Clean Air and Containment Review

ISSN 2042-3268
Issue 21 | January 2015

Contents

Clean Air and Containment Review **is a quarterly journal aimed at users, specifiers, designers, manufacturers, installers and testers of clean air and containment equipment. It publishes articles of topical, technical and historical interest, updates on standards and regulations, news, views and information on relevant events, especially training.**

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

Editorial

We are now in the season of coughs and sneezes, so I thought I would relate two stories from my time in the cleanroom business. The first occurred when I was visiting an aseptic unit in a large hospital. I was standing outside the cleanroom suite, which was in use, when I heard an almighty sneeze from within. I looked at the lady in charge who was standing next to me but she didn't bat an eyelid. I wondered if the person responsible for the sneeze had been wearing a face-mask and, if so, how effective it was. I wondered how many microbes had been released into the room and whether they would be carried away in the airflow to a safe place before they could do any harm. I wondered if the person who had sneezed should have been in the cleanroom at all. Would there be a report of the event and corrective action taken both in relation to the sneeze itself or to prevent future occurrences? Was there a SOP in place to cover safe sneezing? I have read recently that one should sneeze into the inside of a bent elbow (and not into one's hand) so as to avoid spreading germs by touch, but if the SOP specifies a glove change after a sneeze then into the hand might be better. I don't know the answers to any of these points, but I hope that the lady in charge was on the ball and dealt with the issue (no pun intended) as soon as I had left.

The second story, which was in another large hospital aseptic unit, concerned two large flexible film isolators which had very simple transfer chambers for introducing and removing product. These relied on an outward flow of air, when they were opened, to prevent airborne contamination entering the critical workspace inside the isolator. As I recall it, the transfer chambers had no inner doors, only outer doors. There was a lot of concern about isolator technology at that time as it was relatively new and the risks were little understood. The senior pharmacist decided that he needed to satisfy himself, and the authorities, that his isolators were safe, so he laid a series of settle plates around the inside of the isolators and got his staff to cough vigorously through the open doors of the transfer chambers. He reported that there were no growths on the settle plates and that the simple transfer chambers were therefore effective.

Both these stories took place a long time ago. Isolator technology and pharmaceutical regulation have progressed a long way since then as readers of this journal are well aware!

To change the subject, most of us brought up in cleanroom technology have always been obsessed with counting particles in the air. There is a good reason for this. They are comparatively easy to count, especially at 0.5 µm, for which size of particle the sampling time is short enough to be practical. But it doesn't follow that it is the 0.5 µm particles in the air that will damage your product, especially if they remain in the air. In his article on particle deposition monitoring on page 4, Koos Agricola looks at how particle deposition can be measured and makes the point that 'particle deposition determines the rate at which the surface cleanliness at a location will change.' In fact, when we are talking about pharmaceutical products, it is only the particles that actually deposit on the product that can cause harm. Will there perhaps be a time in the future when cleanrooms will be classified primarily by the rate of deposition of particles at critical locations?

John Neiger

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

Clean Air and Containment Review

Issue 21 | January 2015
ISSN 2042-3268

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

EDITORIAL PANEL
Koos Agricola (Holland)
Tim Eaton (UK)
Didier Meyer (France)
Madhu Raju Saghee (India)
Tim Sandle (UK)

PRODUCTION
Clare Beard

SUBSCRIPTIONS
Jill Monk

Published by:
Euromed Communications
Passfield Business Centre,
Lynchborough Road,
Passfield, Liphook, Hampshire
GU30 7SB, UK
T: +44 (0)1428 752222
F: +44 (0)1428 752223
e: publisher@euromedcommunications.com
www.euromedcommunications.com

Clean Air and Containment Review is published quarterly in January, April, July and October

Annual subscription rate £90.00

Practical experiences in particle deposition monitoring

Koos Agricola

Abstract

The rate of deposition of airborne particles determines the risk of product contamination and demonstrates the operational quality of a cleanroom. The particle deposition rate at a particular location and time depends on the deposition velocity and the concentration of particles. The concentration of particles larger than 10 µm cannot be measured easily; therefore the deposition rate of falling particles should be measured.

Specific particle deposition meters, that measure the particle size distribution and rate of particle deposition, have been available since the end of 2013. In the past, particle deposition measurements were complicated and expensive and were therefore only carried out in specific cleanroom applications or to investigate contamination problems. Nowadays it is easy to carry out particle deposition measurement in various cleanrooms where operator activities are important. The new instruments also make real time particle deposition measurements possible. Practical experiences with these instruments in various applications are described in this article.

Key words: cleanroom, cleanroom monitoring, particle deposition, surface cleanliness, operational quality.

Introduction

The most important reason for using cleanrooms is to prevent particle contamination of vulnerable product surfaces. Contamination occurs through particle deposition and by contact transfer with less clean surfaces such as gloves, equipment, tooling, packaging and workbenches.

In relation to the control of particles, the ISO 14644 series of standards (Cleanrooms and associated controlled environments) provides cleanliness classifications of air (Part 1) and surface (Part 9). There are various additional Parts like measurement methods (Part 3) [1, 2].

Particle deposition determines the rate at which the surface cleanliness at a location will change.

Up until 2013 particle deposition measurements were laborious or expensive and did not provide information that could help to reduce the risk of particle deposition.

Particle fall out measurement based on the increase of mass or surface coverage by particles have been available for a long time and accepted in the space industry. Particle deposition in cleanrooms, based on particle size distributions, has been investigated by various research programs [3, 4, 5].

The first easy to use particle deposition meters made use of silicon or glass witness plates [6, 7, 8].

In 2013 the digital holographic measurement [9] of particle deposition was implemented in a commercial available cleanroom monitoring instrument.

Holographic measurement of particle deposition

When a broad coherent laser beam passes through a volume with a low concentration of particles towards a detector most laser beams will reach the detector without meeting a particle. However a few laser beams (a light wave front) will meet a particle and that will disturb the wave front and create a new wave front from each point on the surface of the particle. This leads to a delay in the time for the beam (light wave) to reach the detector, which causes an interference pattern. The interference pattern contains information on the various particles in the path of the light.

By using Fourier transformation techniques these diffraction patterns can be analysed and it is possible to reconstruct a three-dimensional holographic picture of the particles in the volume that the laser beams are passing. When scanning the holographic picture it can be seen that the particles sit on the various surfaces of the inclined glass plates.

This method is used in the APMON system, developed by TNO (Dutch Institute of Applied Physics) and Technology of Sense b.v., to measure particles deposited on inclined glass plates (see Figure 1).

Six glass plates are placed in a sensing device at an angle of 45°. This way both particle deposition and holographic imaging can be performed.

Small particles that fall onto an inclined surface will stick to the position where they hit the glass surface and are kept at this location by van der Waals forces. Only large spherical particles (> 300-500 µm, depending on their specific density) can travel for a certain distance over the inclined glass surface.

By taking a holographic image at regular intervals and comparing these images subsequently, the particle size distribution of the deposited particles at each interval can be determined (see Figure 2).

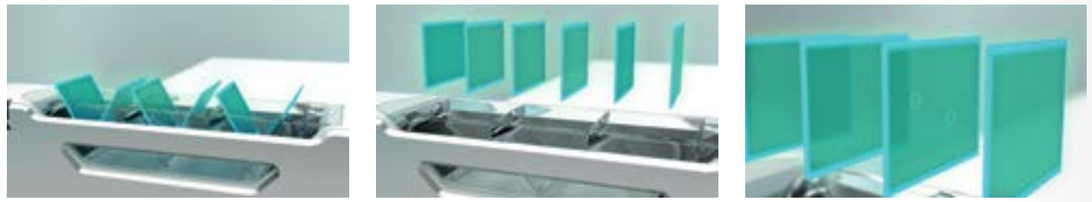


Figure 1: Glass plates that collect depositing particles and are imaged holographically, APMON system courtesy Technology of Sense b.v.

The various sensors can communicate with a base computer through a network or wirelessly. The base computer can show the real-time measurement results on the network. In that way the particle deposition can be monitored at any computer connected to the network.

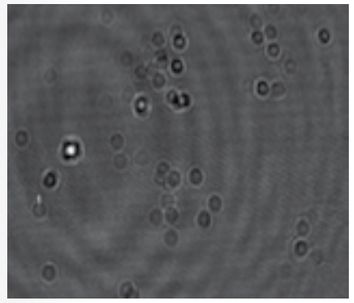


Figure 2: Holographic picture on one glass plate, courtesy Technology of Sense b.v.

Particle deposition measurement results

To show the potential of this particle deposition monitoring method a practical example will be described.

The sensor was placed in an ISO 8 cleanroom where various assembly activities are carried out. Measurement data were collected over a period of one week (7 to 11 April 2014).

The results are shown in Figures 3, 4 and 5. First of all the particle deposition events can be displayed on a real time screen. For each deposited particle the dimensions, shape and cross section are known. For convenience only one dimension is selected to determine the size of each particle. This is the length (largest size) of the particle. This size is larger than or equal to the optical diameter of the particle.

In Figure 3, the number of particles ≥ 20 µm deposited on the sensor every five minutes is recorded (blue line). Sometime high peaks occur. These can arise from cleaning, logistic activities or high activity of the people near the location of the sensor.

The cross-sectional area of each particle is measured and accumulated to calculate the total area coverage. The increase in coverage by particles is shown on the same graph (red line). The scale is given on the right hand side. The resulting coverage after a certain exposure time can be compared with data from a particle fall out meter as used in the space industry.

The particle size distribution can be analysed over a defined time which can be continuous or made up of separate periods. In this example the differential and cumulative particle size distributions per dm^2 over the total measurement period of one week are shown in Table 1. The size bins between 20 and 100 µm are divided in steps of 10 µm and above 100 µm in steps of 100 µm. In ISO 14644-9, the surface cleanliness by particle concentration is classified for particles up to ≥ 500 µm but the table and graphs in this example include larger particle sizes. The differential distribution, shown in Figure 4, is the distribution of the number of particles in each individual size bin. The cumulative distribution is calculated by adding the number of particles of each size bin larger than the observed size.

It can be seen that many large particles can deposit in a cleanroom. Often relatively high numbers of particles > 100 µm are found. This is caused by insufficient cleaning. Similar results are found in many ISO 6 and ISO 7 cleanrooms.

The number of particles in each size bin can be used to calculate the particle deposition rate in terms of the number of particles ≥ D µm per dm^2 or m^2 per hour.

To determine the Particle Deposition Rate (PDR) the number of particles per area should be divided by the time of exposure. As particle deposition of particles ≥ 20 µm only occurs when the cleanroom is in operation, particles are only counted during working hours. The APMON has a timing system that provides for this.

In a cleanroom the airflow will remove most particles < 20 µm and the concentration of those particles can be measured with a particle counter. To determine the (lower) concentration of particles ≥ 20 µm it is better to measure the particle deposition. To be able to derive the PDR for particles ≥ 20 µm sufficient measurement (deposition)

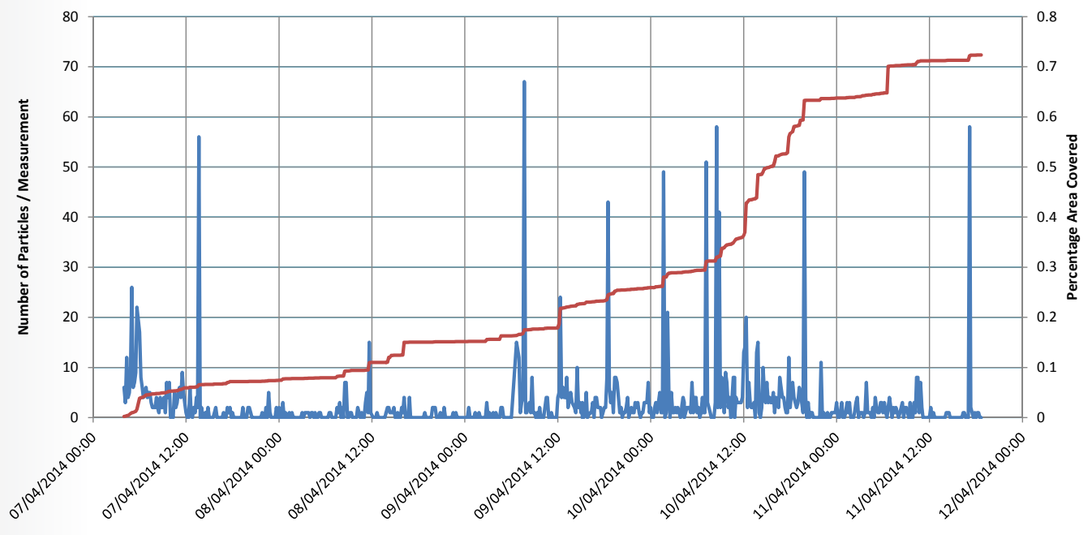


Figure 3: Record of particle deposition events in a cleanroom

area and time are required to be able to detect a statistically significant number of particles.

The author has experience with a measurement system using a XY scanning system with different illumination methods. The cumulative particle size distributions acquired over many years at many different cleanrooms and different applications are summarised in Figure 5. These show the impact of the cleanroom air below 20 µm and a transition between 20 and 30 µm.

In Figure 6 the cumulative particle size distribution of the PDR is shown. A log-log graph is used. Particle sizes are from 10 to 1000 µm. The PDR is expressed in number of particles ≥ D µm per dm^2 per hour.

The particle deposition data can also be expressed in terms of Particle Deposition Class (PDC) as described in [10, 11]. The upper tangent to the PDR curve determines the PDC of the monitored location. The value is determined by taking the maximum of RD^*_D. R_D is the number of deposited particles per m^2 per hour and PDC = $\log_{10} RD^*_D$. In this example the PDC is 5.1. The number of particles ≥ 200 µm determines the PDC.

In the same way a lower tangent can be drawn and a lower PDC can be determined. In this measurement a PDC value of 4.9 is found. The lower value can be reached by improving the operational quality.

Three zones can be observed in the graph shown in Figure 6:

a. Particles ≤ 30 µm,

b. Particles between 30 µm and 100 µm or equal to 100 µm,

c. Particles > 100 µm.

The increase of particle deposition from 30 µm size to the ≥ 20 µm size is influenced by the local air flow.

The middle part is mainly influenced by human contamination (number of people, garments, discipline and working methods). The right hand part of the graph shows the deposition of the very large particles. This part is influenced by the total cleaning program. 'Total' includes all cleanroom surfaces, equipment, tools and incoming goods.

Table 1: Particle size distributions per dm^2 sensor surface

Total number of particles on the sensor		
Particle size in µm	**Differential/dm^2**	**Cumulative/dm^2**
20	2,972	7,104
30	1,384	4,132
40	596	2,748
50	268	2,152
60	192	1,884
70	140	1,692
80	108	1,552
90	84	1,444
100	444	1,360
200	380	916
300	128	536
400	84	408
500	60	324
600	44	264
700	56	220
800	28	164
900	136	136

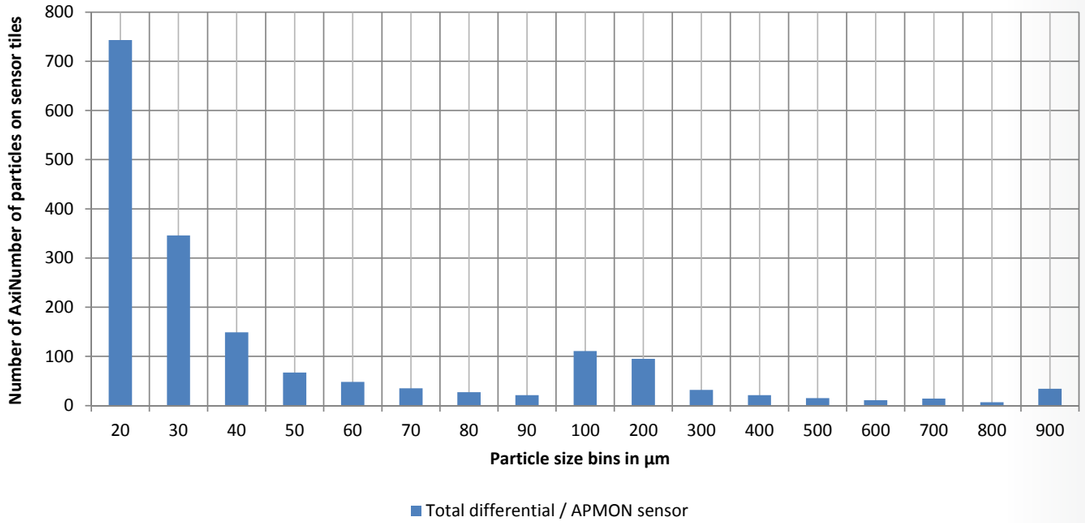


Figure 4: Particle size distribution of deposited particles on the sensor. Note: The sensor is 1/4 dm^2

Potential application of particle deposition measurement

Deposition of particles > 20 µm is determined by the operational aspects of the cleanroom.

There is no deposition of particles > 20 µm in the at rest occupancy state of the cleanroom. Therefore only measurements carried out during working hours are important. Operational aspects are:

- The number of persons
- Their garments
- Their discipline
- Their working method
- The cleaning program
- Cleaning of incoming goods
- Logistics
- Machinery that generates large particles
- Etc.

All these aspects concern cleanrooms in which people are working.

There are many potential applications where measurements could be useful. Examples of potential industries are:

- Space industry
- Automotive industry
- Electronic devices
- Medical devices
- Display industry
- Optical devices
- Operating theatres
- Etc.

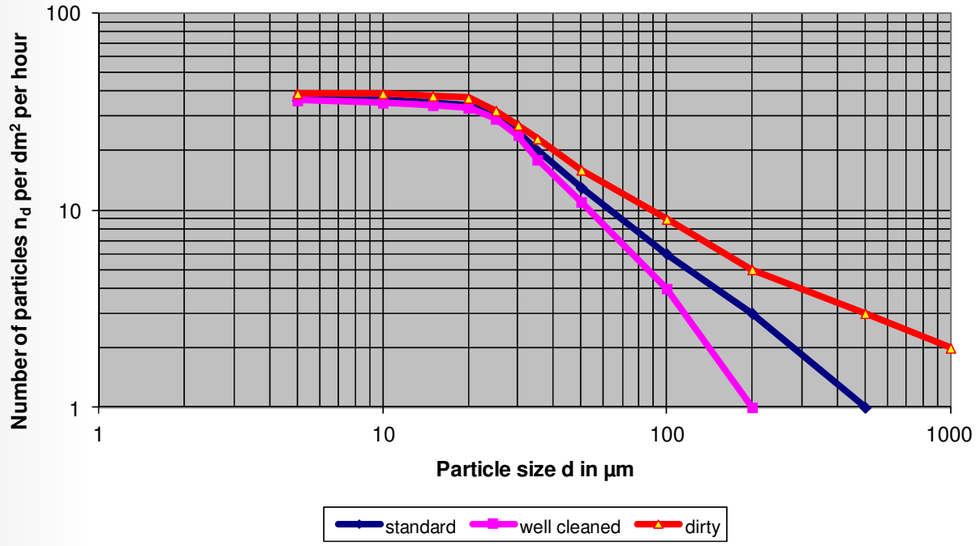


Figure 5: Typical particle deposition distributions

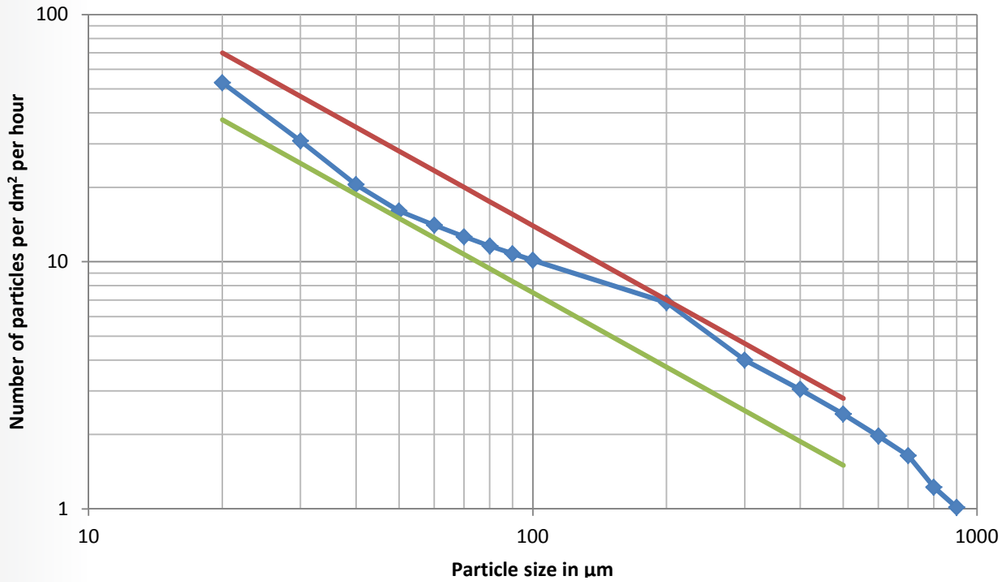


Figure 6: Particle deposition rate shown as cumulative distribution including Particle Deposition Class lines

Particle deposition monitoring can be used to investigate potential sources of contamination and to monitor operational quality.

The data can also be used to optimise the cleaning program. According to ISO 14644-9:2012, the cleanliness of a surface can be expressed in a Surface Cleanliness by Particle concentration class SCP.

SCP = $\log_{10}$ (C_D*D), where C_D is the number of particles ≥ D µm per m^2 and D is the considered particle size.

After cleaning a particular surface, a surface cleanliness of, for instance, SCP 4.7 can be reached. If the maximum allowable surface cleanliness is SCP 6, the time interval between two consecutive cleaning campaigns can be determined from the particle deposition data. The number of particles allowed to deposit is determined by the difference of the achieved and maximum surface cleanliness (SCP 6 – SCP 4.7). The result is equivalent to $10*10^6-0.5*10^6 = 9.5*10^5$ particles ≥ 1 µm per m^2.

In case the PDC is 5, which is 10^5 particles ≥ 1 µm per m^2 per hour. This means that after 9.5 working hours the surface reaches SCP 6 and cleaning is required.

The PDC values for particular particle size can be used to perform risk management. In the example shown, where PDC is 5.1, the risk of deposition of particles ≥ 25 µm on a product surface of 2 cm^2 during 10 minutes can be calculated.

PDC 5.1 gives a PDR of 125,000 particles ≥ 1 µm per m^2 per hour. Therefore the deposition of particles ≥ 25 µm is 125.000/25 = 5,000 unwanted particles per m^2 per hour or 1 particle ≥ 25 µm per product (2 cm^2) per hour. Since the exposure of the product is only 10 minutes, the risk is a factor of 1/6 = 0.2 per product.

The showing of real time particle deposition events on screen can have a positive effect on the awareness of the discipline and activities of personnel. Daily or weekly reports on average PDC values can be displayed in monitoring graphs.

Conclusions

The development of the particle deposition monitor opens the possibility of real time monitoring of particle deposition. Data can be used to find causes of particle deposition and to develop means to reduce the particle deposition at a specific location.

The particle deposition monitor can be used to control the applied solutions.

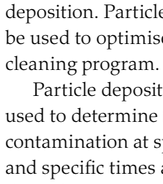
In many cleanrooms the number of large particles is high. Some of these particles are redistributed through the cleanroom and contribute to the particle deposition. Particle deposition data can be used to optimise the cleanroom cleaning program.

Particle deposition can also be used to determine the risk of particle contamination at specific locations and specific times and help to select the right moment to expose vulnerable product surfaces to the cleanroom environment.

Demonstration of particle deposition events, PDR or PDC values and analysis will help to improve personnel awareness and motivation.

References

1. ISO 14644-1, 2 and 3: DIS 2014, Cleanrooms and associated controlled environments: Classification of air cleanliness by particle concentration, Monitoring and Test Methods.
2. ISO 14644-9: 2012: Classification of surface cleanliness by particle concentration.
3. Hamberg O. and Shon E.M., “Particle size distribution on Surfaces in Cleanrooms”, The Aerospace Corporation, Report SD-TR-84-43, El Segundo, USA, 1984.
4. Agricola K. and Geilleit R. (2007); “Classification of Contamination Control Practice”. VDI Wissenforum Reinraum Technik, Basel.
5. Parasuraman D.K., Kemps A.A.M., Veeke H.P.M. and Lodewijks G., “Prediction Model for Particle Fallout in Cleanrooms”, Journal of the IEST, V55-1, USA, 2012.
6. Agricola K. and Weling P. (2008); “Particle Deposition Monitor to reduce cleanroom costs”. Cleanrooms Europe 2008, Stuttgart.
7. Agricola K. (2009); “Quality Assurance of Product Cleanliness”. Cleanrooms Europe 2009, Stuttgart.
8. Agricola K. (2012), “Determination of Operational Quality of Cleanroom by Particle Deposition Monitoring”. ICCCS 2014, Zürich.
9. Singh V.R., Hegde G.M. and Asundi A.K., “Particle field imaging using digital in-line holography, Current Science, Vol. 96, No. 3, 2009. “
10. VCCN Guideline 9, Particle Deposition (2014), www.vccn.nl.
11. Agricola K., “Proposal for the classification of particle deposition”, to be published in ICCCS 2014, Seoul.



Koos Agricola is an Applied Physicist and works in Research and Development at Océ Technologies, a Canon Company, where he has been since 1986. His role includes responsibilities in the cleanrooms and in contamination control for the manufacturing of critical parts of printers, in particular cleaning, coating (including thin films), machine vision and micro-assembly with a focus on Product Oriented Contamination Control.
In his spare time, Koos assists Technology of Sense b.v. as a Contamination Control Specialist. Koos is secretary of the VCCN (Dutch Contamination Control Society), ICCCS (International Confederation of Contamination Control Societies) and ICEB (International Cleanroom Education Board) and a technical expert on ISO/TC 209 Working Groups 1, 3, 11, 12 and 13. Koos is also treasurer of the CTCB-I (Cleanroom Testing and Certification Board – International) and regularly teaches various Cleanroom Technology subjects.

Addressing rouge on stainless steel in biopharmaceutical manufacturing systems

Paul Lopolito

Abstract

This article is a guide on how to treat rouging or discolouration on stainless steel surfaces. The article starts with a description of the different types of stainless steel and how stainless steel develops a chromium-enriched corrosion-resistant layer by passivation either from the oxygen in the air or by chemical means. X-ray photoelectron spectroscopy (XPS) is used to measure the depth of the layer. When stainless steel corrodes, this shows as a discolouration that is known as rouge. Rouge can be anything from reddish brown to blue or black. The article describes three types of rouge that result from deposited oxidized metal particles, in-situ oxidization and high temperatures or steam. Finally the article explains how rouge can be removed and surfaces repassivated. Routine procedures for inspection and treatment are recommended.

Rouge is a corrosion product of stainless steel and can range in colour from reddish-brown to blue or black. The general types of corrosion are: galvanic, pitting, stress, inter-granular, crevice, and microbial-induced.

Introduction

Stainless steel is the primary construction material used for pharmaceutical, biopharmaceutical and food processing equipment. Prized for its unique ability to resist corrosion, stainless steel comes in hundreds of types and subtypes. Austenitic stainless steel is the most common type used for these applications.

The austenitic stainless steels are non-hardened, non-magnetic, easily welded, heat and chemical sterilization resistant, and corrosion resistant. The most commonly used austenitic stainless steels are 304, 304L, 316 and 316L (the "L" refers to low-carbon content, at 0.03% compared to 0.08%). The base metal of 304 and 316 stainless steels is iron (62-65%) which is combined with chromium (16-20%), nickel (8-14%), and other components including carbon, silicon and molybdenum [1].

Stainless steel becomes corrosion-resistant when the metal surface (which must be clean) comes into contact with oxygen to form a non-reactive chromium-enriched passive layer (self-passivation). In addition to naturally occurring passivation, chemicals such as nitric acid, phosphoric acid, citric acid, formulated phosphoric acid/citric acid blends and other chelant[1] formulations can be used to passivate[2-4]. The quality of the passive layer can be assessed by a number of different methods, one of which is x-ray photoelectron spectroscopy (XPS) (see Figure 1). XPS is commonly used to validate chemical treatments.

Rouge types and causes

Rouge is a corrosion product of stainless steel and can range in colour from reddish-brown to blue or black. The general types of corrosion are: galvanic, pitting, stress, inter-granular, crevice, and microbial-induced. Rouge can be classified into three classes or types [5, 6]:

Type I: Oxidized metal particles generated from an external source by erosion or corrosion, which deposit on the downstream surfaces. This rouge is generally easy to wipe off; leaving the underlying stainless steel surface intact (Figure 2).

Type II: In-situ oxidation causing rouge, which is generally tightly adhered and could have underlying surface damage or pits.

Type III: Black oxide rouge generated from high temperatures or steam. The top layers wipe off but often require specific chemical treatment for full removal.

Rouge is found in most biopharmaceutical facilities and is often associated with purified water systems, clean steam systems, buffer preparation tanks (especially sodium chloride or glycine solution preparations), filling lines, vial washers (typically cleaned with hot purified water) and steam sterilisers. Rouge results from exposure to highly aggressive environments, such as purified water or steam systems, chloride or corrosive products, and high temperature stress or erosion conditions. Other conditions that cause rouge are the inclusion of non-stainless steel components or inserts, improper welding, surface defects, and inadequate cleaning or passivation.

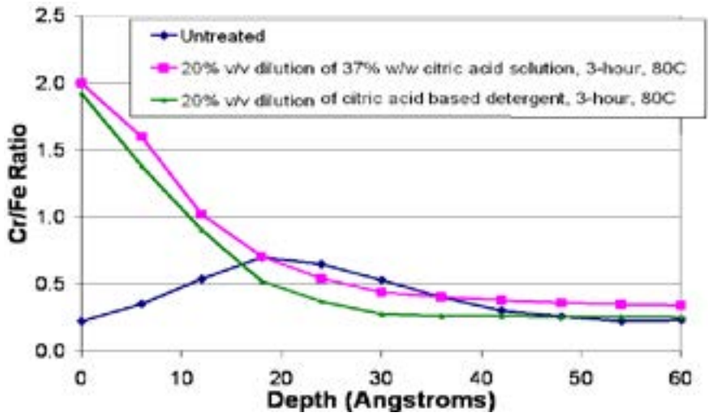


Figure 1: XPS analysis graph with chromium to iron (Cr/Fe) ratio on the x-axis and depth on the y-axis. For this evaluation, mechanically polished, 220-grit finish, 316L stainless steel panels purchased from Metal Samples, Inc. were rinsed with isopropyl alcohol, high purity water, acetone, and again with high purity water prior to passivation. At the end of the passivation treatment, the panels were removed and rinsed with high purity water and allowed to air dry. Evans Analytical Group (EAG) performed the XPS analysis [7].

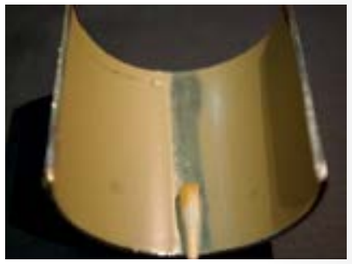


Figure 2: Type 1 rouged pipe
(photo by Amanda Deal)

1. Chelant: Organic compound that can withdraw ions from solution, forming insoluble complexes.

Consistent procedures reduce downtime

Procedures should be in place for cleaning, derouging and passivating new equipment as well as for periodically inspecting in-use water systems and process equipment. New equipment often arrives with particulates and oily residues from buffing, polishing and lubricating compounds. These residues must be removed and the chromium-enriched passive layer restored.

In-use equipment should be inspected for rouge by qualified engineering or maintenance staff. Inspection of the surfaces will help determine whether the equipment needs to be derouged and passivated. If no program is in place, a semi-annual inspection is recommended as a starting point.

Laboratory evaluation can help determine the best conditions (chemistry, concentration, time and temperature) for removing specific types of rouge. A facility's routine acid cleaner, when used at a higher concentration and for a longer time, may effectively remove the rouge and restore the passive layer.

The general procedure for derouging and passivation of 304 and 316 stainless steel surfaces:

1. Determine the type of rouge that is present (laboratory evaluation is recommended)
2. Pre-clean with formulated alkaline chemistry as appropriate
3. Charge the system with a 10% concentration of formulated phosphoric or citric acid-based detergent at 80°C
4. Measure the initial iron concentration in the solution
5. Repeat iron measurement at set intervals until a plateau is reached
6. Add additional formulated phosphoric or citric acid-based detergent to at least a 15% level
7. After a set interval, measure iron concentration again
8. If the iron concentration did not increase significantly, continue agitation for 3 hours at 80°C
9. Repeat steps 5-8 as needed until the surface appears visibly clean or no additional iron is being removed from the surface.
10. Drain equipment, rinse thoroughly with high-quality water and then blow dry with clean compressed air or allow to air dry.

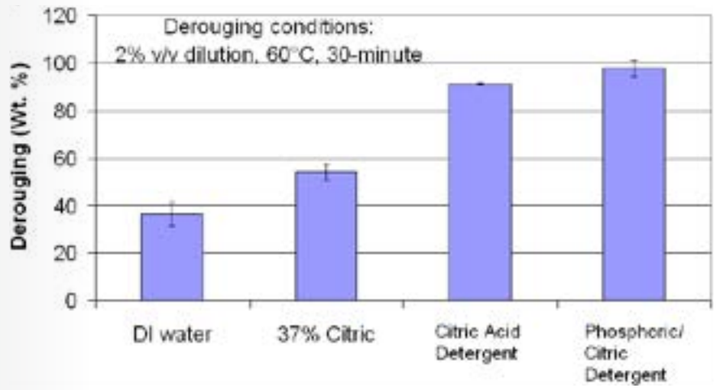


Figure 3: Lab generated rouge removal comparison between water, citric acid, formulated citric acid, and phosphoric/citric acid detergents [8].

Low-level preventive derouging and passivation

Formulated alkaline cleaners are effective at removing most biopharmaceutical process residues from stainless steel surfaces. The standard approach for routine cleaning is to remove organic residues with an alkaline cleaner and follow this with an acid rinse to remove inorganic residues and neutralize the alkaline cleaner. Although this acid rinse is performed at lower concentration and for less time than for derouging and passivation, it can also be an effective method for removing rouge and enhancing the passive layer.

To illustrate this, laboratory rouge was generated by suspending a pre-weighed 304 stainless steel coupon and mild steel coupon in a 1% sodium chloride solution while mixing for one week. The laboratory-generated rouged coupons were then treated with water, citric acid, formulated citric acid or phosphoric acid detergent at 60°C for 30 minutes. The results, shown in Figure 3, indicate that low-level concentration and temperature conditions can remove rouge.

There are potential benefits to using a low concentration acid rinse after an alkaline wash step for regular preventive maintenance derouging and passivation. When compared to completely removing the equipment from the production line to deal with rouge buildup, a low-level clean-in-place approach can be a time, cost and laboursaving method in the long run. In addition, preventive maintenance programs that include

routine inspection of equipment surfaces and piping and specific derouging and passivation procedures can significantly reduce costly equipment downtime.

References

1. Gonzales, M.M. “Stainless Steel Tubing in the Biotechnology Industry,” Biotechnology/ Pharmaceutical Facilities Design, April 30, 2001.
2. Bioprocessing Equipment (ASME BPE 2009) Nonmandatory Appendix E Passivation Procedure Qualification.
3. ASTM, A 967 – 99, Standard Specification for Chemical Treatments for Stainless Steel Parts.
4. ASTM, A 380 – 96, Standard Practice for Cleaning, Descaling, and Passivation of Stainless Steel Parts, Equipment, and Systems.
5. Avery, R.E. and Raney, R. K. “Rouging in Stainless Steel Equipment for Hygienic Services”, European Journal of Parenteral &Pharmaceutical Services, 2008; 13(1): 21-24.
6. Tverberg, J.C., Ledden, J.A., “Rouging of Stainless Steel in WFI and High Purity Water Systems”, Proceedings of Tube 2000, Dusseldorf, 2000.
7. STERIS Corporation, Lab Report 410-300-3308, The Effect of ProKlenz TWO on Passivation of 316 Stainless Steel.
8. STERIS Corporation, Lab Report 410-300-3313, Laboratory Derouging of Simulated Rouge Using ProKlenz TWO.

Paul Lopolito is a technical services manager for the Life Sciences Division of STERIS Corporation (Mentor, Ohio). He currently provides global technical support related to process cleaning and contamination control, which includes field support, site audits, training presentations and educational seminars. Paul has more than 15 years of industry experience and has held positions as a technical services manager, manufacturing manager and laboratory manager. He has authored and published numerous articles on cleaning and contamination control. He earned a B.A. in Biological Sciences from Goucher College in Towson, MD.

A history of isolator and containment technology Part 4: Transfer devices

Doug Throrogood

Abstract

The discussion in this part of the history of isolator and containment technology reviews the development and use of various devices that permit the aseptic transfer of components such as sterile vials, syringes, bottles and other types of container as well as the actual product itself into and out of the aseptic filling area of an isolator or RABS (restricted access barrier system).

Introduction

Some of the systems that permit aseptic transfers, such as pass-through hatches or devices[1], autoclaves and dry heat tunnels, used in current cleanroom technology, have been adapted by isolator and RABS manufacturers and users. With the advent of isolators and RABS, other devices have been developed as well as new techniques for aseptic transfers. Some of the devices are shown in Figure 1.

Note: RTP is rapid transfer port.

The discussion of the various devices will be divided into three sections:

1. The use of systems during the performance of sterility testing.
2. The use of systems for the compounding and transfer of a pharmaceutical product into and out the aseptic area of an isolator or a RABS. Non-sterile compounding of hazardous product is also included as an illustration of the containment aspect of the technology.
3. The use of systems for the entry and exit of sterile containers, components and testing equipment into and out of the aseptic area of an isolator or RABS.

Early pass-through technology

In aseptic manufacture using the classic cleanroom approach the problem of getting sterile materials and components into the cleanroom was to use a double-door autoclave or a dry heat sterilising tunnel. This enabled the transfer of items of filling equipment (autoclave) and sterile containers (dry heat tunnel). For other items, usually to replenish stocks of sterile gloves, garments, etc., as well as items forgotten in the preparation for the filling process, simple double door pass-throughs were used, see Figure 2. Some of these were equipped with HEPA filters and had an air over-pressure profile. Wrapped sterile items were placed in the pass-through and then sprayed with 70% filtered alcohol or another approved disinfectant and allowed to dry. The inner door to cleanroom was then opened and the items were removed. Reliance for asepsis depended upon correctly observed procedures and the effectiveness of the alcohol spray/disinfectant.

Later versions included a diluted peracetic acid spray system to treat the surfaces of stainless steel containers etc. placed in the pass-through. Such a system was developed by Metall + Plastic in Germany, using their expanding seal technology for the doors, an automated peracetic acid spraying system and an appropriate aeration system to remove the vapours after the exposure period. This method was used to decontaminate the external surfaces of sterile stainless steel containers that had to be passed into the sterile filling area, in this particular case for the bulk packing of antibiotic products.

Fedegari in Italy also developed a low temperature decontamination system based on the same concept, using hydrogen peroxide as the decontaminating agent. Furthermore

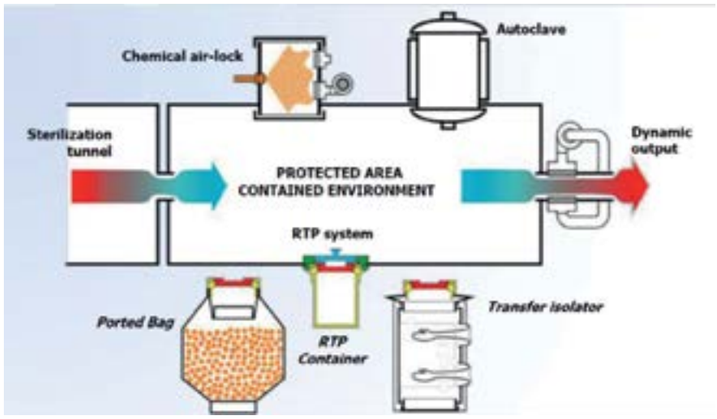


Figure 1: Diagrammatic representation of devices that may be used for the aseptic transfer of materials into and out of a 'protected area contained environment'

Figure 2: Simple two-door pass-through

1. Editor's note: Throughout this paper, the author has used the term 'pass-through'. When discussing isolators, alternative terms are 'transfer chamber' or 'transfer device'.

Fedegari has also introduced a new generation of H_2O_2 vaporizers controlling its concentration within the chamber with a feedback control loop, see Figure 3.

One could also argue that the changing facilities for the operators who were to work in the aseptic filling area could also be considered as pass-throughs. Reliance for maintenance of asepsis was placed on compliance with correct dressing procedures with sterile garments and accoutrements and with the use of sanitising agents prior to entering the aseptic area. An air-pressure 'cascade' ensured that air flowed from the cleanroom into the changing room and thence to the area outside the entry to the changing room.

Figure 3: Fedegari low temperature decontamination chamber

Transfer systems used in sterility testing isolators

As mentioned in an earlier part of this five-part history, sterility testing using isolators became popular and this saw the introduction by La Calhene (now Getinge La Calhene) of an RTP branded DPTE® (double porte à transfert étanche: double door for leak-tight transfer). This device had been developed initially for use in the French nuclear industry for the safe transfer of radio-active materials. La Calhene saw that the same device could be adapted for use with flexible film isolators as a novel way to maintain the integrity of the sterile isolator while making transfers into and out of the isolator.

The DPTE® allowed the connection of a sterile container or bag or even another isolator to the test isolator for the transfer or exit of materials without loss of 'sterility' in the test isolator or the connected items.

The basis of the DPTE® action is simple. There are two parts to the system: an alpha port section and a beta port section. The alpha port is usually installed in a surface such as a wall or the floor of an isolator. It comprises a flange, a seal and a door. The beta port also has a flange, a seal and a door and is connected to a container, another isolator or a suitable device for transfers, e.g. a bag. The seal of the DPTE® is usually referred to as a lip-seal and this is an important component of the entire assembled system.

The alpha and beta sections are connected and, by rotating the beta section approximately 60 degrees, the doors are locked together as one. The alpha side of the unit is then opened with access into the isolator. The external surfaces of both the alpha and the beta section doors remain firmly locked together until the alpha door is closed and a reverse rotation of the beta unit takes place, separating the two doors. These actions are shown in Figure 4. A Getinge La Calhene alpha port is shown in Figure 5 and different sizes of container with beta ports from the same manufacturer in Figure 6.

Obviously the beta container or attached device has to be internally sterile like the isolator. To effect sterilisation of the alpha door a simple beta port with a plastic cap is docked onto the alpha door which is then opened and exposed to the decontaminating agent during the 'sterilisation' of the isolator. At the end of the process the alpha door is closed and the beta cap removed.

Early in the use of the DPTE® on sterility test isolators, a group in the USA coined the phrase 'ring of death'

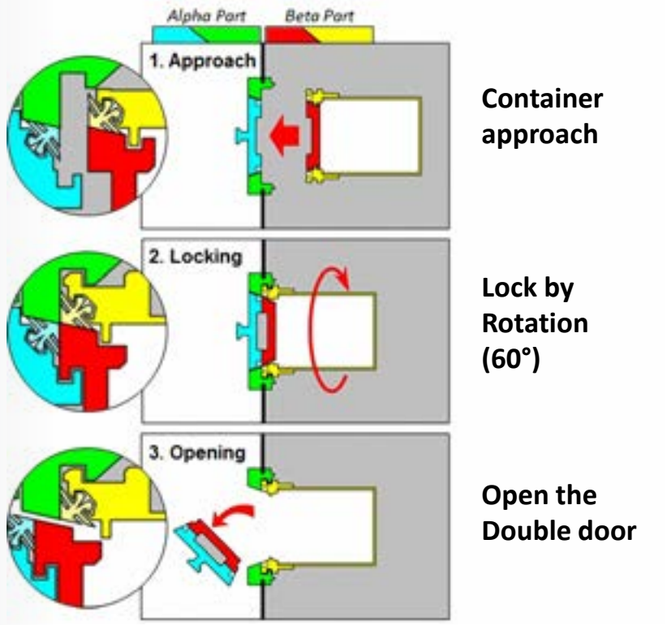


Figure 4: DPTE® mode of connection

Figure 5: Getinge La Calhene alpha port, inside view (the beta port docks onto the outside)

Figure 6: Getinge La Calhene beta ports with plastic containers attached

as they found that a very small (0.1 to 0.5 mm) peripheral band on the lip-seal exposed to the environment outside the isolator was also exposed inside the isolator. This observation raised some concern in the industry.

The author of this current article has, over the years, run many tests to show if any contamination could be transferred, even using deliberately contaminated seals, but under normal GMP conditions it was found not to be a problem. Additional security could be provided by wiping the seals with 70% alcohol or another approved disinfectant. Lubrication was needed occasionally and this was provided by using sterilised silicone oil.

However there remained much concern about the 'ring of death' in the USA and Central Research Laboratories, Chicago produced an RTP where the seal could be heated to above 100 °C in order to 'sterilise' it. They subsequently reverted to a normal design of RTP which is marketed by DE-STA-CO. In common with other RTP manufacturers they offer alpha door diameters of 105,190, 270 and 350 mm.

As mentioned in previous parts of this history, there are over 700 sterility test isolators in use throughout the World fitted with the DPTE® units and there have been no reports of any sterility failure due to the transfer door.

While the DPTE® beta section was usually fitted with a stainless steel or plastic container and the entire unit sterilised internally, other uses included connecting two isolators together and also fitting sterile waste bags to the isolator to hold any materials after the sterility tests had been completed.

In many cases, the rotation of the beta section when connecting to another isolator was overcome by the use of a flexible sleeve that could accommodate the rotation. Early DPTE® or RTP units were not fitted with a locking device and it was possible to remove the beta while the alpha port was still open, thus losing containment and 'sterility'. Later models were fitted with a locking device so that unless a lever was moved inside the isolator the beta section could not be removed. Following the expiry of the patent on the La Calhene DPTE®, other similar devices followed.

Cape Europe offer Optima alpha and beta RTP units and they claim that their RTPs are compatible with the DPTE® of La Calhene. See Figure 7.

M + W Group, Germany, also offer similar RTP designs based on the alpha and beta unit approach. Dynamic Design Pharma, USA, developed a beta port that was reported to be compatible with the La Calhene DPTE® alpha port and the novelty of this design was that the beta port rotated but not the attached container. However not all available RTPs are compatible with La Calhene models and this was reported by La Calhene in a recent report.[1]

The use of sterility testing isolators and the associated transfer units demonstrated the efficacy and the safety of the DPTE®/RTP and the industry adopted these devices for the safe aseptic transfer of product into process isolators.

Figure 7: Optima Alpha port, Cape Europe Ltd.

Figure 8: External view of the SART system, Sartorius GMBH

Transfer of product into and out of process isolators

The containment achieved by using an isolator in the compounding of active pharmaceutical ingredients worked in two ways:

1. Aseptic processing in EU Grade A conditions by filling previously sterilised product into sterile containers.

2. Non-aseptic processing under negative pressure and, usually, EU Grade B or Grade C conditions, in the compounding of hazardous active pharmaceutical ingredients. In this case the finished product was filtered through 0.22 µm filters into sterile vessels for subsequent transfer to an aseptic filling isolator.

There were three ways to achieve these:

1. Directly piped into or out of the isolator using fixed piping in place, subsequently cleaned and sterilised – CIP (clean in place) and SIP (sterilise in place). This type of processing was for large volumes of product prepared on a regular basis.

2. Very small batches of product actually compounded and filled in adjoining isolators, and transferred in small vessels inside the isolators.

3. More commonly by the use of RTP technology where the alpha port was installed in the wall or floor of the isolator and the beta port with an appropriate container was equipped with filters and tubing. This unit would be sterilised in an autoclave. The beta port would be attached to the alpha port, the door opened and the enclosed sterile tubing fixed to the filling head. The product would be sent from an external vessel (sometimes a mobile tank) via a sterilising filter attached to the beta port container. This method allowed for the compounding and filling of various types of product including vaccines, hormonal and cytotoxic drugs.

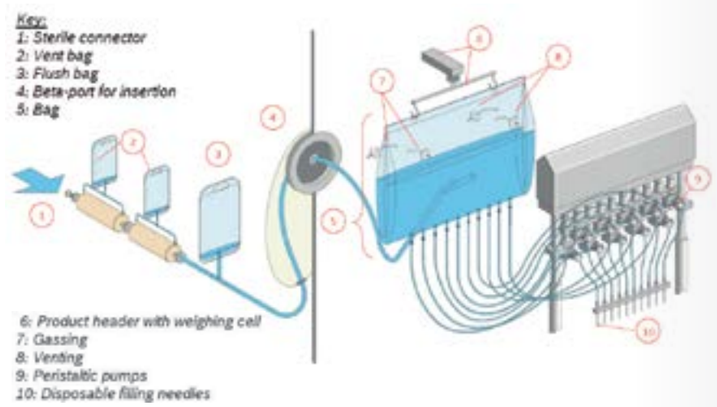


Figure 9: Sterile disposable filling system, Bosch /Sartorius, Germany

As with all systems the components that came into contact with the sterile product to be filled had to be sterilised by a recognised sterilisation process. This meant that filler components had to be sterilised outside of the isolator and introduced via the DPTE® method, or wrapped, placed in the isolator and exposed to the 'sterilising' agent during the decontamination of the isolator.

Recently a new form of aseptic transfer has been developed by Sartorius known as the SART system (Sartorius Aseptic Rapid Transfer), see Figure 8.

This basically was an alpha/beta type port where a sterile line capped at the end by a special closure was inserted and the special end closure removed inside the isolator. Tubing from the filling machine was attached to the exposed entry tube after the removal of the special closure. The asepsis of the system when inserted into the port was provided by knife edge seals similar to the DPTE® seal system.

This type of system has now been superseded by a Sartorius/Bosch disposable filling line where the system is pre-sterilised with filters in place and is complete with balancing sections and filling needles. It requires a special peristaltic pump section, one pump for each filling needle. Again an alpha/beta port type of connection is used, see Figure 8.

As mentioned previously containment is required when compounding hazardous products into tablet or injectable form. Powder handling under such circumstances requires special pass-through systems and a common feature is the use of sterile product in bulk, held in a large vessel, connected to an isolator for transfer through to a powder filling system. In the early days, this was a 25 kg sterile small container (usually an antibiotic product) which was connected manually via a simple aseptic connection consisting of a large diameter flexible tube. Later saw the development of larger powder holding vessels and special docking valve systems.

One example is the Charge Point Pharmasafe® double valve, see Figure 10. It is in a sense the same concept as an alpha/beta port but the components are two parts of a single valve that, when connected, form the whole valve. This is then opened and product allowed to flow through. Powder Systems Limited also offers a similar design. The system offers a very secure and safe way to transfer hazardous powder product with containment claims of < 0.1 µg/m^3.

The transfer of product after being aseptically filled in an isolator is usually carried out by two methods:

1. Small batch sizes can be filled and held in the isolator or an adjoining isolator.

2. For larger batches the isolator filling line is in a sense continuous throughout the batch size.

In the second method, sterile containers, usually from a dry heat tunnel attached to the filling isolator are fed onto the filling line. The product is filled and the container capped. The capped container then exits through a small aperture, known as the 'mouse hole' (see previous articles in this series). Asepsis at the 'mouse hole' was maintained by the over pressure within the isolator causing the air to exit at speeds of up to 2-3 meters per second. Some producers also placed a small unidirectional air flow unit over the exit of the 'mouse hole' This type of filling was adapted for a wide range of sizes of bottles and vials for various heat labile products and also syringes filled with vaccines.

Syringes could be supplied through a dry heat oven or via boxes of pre-sterilised syringes. With the latter it was important that the surfaces of the boxes were sterile before entering the isolator and also when the syringe 'nest' was placed back into the box after the filling and stoppering process. The exit was a modified 'mouse hole'.

Decontaminating the outer surface of the syringe boxes was originally accomplished by the use of large transfer isolators where up to 100 boxes were

Figure 10: Double valve system, ChargePoint Technology, UK

Figure 12: E-beam system for attaching to an isolator, Getinge La Calhene

Figure 11: Two syringe box transfer isolators, Baxter Healthcare, USA

Figure 13: UV system for stopper transfer (outside of isolator), Millipore, USA

Figure 14: UV system for stopper transfer (inside isolator), Millipore, USA

Figure 15: Bioquell Port for rapid bio-decontamination transfers, Bioquell, UK

decontaminated with hydrogen peroxide vapour, see Figure 11. The transfer isolators were then connected to the main filler isolator via a DPTE®.

A later development was the use of e-beam technology to decontaminate the exterior of the syringe boxes. This method has the advantage of speed and also simplicity. La Calhene successfully developed a unit compatible with isolator use, where three small e-beam units were arranged around the conveyor system so that all the external surfaces of the syringe boxes were exposed to a sterilising dose of electron radiation. The syringe boxes were then moved directly into the filling isolator. This type of system, shown in Figure 12, has also now been adopted by other isolator manufacturers.

Entry and exit of containers, components and equipment

Finally there is the introduction of items into the aseptic filling isolator. These mainly consist of filler containers, components and also testing equipment. The transfer of filler containers has been described earlier but testing equipment is usually wrapped and placed in the isolator prior to a 'sterilising' process. As particle counting is normally dealt with by having in-built detection and measuring systems, the main equipment introduced is for microbiological testing.

The closure of aseptically filled vials and bottles needs components such as stoppers and caps plus plunger plugs for syringes and, sometimes, the separate needles.

The main method of transfer of components is to use the RTP system and dedicated disposable plastic bags for the pre-sterilised stoppers, caps plugs and needles. The plastic beta ports that are integral with these bags are also disposable. Different types of chute devices inside the isolator allow direct transfer into the feed hopper bowls.

One unique transfer system, developed by Millipore, utilised intense UV radiation technology. It required a dedicated disposable bag of stoppers, etc. (pre-sterilised) fitted with a short cylindrical sealed cap. On the isolator was fitted a stretcher on which the bag could rest opposite a small circular opening. Inside the isolator was a small door fitted with 6 or 8 small UV tubes.

The door with UV tubes was closed, the cap of the bag introduced through the circular opening and fixed in place. The UV source was activated for 3 minutes during which the surface of the cap was bathed in UV radiation at about 1 to 2 mm. distance. The door was then opened and the cap seal removed allowing the contents of the bag to be emptied into the feed hopper. The system is shown in Figures 13 and 14..

Other methods of stopper transfer evolved around a single large vessel filled with stoppers and attached to a system by which the stoppers were sterilised, treated with silicone and dried. The vessel was detached and moved to the isolator where with a lifting device it was up-ended and attached to the isolator, the exposed section of the connection was decontaminated during the cycle used for the isolator. Companies such as ChargePoint Technology offer this type of equipment.

Finally going back to the original decontamination pass-through at the start of this paper and with the advent of rapid sterilisation methods, various small-pass through devices have been developed where, using hydrogen peroxide vapour technology, items placed in the pass-through can be decontaminated very rapidly, in as little as 20 minutes, depending on load. One such device is shown in Figure 15.

Such 'sterilisable' pass-throughs are now placed between two sterility testing isolators and are used to introduce and remove sterile items as and when required. Bioquell also offers a full size transfer isolator based on the same principle as described at the start of this paper.

i. Rapid Transfer Port Systems- A comparative study by Getinge La Calhene: C.Mounier & C.Guimet, Clean Air and Containment Review, Issue 20, October 2014, p.26-29

Doug Thorogood, Ph.D., studied microbiology and virology in the UK, Belgium and the USA. He has many years' experience in the field of pharmaceutical and medical research as well as QA/QC Regulatory Affairs and Production. He started working in the field of containment in the late 1970s and from that point developed designs, validation procedures and operational systems for a variety of isolators for sterility testing and aseptic filling in 19 countries. He is a specialist in the cleaning and sanitation of enclosures as well as clean rooms and hospital environments.

ISO 14644 series of standards: Progress report

Gordon Farquharson

Introduction

This brief report summarises the state of play following the meetings of ISO/TC 209 'Cleanrooms and associated controlled environments' and its various working groups in Seoul, Korea in October 2014. Updates on some of the work of the working groups that didn't meet in Seoul are also included.

What is a cleanroom?

Originally there was just ISO 14644 Part 1: Classification of air cleanliness by particle concentration. Then other attributes of cleanliness arrived:

- Surface particles
- Chemicals in the air and on surfaces
- Microbes in the air and on surfaces
- Nano-scale particles in the air

Some nations wanted to be able to use any cleanliness attribute alone whilst others believed that we have a particle classified cleanroom first with the other attributes added as required. These other attributes can be termed secondary attributes.

After a big debate there was a realisation that cleanrooms are never actually classified by the secondary attributes or, put another way, the secondary attributes are never subject to a true classification process. What actually happens is that critical control points (CCPs) are identified, target levels of the particular cleanliness attribute defined, appropriate measurement methods selected and a monitoring plan of the CCPs established to ensure they remain in control. The monitoring plan includes reporting and recording the performance, raising an alert for drift from the target level and 'sounding' an alarm when control is lost.

The impact of this change of philosophy is that cleanrooms will be defined first and foremost by air cleanliness by particle concentration with the standards for secondary attributes becoming CCP monitoring standards. Additionally, at the ISO/TC209 meeting a year ago, delegations had agreed that if a secondary attribute were used alone, then the space would be designated as a controlled zone, and NOT a cleanroom or clean zone.

This means that the standards currently under preparation, namely the new bio-cleanliness standard, ISO 14698 (if it proceeds – see later), and ISO 14644-12: classification of air cleanliness by nanoscale particle concentration can be prepared as monitoring standards rather than classification standards. Likewise, in the future, when they come up for periodic review, ISO 14644-8: Classification of air cleanliness by chemical concentration (ACC), ISO 14644-9: Classification of surface cleanliness by particle concentration and ISO 14644-10: Classification of surface cleanliness by chemical concentration can also be re-badged as monitoring standards.

Some nations wanted to be able to use any cleanliness attribute alone whilst others believed that we have a particle classified cleanroom first with the other attributes added as required.

Where now with the new bio-cleanliness standard?

Because of inability of the experts on the working group (WG 2) to reach a consensus after seven years, further work on developing a revised ISO 14698 has been cancelled. The little-used existing ISO 14698-1:2003 and ISO 14698-2:2003 therefore remain in place as confirmed until the next automatic ISO systematic review. The main issue preventing consensus was the non-acceptance by some of the experts of the principle of including a table of microbial cleanliness levels or classes in the standard. In addition, the convenor of the working group had resigned and no permanent replacement could be found. Biologically clean cleanrooms will therefore continue to be defined according to guidelines such as *EU GMP Annex 1:2008: Manufacture of Sterile Medicinal Products and FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice: 2004*. However there is a strong body of interest from European experts that the work of WG2 should not be lost and the possibility of continuing the work in CEN is being explored.

ISO 14644-1 and ISO 14644-2

The new DIS for each of these standards, which have been under periodic review, has been approved by a significant majority of nations through the vote that closed on the 18th November 2014. Much effort has gone into the new DIS for ISO 14644-1 and much has been written about it (see, for example, CACR 17). However, the same is not the case for the new ISO 14644-2 which has now been written with relative speed as a monitoring standard. There is a consensus in the UK, at least, that the present draft is too focussed on continuous monitoring systems and has lost the useful recommendations on periodic testing in the old ISO 14644-2. Periodic testing is a widely used form of monitoring that is perfectly valid for cleanrooms subject to budgetary constraints. Because the voting on these two standards produced a significant number of comments, an extension has been granted to September 30 2015 to allow another working group meeting and an FDIS ballot if these are considered necessary. Thus It is hoped that final publication will be in the third quarter of 2015.

Cleanroom energy management standard

This will become one of the ISO 14644 series. The working group was due to have its first meeting in Chicago in December 2014 under UK convenorship. The work will be based on BS 8568:2013 – cleanroom energy code of practice for improving energy efficiency in cleanrooms and clean air devices with input anticipated from Germany, China and Russia.

Assessment of suitability for use of equipment

Two standards are currently in preparation:

- ISO 14644-14: Assessment of suitability for use of equipment by airborne particle concentration
- ISO 14644-15: Assessment of suitability for use of equipment and material by airborne chemical concentration

The first of these has a normative method for determining equipment suitability that the UK is not happy about. The UK view is that there should be equally weighted evaluation methods looking at a) critical control points in a unidirectional airflow system and b) total emissions. It would be useful if there were a clear reference in the normative section to the relevance of an informative method for evaluation of total particle emissions, especially in non-unidirectional airflow situations.

Design, construction and start-up, ISO 14644-4

After various representations, TC 209 has decided that there should be a periodic review of this standard after all and this will now go ahead.

Gordon Farquharson, B.Sc.(Hons), C.Eng., is a Chartered Consulting Engineer with more than 30 years' experience of quality and safety critical processes, facilities and systems used by industries such as Healthcare, Life Science and, Micro-electronics. His international consultancy, Critical Systems Ltd, is based in the UK, and he is also an executive consultant with PharmOut Pty Ltd based in Australia. Prior to this he was Technical Director of PED Ltd, Tanvec Ltd, and Tanshire Holdings PLC and then Principal Consultant in the Life Sciences division of Bovis Lend Lease.

In recent years, he has been heavily involved in cleanroom and safety containment technology. For cleanrooms, he is active in the development of the CEN/ISO Cleanroom and Contamination Control Standards (EN/ISO 14644 family), revision of Annex 1 EU GMP, revision of Annex 3 of the WHO GMP, preparation of the WHO Pharmaceutical Water GMP. He is Chairman of BSI's LBI/30 Committee and of CEN Technical Committee 243, and is Convenor of WG1 of ISO TC209. In the biosafety arena, he has worked on the application of solutions to BSL 3 and 4, with a special focus on air filtration, enclosure leakage, and systems safety qualification.

He is a founding member, past Chairman, and Honorary Member of the UK Pharmaceutical Healthcare Sciences Society (PHSS), and is active in ISPE, the R3 Nordic Association, and PDA's Science Advisory Board. He is a past chair of the ISPE European Education Committee and was voted ISPE International Member of the year 2001, UK member of the year in 2008, and received the Richard B Purdy distinguished service award in 2009. He is an honorary lecturer at UCL and Manchester University (PEAT & PIAT programmes).

Life-lines

Courtesy of Susan Rogers

Aircraft maintenance (another heavily regulated activity)

Squawks are problem listings that pilots generally leave for maintenance crews to fix before the next flight.
Here are some squawks submitted by pilots and the replies from the maintenance crews.
(P) = Problem (S) = Solution

(P) Left inside main tire almost needs replacement
(S) Almost replaced left inside main tire

(P) Test flight OK, except auto land very rough
(S) Auto land not installed on this aircraft

(P) #2 Propeller seeping prop fluid
(S) #2 Propeller seepage normal – #1 #3 and #4 propellers lack normal seepage

(P) Evidence of leak on right main landing gear
(S) Evidence removed

(P) Dead bugs on windshield
(S) Live bugs on order

(P) Autopilot in altitude hold mode produces a 200 fpm descent
(S) Cannot reproduce problem on ground

(P) Friction locks cause throttle levers to stick
(S) That's what they're there for

(P) Number three engine missing
(S) Engine found on right wing after brief search

(P) Target Radar hums
(S) Reprogrammed Target Radar with the lyrics

WHO adopts ICH quality system philosophy

Dr Hans Schicht

The 2014 report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations[i] has recently been published. From the GMP perspective, only a single new compendium is included among its annexes: a fundamentally revised compilation summarizing the main principles of WHO GMP guidance[ii]. It replaces the previous edition which had been published in 2011[iii].

This new edition reflects the present thinking regarding pharmaceutical quality systems that was first introduced via the ICH Q10 guideline. Topics such as science-based quality risk management, the life cycle approach, periodical trend assessments and learning from experience are addressed throughout the text.

The wide range of GMP and GMP-related matter is covered comprehensively in a total of 58 pages, with a total of 17 headings:

1. Pharmaceutical quality system
2. Good manufacturing practices for pharmaceutical products
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
8. Self-inspection, quality audits and suppliers' audits and approval
9. Personnel
10. Training
11. Personal hygiene
12. Premises
13. Equipment
14. Materials
15. Documentation
16. Good practices in production
17. Good practices in quality control

Between one and five pages are devoted to each topic, with comprehensive guidance provided in an exhaustive but compact and well-structured form. All essentials of general character are addressed. A comparable compilation of main principles does not exist, for instance, in the GMP guideline of the European Union. Therefore, this compendium is useful as a detailed summary of general GMP requirements.

References

i. WHO Expert Committee on Specifications for Pharmaceutical Preparations, 48th report. WHO Technical Re-port Series no. 986, World Health Organization WHO, Geneva (2014).

ii. Annex 2: WHO good manufacturing practices for pharmaceutical products: main principles. Ini, pp. 77-135.

iii. Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Technical Report Series no. 961, World Health Organization WHO, Geneva (2011), p. 94-147.

Hans H Schicht, Dr. sc. Techn, spent 20 years in the field of industrial air conditioning and cleanroom technology before becoming a consultant in cleanroom and contamination control technology in 1991. He has been the representative for Switzerland on the CEN and ISO cleanroom technical committees for many years, Chairman of ICCCS (International Confederation of Contamination Control Societies) and President of SRRT (Swiss Society for Contamination Control). He is a Fellow of the IEST (Institute of Environmental Sciences and Technology) and an inductee to the Cleanrooms Hall of Fame. Dr Schicht has published numerous technical papers.

Regulations that affect cleaning products

James Tucker

The regulatory regime for cleaning and disinfectant products is constantly evolving. Vendors are obliged to keep constantly up to date and it is important that purchasers are aware of the regulations that apply to the products that they purchase. Here are the principal regulations that apply:

The Biocidal Products Regulation (BPR)

The Biocidal Products Regulation (BPR, Regulation (EU) 528/2012) concerns the placing on the market and use of biocidal products, which are used to protect humans, animals, materials or articles against harmful organisms like pests or bacteria, by the action of the active substances contained in the biocidal product. The Regulation was adopted in May 2012 and came into force on 1 September 2013, replacing the Biocidal Products Directive 98/8/EEC (BPD) which has, in effect, been updated with additional weight.

The changes remove the ability for individual country interpretation and also simplify and harmonise all the authorization procedures necessary to allow a company to market a biocide product for use across the EU. They are aimed at ensuring a high level of protection of human health encompassing operators and the environment. They also promote the reduction of animal testing by introducing mandatory data sharing obligations and encouraging the use of alternative testing methods.

Under BPR, all biocidal products*, i.e. all products intended to provide biocidal action, require an authorisation before they can be placed on the market, and the active substances contained in that biocidal product must be previously approved (with certain exceptions, for example: provisional authorisation for new active substances that are still under assessment). A product may have national authorisation if it is to be marketed in that nation alone, or mutual recognition may be applied for if the product is to be marketed in several countries, or there is a new alternative which is an application for EU-wide authorisation in one go.

ECHA (European Chemical Agency) is responsible for the publication of the list of authorised active substances and the list of biocidal products (ECHA Article 95 List) with EU authorisation is published on the ECHA website.

Under BPR, all biocidal products, i.e. all products intended to provide biocidal action, require an authorisation before they can be placed on the market, and the active substances contained in that biocidal product must be previously approved

The BPR regulations apply to every manufacturer and mean that only products containing an approved active substance can be marketed legally. Failure to comply could incur fines, immediate removal from the market and possibly even criminal proceedings for the manufacturer and the end user.

Registration, Evaluation, Authorisation & restriction of CHemicals (REACH)

REACH is a European Union regulation concerning the Registration, Evaluation, Authorisation and restriction of Chemicals. It came into force on 1st June 2007 and replaced a number of European Directives and Regulations with a single system. Although REACH applies primarily to manufacturers and importers of chemical products, users too have certain responsibilities. In particular better information on the hazards of chemicals and how to use them safely will be passed down the supply chain through improved safety data sheets.

The CLP Regulation

European Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures came into force in January 2009 in all EU Member States, including the UK. It is known by its abbreviated form, 'the CLP Regulation' or just plain 'CLP'. The CLP Regulation adopts the United Nations' Globally Harmonised System on the classification and labelling of chemicals (GHS) across all European Union countries, including the UK. The essence of CLP is that Safety Data Sheets are provided for all chemicals so that people using them – either in industry or as consumers – can understand any hazardous effects they could have on human health or the environment and to protect against that harm. It follows that product labels, which must include hazard information from the Safety Data Sheets, will also reflect these changes. CLP must be in place in Europe by June 2015 so any product manufactured after this date will need to be compliant.

Conclusion

Users of biocidal products are advised to familiarise themselves with all the regulations that apply and in particular to ensure that their suppliers are fully compliant and therefore supply only authorised products. Use of non-compliant biocidal products can have serious consequences and also incur serious sanctions. Information on the regulations is available on the websites of UK HSE and ECHA.

James Tucker is Marketing Director at Ecolab Contamination Control. Ecolab Contamination Control provides market leading products and services for the control of microbial contamination in the cleanroom environment to pharmaceutical, biotechnology, healthcare and medical device industries worldwide.

*Biocidal products are active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means.

Bill Whyte awarded Special Commendation by BSI

John Neiger

Left to right: Gordon Farquharson, Chairman of LBI/30, David Bell, Director of External Policy, BSI, Bill Whyte and Sue Barden, Secretary to LBI/30

At the November meeting of LBI/30, the UK BSI Cleanrooms Committee, Dr William (Bill) Whyte was awarded a Special Commendation by BSI, the UK's National Standards Body, in recognition of his exceptional contribution to standards making. The award was presented by David Bell, Director of External Policy at BSI, and Jim Shuker, Head of Strategic Engagement, who also took the photographs. The award was a complete surprise to Bill who was delighted that his work had been recognised in this way.

Bill first joined BSI LBI/30 in 1990 and, as the ISO standardisation process took off, he was nominated as the UK Technical Expert on ISO TC 209 Working Group 5: Cleanroom operations, which had its first meeting in 1995. Around the same time, he was nominated to Working Group 6: Vocabulary. In 1997, when the UK Technical Expert to Working Group 2: Biocontamination was appointed Convenor, Bill took his place as UK Technical Expert. Later on he joined Working Group 1 when it was reviewing ISO 14644-1: Classification of air cleanliness. Serving on so many Working Groups, and with his extensive knowledge of cleanroom technology, he was the ideal person to be UK Head of Delegation at meetings of ISO TC 209, a role which he filled with distinction for many years until he retired from international activities. Happily he continues his involvement with the ISO standards through his regular attendance at LBI/30 meetings where his guidance to current ISO delegates is invaluable.

Bill is uniquely qualified to be a member of this committee, not only because he has a BSc in microbiology and a DSc in engineering, but also because he has made cleanroom technology his specialist subject for the best part of his working life. As the only academic on the committee, his massive contribution has been scientifically based, well-argued and thorough.

Bill has written numerous papers on contamination control and cleanroom design and many of these have formed the basis of his contributions to the standardisation process for cleanrooms. To give one very recent example, a paper published in CACR 20 (October 2014), covers the application of the ventilation equations to the decay of contamination in a cleanroom. One of the conclusions of the paper is that one of the two test methods for room recovery in ISO 14644 Part 3: Test methods, is less reliable than the other. There are many more instances where his papers have thrown light on aspects of cleanroom technology that have been of direct relevance to the development of the cleanroom standards. Incidentally MCP – microbe carrying particle – is a term introduced by Bill himself.

Gordon Farquharson, chairman of LBI/30, writes:

"Dr William Whyte is currently an Honorary Research Fellow in the School of Engineering at the University of Glasgow and has served on LBI/30, the BSI Cleanroom Technology committee, since 1990. What of course this doesn't tell you is the huge impact Bill has had in the field of contamination control and cleanroom technology in the United Kingdom. He has plied his trade for almost exactly 50 years as a scientist, engineer, teacher and researcher. Over the years he has brought all his knowledge, science-based thinking, and attention to detail to the work of standardisation through BSI. He has been a constant friend and inquisitor working with all the experts involved in development of cleanroom and contamination control standards in the United Kingdom, the CEN standards community, and in ISO. His input has often gone unseen as he doesn't appear as chair, convenor etc. His colossal contribution comes from his ability to listen, inspect, assess and challenge what is written and said, and to carefully craft persuasive written and oral contributions. His international credibility and reputation are extremely important in helping to ensure that this contribution to our standards work is not narrow and parochial. When Bill has provided his expertise as a UK expert in CEN and ISO work, his contribution has always been recognised as truly balanced, science-based, and well argued. Bill's academic credentials have brought a further dimension to his contribution to our standards work. As an author of books and numerous papers in the field of cleanroom technology and contamination control, Bill has an ability to craft and write documents with the skill of the teacher and scientific author. Over the years this has been a very important contribution to complement the input of other UK experts.

Bill is a really good person, and whilst he does not suffer fools gladly, he has always made the time to explain his arguments and the essential scientific principles to both his fellow standards volunteers as well as helping BSI's programme management team members understand more about the subject of work."

Bill enjoys music and travel and has always been especially keen on sports, particularly yachting. His main sailing area was in the Clyde and the West Coast of Scotland but he knows the coasts of Greece and Croatia well, and during his year working at the Academic Hospital in Uppsala, Sweden he took his boat over the North Sea and spent two summers sailing much of the coast of Sweden, Finland and Norway. He has also crossed the Atlantic, crewing a yacht from Grand Canaria to St Lucia. He reckons that he has spent about 4 years of his life on a yacht.

However, in his old age (72 years) he only occasionally sails but the yacht is well used by his two sons, and Bill gets the job of maintaining it. Bill is proud of his sons as they have followed on some of his engineering interests and both obtained PhDs at Glasgow University, where they both used cleanrooms in their research. Rather than participating in sport Bill now watches it. He was on the Board of Stenhousemuir Football Club and in the summer watches and helps the local cricket club. Rugby union is another interest and he is a supporter of Glasgow Warriors.

People often ask why Bill does not retire and stop his interests in cleanroom technology. He says that it is good to keep an active mind and when you have worked hard all your life it is difficult to stop. Also, many people retire and spend a lot of their time solving crosswords and other puzzles. What he does is to solve scientific puzzles.

A little while ago, Bill told me that he had been reflecting on the 50 years that he was just about to complete in cleanroom technology. I suggested to him that a historical article might be very interesting for readers of CACR and asked if he would be prepared to write such an article for us. Bill very graciously agreed and suggested that it could be about the work he had carried out on operating rooms in the first half of the 50 years. The result will be a two-part paper on the effect of mechanical ventilation and clothing on airborne microbes and wound sepsis in hospital operating rooms. The paper will cover a very exciting period in the development of operating rooms including the work done by the MRC (Medical Research Council) and by such eminent names from the past as Dr Owen Lidwell, work in which Bill was heavily involved. The two parts will be published in CACR22 (April 2015) and CACR21 (July 2015).

Review of 'Industrial Pharmaceutical Microbiology: Standards & Controls – 2015 Edition' edited by Geoff Hanlon and Tim Sandle

James H Filer

The 2015 edition of Industrial Pharmaceutical Microbiology is a first-rate reference resource for any professional microbiologist, covering a wide range of topics of relevance to the whole industry. The book starts with the role of the microbiologist and the microbiology laboratory, before moving on to specific microbiological and industry controls. It closes with the issues facing some specialised areas of the industry with their own particular microbiological challenges.

All of the well-written chapters offer invaluable guidance to a pharmaceutical microbiologist, however there are a few chapters which I find especially apposite, based on recent regulatory inspection trends:

The chapter covering microbial risk assessments for cleanrooms introduces the fundamentals of contamination transfer into an operational cleanroom from a range of specified sources. It proposes a model to map the possible sources of contamination against the means of control intended to mitigate those risks; based on source strength, proportion of contamination transferred, and the time available for that contamination to occur. The resulting risk factor, expressed in terms of potentially contaminated final product units, allows the microbiologist to make an assessment about whether those in-process controls are adequate to meet the required sterility assurance level.

The environmental monitoring chapter gives a useful background into the role the program plays in the overall sterility assurance at a facility. The current best practice of using a formal risk analysis tool is covered in detail, helping ensure appropriate monitoring of critical control points. The various monitoring methods and media are discussed, with their pros and cons and validation requirements.

The rapid microbiological methods chapter discusses the regulatory expectations for RMMs, before giving a thorough overview of the available technologies, their common uses and the available commercial systems. The section on validation of RMMs offers myriad examples of typical validation considerations, focussing on the expectations of USP, EP and PDA.

an invaluable reference to anyone involved in pharmaceutical microbiology

The chapter on auditing the microbiology department opens with an extensive list of microbiology-related FDA 483 citations covering a wide range of topics in order to set the scene for what is perhaps the most extensively audited department in a pharmaceutical manufacturing facility. The chapter follows a logical audit path from the high level microbiological control strategy through specific tests, media, equipment and controls, each with typical questions an auditor may ask to show whether a laboratory complies with cGMP. Although aimed at the auditor, this chapter offers microbiologists an accurate audit roadmap to perform mock reviews of their own facilities in preparation for regulatory inspection.

An introduction to the different grades of pharmaceutical water includes details on production methods, the design principles of water generation systems, as well as its storage and distribution. The microbiology of these systems is discussed in great detail and includes clear guidance on the use of appropriate methods to monitor a water system. Immediately after this section comes the excellent chapter on biofilms, containing great detail on how and why biofilms form, the science of bacterial adhesion and how biofilms adversely impact pharmaceutical manufacturing processes. The author discusses biofilm control, focussing on prevention of biofilm formation, but providing strategies for removal of biofilm. This is the most detailed discussion of biofilm that I have read, and explains many of the associated phenomena that I have often perplexed me over my career in microbiology.

The chapter titled Containment System Integrity is a great discussion of the science of applying a microbiological challenge to a product's container/closure system to verify integrity. The author candidly discusses the challenges of using these methods and the potential pitfalls in applying them in practice, not least of which are the perils of using an inappropriate positive control; something I have seen several integrity studies fall foul of.

The final must-read chapter is the one covering aseptic process simulations, which as you would expect, offers detailed advice on factors to consider. However the discussion about how "worst case" a simulation should be is, in my opinion, one that all pharmaceutical microbiologists should read to avoid the practice of stressing your simulation far beyond anything remotely realistic in routine manufacturing.

Overall a very useful, well-edited book that will be an invaluable reference to anyone involved in pharmaceutical microbiology.

James Filer, Global Quality Compliance Executive – GE Healthcare, has a BSc in Industrial Microbiology and an MBA. He has worked in the pharmaceutical industry for 20 years, initially for Amersham International and then GE Healthcare, mostly in roles relating to sterility assurance. He is a technical expert on BSI LBI/30 and the UK principal expert on ISO TC 209, Working Group 2 – Biocontamination.

Nitritex: Only too pleased to help...

Following the outbreak of the Ebola virus in West Africa, Nitritex Ltd was among the first to donate and help the Emergency Ebola Appeal from Scotia Aid-Sierra Leone, a charity which was set up in 2010 to improve the lives of the people of Sierra Leone through educational and social programmes, with the emphasis on helping the large numbers of children whose lives are controlled by the streets.

Nitritex Ltd was happy to donate seven pallets of Personal Protection Equipment (PPE) including disposable coveralls, aprons, and over 200,000 gloves to protect the healthcare workers helping to save lives during this crisis.

For more information on the work carried out by Scotia Aid please visit www.scotiaaid-sierraleone.org.uk or if you would like to make a donation please visit https://www.justgiving.com/scotiaaid

For more information on the PPE available from Nitritex Ltd please visit www.bioclean.com

PPE from Nitritex ready for shipping to Sierra Leone as a donation to the Emergency Ebola Appeal

Bassaire and ISD Solutions deliver state-of-the-art clean room manufacturing facility for The Nutrition Group

In a joint development, clean air engineering specialist Bassaire and composite panel construction company ISD Solutions have completed a new state-of the art ISO class 8 clean manufacturing facility for the UK's fastest growing contract manufacturer within the health supplements and sports nutrition markets.

The 1,365m^2 cleanroom suite is constructed with a fixing-free flush finish using ISD's PIR composite panels for walls and ceilings, with some 60 specialist doors, and is served by a dedicated air handling unit with HEPA-filtered air to provide good air movement and positive pressure for GMP.

"Together with ISD we have value engineered a turnkey solution to meet the strict clean production requirements of The Nutrition Group," explains Rachel Utting, project manager at Bassaire.

"Composite PIR panels incorporating a 'clean safe' plasticised finish are an ideal construction solution for clean room and pharmaceutical environments," explains Andy Hudspith for ISD Solutions.

See: www.bassaire.co.uk and www.isd-solutions.co.uk/isd-divisions/retail-division

New Lighthouse ApexR5 remote particle monitoring from DOP Solutions

In collaboration with Lighthouse Worldwide Solutions, DOP Solutions has recently added the 1 CFM (28.3 LPM) ApexR5 Remote Particle Counter to its range of cleanroom monitoring instruments. Delivering an increased range of specifications guarantees the critical data logged is of the highest accuracy. With its newly designed sloped front face and sealed connections, the ApexR5 is compatible with all decontamination processes (including H_2O_2 vapour) and meets the stringent requirements of today's technology driven industries.

New features include a validation mode, hot swap smart bracket, optional 4 channels and real-time viewing on tablets or smartphones, all at a cost-effective price with a two year warranty. The ApexR5 offers unmatched performance, accuracy and reliability with its long-life laser diode sensor and sensitivity of 0.5 microns.

Please contact DOP Solutions for advice, prices or demonstrations at sales@dopsolutions.com or +44 (0)1462 676446, or visit www.dopsolutions.com

Lift-off for CRC space technology project

Work has started on site to deliver a cleanroom facility for RAL Space that will be out of this world, according to design and build specialists Clean Room Construction (CRC).

The 1,372 square metre facility at the space and technology centre in Didcot in Oxfordshire is one of the tallest cleanroom facilities ever built by CRC. When completed, the suite of 15 cleanrooms and 5 changing areas will be used to assemble and test satellite instrumentation.

CRC is working with Willmott Dixon Construction Ltd to deliver the project. The specification includes cleanrooms with walk-on and suspended ceilings, some of which exceed 12m in height, and a requirement for self-supporting modular wall panels including 6.5m by 6m roller door access. Three cleanrooms will be used for optical testing and laser alignment projects. Facilities comprise Class 5 and 6 cleanrooms for the assembly, integration and test of space hardware, including the largest thermal vacuum calibration facility in the UK.

CRC is responsible for the testing, validation and commissioning of the facilities too.

RAL Space is the space department of the Science Technology Facilities Council which provides world-leading research and technology development, space testing facilities, instrument and mission design capability.

CRC Managing Director Steve Lawton said: "Clean Room Construction is the most experienced cleanroom design and build specialist in the UK and we are very proud to be working with Willmott Dixon Construction Ltd to deliver a space-age facility for a leading technology centre."

www.crc-ltd.co.uk

A Sea and Land Surface Temperature Radiometer (SLSTR) being prepared for thermal vacuum calibration at RAL Space. The new cleanrooms will accommodate the largest thermal vacuum calibration facility in the UK. Photo courtesy of Science Technology Facilities Council (STFC).

Cleanroom Istanbul 2015 Cleanroom Technology, Maintenance and Equipment Exhibition

Akdeniz Tanitim is very pleased to announce the first Cleanroom Istanbul exhibition for cleanroom technology, maintenance and equipment.

Facility managers and cleanroom professionals who design and engineer "extraordinary spaces" will come together at the "one and only" Cleanroom Exhibition of Turkey from 16th to 18th April 2015. This will be held at the Lütfi Kırdar International Congress and Exhibition Center (ICEC) in Istanbul.

Nowadays many special industrial plants, medical facilities and R&D departments require very hygienic and extremely sterile spaces which should be designed and engineered by experts using high-tech materials, equipment, control techniques, management models and certification and risk management systems.

Cleanroom Istanbul 2015 will be an appropriate business platform for all concerned to present materials, products, technology and services for the increasing demands of organisations that require cleanrooms. All interested parties are invited to Cleanroom Istanbul 2015, to establish new business contacts in this rapidly developing field and to take a place in the future-oriented market of Turkey.

www.expocleanroom.com

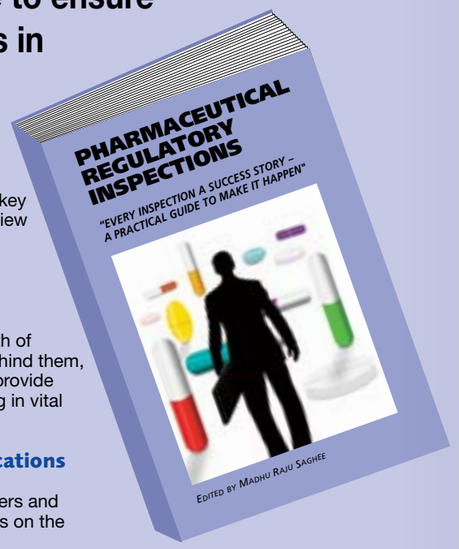
Irish Cleanroom Society

Do you want a share of the Irish Cleanroom Industry?

- The Irish Cleanroom Society is THE forum for the interchange of ideas and information within the Irish Cleanroom Industry and world wide
- The ICS is the voice of the Irish cleanroom industry to Government and the EU
- Receive the ICS newsletter FREE
- Get preferential rates for seminars and ICEB training courses held in Ireland and England
- Access the ICS web library of papers and training seminars
- Present your Company on the ICS vendor webpage

The Irish Cleanroom Society (ICS) is a not for profit membership subscription based organisation formed in 1998 to represent Cleanroom professionals in Ireland. The ICS is affiliated to the International Confederation of Contamination Control Societies (ICCCS) Our main focus is to offer better knowledge and awareness of Cleanroom technology to professionals involved in semi conductors, medical technology, pharmaceutical, healthcare and food industries. We do so by organising educational programmes, seminars, and exhibitions and by providing up to date information. For more information, subscription rates and membership application forms please go to our website at www.cleanrooms-ireland.ie

A unique and comprehensive guide to ensure regulatory compliance and success in pharmaceutical regulatory inspections



In over 600 pages and twelve chapters this unique book provides a focussed account of regulatory issues from pre-approval inspections and the inspection itself to post-inspection and maintaining compliance. This is a book that every pharmaceutical company will wish to study before and during any inspection process to ensure a successful outcome.

Complete Remit

The book is a fully detailed and practical guide *containing pragmatic and up-to-date advice* and insight to help any pharmaceutical organisation prepare for GMP Inspections, understand key regulatory issues and review inspectorate trends and findings.

Expert Advice

The authors, with a wealth of regulatory experience behind them, express their views and provide useful tips for succeeding in vital regulatory inspections

International Applications

For a full list of the chapters and authors see further details on the Euromed website

order online at www.euromedcommunications.com
Or contact the publishers: email: publisher@euromedcommunications.com;
Tel: +44 (0)1428 752222; Fax: +44 (0)1428 752223.

ENVAIR
Integrity in clean air

Creating the perfect **working environment**

With our many years of global experience, Envair have a proven ability for delivering high performance and cost effective solutions for specialist ultra-clean and containment engineering associated with primary & secondary pharma manufacture and biotechnology research to fully compliant GMP sterile drug dispensing and radioactive drug preparation.

Long established UK manufacturer of:

- > Hospital Pharmacy Isolators
- > Microbiological Safety Cabinets
- > Powder Handling Booths
- > Unidirectional Airflow Cabinets & Rigs
- > Radiopharmaceutical Isolators
- > Laboratory Fume Cupboards
- > Glovebox Isolators
- > Custom & Bespoke Containment

PHARMACEUTICAL | BIOTECHNOLOGY | RESEARCH | HEALTHCARE

Call our dedicated sales team today: ✆+44 (0)1706 228416 www.envair.co.uk

Berner Cleanroom Gloves

First class glove protection comes as standard

8 hours+ chemical safety

When your safety is at stake, our Berner range of protective cleanroom gloves offer market leading resistance in handling hazardous materials.

Berner gloves are fully certified PPE Category III offering over 8 hours of chemical resistance, without compromising on comfort or touch sensitivity.

Suitable for high risk applications and compatible up to ISO Class 5, our complete Berner range of latex, neoprene and nitrile gloves set the standard in quality cleanroom protection.

Try for yourself and order FREE samples today!

Helapet
A CliniMed® Group Company

Helapet Limited
Telephone 0800 0 328 428
E-mail sales@helapet.co.uk
www.helapet.co.uk

Download our brochure

Events

Dates	Event	Organiser
2015		
February 18	Seminar and Workshop: Sterilisation, Sanitisation & Disinfection – Requirements of effective contamination control and the appropriate steps to manage deviations, Abingdon, UK	PHSS
February 23-24	24th Annual Aseptic Processing Technology Conference, Baltimore, Maryland, USA	ISPE
April 16-18	Cleanroom Technology, Maintenance and Equipment Exhibition, Istanbul, Turkey	Akdeniz Tanitim
April 21-24	8th Annual Meeting of the European Biosafety Association: Orchestrating a (bio)safe EBSAworld, Vienna, Austria	EBSA
April 27-30	ESTECH 2015, Danvers, Massachusetts, USA	IEST
May 10-12	R3 Nordic 45th Symposium and Exhibition, Lillestrøm, Norway	R3Nordic
May 19-21	Lounges Stuttgart Multi-sector fair, Stuttgart, Germany	Inspire Gmbh
June 15-19	ACHEMA, Frankfurt am Main, Germany	DECHEMA
November 9-12	2015 IEST Fall Conference, Chicago, USA	IEST
November 17-19	A3P Congress, Biarritz, France	A3P

Training courses

IEST (Institute of Environmental Sciences and Technology)		
2015	**Event**	**Location**
February 11	Practical Guide for Meeting ISO 14644-2 "Monitoring Plan" Requirements	Freemont, California, USA
March 25	Cleanrooms, HVAC System Design, and Engineering Fundamentals	Arlington Heights, Illinois, USA

ICS (Irish Cleanroom Society)		
2015	**Event**	**Location**
March 4	CTCB-I Cleanroom Technology Advanced course and Examination	Dublin, Ireland
November 3-5	CTCB-I Testing and Certification	Dublin, Ireland

CTCB-I /Netherlands (VCCN)		
2015	**Event**	**Location**
April 22-24	Cleanroom Testing & Validation Lecture only (in Dutch) 2 days Associate and 3 days Professional	Boven Leeuwen, The Netherlands
November 17-19	Cleanroom Testing & Validation Lecture only (in Dutch) 2 days Associate and 3 days Professional	Boven Leeuwen, The Netherlands

R3Nordic with Chalmers University of Technology		
2015	**Event**	**Location**
September (Date TBA)	CTCB-I Certification, Associate and Professional Levels	Göteborg, Sweden

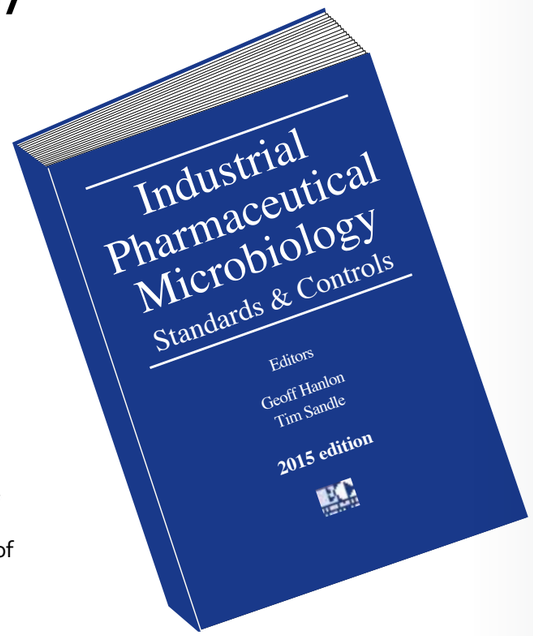
Note that:

- ICEB and CTCB-I certifications are explained on the ICS, ICEB and CTCB-I websites
- The Academy for Cleanroom Testing (ACT) is a part of DOP Solutions, a commercial company that provides cleanroom testing and monitoring equipment, and training
- All CTCB-I courses run by ACT are under the auspices of the Irish Cleanroom Society (ICS).

ACT (Academy for Cleanroom Testing)		
2015	**Event**	**Location**
February 17	HEPA Filter testing	Letchworth, UK
February 18	Cleanroom Certification to ISO14644	Letchworth, UK
February 19-20	Safety Cabinet Testing	Letchworth, UK
March 16	HEPA Filter testing	Durban, South Africa
March 17	Airflow measurement and testing	Durban, South Africa
March 18	Cleanroom Certification to ISO14644	Durban, South Africa
March 19-20	Safety Cabinet Testing	Durban, South Africa
March 24-26	CTCB-I Testing and Certification	Durban, South Africa
May 12	Cleanroom Technology (CTCB-I)	Letchworth, UK
May 13	HEPA filter testing	Letchworth, UK
May 14	Airflow measurement and testing	Letchworth, UK
June 23-25	CTCB-I Testing and Certification	Letchworth, UK
July 13	Airflow Measurement and Testing	Letchworth, UK
July 14	HEPA filter testing	Letchworth, UK
July 15	Cleanroom Certification to ISO14644	Letchworth, UK
November 3-5	CTCB-I Testing and Certification	Dublin, Ireland
November 23	HEPA filter testing	Letchworth, UK
November 24-25	Safety Cabinet Testing	Letchworth, UK
November 26	CTCB-I Cleanroom Technology	Letchworth, UK
November 27	Airflow Measurement and Testing	Letchworth, UK

Expert Guidance on Industrial Pharma Microbiology

Edited by Geoff Hanlon
and Tim Sandle



Industrial Pharmaceutical Microbiology: Standards and Controls provides clear, practical and up-to-date guidance for handling virtually every compliance and operational challenge associated with pharmaceutical microbiology.

In over 600 pages and 25 chapters this updated and revised book covers the entire spectrum of industrial pharmaceutical microbiology, as applicable to pharmaceuticals and healthcare. The book is divided into three sections: A) The Role of the Microbiologist and the Microbiology Laboratory B) Microbiological Control and Industrial Processes and C) Regulatory Aspects of Industrial Pharmaceutical Microbiology

Expert Advice

A team of twenty-four international authorities will assist you in all your questions concerning regulatory expectations in areas such as microbiological audits, rapid microbiological methods, conducting risk assessments, both proactive in terms of minimising contamination, and reactive in terms of addressing microbial data deviation; and also ensuring that processes meet "quality by design" principles.

International Applications

Connect instantly with regulations and current best practices on everything from disinfectants to sterility testing; environmental monitoring to hazard analysis; and from pharmaceutical processes to biological indicators. All of this is developed from an international perspective, where different regulations are compared and contrasted together with insightful commentary as to best practices.

This new second edition is an excellent reference work for those working in industrial pharmaceutical microbiology. It covers all aspects of this complex subject with contributions from many leading figures in the field and is highly recommended

European Journal of Parenteral and Pharmaceutical Sciences

This book is not simply about the science of microbiology for it takes the science into to the industrial setting and offers invaluable advice on how to apply it to the manufacture of pharmaceutical and healthcare products, and for keeping such products within microbial control. A further strength with the book is its topicality, in having the most recent regulations and standards. The book features 25 chapters covering environmental monitoring, water systems, vaccines, safety, biological indicators and microbiology laboratory management. Picking the stand-out chapters is difficult, because there are so many good ones. … In summary this book is essential for every pharmaceutical laboratory: scientific, topical and practical.

Pharmig

order online at www.euromedcommunications.com
Or contact the publishers: email: publisher@euromedcommunications.com;
Tel: +44 (0)1428 752222; Fax: +44 (0)1428 752223.

Cleanroom EXHIBITION

Cleanroom Technology, Maintenance and Equipment Exhibition

16th-18th April 2015

ICEC – Lütfi Kırdar International Congress and Exhibition Center
İSTANBUL/TURKEY

Organiser AKDENİZ TANITIM

www.expocleanroom.com

İstanbul Lütfi Kırdar ICEC

MADE IN CLEANROOMS
PROCESS MATCH
FOR CLEANROOMS

By The Book

You can take it as read that, at Ecolab, our regulatory department constantly monitors the latest industry regulations to ensure that our products and processes are always compliant.

As market leaders in contamination control we are always looking to the future, and that means planning for the latest advice from relevant regulatory bodies. Recently, we've been making changes to the way we register and label our products to adhere to the most up to date advice from the EU.

The Biocidal Products Regulations' (BPR) authorized list of active substances acceptable for use in biocides requires products to be registered with the European Chemicals Agency (ECHA). The consequences of non-compliance are disruptive and expensive; continuity of supply may be compromised when an unauthorized product is removed from the market, causing production disruption, downtime, and urgent change control and validation to implement a replacement. You may also be fined if you use a unauthorized product as a biocide.

By using Ecolab's products, you are assured that you are using products that will be supported through the BPR. Importantly, this legislation also applies to pharmaceutical companies manufacturing their own biocide for internal use. If it's not registered according to BPR, it's not valid for use as such.

Additionally we are making changes to our product labels in accordance with the Classification Labeling and Packaging Regulation (CLP), ensuring any hazards associated with the use of our products are clearly indicated in line with new global standards. We also register our products under the REACH directive[1] to ensure the highest level of safety for users and the environment.

Our products are always up to date with the latest regulatory requirements, so you can use them with absolute confidence. Are you sure other suppliers can say the same?

Our unrivalled range of alcohol & biocide sprays all feature our unique SteriShield Delivery System (SDS).

As the only fully validated trigger spray system compliant with the new MHRA guidelines[2], the SDS can further reduce the possibility of risk. Visit ecolabcc.com for more details.

TO FIND OUT HOW WE CAN HELP CONTROL CONTAMINATION IN YOUR FACILITY, PLEASE CONTACT YOUR ECOLAB CONTAMINATION CONTROL EXPERT, EMAIL US AT INFOCC@ECOLAB.COM OR CALL +44 (0)2920 854 390

CONTAMINATION CONTROL WITHOUT COMPROMISE

ECOLAB CONTAMINATION CONTROL
Brunel Way
Baglan Energy Park
Neath SA11 2GA UK
02920 854 390 (UK)
+44 2920 854 395 (Export)
www.ecolabcc.com

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

1. Registration, Evaluation, Authorization and Restriction of Chemicals
2. MHRA Guidance for MS Holders Version 1, App 2, Sec 3. 5.20

ECOLAB®
Everywhere It Matters.™