are penetration, permeation and degradation?

Penetration

Penetration is the movement of a chemical and/or micro-organism through pinholes or other imperfections in a protective glove material at a non-molecular level.

Permeation

Permeation is the process by which a chemical moves through a protective glove material at a molecular level. Permeation involves the following:

- absorption of molecules of the chemical into the contacted (outside) surface of a material;
- diffusion of the absorbed molecules within the material;
- desorption of the molecules from the opposite (inside) surface of the material.

Degradation

Degradation is the change in one or more physical characteristics of a glove caused by contact with a chemical. Indications of degradation are flaking, swelling, disintegration, embrittlement, colour change, dimensional change, appearance, hardening, softening, etc.

What are the main changes in each part of the standard?

Part 1 – EN374-1:2016 Terminology and performance requirements for chemical risks:

- Permeation testing still requires three samples taken from the palm.
- New requirement for gloves 400mm or longer – 3 ADDITIONAL samples must be taken from the cuff area and tested for permeation and degradation.
- The new standard includes 6 additional chemicals highlighted in blue in Table 2.
- The permeation performance levels, shown in Table 3, remain unchanged.
- Gloves are now separated into 3 classification types based on permeation performance: TYPE A, TYPE B or TYPE C.

Table 1: The four parts of the standard

EN ISO 374-1:2016	Protective gloves against dangerous chemicals and microorganisms Part 1: Terminology and performance requirements for chemical risks
EN 374-2:2014	Protective gloves against dangerous chemicals and microorganisms Part 2: Determination of resistance to penetration
EN 374-4:2013	Protective gloves against dangerous chemicals and microorganisms Part 4: Determination of resistance to degradation by chemicals
EN ISO 374-5:2016	Protective gloves against dangerous chemicals and microorganisms Part 5: Terminology and performance requirements for micro-organisms risks

Table 2: Listed chemicals

	Chemical	Cas number	Class
A	Methanol	67-56-1	Primary alcohol
B	Acetone	67-64-1	Ketone
C	Acetonitrile	75-05-8	Nitrile compound
D	Dichloromethane	75-09-2	Chlorinated hydrocarbon
E	Carbon disulphide	75-15-0	Sulphur containing organic compound
F	Toluene	108-88-3	Aromatic hydrocarbon
G	Diethylamine	109-89-7	Amine
H	Tetrahydrofuran	109-99-9	Heterocyclic and ether compound
I	Ethyl acetate	141-78-6	Ester
J	n-Heptane	142-85-5	Saturated hydrocarbon
K	Sodium hydroxide 40%	1310-73-2	Inorganic base
L	Sulphuric acid 96%	7664-93-9	Inorganic mineral acid, oxidizing
M	Nitric acid 65%	7697-37-2	Inorganic mineral acid, oxidizing
N	Acetic acid 99%	64-19-7	Organic acid
O	Ammonium hydroxide 25%	1336-21-6	Organic base
P	Hydrogen peroxide 30%	7722-84-1	Peroxide
S	Hydrogen fluoride 40%	7664-39-3	Inorganic mineral acid, contact poison
T	Formaldehyde 37%	50-00-0	Aldehyde

Note: The six extra chemicals are not more aggressive than the existing 12; they were added because they are more representative of chemicals in the modern industrial environment.

Table 3: Permeation performance levels

Breakthrough Time BTT (mins)	Performance level
>10	Level 1
>30	Level 2
>60	Level 3
>120	Level 4
>240	Level 5
>480	Level 6

Table 4: Performance level and number of chemicals required for each type

Classification	Minimum Performance Level Required	Minimum number of chemicals from the 18 listed
Type A	2 (min 30 minutes breakthrough)	6
Type B	2 (min 30 minutes breakthrough)	3
Type C	1 (min 10 minutes breakthrough)	1

Table 4 lists the performance level and number of chemicals required for each type.

- New pictograms to depict permeation performance, with Type above and letters underneath (Type A & B) denoting which chemicals the gloves have been tested against – see Figure 1.

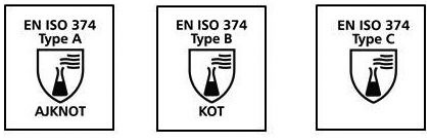

Figure 1: New pictograms

Note: The pictograms Type A, Type B or Type C are mandatory on all gloves covered by this standard

- The beaker icon from EN 374-1: 2003 indicating low level protection has been eliminated – see Figure 2.

Figure 2: The eliminated icon for low level protection

- New requirement that degradation resistance test is carried out per EN 374-4: 2013.

Test must be carried out for each test chemical claimed in the Type classification.

- The following warnings are required to be added to the packaging of gloves:

"The information does not reflect the actual duration of protection in the workplace and the differentiation between mixtures and pure chemicals."

"The chemical resistance has been assessed under laboratory conditions from samples taken from the palm only and relates only to the chemical tested. It can be different if it is used in a mixture."

"It is recommended to check that the gloves are suitable for the intended use because the conditions in the workplace may differ from the type test depending on temperature, abrasion and degradation."

"When used protective gloves may provide less resistance to the dangerous chemical due to changes in physical

properties. Movements, snag, rubbing, degradation caused by the chemical contact etc. may reduce the actual use time significantly. For corrosive chemicals, degradation can be the most important factor to consider in selection of chemical resistant gloves."

"Before usage inspect the gloves for any defect or imperfection."

- Reusable gloves must have instructions for decontamination
- If no decontamination instructions then gloves are are single use and must be labelled "For single use only"

Part 2 – EN 374-2:2014 Determination of resistance to penetration

- This part replaces EN 374-2:2003, which specified the test method used for the penetration resistance of gloves that protect against dangerous chemicals and/or micro-organisms (water leak and air leak test).
- Testing for protection against micro-organisms is no longer included and is covered by the new standard EN 374 5: 2016.
- It acknowledges that the air leak test is not appropriate for non-homogenous gloves
- The claimed AQL for pinhole testing during production is no longer a part of type examination certification.
- Performance levels (AQL) for use in production control are still given in Annex A (informative) and shown here in Table 5.

Part 3 – EN 374-3:2003 Determination of resistance to permeation by chemicals

- This part has been withdrawn and replaced by test method EN 16523-1:2015.

Part 4 – EN 374-4:2013 Determination of resistance to degradation by chemicals

This part describes the mandatory test for all gloves that offer chemical protection. The puncture resistance of the glove material is measured after continuous contact of its external surface with a challenge chemical. The test is carried out using the following method:

- 6 specimens are cut from each of 3 gloves
- For each glove 3 specimens are exposed to test chemicals and 3 specimens are unexposed
- Exposure to chemical is for 60 mins
- Standardised puncture stylus used to measure peak force required to puncture the specimen
- Degradation is the average change in force required from unexposed to exposed as %
- No Pass/Fail

There is also a non-mandatory weight change test (Annex B) which consists of:

- Cut same finger off three gloves and weigh individually
- Immerse each finger in a beaker of test chemical and weigh down
- After 60 minutes reweigh the fingers
- Calculate the % change based on starting weight
- No Pass/Fail

Part 5 – EN ISO 374-5:2016 Terminology and performance requirements for micro-organisms risks

Part 5 specifies performance requirements for gloves that protect the user against micro-organisms. It has been taken out of the old Part 2 and developed.

- There are now two classifications

a. Protection against bacteria and fungi

b. Protection against viruses, bacteria and fungi

- A glove claiming protection from bacteria and fungi must carry the pictogram and warnings shown in Figure 3.

Table 5: Performance levels

Performance level	AQL	Inspection level
Level 3	<0.65	G1
Level 2	<1.5	G1
Level 1	<4.0	S4

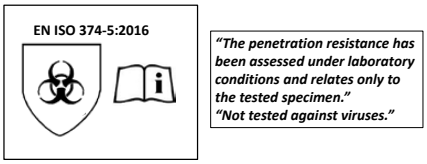

Figure 3: Pictogram and warning for gloves claiming protection from bacteria and fungi

- All gloves claiming micro-organism protection must have been penetration tested as outlined in Part 2 of the standard
- Gloves claiming protection from viruses require additional penetration testing according to ISO 16604:2004 Clothing for protection against contact with blood and body fluids — Determination of resistance of protective clothing materials to penetration by blood-borne pathogens — Test method using Phi-X174 bacteriophage :

a. Test uses a nutrient broth containing a virus is forced against the glove for specified time and pressure pattern

b. Glove is elastomeric – mesh inserted into test chamber to prevent ballooning and distortion of the test results

c. Visual detection of penetration plus assay procedure to detect the presence of virus

- The detection of any permeation constitutes a test failure
- A glove claiming protection from virus, bacteria and fungi must carry the pictogram and warnings shown in Figure 4.

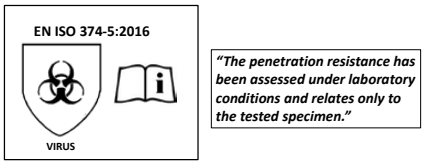

Figure 4: Pictogram and warnings for gloves claiming protection from virus, bacteria and fungi

Summary

- Chemical protection is redefined as Type A, B and C, representing high, medium and low protection respectively
- Permeation test method now covered by a new, universal standard EN 16523
- Glove degradation now must be tested – even though there are no pass/fail criteria set
- Pinhole AQLs are removed from type examination testing
- One glove per size air and water leak tested with a minimum total of four gloves tested

- Protection from micro-organisms now treated as separate tests with two levels of protection – bacteria and fungi or viruses, bacteria and fungi

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New energy standard

ISO 14644-16:2019 – Part 16: Energy efficiency in cleanrooms and separative devices

This standard was published in June 2019 and the Scope reads:

This document gives guidance and recommendations for optimizing energy usage and maintaining energy efficiency in new and existing cleanrooms, clean zones and separative devices. It provides guidance for the design, construction, commissioning and operation of cleanrooms.

This document covers all cleanroom-specific features and can be used in different areas to optimize energy use in electronic, aerospace, nuclear, pharmaceutical, hospital, medical device, food industries and other clean air applications.

It also introduces the concept of benchmarking for the performance assessment and comparison of cleanroom energy efficiencies, while maintaining performance levels to ISO 14644 requirements.

To order, visit https://www.iso.org/standard/66331.html

Cleanroom regulatory trends: A review of FDA warning letters

Tim Sandle

Abstract

Cleanrooms remain a central focus of regulatory inspections and it is good practice for those working within pharmaceuticals and healthcare to assess regulatory trends. This task is difficult within Europe, where only broad overviews are released (due to data privacy restrictions) and it becomes complex when assessing output from U.S. FDA, given the hundreds of warning letters issued. To assist with this process, this article assesses recent FDA warning letters and draws out the main trends and significant non-compliances relating to cleanroom design, testing and operations.

Introduction

Deficiencies relating to cleanrooms and practices within cleanrooms remain areas commonly cited by regulators. While information relating to inspections by European regulators tends to remain undisclosed, protected by data privacy legislation (save occasional overarching summaries issued by the MHRA) (1), the U.S. Food and Drug Administration places all warnings letters documenting Current Good Manufacturing Practices (CGMP)[i] concerns into the public domain (2). A review of FDA issued warning letters for the period March 2017 to March 2019, in relation to cleanrooms, reveals a number of concerns in relation to this aspect of pharmaceutical operations. Evaluating these warning letters over a two-year period provides an indication of the types of cleanroom-related areas that inspectors are more inclined to look into when conducting pharmaceutical facility inspections, and also the areas where pharmaceutical companies have been found not to be meeting the expected level of CGMP.

This article draws out the main cleanroom-related themes from FDA warning letters over a two-year period, with the intention of providing a benchmark for those operating cleanrooms within the pharmaceutical or healthcare sector to review their practices against. Given the relative criticality of the operation, the majority of the warning letters relate to sterile products manufacturing (most notably for aseptically filled products). However, many of the findings will be of interest to those who work within any type of pharmaceutical or healthcare activity which takes place within a cleanroom environment and where CGMP is required.

U.S. FDA and warning letters

The Food and Drug Administration (FDA) is an agency of the United States Department of Health and Human Services, and it is one of the United States federal executive departments. With CGMP inspections, FDA inspectors assess whether the manufacturer is compliant with CGMP. The scope of CGMP includes ensuring that all manufacturing operations are performed in accordance with the relevant marketing authorisation and published guidelines. The purpose of an inspection may vary somewhat in the details; however, all inspections are designed to:

- Determine if violations of law within FDA's jurisdiction are occurring, and if so,
- Obtain voluntary correction by the inspected entity, or
- Develop the necessary evidence to support FDA enforcement action if voluntary correction is not promptly forthcoming or is ineffective.

The FDA commonly adopt a systems-based approach to inspections, taking samples from six different systems – Quality System, Facilities and Equipment System, Materials System, Production System, Packaging and Labelling System and Laboratory System – in order to assess an organisation's adherence to CGMP (3).

Where deficiencies are noted following an inspection, these are documented on a form 483. An example of a warning letter is shown in the box. If the manufacturer's response to the 483 is deemed inadequate by the FDA, the agency will issue a warning letter to the manufacturer stating that the manufacturer has violated a CGMP rule in a federally regulated activity. The reasons for the violation(s) are listed out, and these are published on the FDA website.

Warning letters are issues as set out under the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), section 501 CGMP (4), which "includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

FDA inspection trends relating to cleanrooms

During 2017 the FDA released 476 warning letters (of which 52% were applicable to pharmaceuticals and healthcare, with 8% relating to medical devices). Of these, 114 related to CGMP violations (it is noteworthy that in 2015 there were only 42 individual warning letters for CGMP violations). For 2018, the warning letters containing CGMP violations rose to 127.

This author has undertaken a review of all CGMP warning letters issued across a 24-month period (March 2017 to March 2019), some 271 warning letters and the main issues and trends either relating directly to cleanrooms or key operations that take place within cleanrooms have been drawn out and these are discussed below.

Environmental monitoring

Microbiological environmental monitoring is an important means to assess whether cleanrooms remain in

i. The FDA tends to discuss GMP in terms of 'CGMP', Current Good Manufacturing, Practice, in contrast to Europe, where 'GMP' tends to be used.

a state of environmental control and unsurprisingly this activity is a key focal point during inspections. While there still remains some basic observations about the design of environmental monitoring (with one company, for instance, being cited for not including any air monitoring whatsoever), more recent FDA concerns pertaining to environmental monitoring have generally related to data integrity issues. These include the lack of contemporaneous recording of data, such as not labelling environmental monitoring samples at the point they are taken in the production facility or failing to record all information relating to the sampling activity onto each sample (such as only recording the exposed and collected time onto one settle plate from a set). Several companies have been called out for not undertaking growth promotion testing on the culture media used to assess cleanrooms or, where such testing is undertaken, for not including environmental isolates within the test panel. Connected with culture media are comments in some letters about lack of written procedures to ensure that prepared media consistently meets appropriate standards of quality and purity.

The main issue, however, relates to colony counting. Examples from the warning letters range from suspected causes of fraud, where zero colonies have been recorded but where the inspector has re-examined plates and found there to be colonies; an infraction whereby a microbiologist reporting plates as having one colony when, in the inspector's view, the plate contained two colonies side-by-side; disposing of samples prior to incubation (in relation to an abandoned environmental monitoring session); or with not using colony counters (equipped with light-sources and magnifying glasses) to record colonies. The concern with plate reading probably accounts for the inclusion of the topic in the FDA 2018 question and answer document on data integrity (5), which infers that there should be a second check in place to verify plate counts.

Data integrity appears in many warning letters, beyond issues affecting cleanrooms. While there are no instances of particle counters being called out for not meeting data integrity requirements it is good practice to ensure that particle counters are compliant and meet the trends within the warning letters. FDA inspectors tend to cite:

- Lack of control over access to computerized systems (password protection).
- Non-contemporaneous record-keeping.
- Lack of audit trails.
- Deletion, falsification, alteration, or other manipulation of data.

Also linked with environmental monitoring is the recurrent finding of inadequate root cause investigation where microbial contamination has

Example text taken from an FDA Warning Letter, issued to a manufacturer of sterile products based in South Korea in October 2018.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).
Your operators' poor aseptic practices during set-up and filling operations for your sterile **(b)(4)** solution posed a significant risk of microbial contamination. During filling set-up, an operator touched the **(b)(4)** between an ISO-7 and ISO-5 area. The operator then continued equipment set-up activities in the ISO-5 zone without disinfecting his hands, which could transfer microorganisms from the ISO-7 area to the surfaces and components in the ISO-5 aseptic filling zone. Also, on Jan. 30, during filling of an **(b)(4)*** solution on Line **(b)(4)**, our investigator observed operators stopping the lines and opening the **(b)(4)** to clear bottle jams more than 10 times in a 90-minute period. On several occasions, operators leaned their heads and torsos inside the **(b)(4)** over open bottles. They restarted the line without clearing open bottles that may have been contaminated by their interventions.

In your response, you stated that you will make changes to the filling line and will train operators on movement in filling rooms. Your response was inadequate because you did not sufficiently assess the adequacy of your aseptic filling line design. You did not provide a detailed plan for qualifying changes to your filling line by conducting media fills and smoke studies. You also did not provide any details on operator training.

Furthermore, FDA cited a similar CGMP violation regarding inadequate design of your aseptic line in an April 2014 inspection.

In response to this letter, provide:

- Your plan to assure strict adherence to appropriate aseptic practices and cleanroom behaviors. Specify how your firm will ensure routine and effective supervisory oversight during manufacture of each batch. Also, describe the frequency of quality assurance oversight, such as audits, during aseptic processing and other operations.
- A thorough risk assessment that evaluates how poor aseptic technique and cleanroom behavior such as that observed during the inspection may have affected quality and sterility of your drugs.
- Comprehensive, independent identification of all contamination hazards specific to your aseptic processes, equipment, and facilities. Provide an independent risk assessment that covers, among other things, all human interactions with the ISO-5 area, equipment placement and ergonomics, air quality in the ISO-5 area and surrounding room, facility layout, personnel flow, and material flow.
- A detailed corrective action and preventive action (CAPA) plan, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve aseptic processing operation design, control, maintenance, and personnel qualification.

*** (b) (4) indicates redacted content relating to the company in question.**

been isolated within the cleanroom. This appears particularly so where organisms with a theoretical greater resistance to disinfection agents have been recovered, such as fungi or bacterial spores.

Aspects of the cleanroom environmental programme, in relation to either the frequency or scope of monitoring are also cited. As an example, it was noted with one company that environmental monitoring did not include the cleanroom within which sterility testing takes place.

Environmental monitoring criticisms also extend to insufficient trend monitoring. Environmental monitoring is seldom about individual results, either within range or excursions; a true picture of the state of control can only meaningfully be derived from assessing trends. In some cases, organisations were not assessing trends; in other circumstances the FDA considered the trend to be over too short a time period (such as just one week, taking one example).

There are many other examples of environmental monitoring inadequacies, including:

- Not carrying out a sufficient number of identifications of microbial contaminations.
- Not looking for patterns in relation to the microbial species identified.
- Insufficient sampling, including one case where personnel finger plates were "from left and right hands on alternate days", which the FDA, quite rightly, considered to be "unacceptable".
- A failure to justify sampling locations, and associated action and alert limits
- Not ensuring all locations are sampled at appropriate frequencies.
- Not assessing cleanrooms following a period of shutdown to assess the impact of maintenance works upon the environment.
- Not clearly defining circumstances under which investigation of an adverse trend or out-of-limit result is triggered.
- Inadequate investigations into occurrences where contamination hazards have been identified.
- Poor sampling SOPs, as with procedures that did not include instructions for the location and duration of samples collected within cleanrooms.

Summing up these observations, it is of importance that the environmental monitoring programme is continually maintained and that thorough investigations are undertaken and documented.

Aseptic technique

A number of warning letters take issue with the aseptic practices performed by cleanroom personnel, as observed by inspectors. With the first three months of 2019, for example, three warning letters discuss poor aseptic behaviours including failure to log interventions of the aseptic core in the batch records and with operators making rapid movements, instead of the slow and deliberate movements that are necessary for good aseptic practice. There is a trend apparent from more recent warning letters where FDA inspectors are closely observing (either directly or via video footage) the practices of operators when performing aseptic processing activities. Other poor aseptic practices mentioned are with the use of gloves that were found to be non-integral.

Further with gloves, there are several instances of personnel monitoring being deemed to be inadequate because staff did not sanitize their gloved hands prior to undertaking a critical activity or before performing environmental monitoring. The interaction between the aseptic core and the surrounding environment is also regularly highlighted as a concern (the barrier between EU GMP Grade A and Grade B environments). One finding concerns operators being observed touching gowns and other objects outside of a Grade A unidirectional cabinet and then returning their gloved hands into the Grade A without sanitizing the entire surface of their hands. Connected with environmental monitoring, where personnel have recorded several microbial counts from glove finger plates, two organisations have been criticised for failing to take appropriate action.

Cleanroom design

Inadequate cleanroom design features in a few warning letters. This is primarily in relation to space (such as with the space not permitting effective equipment segregation); with having too many operators inside cleanrooms (or not justifying how many operators can be present within a cleanroom); or to poorly defined process flows. Another area that appears with some regularity across the warning letters relates to fabric, either for older facilities (maintaining aging pharmaceutical plants in an area of great challenge) or where the fabric is in a poor state, such as rouging where a chlorine disinfectant has contacted stainless steel, or with a case where an ISO class 8 cleanroom (EU GMP Grade C) has not been completely 'vinyled', with the vinyl only extending part way up each wall. To address such concerns, maintenance issues should be mitigated by conducting routine and frequent checks of both the condition of the area and the equipment, ensuring that any damage is quickly repaired.

A different design issue in one warning letter is linked with HEPA filter integrity test failures (linked to seals around the filters). A company recorded failures in March of 2018; did not conduct root cause analysis until a month later; and by June of the same year had yet to implement a new design for HEPA filter housing.

Cleanroom assessments

The most common deficiency in relation to the assessment of cleanrooms is with airflow visualisation studies, which are required for ISO 14644 class 5 areas (EU GMP Grade A equivalent). This is either with a failure to conduct airflow studies; only conducting airflow studies 'at rest' rather than 'in operation'(necessary to show what happens when there is an intervention into the aseptic core); or with a failure to adequately react to the findings, such as air showing turbulence when it should be unidirectional. Exemplifying the greater emphasis upon environmental control, one company who elected to compensate inadequate airflow through 'additional' environmental monitoring was pulled up for attempting to justify bad practice. This was in relation to the stopper bowl within a filling machine disrupting the unidirectional airflow, creating a risk for microbial contamination.

Connected with airflow is the failure by some companies to assess air exchange rates and with not recording airflow

velocity readings in unidirectional airflow devices. Interestingly, in terms of terminology, a number of the warning letters continue to use the word 'laminar'. Another finding is with no alarms being in place for unidirectional airflow devices, which means there is no mechanism for altering cleanroom operators in case of a loss in HEPA filtered air. The same warning letter mentions that there is no uninterrupted power supply system for the cleanrooms or unidirectional airflow devices.

Further with monitoring, another company is noted for not having any process of continuous monitoring of differential pressure and with this the absence of any alarm mechanism for altering cleanroom operators in cases of low or negative pressure differentials. The issue of pressure alarms extends to several cases where companies do not have active alarms operating in airlocks.

Taking cleanroom design and assessments together, to reduce the chance of receiving a warning letter, organisations should review the design features of a cleanroom on a regular basis and take appropriate corrective actions to ensure that airflows are maintained, especially when personnel are operating within a critical area.

Media simulation trials

Media simulation trials represent an important assessment step for aseptic processing. FDA warning letters cite inadequate media simulation trials on a number of occasions. The more common reasons for this are running media fills which are not considered to be representative of actual predict fills; insufficient environmental monitoring during media fills; and the failure to incubate all filled and integral units during the course of the media fill (with vials excluded for reasons such as under- or over-filling of culture media). Each of these is cited as a sterility assurance concern.

Cleaning validation

There are numerous examples of a failure to adhere to appropriate cleaning validation of equipment and utensils. The main failing appear to be the inadequate development of the cleaning validation protocol, which has led to a poorly executed cleaning validation study. The FDA are also willing to criticise what they determine to be inadequacies with cleaning cycles, such as the absence of an acid or caustic rinse, or with inadequate rinsing of cleaning solutions using Water-for-Injections (WFI). Furthermore, while cleaning validation can be both automated and manual, the FDA appears to be especially concerned about the uncontrolled and inconsistent nature of manual cleaning practices.

Disinfection

Several different points are made in the warning letters about disinfection. This rests on a number of areas, including the inability to clean and to disinfect adequately, such as missing out some parts of the cleanroom or having equipment within the cleanroom which does not facilitate the effective cleaning of the room (such as fixed items which cannot be easily cleaned around or underneath). In some cases, the cleaning and disinfection programme is classed as unsatisfactory due to the recovery of 'objectionable microorganisms' (such as Gram-negative bacteria in aseptic processing areas). With one of these cases, the company in question was found to be making up disinfectant solutions with mains water instead of purified water, with the mains water being the source of the undesirable microorganisms. In other cases (and there are several examples) companies have been criticised for not having a sporicidal agent as part of their disinfection programme and with not using sterile disinfectant solutions within their aseptic processing areas.

The lack of disinfectant efficacy studies also features in warning letters, or where disinfection efficacy studies are deemed to be inadequate. The FDA do not accept suspension tests for the evaluation of disinfectants and instead expect the surface test. For surface (or 'coupon') testing some organisations have been cited for not conducting testing on a representative range of surfaces (or, alternatively, with not having a risk assessment in place to justify surface selection). Given the range of different surfaces found within a typical pharmaceutical facility, opting to only assess disinfectants on stainless steel, glass and vinyl is most likely to be assessed as insufficient in the eyes of the FDA.

Cleaning techniques are also called into question in some warning letters. This includes operators 're-contaminating' areas that have recently been cleaned (as with not cleaning from the back of the room and working towards the room exit) to using inappropriate cleaning techniques (such as not using a double or triple bucket system) and to using inappropriate tools (there was one incident of a wire brush being used inside a cleanroom).

Quality agreements for cleanroom activities

The FDA expects quality agreements to be in place (and up-to-date) between pharmaceutical firms and their contractors. A quality agreement is a comprehensive written agreement that defines responsibilities of the Quality Units of each party in contract manufacturing of drugs subject to CGMP. Within quality agreements, both parties can define, establish, and document the responsibilities of parties involved in the contract manufacturing of drugs subject to CGMP. In this context, two warning letters note that organisations did not have quality agreements in place with cleanroom garment suppliers. Although not specified in warning letters, it is additionally important to ensure that quality agreements exist for companies contracted to undertake particle classification of cleanrooms according to the ISO 14644 standard.

Written procedures and risk assessments

A common finding across CGMP activities, and with a number of the topics touched upon in this article pertaining to cleanroom operations, is with pharmaceutical and healthcare organisations not establishing or following written procedures. This includes procedures that should enable contamination control measures to be followed. Linked to standard procedures, there are several examples where risk assessments have either not been written; of where risk assessments are deemed inadequate (one Failure Modes and Effects Analysis for a cleanroom neglected to make any reference to pressure differentials, as an example); or where items that came out as a high risk have not been addressed.

Summary

This article has looked at the main topics and trends from FDA warning letters relating to cleanrooms and the activities that take place within them. Whilst an article such as this can only highlight and briefly discuss the main issues, it can provide an indicative benchmark for those working in pharmaceutical and healthcare cleanroom environments to consider.

What is clear from the number of warning letters issued and the topics that appear within the warning letters is that the FDA continues to focus investigatory efforts on the manufacture of drugs, both in the U.S. and internationally. Central to these concerns are cleanrooms and cleanroom practices. Moreover, according to the commentary within the letters, the FDA finds many responses to warning letters to be deficient due to poor documentation and lack of proof of corrective actions. This latter point would suggest that attention needs to be paid to building a strong quality management system and with ensuring that this is aligned to support cleanroom design, operations and practices.

References

1. Sandle, T. (2017) MHRA annual deficiency review highlights sterility assurance issues, *GMP Review*, 16 92): 4-7
2. FDA. Inspections, Compliance, Enforcement, and Criminal Investigations – Warning Letters at: https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
3. Barr, D. and Sandle, T. (2014). System Based Approach to Inspections. In Saghee, M.R. (Ed.) *Pharmaceutical Regulatory Inspections*, Euromed Communications: Passfield, UK, pp119-182
4. U.S. government. Public Law 112-144, 126 Stat. 993, Amendment to the Federal Food, Drug, and Cosmetic Act as passed by the 12th Congress https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf
5. FDA. Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry, U.S. Department of Health and Human Services, December 2018 at: https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf

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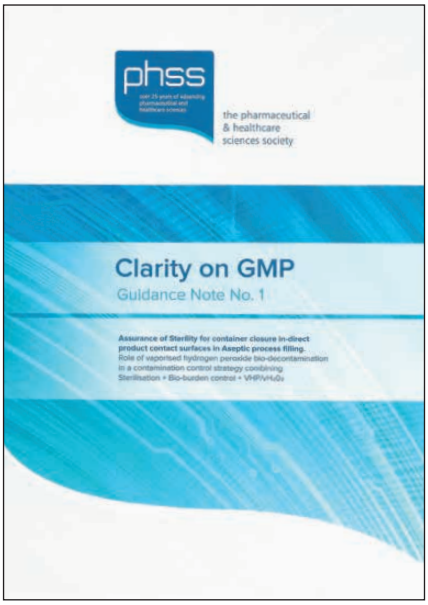
Clarity on GMP from PHSS, a critique of Guidance Note No. 1

Tim Coles



Abstract

The recently-published PHSS Guidance Note No. 1 was drafted largely in response to the MHRA blog which described the vapour phase hydrogen peroxide (VPHP) bio-decontamination process as "incredibly fragile". Whilst the guidance note offers some very useful information to support users of the VPHP process, it is not entirely clear in places. This critique seeks to clarify and expand on a number of points in the note, to bolster confidence in the VPHP process, and to assure users that if due consideration is applied, the process may be considered robust.

Introduction

The full title of this guidance note which was published at the end of 2018 is: **Clarity on GMP, Guidance Note No.1, Assurance of Sterility for container closure in-direct product contact surfaces in Aseptic process filling, Role of vapourised hydrogen peroxide bio-decontamination in a contamination control strategy combining Sterilisation + Bio-burden control + VHP/vH_2O_2.**

The note essentially follows on from the recent MHRA blog which described the VPHP bio-decontamination process as "incredibly fragile". The blog led to some consternation in the industry, to the extent that some operators interpreted it as a signal that the process should be discontinued. The guidance note is therefore a welcome attempt at explanation and clarification. Indeed, it does offer a lot of useful information, and although mostly targeted at aseptic filling operations, it provides useful background for any application of the VPHP process. That said, there are still some points which could benefit from further comment and additional clarification.

VHP®/vH_2O_2

The note refers to the process of bio-decontamination using vapour phase hydrogen peroxide (VPHP) throughout as "VHP®/vH_2O_2". No explanation is offered for this terminology, which will puzzle some, and confuse others. "VHP®" is the trademark of the Steris Corporation, manufacturers of hydrogen peroxide vapour generators. "vH_2O_2" is used to denote the VPHP process provided by other suppliers, notably Bioquell Ltd. Unfortunately, use of the terminology "VHP®/vH_2O_2" hints at two possible regimes, or types of gassing cycle, the former being notionally "dry" and the latter being notionally "wet". It has long been shown that this delineation simply does not exist, and that in essence, all VPHP processes work in the same way, and this probably includes the aerosol systems on offer (Reference 1). It would aid the reader if the guidance note simply used the very clear term "VPHP".

Sterilisation

The note very much labours the point that the VPHP process cannot be regarded as true sterilisation. For the most part, the equipment suppliers do not claim that the VPHP process is anything other than a bio-decontamination and, generally informed operators will be aware of this limitation. The note does then go on to provide useful information as to how to address the limitations of the process. Mention is made of the need to minimise surface occlusion in the isolator load pattern, and also the need for effective cleaning prior to the application of VPHP. However, these issues are tackled in a rather roundabout description, again leading to potential confusion.

Particle size

The note also labours the size difference between molecular hydrogen peroxide and aerosol droplets. This is completely irrelevant to the VPHP process. There is no parallel whatsoever between individual molecules and aerosol droplets. This issue has been addressed in the previous reference paper (Reference 1).

"It would be a huge step forward if the industry were to apply the technically-correct phrase "micro-condensed hydrogen peroxide" (MCHP) universally."

Micro-condensation

Somewhat strangely, whilst the guidance note clearly accepts the concept of micro-condensation, the inexact and potentially confusing term "deposition layer" is used. The rapid sporicidal effect of the VPHP process is produced by the formation of invisible micro-condensation hydrogen peroxide solution at high concentration. It would be a huge step forward if the industry were to apply the technically-correct phrase "micro-condensed hydrogen peroxide" (MCHP) universally.

Humidity

The note states: *"…water molecules in the environment at cycle start can be a barrier to vH_2O_2 molecule distribution via inherent localised bonding or incoming molecules being attracted to preferential sites where surface condensate layers have formed."* Which is a very circumspect way of saying that the relative humidity of the air in the isolator matters. Basically, if the humidity at the start of the cycle is too high (specifically above 50%), then frank, visible condensation will form, which reduces the efficacy of the process.

Vapour and aerosol

The note makes mention of aerosol application hydrogen peroxide solution but does not go on to discuss or clarify this, other than stating: *"…not all processes that apply H_2O_2 are equal or comparable"*. The note appears to be disparaging of aerosol processes.
To describe the effect briefly: when a true aerosol of hydrogen peroxide is introduced into an isolator, the large surface area of the droplets allows the hydrogen peroxide molecules, which have a much lower vapour pressure than their companion water molecules, to leave the droplets and form MCHP.
To this extent, the true aerosol process is the same as the vapour process – both methods simply deliver MCHP. Whilst every aerosol generator / gas generator / isolator / load pattern arrangement will be different, requiring different cycle development, the basic mode of action is the same at isolator surfaces.

Hydrogen bonding

It is a significant drawback of the MCHP process that the aeration phase takes a long time, often very much longer than the rest of the cycle. The cause of this effect has been described as "absorption" or "adsorption" of peroxide into or onto, the materials of the isolator and the load. The note ascribes the effect to hydrogen bonding and, although this may in part be true, it presents a new and potentially confusing element to the operators.
It may be preferable to simply note the need to allow for the adequate de-gassing of hydrogen peroxide from surfaces during the aeration phase.

Cycle development

Within a paragraph which consists of a single very long sentence, the note states *"…the qualified VHP®/vH_2O_2 cycle used to render surfaces free of CFU recovery in a Grade A aseptic processing environment after a sterilisation process… should be justified via a risk based approach with consideration to science, process integration, impact from process variables, inherent contamination, penetration limitations of VHP®/vH_2O_2" and surface exposure for bio-decontamination"*.
It would be very much clearer if mention were made of the need for cycle development, followed by a brief description of the steps required to complete a cycle development exercise.

"The blog led to some consternation in the industry, to the extent that some operators interpreted it as a signal that the process should be discontinued."

Death kinetics

Mention is made in the guidance note of "death kinetics", with the suggestion that these can be extrapolated to offer a theoretical log 12 sporicidal reduction. This assumes that the concept of D-Value is valid for the MCHP process, and this is in some doubt. Given that the sporicidal process is caused by the formation of MCHP, it is hard to see how the process puts a linear stress onto the test spores over a given time period. Furthermore, such a time period would be hard to quantify, certainly in terms of establishing the point at which it commences.
The MCHP process is surely not a time / concentration effect.

More fragile than autoclaving?

The note indicates that although log 6, or indeed log 12, may be demonstrated by the MCHP process using biological indicators, this does not necessarily mean that adjacent surfaces are sterile. This is true. However, the same is equally true for almost any sterilisation process. All have to be validated, and all have to be regulated. Autoclaving is fraught with potential for failure - is it really less fragile than the MCHP process? The robustness of the VPHP process is supported elsewhere (Reference 2).

Editing

Finally, whilst the content of this guidance note is important, the layout of the information, and quality of writing need to be improved in order to make this valuable information more easily accessible to those who need to put it into practice. The services of a competent scientific editor could usefully be employed. Even the title and sub-title of the note, reproduced verbatim at the head of this critique, are poorly-conceived.

References

1. Coles, T. Understanding the hydrogen peroxide vapour sanitisation process and introducing the MCHP concept, a personal account. Clean Air and Containment Review 2016. Issue 25: 12-14.
2. Meyer, D. H_2O_2 surface sterilisation: a definitely robust process for routine use in isolators Clean Air and Containment Review 2018. Issue 36: 6-8.

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

Ecolab's new sporicide balances effective disinfection with user acceptability

The use of sporicidal disinfectants in cleanrooms can present a significant health and safety challenge with a reputation for being aggressive and unpleasant to use.[i]

Ecolab Life Sciences has developed an innovative solution. Klercide Sporicidal Enhanced Peroxide (KSEP) provides the perfect balance between fast broad spectrum with sporicidal efficacy, and greater user safety and acceptability.

The product's patented formulation allows a much lower 1.5% concentration of hydrogen peroxide (H_2O_2), to be faster acting and equally effective as a standard 6% solution.

Jocelyn Romanis, Ecolab's European Cleanroom Marketing Manager, said: "We are convinced KSEP offers a game-changing sporicidal solution, helping our customers achieve their environmental goals whilst improving compliance with SOPs." For more information, visit www.ecolablifesciences.com or call your Ecolab Life Sciences account manager.

i. USP <1072> 'The daily application of sporicidal agents is not generally favoured because of their tendency to corrode equipment and because of the potential safety issues with chronic operator exposure.'

Lab Innovations hosts The Cleanroom Hub

Lab Innovations, at the NEC, Birmingham on 30 & 31 October, is the UK's only trade show for laboratory professionals across all sectors.

A key area of Lab Innovations is a dedicated zone for suppliers of cleanroom equipment. The Cleanroom Hub not only showcases novel laboratory and cleanroom products, it also incorporates a seminar pod with CPD-accredited educational presentations for cleanroom professionals, a networking lounge and dedicated exhibitor pavilion. Seminars in the Cleanroom Hub will focus on regulation and legislation in the cleanroom, and how to ensure sterilisation in environments where contamination needs to be controlled. Visitors can learn how to successfully prepare for audits, to ensure proper quality and specifications are being met.

The significant increase in cleanroom attendees in 2018 demonstrates the clear demand for products and information relating to the cleanroom, and this zone is set to create another buzz at Lab Innovations 2019.

Free advance registration for all visitors at www.lab-innovations.com.

EECO2's Mobile Energy Monitoring Unit (MEMU) eligible for Enhanced Capital Allowance (ECA) tax scheme

EECO2's Mobile Energy Monitoring Unit (MEMU) is now listed on the Energy Technology List for UK and the Triple E Register for Ireland making it eligible for the Enhanced Capital Allowance (ECA) tax scheme for businesses in the UK or the Accelerated Capital Allowance (ACA) scheme in Ireland. These schemes allow businesses to write off the entire cost of any listed product against taxable profits.

The MEMU is an independent metering, monitoring and targeting system. It is simple to install utilising wireless communication between sensors and can be tailored to meet a client's specific requirements. The MEMU helps identify the largest energy consuming equipment and supports energy managers in making more informed decisions. It can be used to prove energy savings by measuring usage before and after implementation of a project.

For more information on the MEMU visit www.eeco2.com/memu or contact EECO2 at info@eeco2.com or +44(0)1625660717.

BioClean™ Isolator Sleeve/Glove System

BioClean Sterile nitrile isolator sleeve/glove systems are a fully validated sterile (Sterility Assurance Level (SAL) 10-6) and cleanroom processed and packed ready to use 'out of the bag' system, with no further processing required prior to initial use. Available in two configurations – 32"/813mm or 36"/914mm long systems with either an ambidextrous or hand specific polychloroprene sterile glove attached by a channel ring and 'O' ring, they are individually triple bagged and packed in easy tear PE packaging. Both sleeve and glove have been tested against ASTM D6978 standard for cytotoxic drugs and comply with EN ISO 374 & EN 420.

For more information please visit www.bioclean.com

Cherwell announces new microbiology product specialist

Hamish Hogg – Cherwell Laboratories' new Microbiology Product Specialist

Cherwell Laboratories has announced the appointment of Hamish Hogg as Microbiology Product Specialist, affirming the Company's continued focus on providing high quality products, supported by excellent customer service.

Providing direct technical and applications support to customers and distributors of Redipor® Prepared Media, Hamish will also maintain and share Cherwell's understanding of regulatory requirements and scientific advances. Thus, ensuring the Company sustains its expertise and continues to offer up-to-date products, services and advice.

Hamish holds a Master's degree in Biomedical Sciences and has a number of years' experience based in Clinical Microbiology Laboratories before working in the medical devices industry. As a Technical Support Specialist for Cepheid, and more recently as a Urinalysis Product Specialist at Sysmex, he focused on providing technical expertise and managing customer relations.

To stay current with the latest industry developments, Hamish will be attending the various meetings that Cherwell participates in during the year, such as Pharmig, PHSS and NHS QA symposium.

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

Customer satisfaction at Crowthorne Group

"Action speaks louder than words, and when our customers speak, we take action!"

'Reliable', 'high quality', 'useful' and 'good value for money' are the phrases used by our customers in the 2018 Crowthorne Customer Satisfaction Survey.

After a year of hard work and customer liaison we're proud to announce that the overall level of customer satisfaction has risen to 91% (from 81% in 2017).

East Sussex Healthcare illustrate how we're doing our best to accommodate the needs of our customers, *"Crowthorne Hi-Tec Services have provided a service to the East Sussex Trust Pathology department for several years and we have always found their work highly professional. The servicing team are very accommodating regarding dates for the work and the engineers provide an excellent and efficient service."*

We'd like to thank our customers for taking the time to respond to our survey. Increasing the survey response rate by over 100% has given us more data on which to base our business strategy and develop our products and services.

Find out more (or get in touch) at www.chts.co.uk.

Another prestigious completion by CRC

Clean Room Construction (CRC) has successfully handed over a £2 million cleanroom facility to the world-leading university, King's College London.

CRC designed and installed an atomic layer deposition cleanroom facility and two optics labs, at the Strand site on schedule. The two-stage design and build project, which has been integrated into the university's IT, fire alarm and security systems, included Class 5 and Class 6 cleanrooms with shared changing room and service chase.

Steve Lawton, CRC's Managing Director, said: "King's College London is one of the world's most prestigious universities, known for its cutting-edge research and global connections. Clean Room Construction is very proud to have collaborated with the university to deliver these first class facilities."

"Our team worked at basement level, stripping out the existing facilities before starting the new build within a busy teaching and learning environment. This meant that all work had to be carried out while the university continued to function. We liaised daily with the university's management to ensure we kept any noise or disruption to an absolute minimum."

www.crc-ltd.co.uk

Envair recognised as Major Equipment Supplier in Facility of the Year Award to Eli Lilly and Company

Envair Limited is very proud to have received this message from Eli Lilly and Company:

"I would like to take this opportunity to congratulate your company for being a part of one of this year's ISPE 2019 Facility of the Year Award winning projects. Eli Lilly and Company is recognized as a Process Innovation Category Award Winner for their "IE2 Small Volume Continuous Facility" Project and they've included your company as one of their key participants and supply partners in the project.

ISPE's Facility of the Year Awards is an annual program that recognizes state-of-the-art projects utilizing new, innovative technologies to improve the quality of products, to reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery.

Winning a FOYA Award is very much a group effort of, not only members of the owner company's project team, but also the many supply partners who've helped them meet their goals. As a supply partner, we hope you are equally excited to share in the project's success."

Winner Page: https://ispe.org/facility-year-awards/winners/2019/process-innovation

For more information about Envair, please visit www.envair.co.uk

Sign up today for Cleanroom Guangzhou Exhibition 2019!

Slated for this **August 16th to 18th**, at **China Import & Export Fair Complex**, Asia-Pacific Cleanroom Technology & Equipment Exhibition (**Cleanroom Guangzhou Exhibition 2019**), is expected to call together 150+ Premium Exhibitors and 9000+ Professional Buyers worldwide!

Many big names and brands have confirmed their participation, including Hollingsworth & Vose, TSI INSTRUMENT, CAMFIL, DYNACO, Ahlstrom, Tongxin Purification, Meditech Technology, and etc, guaranteeing a fest of cutting-edge clean room products and solutions!

Co-organized by Guangdong Association of Cleanroom Technology (GACT), and supported by other 30+ trade bodies, such as ICCCS, CCCS, VCCN, KACA, JACA, and etc, the show will invite its visitors mainly from sectors like pharmaceuticals, electronics, food processing, clean room engineering, and etc.

Sign up today via grand2@grahw.com

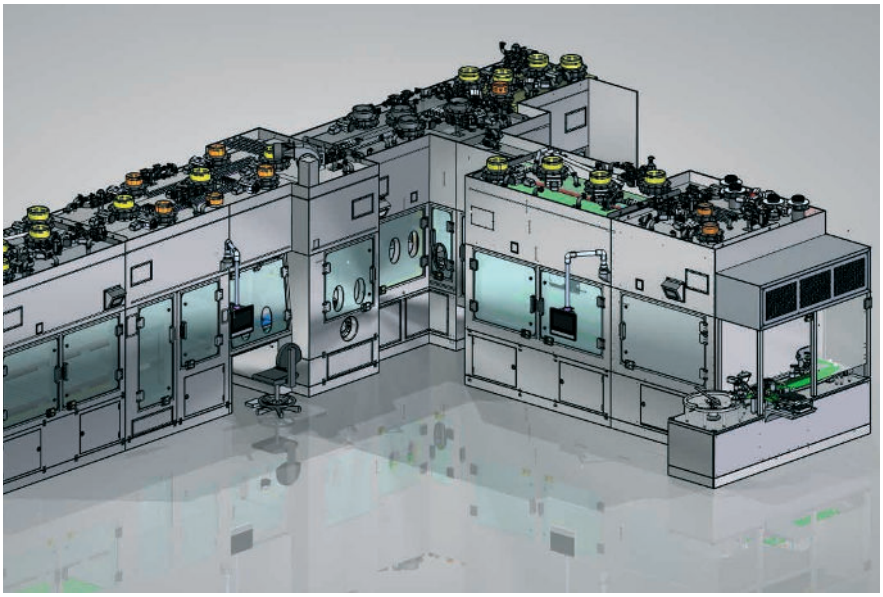
PMS: Industry experts combine to create safer intravenous delivery

The Italian Biochemical Institute, Comecer, and Particle Measuring Systems share expertise to develop and manufacture a safer intravenous solution.

Rome, Italy – The Italian Biochemical Institute (IBI) "Lorenzini", Comecer, and Particle Measuring Systems (PMS) recently partnered to leverage and combine the expertise of each entity to design a new drug delivery system and a filling line to safely and effectively manufacture it. A Quality Risk Management (QRM) approach was used as the basis to meet the distinctive needs of the aseptic filling line and ensure that regulatory needs were met.

This partnership started when IBI designed a new approach to drug infusions deliveries, patented as Espresso®. "Espresso® was created to ensure the safe delivery of sterile intravenous medication to patients", said J. Khevenhüller, CEO at The Italian Biochemical Institute (IBI). "Following the initial project, we needed a way to safely mass produce Espresso®. However, because of its unique design, existing filling lines could not meet our needs, so we contacted Comecer to create something new."

Nina Morton, Particle Measuring Systems, Boulder, CO 80301, Tel: 303-443-7100 nmorton@pmeasuring.com



Cleanzone trade fair experience enriched by numerous events

In addition to the exhibitors' new products and services, the international Cleanzone trade fair (19th-20th November) for contamination control and cleanroom technology will yet again be featuring an extensive supporting programme.

Cleanzone is once again offering a wide range of events in 2019 that enrich the trade fair experience, promote knowledge transfer and support innovations and new talent such as the DRRI Research Award and the Cleanroom Future Award.

The Cleanzone Conference – the heart of the event programme – boasts an entirely new format this year. With a compact presentation programme, it shines a spotlight on the topics that are important to the industry's future and comprises the central presentation area at the trade fair. For the first time, the German Cleanroom Institute (DRRI) and the VDI Association of German Engineers will be content partners of the event.

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

STERIS Launches ProKlenz® Foam High Performance Alkaline Cleaner and ProKlenz® RESTORE High Performance Acid-Based Cleaner

STERIS announces the global launch of ProKlenz® FOAM High Performance Alkaline Cleaner and ProKlenz® RESTORE High Performance Acid-Based Cleaner. Both products have unique applications for use in cGMP manufacturing.

ProKlenz FOAM Cleaner is particularly effective against fats, oils, and organic soils for use on large manufacturing equipment for a vigorous clean without high levels of manual scrubbing. The high foaming system with emulsification and dispersion properties promotes cost-effective and efficient cleaning, even at low use-concentrations.

ProKlenz RESTORE Cleaner is an engineered detergent with biodegradable surfactants for type I rouge removal and all-purpose cleaning. Unlike other commonly used derouging agents, ProKlenz RESTORE Cleaner performs better at lower temperatures and concentrations to remove type I rouge.

ProKlenz FOAM Cleaner and ProKlenz RESTORE Cleaner are globally available for use in pharmaceutical, biotechnology, cosmetic, and nutraceutical industries. These products have an extensive documentation package to meet your validation objectives and are supported by the STERIS Technical Services team. For more information about this and other STERIS formulated chemistry products, please visit www.sterislifesciences.com.

To learn more about STERIS and its mission, please visit www.steris.com.

Events

Dates	Event	Organiser
2019		
September 10	PHSS Annual Conference 2019 in association with UCL Q3P, London, UK	PHSS
September 18-19	Making Pharmaceuticals, Milan, Italy	Step Exhibitions
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 28-19	Pharmig 26th Annual Microbiology Conference, Nottingham, UK	Pharmig
2020		
April 27-30	ESTECH, Minniapolis/St.Paul, Minnesota	IEST

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2019	**Event**	**Location**
August 1	Designing and USP 797/800 Compliant Compounding Pharmacy	Schaumburg, Illinois
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

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**
September TBA	CTCB-I Cleanroom Technology	Dublin
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

Life-lines

Quotations of Albert Einstein

If you can't explain it simply, you don't understand it well enough.

The true sign of intelligence is not knowledge but imagination.

Logic will get you from A to B. Imagination will take you everywhere.

The world is a dangerous place to live; not because of the people who are evil, but because of the people who don't do anything about it.

I know not with what weapons World War III will be fought, but World War IV will be fought with sticks and stones.

Our task must be to free ourselves by widening our circle of compassion to embrace all living creatures and the whole of nature and its beauty.

It is the supreme art of the teacher to awaken joy in creative expression and knowledge.

Any man who can drive safely while kissing a pretty girl is simply not giving the kiss the attention it deserves.

Great spirits have always encountered violent opposition from mediocre minds.

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