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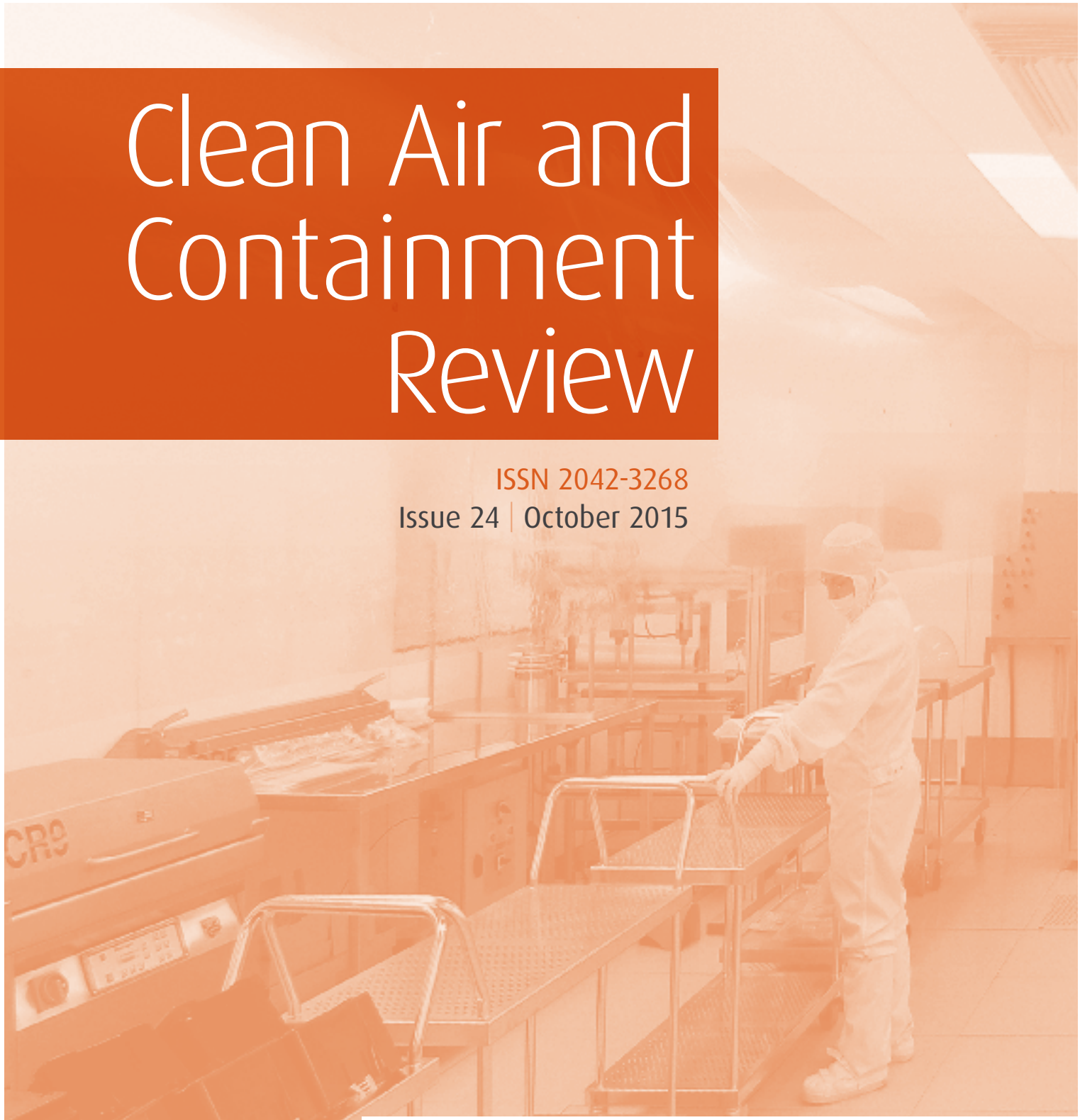

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EUROMED communications
Passfield Business Centre, Passfield
Liphook Hampshire, GU30 7SB
T: +44 (0)1428 752222
F: +44 (0)1428 752223
e: publisher@euromedcommunications.com
www.euromedcommunications.com

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.**

Editorial

I must be getting old. The things that came to mind when I set about writing this editorial are mainly flashes from the past, like the design engineer who always spent a full morning explaining his manufacturing drawings to his manufacturer instead of just mailing them. A couple of hours at the design stage might have been worthwhile, but for a final drawing??? Another design engineer, when asked to show me the test ports for testing HEPA filters upstream and downstream, thought that the provision of access points was the responsibility of the test engineer! (I might have mentioned that one before). And there was yet another design engineer who believed so strongly in evidence based practice that, when an obvious design fault in a standard product was pointed out that could have led to a serious failure, he asked if the quality management system had thrown up any customer complaints that demanded action!

Coming back to the here and now, those of us who work in this industry are living in exciting times. The final drafts of two important revised standards have been circulated to the national standards bodies following their ISO Systematic Reviews – ISO/FDIS 14644-1, Cleanrooms and associated controlled environments - Part 1 'Classification of air cleanliness by particle concentration' and ISO/FDIS 14644-2 Cleanrooms and associated controlled environments - Part 2 'Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration'. Various things have been addressed in these revisions: in Part 1 the impracticality of counting small numbers of 5µm particles and the adoption of a better statistical approach to sampling and evaluation of data, and in Part 2 emphasis on the requirements of a monitoring strategy.

There are many aspects to product contamination. In the previous issue of this journal, Bill Whyte, in his paper 'The effect of mechanical ventilation and clothing on airborne microbes and wound sepsis in hospital operating rooms' wrote "It was found that 30% [of microbe carrying particles] deposited [into the wound] directly from the air and the remainder appeared to deposit first onto patient drapes, gloves, instruments etc. before being transferred into the wound." So as well as understanding airborne concentration of particles, we also need to understand deposition of particles from the air. Well two papers in this issue cover just that. Bill Whyte in yet another learned paper writes about airborne particle deposition in cleanrooms, see page 4 and Koos Agricola writes about POCC (product orientated contamination control), see page 10. POCC might well be something that can be applied in aseptic transfers, which is what Tim Sandle writes about on page 18. Perhaps the focus in the cleanroom industry will move towards measuring what might reach the product, rather than what is in the air. Interesting!

I am aware that CACR has been light on containment and has focussed largely on clean air, but in this issue, to redress the balance, we have a fascinating article by Allan Bennett et al on the Ebola diagnostic facilities that the government commissioned for Sierra Leone from PHE, see page 24.

Biosafety is also the background to a novel by Ken Follett which I can thoroughly recommend if you enjoy a good adventure. In 'Whiteout,' published in 2004, the plot concerns the theft of the fictional deadly Mandoba-2 virus from a BSL4 laboratory. Like all Ken Follett's books, the story is well-told, the adventure is gripping and the background appears to be well researched.

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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)
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PRODUCTION
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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

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Airborne particle deposition in cleanrooms: Deposition mechanisms

W Whyte[1], K Agricola[2] and M Derks[3]

[1] School of Engineering, University of Glasgow, UK; [2] VCCN, Dutch Contamination Control Society, Leusden, the Netherlands; [3] Lighthouse Benelux BV, Boven-Leeuwen, the Netherlands.

Abstract

This article discusses the mechanisms of particle deposition onto cleanroom surfaces. The main mechanism for particles above about 0.5µm is gravitational settling. Turbulent deposition and electrostatic attraction can also occur at all particle sizes, and for particles below 0.5µm Brownian diffusion is important. Measurements of particle deposition rates (PDRs) were made of particles ≥10µm on witness plates orientated in different directions and exposed in different ventilation conditions, and it was concluded that over 80% of particles were deposited by gravitational sedimentation, and probably more than half of the remainder by turbulent deposition.

Introduction

Cleanrooms are classified by the airborne particle concentration according to the method given in ISO 14644-1:1999. However, the concentration of airborne particles does not directly measure the likely amount of surface and product contamination, and the best method is by determining the particle deposition rate (PDR) onto a surface adjacent to the product. Discussion of this will be contained in a further article.

There has been a considerable amount of research into the behaviour of particles in air and their deposition onto surfaces, as demonstrated in the publications of Hinds (1999) and Lui (2010). Investigations of particle deposition in cleanrooms have also been reported but these have been mainly concerned with deposition of small particles (≤1µm) during semiconductor manufacturing (Lui and Ann, 1987; Wu et al, 1989; Copper et al, 1990; Pui et al 1990). Also, much of the published information on particle deposition in cleanrooms has been theoretical, and the effect of turbulent deposition largely disregarded. This article reviews some of the published information relevant to surface deposition in a variety of cleanrooms, especially from larger particles (≥10µm), and reports on the results of an experimental investigation into the importance of different deposition mechanisms, including turbulent deposition.

Possible mechanisms of surface deposition of particles in cleanrooms

There are a number of mechanisms that cause airborne particles to deposit onto surfaces, although not all are important in cleanrooms. These deposition mechanisms are discussed in detail by Hinds (1999) and Liu (2010) and are: gravitational settling, turbulent deposition, electrostatic attraction, Brownian diffusion, impaction, interception, turbophoresis and thermophoresis.

The transfer of airborne particles to surfaces in cleanrooms can be considered in two stages. Airborne particles are transferred from the general area of a cleanroom to the layer of air next to a surface, and then transferred through the layer to the actual surface. As air passes over a surface, the surface drag slows the air velocity down so that it approaches zero at the surface. However, as the distance from the surface increases, the velocity increases until it reaches that of the general cleanroom area. The area next to the surface is known as the 'boundary layer' and the area outside that layer is known as the 'free flow' area. The thickness of the boundary layer in a ventilated room will be a few centimetres, but this varies. The transfer of particles from the free flow area to the boundary layer is mainly by (a) air movement and turbulence caused by mechanical ventilation, (b) gravity, and (c) Brownian diffusion. In addition, electrostatic forces will attract particles that are relatively close to a surface. When the particles reach the boundary layer they will be deposited onto the surface and retained. The particles can be deposited by one or more of the following mechanisms.

a. An important deposition mechanism is gravitational settling, where particles settle onto surfaces under the influence of gravity. This is less important with small particles, as they sediment slowly e.g. a 0.5µm spherical particle settles at about 0.0008 cm/s. However, deposition velocity increases in proportion to the square of the particle diameter, and with larger particles it is a dominant mechanism e.g. 5µm and 50µm spherical particles have a settling velocity of about 0.08 and 8 cm/s, respectively.

b. Turbulent deposition occurs when air turbulence deposits particles onto a surface and particles greater than about 1µm are deposited by their inertia. The greater the air turbulence, the more particles will deposit onto a surface.

c. Most airborne particles have electrical charges on their surface, and are attracted to oppositely-charged surfaces. This mechanism can be a dominant force in some situations, but cleanrooms are generally designed and constructed to avoid large electrostatic charges on critical surfaces, so as to minimise the attraction of particles. Electrostatic charges are additionally minimised during manufacturing by electrically grounding materials and by the use of ionizers. Electrostatic attraction can be an important deposition mechanism but only in certain circumstances.

d. Small airborne particles below about 0.5µm are bombarded by air molecules and particles and this causes a random movement in the air known as Brownian motion, and the diffusion of these particles through air allows them to collide with surfaces, where they are retained.

e. Impaction is an important mechanism in the removal of particles by air filters, and occurs when an airstream flows round surfaces, such as fibres in filter media. If the velocity is sufficiently high and the particles are of sufficient size and inertia, the particles will not move with the air stream but are thrown onto the surface, where they are retained.

f. Interception is another important mechanism in the removal of particles in air filters and occurs when airflow brings a particle very close to a surface, such as a filter media fibre, where they are attracted and retained.

g. Thermophoresis occurs when a surface is colder that the surrounding air. This deposition mechanism can be important in particles less than 0.5 µm, but the effect decreases as the particle size increases and there is little deposition of particles over 10µm. Cold surfaces are normally not found in cleanrooms and such a mechanism is unlikely to be important.

h. Turbophoresis occurs when turbulence pushes particles into areas of low turbulence, such as a boundary layer, and there is insufficient turbulence to push the particles out of the area.

Taking account of the air velocities, differential temperatures, and other prevalent conditions in cleanrooms, the conclusions that can be drawn are that the dominant deposition mechanisms in cleanrooms are likely to be a) gravitational deposition, b) turbulent deposition, and c), in certain conditions, electrostatic deposition. If particles are below 0.5µm, Brownian diffusion is also important, but owing to the larger particles studied in this article, this mechanism is not considered in further detail.

The rate of deposition of particles onto a surface is known as the particle deposition rate (PDR) and is calculated by means of Equation 1.

Equation 1

$$\text{PDR (no./dm}^2\text{/h)} = \frac{\text{number of particles deposited/dm}^2}{\text{time of deposition (hours)}}$$

The PDR is calculated as the number of particles that deposit onto a standard surface area in a standard time, and in this article the units are number/dm²/h as this gives results close to actual counts found on witness plates. The PDR can be determined for discrete (also known as differential) sizes of particles, but as contamination problems in cleanrooms are normally caused by *all* particles over a stated size, it is the cumulative size that is normally measured in cleanrooms, and discussed in this article.

Experimental equipment and methodology

The cleanroom used in these experiments was a non-UDAF type with a floor size of 6m by 4.2m i.e. a floor area of 25m². The height of the wall was 2.7m, and the room volume 67.5m³. HEPA-filtered air was normally supplied by nine fan-filter units in the ceiling, with each supplying 450m³/h. This gave a total air supply of 4050m³/h, and an air change of about 60 per hour. The cleanroom air was extracted at five grilles located on the walls at floor level. The differential pressure between the cleanroom and outside areas was maintained at 15 Pa.

To obtain a higher particle concentration than normal during the experiments, and ensure that the PDR was high enough for experiments to be completed in a reasonable time, only two of the fan/filter units were switched on. These gave a total air supply of 900m³/h and air change rate of about 13 per hour. The air outlets of the fan-filters in the ceiling did not have air diffusers, and to assist the mixing of supply and cleanroom air, the location of the two active fan-filter units was about one third of the way along the length of the cleanroom, with the sampling location about two thirds.

Experiments were also carried out when all fan-filter units were switched off, and this condition was known as the 'unventilated' condition. Unidirectional airflow conditions were also investigated but, to obtain a high particle concentration, unventilated room air was used and directed by a table fan to the sampling location in a unidirectional manner.

To obtain similar types and size distribution to airborne particles normally found in a cleanroom, the cleanroom was occupied during the experiments by three people. To achieve a suitably-high concentration of particles, the people did not wear cleanroom clothing but their ordinary indoor clothing. The exception was the person who manipulated the witness plates, who wore a full set of cleanroom clothing and gloves, but only during the manipulation. The three people mainly sat and talked, worked with their computers, and occasionally walked about the room. They sat at the end of the cleanroom where the filtered air was supplied and the table fan located.

Clean glass witness plates of 12 cm diameter (with a measuring area of 49cm²) were exposed in the cleanroom for approximately 90 minutes and, after exposure, the particles on the surface were immediately counted and sized. This was carried out automatically by means of a HE850 Particle Deposition Measurement (PDM) instrument (SAC, Netherlands), which used an image recognition method. The instrument counted the number of particles on the witness plates in the following cumulative sizes: ≥10µm; ≥25 µm; ≥40µm; ≥50µm and ≥100µm, with a definition accuracy of +/-5µm.

The area of the top surface of each particle was determined and the equivalent diameter of a spherical particle was calculated by means of the following equation:

Equation 2

$$\text{Equivalent particle diameter} = \sqrt{\frac{4A}{\pi}}$$

Where, A is the area of top surface of the particle.

The number of particles on the surface of the witness plate after exposure was counted, and the background count on the witness plate after cleaning was deducted. The PDR was then calculated as the number of particles deposited per dm² per hour.

Experimental investigations of particle deposition

An experiment was carried out in the cleanroom to ascertain the relative importance of the different particle deposition mechanisms by using witness plates orientated in different directions and in dissimilar ventilation conditions. Previous results obtained from a similar experiment carried out with microbe-carrying particles (MCPs) are also reported. Another experiment is reported in which the protective effect of one surface placed above another to reduce particle deposition was investigated.

Witness plate orientation study

Four clean witness plates were inserted into steel holders mounted on a 14 cm polycarbonate box shown in Figure 1. One witness plate was mounted horizontally on the top of the box and faced upwards, the second was on the bottom facing downwards, and the third and fourth were mounted vertically on the front and back of the box. The mounting box was suspended on metal stands and about 1m from the floor.

Three ventilation conditions were studied:

1. Unventilated cleanroom: the air supply to the cleanroom was switched off. However, the air was not completely 'still', as it was stirred when personnel moved, and the air intake and exhaust of the airborne particle counter and membrane sampler were within a metre of the witness plate holder.
2. Non-unidirectional airflow: the air change rate was set at 13 per hour.
3. Unidirectional airflow: the air in the unventilated cleanroom was blown in a unidirectional manner by a table fan at a velocity of 0.75m/s towards the box holder. This velocity was greater than normally found in unidirectional airflow but was necessary to overcome the disturbing effect of the downflow of the supply air from the two fan/filter units in the ceiling. One vertical witness plate directly faced the airflow and the other faced backwards.

The PDR of a range of particle sizes ≥10µm was determined for each ventilation condition, and this information will be given in a future article. However, shown in Figure 2 are the PDR values calculated as an average of the three ventilation conditions. Also given in Figure 2 are the PDR values for each cumulative size as a percentage of the total PDR. The latter graph allows the average size of particles (50% value) in the distribution to be ascertained. This is about 30µm, although it must be understood that this is the average value of the sizes measured above 10µm.

Table 1 shows the PDRs of particles ≥10µm obtained from the four witness plates orientated in different directions in the three ventilation conditions. Each result is the average of two tests.

It can be seen in Table 1 that substantially greater PDRs were obtained on the top plates. It can be assumed that particles on the top plates were deposited by all mechanisms, including gravity, but the other three plates had no gravitational deposition. Therefore, the proportion of non-gravitational deposition on each witness plates (other than the top ones) can be obtained by dividing a plate's PDR by the PDR on the corresponding top plate. These proportions are given in Table 1 as a percentage, and in parentheses. In the bottom row of Table 1, the average PDR and percentage of non-gravitational deposition is given for each ventilation condition. Excluding the unventilated condition, which would never be used in a cleanroom, an overall average percentage of non-gravitational deposition was also calculated. This was 18% and, therefore, the overall percentage of deposition by gravity by particles ≥10µm was 82%.

The witness plates were set up in different orientations not only to ascertain the importance of gravitational deposition but to obtain an indication of the importance of turbulent deposition. It can be seen in Table 1 that the average non-gravitational deposition in the unventilated cleanroom was 11%, with little variation caused by the orientation of the witness plates. Although the air in the unventilated cleanroom was not perfectly still, the particle deposition owing to turbulence must have been low, and any additional non-gravitational deposition found in the 13 air change/hour conditions was likely to have been caused by turbulence. Table 1 shows that the non-gravitational deposition in the non-UDAF ventilation condition was 22%, which was double that in the unventilated condition of 11%.

In UDAF conditions, the magnitude of the non-gravitation deposition was dependent on the orientation of the plate to the unidirectional airflow. When unidirectional airflow passes the cube holding the witness plates, the air flow and turbulence change. Figure 3 shows a CFD simulation of air flowing passing a cube of the same size and at the same velocity as that used during the experiments. The CFD simulation was obtained by use of ANSYS Fluent solver, assuming transient airflow

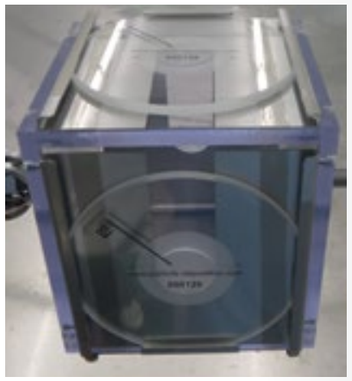


Figure 1: Box holder with witness plates as seen from the front

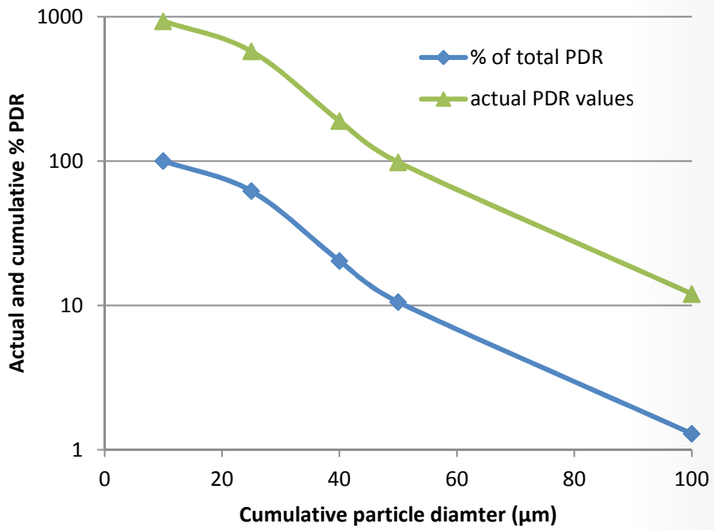


Figure 2: Distribution of actual values of the PDRs and percentages of the total PDR

Table 1: PDR (no./dm²/h) of particles ≥10 µm during different ventilation conditions

Orientation of plate	Ventilation condition		
	13 AC/h	unventilated	unidirectional
Top	612	874	1305
Bottom	168 (27%)	89 (11%)	108 (8%)
Front	106 (17%)	86 (10%)	166 (13%)
Back	132 (22%)	126 (14%)	263 (20%)
Average of non-gravitational deposition	135 (22%)	100 (11%)	179 (14%)

AC/h = air changes per hour

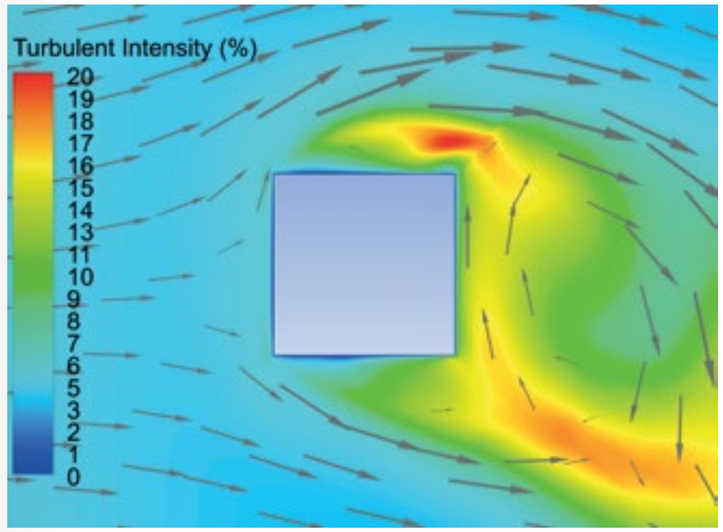


Figure 3: CFD simulation of airflow around cube

and using a SST k-ω turbulence model. The turbulent intensity of the air approaching the cube was set at 5%, and the intensity round the cube calculated and shown in Figure 3. It can be seen that the greatest turbulent intensity was in the rear of the cube, with lesser intensities at the side and front. These results can largely explain the differences in particle deposition around the cube that are given in Table 1, where it can be seen that the highest non-gravitational deposition was at the back of the cube (20%), less in the front (13%), and the least at the cube's sides (8%).

The results given in this section can be summarised, with respect to non-gravitational deposition, as follows: (a) there was a doubling of non-gravitational deposition in the 13 air changes per hour condition compared to the unventilated condition and, (b) a near-doubling in UDAF conditions in the area with the greatest turbulence at the rear of the cube. These results suggest that turbulent deposition may account for at least half of the non-gravitational deposition. The remaining deposition could also have been caused by turbulent deposition, or it could have been caused by other non-gravitational mechanisms, such as electrostatic attraction, and this possibility is now discussed.

Electrostatic deposition on the witness plates

The witness plates used in these experiments were made from glass. They were inserted into metal holders fitted with Teflon tape to avoid the glass coming into contact with the metal and being scratched. The metal holders were attached to a box made from polycarbonate plastic. Because of the electrical insulating properties of these materials, any electrostatic change on the witness plates would not be easily dissipated from the surface. Before being exposed to particle deposition, the plates were cleaned with a cleanroom wipe, which would produce an electrostatic surface charge. However, the handling of a witness plate during its mounting into the holder and the exposure to air might cause changes. Measurements were therefore made of the static field charge to ascertain the likely charge that would be present during the experiments.

The field voltage was measured by an Elektrofeldmeter EFM 022 at a distance of 20mm from the plate surface. The witness plates were wiped with a cleanroom wipe and inserted into the box holder and the field voltage measured. The charge varied, with a field voltage of between -300v and +500v.

Previous experiments on the deposition of airborne microbe-carrying particles

Similar experiments to those described in the previous section have been carried out on airborne microbe-carrying particles (MCPs) by Whyte (1986). Petri dishes of 140mm diameter containing nutrient agar were inserted into a holder and orientated in the same way as described in the previous section. They were then exposed to ventilation conditions similar to those previously described, namely, (a) still air, (b) air changes equivalent to 30 per hour, and (c) unidirectional airflow of 1.0 m/s. The Petri dishes were exposed to deposition from naturally-occurring MCPs dispersed by a person active in the room for several hours and, after incubation, the resulting microbial colonies were counted. The results were analysed in the same way as discussed in the previous section, and given in Table 2.

An important difference from the experiments with particles ≥10µm reported in the previous section was that MCPs were deposited onto nutrient agar, and not onto glass witness plates. Nutrient agar contains about 95% water, and would be expected to have no electrostatic charge. The charge was measured and the assumption shown to be correct.

The overall non-gravitational deposition on the Petri dishes was found to be 6%, i.e. 94% of the MCPs came from gravitational deposition. It can be seen in Table 2 that the average non-gravitational deposition in still

air, and in the 30 air changes per hour, was the same i.e. 5%. In the UDAF condition, the backward-facing plate had the greatest amount of deposition (15%), the forward-facing plates less (5%), and the downward-facing plates, the least (2%), showing the same trend as the experiments carried out with particles ≥10µm. These results showed that in these conditions, when electrostatic attraction is not present, the overall percentage of gravitational settling is greater (94%), and that most of the remaining deposition (6%) is likely to be accounted for by turbulent deposition. However, the size distribution of MCPs is smaller than the particles ≥10µm and this may account for a lesser amount of turbulent deposition. The sizes of the airborne MCPs were not measured, but it has been well established that MCPs in occupied and ventilated rooms are dispersed by people on skin and clothing particles. These MCPs have an average aerodynamic particle diameter of about 12 µm (Noble, Lidwell and Kingston, 1963), and Whyte et al (2012) have reported that the size distribution ranges from about <1 µm (with an occurrence of 1%) to >50 µm (with an occurrence of 5%). This MCP size distribution is smaller than of particles ≥10 µm, which are shown in Figure 2 to average about 30µm. However, the equivalent particle size as measured by the PDM instrument is based on a measurement of the surface area of the top of the particle and does not take account of the thinness of the flake-like skin particles. In addition, the size distributions of MCPs are measured as aerodynamic diameters, which will be affected by the flake-like shape of the particle and have slower deposition velocities, and therefore appear smaller than the size measured by the PDM. These two reasons will therefore account for at least part of the difference between the size distributions, although it is not clear if this explains the full difference.

Parallel witness plate study

Shown in Figure 4 is a photograph of the two metal holders used to hold two witness plates parallel to each other. The two witness plates were 10 cm apart and about 1 metre from the floor, with one plate placed exactly above the other. Tests were carried out with plates exposed for about 90 minutes in each of the three air movement conditions. In the case of unidirectional airflow, the air velocity passing between the plates was 0.5m/s.

The PDR of particles ≥10µm was measured on each plate in the three ventilation conditions and calculated as a percentage of the total PDR from both plates. These percentages, which are given in Table 3, are all similar and close to 50%.

Discussions and conclusions

The mechanisms of airborne deposition of particles onto surfaces have been reported in the scientific literature and reviewed in the introduction to this article. It was concluded that in cleanrooms the most important mechanisms were gravitational settling, turbulent deposition and, in certain circumstances, electrostatic attraction. Brownian diffusion was also important, but only for particles of a size less than about 0.5µm. Measurements of the PDR on witness plates orientated in different directions and in three air movement conditions were carried out to help to resolve the question of the relative importance of these deposition mechanisms.

The particle deposition rates (PDRs) of particles ≥10µm were measured on witness plates exposed in four different directions in a cleanroom. Most of the deposition occurred on the upward-facing plates, and gravitational deposition account for 82% of the overall deposition. The deposition mechanisms of the remaining 18% of particles deposited by non-gravitational means were likely to be turbulent deposition or electrostatic attraction, and these possibilities were investigated.

Experiments carried out into the deposition of particles ≥10µm onto witness plates orientated in different directions and airflow conditions suggested that at least half of the 18% of the non-gravitational deposition was caused by turbulent deposition. This finding was supported by previously-reported experiments carried out on microbe-carrying particles using nutrient agar plates, and therefore depositing onto surfaces free of electrostatic charge. In that situation only 6% was non-gravitational but differences in the size distribution could be a contributing cause.

The electrostatic field charge on the glass witness plates used in the particle

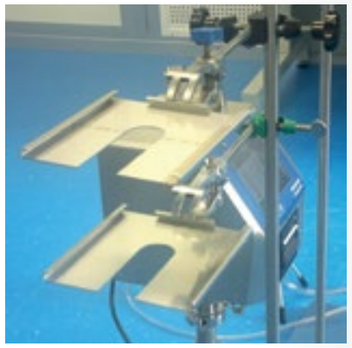


Figure 4: Two parallel witness plate holders with an airborne particle counter in the background

Table 2: Number of MCPs deposited on nutrient agar plates

Orientation of plate	Ventilation conditions		
	30AC/h	unventilated	unidirectional
Top	229	150	158
Bottom	5 (2%)	9 (6%)	3 (2%)
Front	14 (6%)	9 (6%)	8 (5%)
Back	12 (5%)	6 (4%)	24 (15%)
Average of non gravitational deposition	5%	5%	7%

Table 3: Percentage of particles ≥ 10µm deposited on the lower or upper plates

Cumulative particle size ≥10 µm	Ventilation condition					
	13 AC/h		No ventilation		Unidirectional	
	Lower	Upper	Lower	Upper	Lower	Upper
	51.9%	48.1%	49.5%	50.5%	51.3%	48.7%

experiments was measured at 20mm from the surface and found to range from -300v to +500v. This charge would attract particles and could account for some of the non-gravitational deposition, although the exact proportion was uncertain.

Experiments carried out on the deposition of particles on parallel plates gave an additional insight into particle deposition in cleanrooms. As gravitational deposition was the dominant mechanism in these experiments, it might be expected that a plate located directly above another plate, and 10cm apart, would protect the lower plate from particle deposition. This method of protection is used in cleanrooms to minimise surface contamination but it is clear that it cannot be relied upon. The result was a little surprising but can be explained. Air turbulence above the top and bottom plates should be similar and give a similar amount of turbulent deposition. Any electrostatic deposition should also be the same. Cleanroom air passing between the two plates will have a turbulent movement in which the particles will move up and down but these movements should balance each other out, and the downward gravitational sedimentation of particles should largely determine the PDR. It should, therefore, be expected that the two parallel plates will have similar PDRs. It can be anticipated that in cleanroom areas where deposition might not be thought to occur but room air can flow in and out, deposition will occur and the PDR will be similar to that found in the general cleanroom area.

Further investigations into the PDR in a cleanroom will be reported in a further article, along with the relationship between the PDR and airborne particle concentration. Methods that can be used to calculate airborne particle contamination of products, and the cleanliness class of cleanroom required for an acceptable amount of product contamination, will also be discussed.

References

1. Cooper DW, Miller RJ, Ang JJ and Peters MH (1990). Deposition of submicron aerosol particles during integrated circuit manufacturing: theory. Particulate Science and Technology, **8**, pp.209-224.
2. Hinds WC (1999). Aerosol technology: properties, behavior, and measurement of airborne particles: second edition. John Wiley and Sons, New York. ISBN0-471-19410-7.
3. ISO 14644-1: 1999. Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness. International Organization for Standardization, Geneva, Switzerland.
4. Liu D (2010). Particle deposition and enclosure studies. In 'Developments in surface contamination and cleaning-Volume Two; Particle deposition, control and removal'. Edited by Kohli, R and Mittal, KL. William Andrews Publication, Oxford, UK. ISBN-13: 978-1-4377-7830-4.
5. Lui BYH and Ahn K (1987). Particle deposition on semiconductor wafers. Aerosol Science and Technology, **6**, pp.215-224.
6. Noble WC, Lidwell OM and Kingston D (1963). The size distribution of airborne particles carrying micro-organisms. Journal of Hygiene, **61**, pp.385-391.
7. Pui DYH, Ye Y and Lui BYH (1990). Experimental study of particle deposition in semiconductor wafers. Aerosol Science and Technology, **122**, pp.795-804.
8. Whyte W (1986). Sterility assurance and models for assessing airborne particle contamination. Journal of Parenteral Science and Technology, **40**, pp188-197.
9. Whyte W, Hejab M, Whyte WM and Green G (2010). Experimental and CFD airflow studies of a cleanroom with special respect to air supply inlets. International Journal of Ventilation, **9**, pp.197-209.
10. Whyte W, Green G and Whyte WM (2012). Removal of microbe-carrying particles by high-efficiency air filters in cleanrooms. International Journal of Ventilation, **10**, pp.339-351.
11. Wu JJ, Miller RJ, Cooper DW, Flynn JF, Delson DJ and Teagle RF (1989). Deposition of submicron aerosol particles during integrated circuit manufacturing: experiments. The Journal of Environmental Sciences, January/February, pp.27-28 and 43-45.

W (Bill) Whyte, B.Sc. (microbiology), D.Sc. (mechanical engineering) and Honorary Research Fellow at Glasgow University, has been involved with cleanrooms for over 50 years. He has published over 140 reports and papers and written two major books on the subject. He is a founder and former chairman of the Scottish Society for Contamination Control and the Cleanroom Testing and Certification Board - International. He is a member of the BSI committee involved in the writing of cleanroom standards. He has extensive experience as an industrial consultant and running cleanroom courses.

Koos Agricola is an Applied Physicist and has worked in R & D at Océ Technologies, a Canon Company, since 1986. His responsibilities include contamination control in cleanrooms for the manufacture of critical parts. 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, 4, 11, 12 and 13 and CEN/TC243 Working Group 5. Koos is treasurer of the CTCB-I (Cleanroom Testing and Certification Board – International) and regularly teaches various cleanroom technology subjects.

Martin Derks is a skilled electronics engineer and has worked as calibration engineer and contamination control equipment expert for Philips Semiconductor where his role included responsibilities for cleanrooms, contamination control equipment for cleanrooms, maintenance and service. After 10 years as sales engineer for a manufacturer of particle counters, Martin became managing director for the European Headquarters of Lighthouse Worldwide Solutions. This company supplies contamination monitors for various cleanroom industries, like pharma, medical and semiconductor.

Product Oriented Contamination Control (POCC)

Koos Agricola

Summary

Product Oriented Contamination Control (POCC) is a systematic method to determine contamination causes of product failure and to determine potential critical control points. A risk assessment then helps to prioritise the critical control points and to determine the type of contamination control solution that would reduce the risk of product failure due to particle contamination during manufacturing.

Introduction

When developing a product that needs a clean environment for manufacturing it is difficult to specify the proper cleanroom facilities. In many cases products are manufactured in a cleanroom that is too high grade and sometimes in one that is too low grade. But even when specifying the correct clean environment the results can be poor because of the way the cleanroom is used. It would be easier to find the right solution if the risk at each process step (location and/or moment) is known.

Product Oriented Contamination Control (POCC) describes a method that the writer uses when analysing the clean manufacturing of new or existing products. The method is applied for technical products that are sensitive to particle contamination, but this method of analysis could be applied to other products and other contaminants.

Product

In this paper a product is an object created as a result of a process and serves a need or satisfies a want. A product is a commercially distributed object that is a tangible item, the output or result of a fabrication, manufacturing or production process or a functional part of such an object.

A product is of good quality when it has the specified or anticipated combination of tangible and intangible attributes, i.e. benefits, features, functions, uses, that the seller offers to the buyer and it serves the purpose(s) it is made for.

If the product can lose its quality by contamination during manufacturing, some kind of contamination control system has to be established during the fabrication. Therefore the types of contaminants and their quantity and dimension should be determined. Furthermore, the critical location and/or moment of time during the manufacturing process should be determined. A risk assessment will help to determine the proper contamination control actions.

Contamination Control

A vulnerable product surface can be contaminated by particles through deposition or by contact transfer. Depending on the size, type and number of particles and the product surface, particles can disturb the function of the part, and the subassembly and finally the end product.

Particle contamination can cause opens and shorts in electronics, barriers in semiconductors, distortion of optical information, blockage of an air or liquid channel or orifice, geometric misfits, malfunction of mechanical components and many other type of defects.

Particle contamination can be reduced by preventing contact with and exposure of the critical surface. The particle deposition rate should be limited to reduce the risk of deposition of critical particles on critical surface when exposed and on surfaces that will come into contact with critical product surfaces. Particle deposition is controlled by clean air and clean surfaces. Contact transfer is controlled by clean surfaces.

To create clean air a cleanroom, cleanzone or separative device is required. In such a controlled environment filtration, circulation and overpressure are applied to provide clean air. Several measures are taken to reduce the generation of particles. Everything entering the cleanroom is cleaned, the number of people in the cleanroom is limited, the people follow special entry procedures and wear cleanroom garments, and all surfaces are cleaned frequently. Unnecessary surfaces are avoided and all surfaces should be cleaned to a level that critical particles cannot enter the air and/or cannot be distributed through the room.

The cleaning of surfaces helps to keep the air sufficiently clean. Contact surfaces need special attention. They need to be cleaned more frequently.

Air cleanliness is expressed in air cleanliness classes by particle concentrations according to ISO 14644-1. Surface cleanliness is expressed in surface cleanliness classes by particle concentrations according to ISO 14644-9 (see [2]). Particle deposition can be expressed in particle deposition classes according to the VCCN guideline 9 (see [3] and [4]).

POCC method

POCC is a systematic approach to find relevant critical contamination control points, where contamination control solutions for the manufacturing of a vulnerable product should be implemented.

The POCC method should be performed by a multidisciplinary team consisting of people from different trades and professions, e.g. mechanics, electronics technicians, physicists, chemists, engineers, operators, cleaners etc..

The POCC method consists of the following 10 steps:

1. Analyse how the product functions;
2. Determine potential failures;
3. Investigate where the potential failures could occur;
4. Investigate when the failure could occur;
5. Analyse what could cause the failure;
6. Investigate possible contamination routes;
7. Quantify contamination by measurements;
8. Perform a risk analysis;
9. Determine conclusions;
10. Find solutions and implement them.

Each step is described and discussed below.

Step 1: Analyse how the product functions

To be able to determine when a product fails, first the main function(s) of the product should be described and listed. Separation into primary and secondary functions is useful in determining the severity of different types of failure. The functions of the product can be physical (mechanical, electrical, optical, thermal etc), chemical or biological in nature. It is important to investigate the functions based on the intended use of the product. This analysis will lead to a listing of specific primary and secondary functions of specific parts in the product, which will be used in the next step, Step 2.

The manufacture of a digital camera is a good example of the application of POCC. A digital camera has a combination of different functional systems (see Figure 1 and [1]) including optical, mechanical, electronic, to capture an image and image processing, to present it as a digital picture. The user interface consists of an interactive display and some switches. All these systems should function in a synchronised way. The quality of the camera is determined by the manufacturing processes of the various individual parts, the assembly of the subassemblies and the assembly of the final camera.

The primary function of a digital camera is to take sharp digital pictures. Secondary functions are the optical zoom, various digital correction methods using light and/or acceleration sensors and actuators, data processing and storage. A camera consists of many parts that can be divided into a number of functional units (see cross section in Figure 2):

Figure 1: Example of a digital single lens reflex (SLR) camera

- The lens system transfers the light image onto the image sensor
- The image sensor transfers the analogue image into a digital image,
- The electro-mechanical system provides the settings and actions required to take a picture.
- The image processor transfers the digital image into a picture that can be displayed
- The display is used to show the image of the object to be photographed, the resulting picture and certain components of the user interface.
- The electronic controller with battery processes and synchronizes the settings and the action required to make the picture.
- The mechanical housing protects all the vulnerable parts and contains the user interface components.

The optical, mechanical and sensor parts of the camera will be discussed to explain the POCC method.

Step 2: Determine potential failures

The list of primary and secondary functions from Step 1 is used to predict the type of potential failure(s) per function that can affect the functionality of the end product. One can also include failures and disturbances that were experienced during development, because these could occur again. Comparable products or competitive products can be used for inspiration. This investigation of potential failures is both theoretical, a process of reasoning, and practical, an investigation of past, present and/or created failures. Sometimes it is useful to go back to the previous Step and then to the following Step to complete the list of potential failures for this Step.

For each type of potential failure, the degree of failure or severity can be assessed. Potential failures could include:

- Not fulfilling the described function (specification),
- Fulfilling the function, but at a lower level (out of specification),
- Reduced product life,
- Appearance of the product,
- Etc.

The objective of the list of potential failures is to find solutions to reduce failure caused by contamination. It is always possible that a product doesn't fulfil its specification because of bad

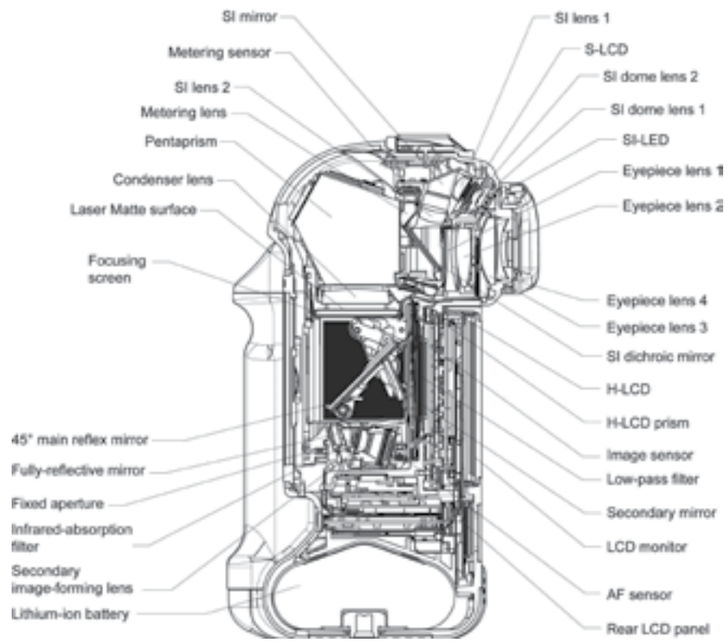


Figure 2: Cross section of digital SLR camera

quality parts that are defective for reasons other than contamination.

When looking at the camera, the main functions are:

- The lens system projects the optical image onto the sensor. Contamination can obscure or distort the image that is projected onto the sensor. Sharpness may be reduced and the number of optical defects increased if there are particles in between the lenses and/or on the lens system (see Figure 3).
- The mechanical part of the camera houses the main functional parts, including the touch screen as user interface, and the mechanical devices for focussing, setting the diaphragm, opening and closing the shutter, flipping the mirror, setting switches. Defects caused by particles could lead to failure to take pictures at all or taking pictures with the wrong settings (see Figure 4).
- The image sensor transfers the optical image into a digital image. Contamination on the sensor will disturb this transfer. Particles inside the sensor chip or its electrical connections can cause defects in the digital image (see Figure 5).

All the described parts up to the assembled camera are sensitive to particle contamination. However the manufacturing processes for the different components at the various manufacturing stages have different risks. For each failure, it should be determined where, when and how it might occur.

Step 3: Investigate where the potential failures could occur

Using the list of primary and secondary functions from Step 1 and the list of potential failures from Step 2, the following points should be considered:

- Where these functions are inside the product.
- Which parts are important to make the product work?
- Which interface(s) are important for this function?
- Where inside the product will a defect cause failure?
- At which product surfaces could contamination cause the potential failure?

Taking the digital camera again as an example:

- Contamination on a lens surface under, in or on the coating can distort the optical image,
- Contamination in a moving part of the mechanical system can disturb the internal operation,
- Contamination on the image sensor or in an interconnection between the sensor chip and the electronics can disturb the digital image.

Figure 3: Lens system of digital SLR camera

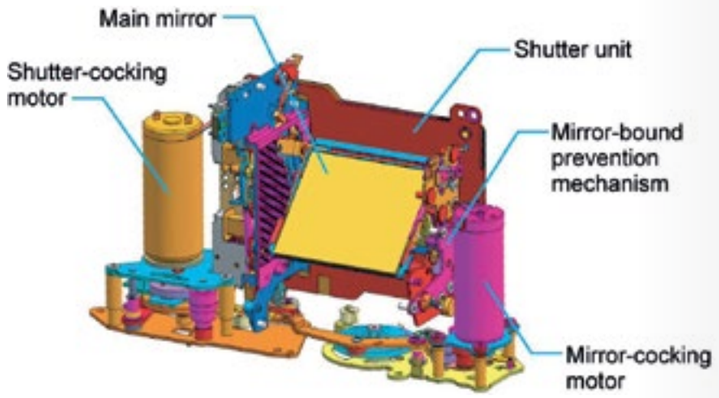


Figure 4: Mechanical system of a digital SLR camera

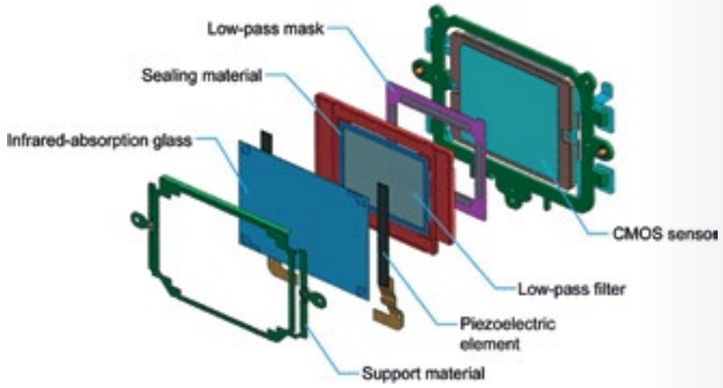


Figure 5: Light sensing device of SLR camera

Step 4: Investigate when the failure could occur

The location of the interface or surface inside the product, that can cause failure, determines when as well as where in the manufacturing process the contamination can occur. The critical surface of this part is followed in time and place through the process flow to search for potential contamination locations. This investigation can be started at the supplier and finish at final assembly or even delivery of the product. A cleaning process in the process flow could be used as a decoupling point and so used as a starting point. Look for potential causes for each potential failure.

When could contamination of a quality determining (critical) surface occur:

- When is the critical surface exposed?
- When does the critical surface make contact with another surface?

The answers should lead to:

- Process steps where the surface can become contaminated,
- Locations where the surface can become contaminated,
- Tools or packaging that make contact with the critical surface.

In the camera example some contamination locations are:

- In lens manufacturing: during polishing, before or after coating or lens assembly, during packing, during exposure after unpacking, where the tools are used to handle it, in the assembly line, after assembly, etc.
- For critical mechanical parts: exposure after unpacking or cleaning, during assembly, in contact with handling tools, etc.
- For the C-MOS wafer, only the good sensor chips are selected. Critical moments occur during the backend assembly (dicing, wire bonding and moulding), packing, transport, exposure after unpacking, in the assembly line, in contact with handling tools, etc.

Step 5: Analyse what could cause the failure

At each critical location the type of contamination that could cause the failure is investigated. What is the nature of the particle that can cause the failure? A particle can be conductive or nonconductive, charged or uncharged, organic or non-organic, transparent or opaque, compressible or not etc. What particle size will cause a defect? In what direction will this size cause the problem? If the particle is incompressible the height can disturb the geometry of two planes that are put together. On an optical surface the area of the particle on the surface can be important.

The particle size that will cause a defect is the critical particle size. Often more than one particle smaller than the critical particle size can cause a defect, for instance when a cluster or a particular distribution is formed. So then the size and location of such clusters is important. It is also useful to know which smaller particles will not affect the product function. This way a critical particle size distribution can be deduced.

Critical particle sizes can be determined by reasoning, but also practical experiences can help to find the critical values. In some cases experiments with test particles can help to find the critical values.

There will be a different result when using a theoretical and a practical approach. Mostly theoretical deduced values are smaller than those found in real failing products. The reason is that there are often compensating factors. A particle could be compressed or fall within the roughness of a surface.

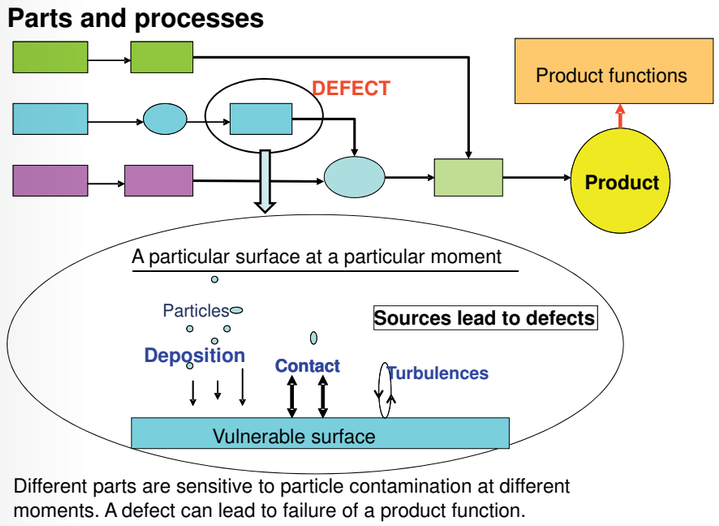


Figure 6: A particular surface at a particular moment

Step 6: Investigate possible contamination routes

When the location, size, number and characteristic of the contaminating particles is found, the possible routes of contamination should be investigated. It is useful to mark the location of potential contamination in the process flow and map this location on the production area (factory floor). Therefore a schematic process flow of the part or product should be made, for instance: unpacking, cleaning, coating, assembly, testing and packing (see Figure 6). This process flow and the locations of possible contamination can be projected onto the map of the facility.

The main routes of contamination are the transfer by contact and deposition of particles onto the vulnerable surface.

Particle transfer by contact

When the clean product surface come into contact with a less clean surface particles will be transferred onto the product. The particle transfer depends on the surface cleanliness, the contact area, the number of contacts and the nature of both surfaces. The transfer between hard surfaces is less than between flexible surfaces.

Contact transfer can also take place via intermediate surfaces (cross contamination). For instance a glove can touch a dirty surface, pick up many particles and then transfer to a product surface by contact.

Particle deposition

The behaviour of a particle depends on mass, size and shape, electrostatic charge, local air flow and local surface properties. Particles have various shapes like a sphere, potato, crystal, flake, straight or curled fibre etc. Particles in the air can be deposited onto the product surface. This depends on their deposition velocity. Small particles have a low deposition velocity and will be removed by the air circulation. Larger particles have a greater mass and can deposit. This is mostly the case with macro particles > 5 µm. Their concentration is low and difficult to measure. Particles can also possess a certain momentum, because the source was moving or the surface that carried and released the particle had a certain motion. Turbulent air movements can give particles enough momentum to deposit on a product surface even if this is vertical or a horizontal underside.

Local turbulent air flow can also cause re-entering large particles into the air which will deposit somewhere else.

The particle deposition rate (PDR) is equal to the particle deposition velocity times the concentration in the air. Both depend on the particle size (see [7], [8] and [9]).

The major factor in particle deposition is the total number of macro particles in the room or cleanroom. This is determined by the total surface area, its surface cleanliness and the sum of all the particle sources. Particles sources are people and friction points of moving parts of equipment (tools and machinery). Particle deposition increases when there is activity by people. They generate, transport and distribute particles.

The air flow in the cleanroom will remove most particles < 15 µm. Large particles will not be removed by air flow. However local unidirectional air flow can be used to move depositing particles away from the vulnerable product surface.

One should bear in mind that a unidirectional flow can also transport particles towards the vulnerable product. Turbulent air flow is unpredictable and can cause unexpected particle transport.

Particles on surfaces can only be removed by cleaning. Therefore cleaning is as important as the air treatment in a cleanroom and in some products it is even more important.

Layout

An overview of potential contamination routes can be visualised by the following steps:

- Make a process flow diagram
- Project this onto a map of the factory floor
- Mark different levels of cleanliness requirements with a colour
- Specify product / process requirements
- Specify the required surface cleanliness
- Specify the required minimal Particle Deposition Rate (PDR)
- Outline the routing of goods and people.

At each critical location more details of the contamination route can be noted, like: environmental condition, routing, exposure, handling, quality checks and regulations.

This layout can also be used to optimize the routing of material, goods, people and products. It can be used to set air cleanliness, surface cleanliness and particle deposition rate levels by using the associated classifications (see [3] and [4]) . This can be used for the design of the cleanroom and/or cleaning program.

This analysis should identify a number of locations and the measures that should be taken. The effectiveness of these measures can be established by collecting data and applying FMEA[i] to prioritise the potential defects and failures. That will be done in the next two steps.

Step 7: Quantify contamination by measurements

In an existing production it will be easy to collect relevant data. If the product is still under development it is hard to collect data. Sometimes prototype products are made in a laboratory or development environment or even in a pilot plant. Data from these processes and facilities should be used if available. If the product design is still on the drawing board there is no measurement data. If possible data should be collected from similar products and/or processes. In a laboratory or pilot plant, limited relevant data can be collected, but there is an opportunity to study the sensitivity of the product to different contamination levels. During this stage there is a good opportunity to find the optimal design, processes, process flow, facilities and working methods. In case of an existing production process the available data can only be used to improve operational quality at relevant locations and, sometimes, make small process changes.

The following measurements in cleanroom can give useful information:

- Air cleanliness (particle counting: measurement and/or monitoring data),
- Surface cleanliness (direct or indirect measurement of parts, tools, work and cleanroom surfaces),
- Particle deposition rate (manually with witness plates and microscope or with a particle deposition measurement or monitoring instrument),
- Product analysis (under which circumstances is the product OK and when not)
- Location defect in product (which function fails, where, when and why)
- Product failure analysis (what is the cause of the failure, try to find the killer particle(s))

These data will be used in the risk analysis and the search for effective solutions.

Using the final assembly of the camera as an example (see Figure 7), a fictitious

Figure 7: Final assembly of SLR camera

i. FMEA is Failure Mode and Effects Analysis, a systematic technique first developed by reliabiity engineers in the late 1950s for failure analysis.

simplified quantitative analysis of three critical surfaces during assembly is given.

The maximum allowable number of critical particles determines the upper limit of the surface cleanliness of a part or product. If the initial surface cleanliness is known or sufficiently low the upper limit of the surface cleanliness can be used to determine the upper limit of the particle deposition rate (required Particle Deposition Class).

Particle deposition monitoring can be applied to check if particle deposition rate at this location is in control. Real time particle deposition monitoring with an APMON will show the moments of higher particle deposition and associated particle sizes.

Example 1: Optical part

Assume the optical part has a vulnerable critical surface area A of 40 mm^2 or 4.10^{-5} m^2 and the critical particle size d_c is 10 µm. If no more than 1 particle per 10 parts is allowed, then the maximum number of critical particles is N_{10} =0,1 per part.

Therefore the Surface Cleanliness[ii] by Particle Concentration should be better than
$S = \log_{10} (N_{dc} .d_c /A) = \log_{10} (0,1*10/(4*10^{-5}) = 4.4$ or SCP Class 4,4.

If particle deposition is the only contamination route, the Particle Deposition Rate PDR (in particles per m^2 per hour) can be determined when the initial surface cleanliness class SPC_0 is known or sufficiently low. The PDR is the change of surface cleanliness during exposure.

Assume the initial surface cleanliness class of the optical part is SCP Class 3 and the exposure time t is 2 hours. Then the PDR should be smaller than $(10^S-10^{SCP0})/t = (10^{4,4}-10^3)/2) = (25.119-1.000)/2 = 12.060$. The required Particle Deposition Class PDC = $\log_{10}$ PDR = 4,1 or lower.

In case SCP_0 is sufficiently low then $PDR = 10^S/t = 10^{4,4}/2 = 12.560$ and PDC = 4,1.

Example 2: Mechanical part

Assume the mechanical part has a vulnerable area A of 1 cm^2, the critical particle size is 50 µm and not more than 1 particle per 5 parts is allowed. This means that the number of critical particles N_{50} = 0,2 per part. Then the Surface cleanliness should be SCP class 4 ($S = \log_{10} (0,2*50/10^{-4})$ or better.

Assume the mechanical part is cleaned to a surface cleanliness level SCP class 3,2 and is exposed for 1 hour. If deposition is the only contamination route, the PDR (in particles per m^2 per hour) should be smaller than $PDR = (10^4-10^{3,2})/1,5 = (10.000-1.585)/1= 8.415$ or PDC 3,9.

Example 3: Image sensor part

An image sensor part is cleaned to a surface cleanliness level SCP class 3. Assume the vulnerable area A is 10 mm^2 and this is exposed for 0,5 hour. The critical particle size d_c > 1 µm and not more than 1 particle per 20 parts is allowed. Then the number of accepted critical particles per part N_1 =0,05 and the Surface Cleanliness by Particle concentration Class should be better than SCP class 3,7 ($S = \log_{10}(0,05*1/(1*10^{-5})$.

If deposition is the only contamination route the PDR per m^2 per hour should be smaller than $PDR = (10^{3,7}-10^3)/0,5 = (5.000-1.000)/0,5 = 8.000$ or PDC 3,9.

In addition to particle deposition, contact transfer is a mechanism that could be quantified. One can measure the surface cleanliness of the contact surfaces and take an average transfer efficiency of 10 % of the particles from the less clean surface. So if the critical particle size is 20 µm and the surface cleanliness of a tool with contact area of 5 cm^2 has a surface cleanliness of SCP class 5 then 10 % of $10^S.A/d_c$ can be transferred. So $N_{dc} = 0,1*10^5*5.10^{-4}/20 = 0,25$ per contact or one critical particle per 4 contacts.

The number of particles transferred to the critical surface by contact should be added to the particles deposited during exposure at a measured or required particle deposition rate.

Step 8: Perform a risk analysis

Steps 1 to 7 lead to a list of potential failures, possible causes and potential critical locations. The critical locations could be treated as critical control points according to the HACCP (Hazard Analysis and Critical Control Point) approach. One has to set limits on relevant parameters at relevant locations and then monitor them. These measures will be more effective at some points than at others. A risk analysis with the use of available data can help to prioritise the potential failures and to develop effective solutions. A risk analysis can also be done if not enough data are available. Often one knows more than one realizes. If it is not known which particle size can cause a problem, it is possible to estimate which one will and which one won't. If the exact vulnerable surface is not known, then at least a maximum size can be stated.

A good method to use for the risk analysis is Failure Mode and Effects Analysis (FMEA) since this method generates a Risk Priority Number RPN. Application of this engineering technique to contamination control problems in pharmaceutical manufacturing is described in [10]. From the first three Steps in the POCC procedure the **Severity S** of a potential failure is already known and qualified by the POCC team. In Steps 4 to 7 the location, contamination and route of contamination are found and where possible quantified. This information can be used to quantify the **Occurrence O** (chance of contamination). If there is no hard data the team can try to reason and decide whether the chance of occurrence is high or low.

In FMEA it is assumed that when a part is defective or does not fulfil the specification, and this can be measured or detected, the part can be rejected and replaced by a good part. In that case the **Detectability D** should also be included in the determination of the risk number.

The **Risk Priority Number RPN = S*O*D**.

The values of S, O and D are determined by all the members of the FMEA team. A quantitative number is given to scale the Severity, Occurrence and Detectability. Depending on the extent of available information one can choose a scale of 1 to 5 or 1 to 10 for the Severity and/or Occurrence. A scale of 1 to 3 or 1 to 5 can be used to quantify the Detectability with the lowest value representing the highest Detectability. If, in all the potential failures that are compared, Detectability is not included, this can be set to 1. The result of the FMEA

ii. Surface Cleanliness by Particle concentration SCP class S: $N_d/A = 10^S/d$ per m^2; The Particle Deposition Rate PDR is also the change of surface cleanliness during exposure; $PDR = (N_d-N_{d0})*d/(A*t) = 10^{PDC}$; PDC is Particle Deposition Class = $\log_{10}$ PDR (see [4]. [5] or [9]).

is a list of potential failures with an RPN. When looking for solutions one can start with the risk with the highest RPN.

As an example the coating of a lens is taken. The critical area is 12 cm^2. If there is one opaque particle larger than or equal to (≥) 50 µm or 3 particles ≥ 20 µm the part is rejected. So the Severity S = 5 (scale 1-5).

To determine the Occurrence O, in this example only particle deposition is taken into account. Assume the exposure time t is 2 hours and the Particle Deposition Class PDC = 4,3, then the PDR is $10^{4,3}$ = 20.000 per m^2 per hour. The chance of deposition of particles ≥ 50 µm is $PDR*t*A/d_c = 20.000*2*12*10^{-4}/50 = 1$ so the Occurrence will be high and O = 5.

The chance of deposition of particles ≥ 20 µm is then: $20.000*2*12*10^{-4}/20$ = 2,5. Since 3 particles are acceptable the Occurrence can be set at a lesser value O = 3.

Since particles > 50 µm can be detected very well, then D = 1 (scale 1-3), but particles > 20 µm are more difficult but not impossible so D =2.

If there are more than 10 particles > 10 µm the quality is not so good. The Severity is medium S = 3. These smaller particles cannot be detected, therefore D = 3. The Occurrence or the chance of deposition of particles ≥ 10 µm is $20.000*2*12*10^{-4}/10 = 5$ and can be set at O = 2.

With these qualifications the Risk Priority Number for the different particle sizes can be calculated:

- $RPN_{50} = S*O*D = 5*5*1 = 25$;
- $RPN_{20} = 5*3*2 = 30$;
- $RPN_{10} = 3*2*3 = 18$.

So the priority order is RPN_{20} - RPN_{50} - RPN_{10}.

Step 9: Determine conclusions

The result of the FMEA is a list of potential failures with an RPN. Based on this list plans can be made to reduce the potential failures with a high RPN. The reason the RPN is high can indicate a direction for the optimal solution. If Severity is high, maybe the product design could be changed. If Occurrence is high the contamination route should be reduced (less exposure, less dirty contact, lower particle deposition, clean airflow, separation between operator and product etc.). If the Detectability is high a measurement method could be introduced and/or product or process design should be changed to make detection possible.

When making the list, potential failures and prioritisation of potential actions may be included. In many cases reduction of vulnerability, chance of contamination, exposure, particle deposition or particle transfer will decrease the RPN. Also improvement of detectability can help in case action based on the detected values can be taken.

In the example of the lens coating RPN_{20} should be reduced first. To reduce RPN_{20} the Detectability could be improved, then the use of contaminated products can be avoided. The Occurrence can be reduced by decreasing the exposure time and/or particle deposition rate. This will impact the Occurrence of the other critical particle sizes. The Severity could be influenced by reducing the sensitivity of image correction to the defect.

Step 10: Find solutions and implement them

The priority list with potential failures and risk priority number is used to create solutions. When searching for solutions the goal is to reduce S, O and/or D. The product could be redesigned to be less vulnerable to decrease the severity. The major contribution is often reduction of the chance of particle contamination occurring. Factors are exposure, contacts, air and surface cleanliness. There are many solutions the POCC team should be able to think off. A contamination control expert could help to make suggestions for potential solutions.

The type of solution that can be implemented depends on the degree of freedom to change and the costs and benefits. The degree of freedom depends on the product, process, cleanroom and regulations. When one of these aspects can be changed, an optimal solution can be implemented.

Processes, equipment, process sequence, facilities and product design can be changed or optimised.

When looking for solution the vulnerability of the product could be reduced by changing the design of the product and/or manufacturing process sequence. The exposure could be reduced by changing the routing or improvement of the exposure environment. The operational quality and/or classification of a cleanzone or cleanroom could be improved. A separative device could be applied. A critical process could be executed by a (simple) robot to avoid contamination by people. Tooling aids can be made or improved.

In case of an existing production process in an existing cleanroom and process facility, the operating quality of the cleanroom can be improved. The operating quality or particle deposition class is determined by the way the cleanroom is used and depends on the cleaning program, the number of people, their discipline, the cleanliness of the goods brought into the cleanroom and various other operational aspects that can be described in Standard Operating Procedures.

Conclusion

In this paper the POCC method is described briefly. The POCC method can be applied to specific parts of a manufacturing process. A digital camera has been used as an example to understand the relationship between product functionality, failure and potential causes. However a camera is too complicated a product to demonstrate all the steps.

Risk analysis can be applied to look for the most effective contamination control measures. Particle deposition measurements are useful to determine that the contamination and to demonstrate the production process is under control.

The POCC method stimulates communication between different disciplines and professions. It makes it clear where and which type of contamination control measures are required.

References

All figures and picture are taken from [1] with the kind permission of Canon.

1. "Canon EOS-1D Mark IV", Jon Faur, www.fdtimes.com, 10/19/2009 and https://www.youtube.com/watch?v=Lkv0Sc2MxP8.
2. "Strategisch strijden tegen stofdeeltjes", Koos Agricola en Cora Oostendorp, VCCN 2009, *www.vccn.nl*.
3. ISO 14644-1, 4, 5 and 9: Cleanrooms and associated controlled environments: 1: Classification of air cleanliness and 9: Surface cleanliness of surface cleanliness by particle concentration.
4. VCCN Guideline 9, Particle Deposition (2014), *www.vccn.nl*.
5. "Proposal for the classification of particle deposition", Koos Agricola, *ICCCS symposium 2014, Seoul*.
6. "Airborne particle deposition in cleanrooms: deposition mechanisms", W. Whyte, K. Agricola and M. Derks, *to be published in Clean Air and Containment Review 24*.
7. "Quality Assurance of Product Cleanliness". Koos Agricola (2009); *Cleanrooms Europe 2009, Stuttgart*.
8. "Determination of operational quality of cleanroom by particle deposition monitoring". K. Agricola; *ICCCS conference 2012, Zürich*.
9. "Practical experiences in particle deposition monitoring", K. Agricola, *ICCCS symposium 2014 in Seoul and rewritten for Clean Air and Containment Review 21*.
10. Risk management and risk assessment for pharmaceutical manufacturing, Tim Sandle, Microbiological Solutions 2013, *www.pharmamicroresources.com*.

There is a biographical note for Koos Agricola on page 9.

Importance of risk assessment for aseptic transfer in pharmaceutical compounding

Tim Sandle

Abstract

Aseptic transfer is a critical contamination control issue, carried out over a series of stages. If any stage is performed in an uncontrolled manner then microbial contamination of a product can occur. Contamination risks can arise from a number of sources, including incoming materials, air and personnel. To address these risks appropriate controls include controlled environments, personnel gowning and behaviour, and the use of disinfectants. This article considers the key risks and risk mitigation strategies using a case study of aseptic transfer within a pharmacy unit for the purpose of preparation or compounding of a medicinal drug product.

Introduction

Aseptic transfer applies to various aspects of pharmaceuticals and healthcare, covering everything from the inoculation of agar plates in a microbiology laboratory to the transfer of items into a cleanroom as part of sterile products manufacturing or pharmaceutical compounding. Across this range of applications the overriding requirement is asepsis, to either render the material free of microbial contamination (through bioburden reduction) or to prevent adventitious contamination, from operators or the environment, affecting the quality of the product or materials.

This article focuses on the best practices for aseptic transfer within a pharmaceutical facility or pharmacy specialising in drug compounding. Compounding is a process whereby the facility combines, mixes, or alters ingredients of a drug to create a medication suitable for the needs of patients. This can range from the larger scale production of intravenous bags of nutrient fluid for babies to the preparation of individual cytotoxic drugs.

With these activities microbial contamination in the environment can result in product adulteration and, in turn, in a potential infection of the patient. In order to minimise the possibility of cross-contamination, a risk-centric approach is required. This is a topical subject in light of several high profile product contamination events which have occurred worldwide (some with serious consequences for patients)[i]. These cases demonstrate that microbial contamination risks remain an ever present concern. The article considers where these risks arise from and the types of risk mitigation step that can be implemented. Mitigation steps require the use of strict biocontamination control measures. The article also emphasises the importance of environmental monitoring.

Contamination risks

Microbial contamination risks can arise from the environment (with microorganisms on surfaces or carried on particles in the air-stream); from personnel; or from the product. Environmental contamination can arise from material containers and packaging or from the cleanrooms where processing takes place. These areas are discussed below.

Environmental risks

Airborne environmental risks are controlled through cleanrooms and clean zones. Cleanrooms will be of different grades, with in-coming materials typically held in an EU GMP Grade D area. Here outer packaging should be removed. Items are then transferred into Grade C cleanrooms and then into Grade B. In the Grade B area assembly will occur, prior to transfer of kits and products into a Grade A zone. The Grade A zone is typically an isolator. Within the Grade A zone dispensing, along with any required final formulation, will take place.

Cleanrooms should be designed with the protection of product quality in mind. Control is achieved through the use of HEPA (high efficiency particulate air) filters; pressure differentials between rooms of different grades; and an appropriate airflow system. Turbulent, or non-unidirectional airflow, dilutes airborne contaminants down to an acceptable level and keeps smaller particles in suspension as the air is removed[ii]. This type of airflow is used in the lower grade areas. Unidirectional airflow provides a supply of clean air to the critical work zone and any contamination generated is removed in the airstream. This type of airflow is used in the highest grade areas such as Grade A. The use of an isolator creates an additional barrier between personnel and the product being handled.

With the cascade of increasing cleanroom standards described, not only should the concentration of airborne particulates reduce but there should also be a reduction in microbial numbers and in the diversity of the microbial species. Spore forming organisms, for example, will more likely be present in Grade D areas, where packaging is removed, than in Grade C or B environments where outer packaging is not present. Therefore, the careful removal of packaging layers and effective disinfection are important[iii]. In the higher graded areas the most common types of contamination are from skin bacteria, such as Staphylococci and Micrococci[iv]. Nevertheless, the risk of microorganisms that are more challenging to kill with standard disinfectants remains, and thus the assessment of risks should extend to the possibility of endospore forming bacteria being present (see below).

With the cleanroom cascade and process flow (Figure 1), the objective is to reduce bioburden by disinfection as the different layers of wrapping are removed. Care should also be taken to avoid recontamination from personnel practices, inadequate cleaning and disinfection; or cleanroom operation environmental failures. The most important stage of aseptic transfer is into and out of the Grade A zone. For optimal contamination control, the Grade A zone will be an isolator.

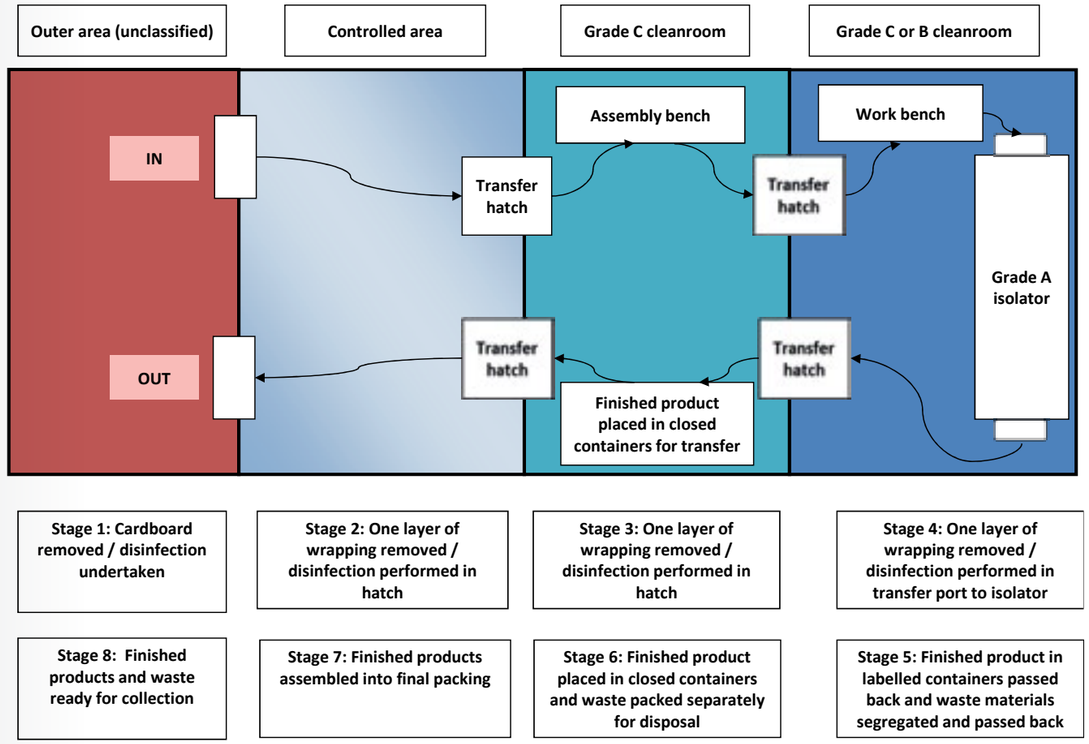


Figure 1: Simplified diagram of a typical aseptic transfer process for aseptic compounding

Personnel risks

Modern cleanrooms are generally well-designed; the main risk variable is people. People are the most significant source of contamination during the aseptic processing of medicines. This can be due to errors with gowning and use of gloves and masks; general behaviours; and a tendency to touch one object or surface and then another. Nonetheless, personnel risks can be reduced through[v]:

- Good quality gowns and standardised gowning techniques;
- The use of gloves, masks and head covers;
- Appropriate training;
- Controlled behaviours;
- Regular glove sanitisation (70% isopropyl alcohol is the most effective);
- Reducing direct personnel intrusions into the processing zone.

Attention should also be given to ergonomics, particularly when using an isolator. The better the design, the more comfortable the operator is, and the less likely the operator is to make errors[vi].

Product risks

Contamination risks can arise from the product itself and its associated components. This can happen if the product is not sterile due to issues with sterilising grade filtration or with an intended terminal sterilisation cycle, or materials are not sterile, or where packing used for components has been compromised. These factors can be addressed through identity checks on materials and careful handling; the latter leads into risk mitigation through practising biocontamination control.

Biocontamination control

Although the risks described above are faced by pharmaceutical processes during each work session, experience suggests that, in most cases, the risk of product contamination and, subsequently, patient infection is low. When incidents occur these are normally through a breakdown of a system (such as a HEPA filter becoming damaged) or a failure to follow an established system (such as a failure to disinfect at the appropriate stage). To further negate these risks, there are practices that can be undertaken with strengthen risk control. These are examined next.

Contamination transfer

Arguably transfer is the weakest link in the biocontamination process. To mitigate the risk, disinfection is necessary at each transfer stage (the stages are represented in Figure 1, above). Items transferred include medicinal products, active ingredients, needles, Luer connectors, and so on.

At the start of the process, such items should be held in the lowest grade of cleanroom, within protective packaging. The storage of paper and cardboard in the preparation room should also be avoided (any outer packaging that has been exposed to outside air should ideally not be taken into a cleanroom). Items should be removed from storage boxes and spayed and wiped with disinfectant on transfer into the cleanroom. Items can then be taken through the necessary stages, via transfer hatches, to reach the Grade A workzone. Some transfer hatches are fitted with localised airflow. Items at these stages should have an outer wrapper removed and then be disinfected. Items should be double or triple wrapped. An example of a triple wrapped item is shown in Figure 2.

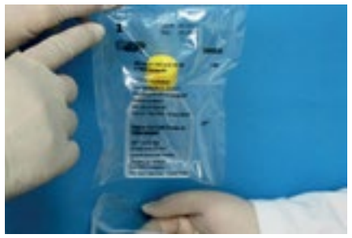


Figure 2: A triple wrapped item (outer layer removed)

The wiping process, whether by 'wipe-and-spray' or using pre-saturated wipes, is preferable to simply 'spraying.' Studies suggest greater microbial kill is obtained through the act of wiping[vii]. One problem is that wiping is often inconsistent, especially where removing bacterial spores is a concern. Here the ability to remove spores is effected by the spore surface structure and the weave of the wipe, as well as the technique of the person carrying out the task (it is common for wiping techniques to be poorly defined). It is important that the number of wiping motions and the requirement to use a different side of the wipe for each wiping motion is practiced (this is commonly either the three-fold or four-fold technique).

An example of a wiping technique is:

- Wipe the surface to be sampled using a saturated wipe.
- Hold the fingertips together and apply a gentle but firm pressure.
- Use an overlapping 'S' pattern to cover the entire surface with horizontal strokes (see Figure 3).
- Fold the exposed side of the wipe in and wipe the same area again using vertical 'S'-strokes (see Figure 4).
- Fold the exposed side of the wipe in once more and wipe the same area using diagonal 'S'-strokes (see Figure 5).

In addition, the contact time for the disinfectant needs to be observed. With wiping of product vials, particular attention should be paid to the rubber septa of vials and the break lines of ampoules. Over-seals should therefore be removed at the first sanitisation stage.

In selecting between pre-impregnated sterile wipes and wipes onto which a disinfectant is sprayed, pre-saturated wipes add greater consistency since spraying biocide into dry wipes may leave some portions of the wipe with limited biocide. Pre-saturated wipes are prepared in a manner where the disinfectant is uniformly applied across the surface. Pre-saturated wipes should be assessed to show that they are low particle shedding.

Furthermore, some transfer hatches are "locked" for a set time period. This is both to allow for adequate "clean air" changes to occur within the hatch before the inner doors are opened; and to ensure that a suitable contact time, between the item and the disinfectant, is achieved[viii]. Materials should be dry before proceeding to the next stage.

The closer the process is to the EU GMP Grade A zone, the more important it is that the disinfectant used is a sporicide. Some would take a counter view and argue that a sporicide should be used at the early stage, where the bioburden is theoretically greater. This issue can be examined through profiling and characterisation of the microorganisms recovered. The use of a sporicide, at the appropriate stage, is important, given the risk of bacterial endospores which might be carried through from outer packaging or result from an environmental control failure. Alcohol based disinfectants, which have traditionally been used, are not sporicidal.

Periodic verification of sanitisation effectiveness should be carried out at intervals based on a risk assessment. This will require an assessment of the typical bioburden recovered from materials transferred through each stage. For product vials, rolling a representative vial across an agar plate or immersing a vial into microbiological broth culture medium are common bioburden assessment methods. Such methods are more effective than swabbing.

Barrier technology

The use of isolators during final processing and formulation provides an effective means for ensuring biocontamination control. This is because such devices provide a physical barrier between the operator and the product. As an additional measure, isolators can be decontaminated, either through a validated bio-decontamination process or through periodic spraying with a sporicidal disinfectant. The greatest advantages can be realised through hydrogen peroxide vapour rapid gassing systems. Gassing systems are expected to demonstrate a reproducible six log reduction in *Geobacillus stearothermophilis* spores. However, such technology is often unaffordable in the hospital pharmacy sector and manual disinfection is commonplace. It is important with manual disinfection that the disinfectant is suitable and has been qualified through efficacy studies according to a recognised standard.

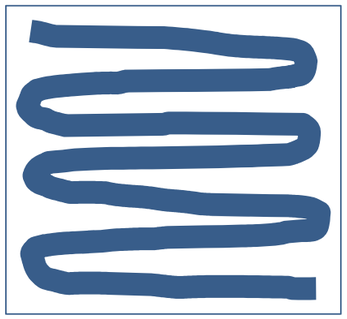


Figure 3: Horizontal 'S' shaped wiping technique

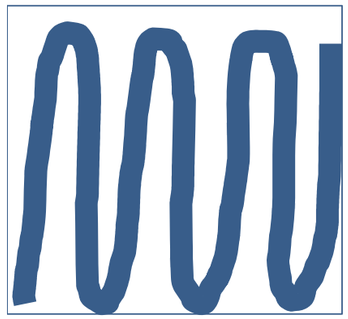


Figure 4: Vertical 'S' shaped wiping technique)

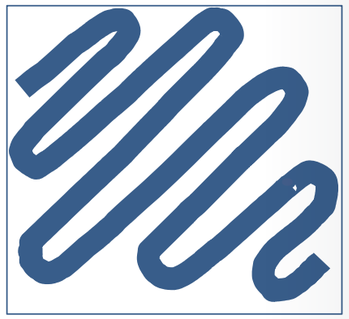


Figure 5: Diagonal 'S' shaped wiping technique)

Aseptic manipulations

When carrying out aseptic operations and manipulations of product, any product exposure must be carried out under localised Grade A airflow protection and the time of exposure kept to a minimum. Good design of the workspace is important. The airflow above and around the product containers must be unobstructed.

With manipulations, personnel must adopt a disciplined 'no-touch' technique to avoid contact with any surface which will be in contact with the product. This is especially important for the ends of transfer tubing, needle tips and vial closures.

The risk of contamination ingress can be assessed through risk based studies, such as the use of Whyte and Eaton's contamination transfer equation,[ix] for which the simplified version reads:

Number of microorganisms deposited into a product:

Deposition rate of microbe carrying particles (no/cm²) x Area of product exposed (cm²) x Time exposure (seconds)

The deposition rate of microbial carrying particles can be estimated through settle plate exposure, provided the plates are positioned in suitable locations and exposed for the duration of the activity.

Closed system

In traditional aseptic processes, drugs are compounded using syringes and needles (into or out or vials or other syringes). This process, while necessary, is cumbersome and carries the risk of cross-contamination. More advanced systems are available (as discussed below). Where syringe-and-ampoule transfer remains the most appropriate, only single entry to ampoules must be practiced.

The greater use of closed systems and single-use sterile disposable technology, introduced in the last decade, has helped to lower contamination risks. Examples include sterile bags and aseptic connectors. Many of these are made of plastics that are subject to gamma radiation for sterilisation[x]. In combination, bag technology and interlocking connectors allow the transfer of fluid from a reagent into a medical device or for the mixing of two materials together (as with pharmaceutical drug compounding.)

More advanced transfer systems use docking ports, which allow the transfer of fluid into a cleanroom or an isolator. Bags can be pre-filled with vials and closures and subject to a sterilisation process. Such bags can then be passed ino the Grade A environment.

An important consideration with plastic disposable systems is whether there is a risk of leachables or extractables[xi]. This can occur when a fluid or powder comes into contact with the plastic. The risk is dependent upon time, temperature and pH and any study run to assess this must take into account the maximum hold time.

Other control measures

Other measures that can be taken to minimise contamination risks include:

- Controlled entry of personnel into the processing area;
- Maintaining the integrity of the aseptic processing area, and monitoring the work area (such as an isolator) and its environment;
- Disciplined handling and preparation of starting materials, especially disinfection before transfer into the critical zone (in line with the section above);
- Correct loading and positioning of materials within the critical zone of the controlled workspace;
- Practicing good aseptic processing techniques during manipulation of the product, including 'no-touch' of critical surfaces;
- Segregation and flow of materials to ensure no inadvertent cross-contamination or substitution of products;
- Removal of product and waste materials from the processing area;
- Effective post-activity cleaning and disinfection.

In addition completing all required documentation helps to verify that each control measure is in place and that the necessary steps have been completed. Documentation is a requirement of Good Manufacturing Practice (GMP).

Environmental monitoring

Where risks cannot be wholly eliminated, then environmental monitoring should take place. Importantly, environmental monitoring is not a substitute for poor control. Environmental monitoring should be conducted once controls have been reviewed and risk assessed; thus the purpose of monitoring is to verify the suitability of controls and to assess how well control is being maintained over time.

Environmental monitoring is very much bound-up with risk assessment and risk methodologies should inform about monitoring locations. Sites for monitoring should be orientated towards points of greatest product contamination risk, such as fingers of operators in close proximity to the product (for finger dabs). Other monitoring sites should be chosen for the assessment of cleaning and disinfection efficacy.

In terms of aseptic operations, finger dabs taken by operators at the end of the activity provide important information as to the risk of contamination transfer. A key metric is the incident rate, more so than the level of counts obtained. In a well controlled facility the incident rate should be below 1 percent. A rate above 5 percent would suggest operator activities are potentially out of control.

Other important samples are air samples, especially settle plates which can provide information about contamination rate transfer (in relation to the formula presented earlier) and post-activity contact plates, which can give an indication of whether the typical bioburden on the in-coming materials has been affected by levels of environmental contamination outside of the norm[xii].

With environmental monitoring, examining data for trends provides useful information about the state of control. Data can be analysed for total counts, incident rate and the types of the microorganisms recovered.

Conclusion

This article has outlined the process of aseptic transfer within a typical pharmaceutical compounding or hospital pharmacy setting. The article has presented the main risks and risk stages and has gone on to show how these primary risks can be mitigated. The most important of these mitigation steps is with the use of disinfectants. Here, at the appropriate stages, a sporicidal disinfectant should be used and its application undertaken with a defined

wiping technique. The article ended with a brief consideration of environmental monitoring. The review of trends drawn from the monitoring programme is an important activity and it can inform about a potential out-of-control situation arising.

References

i. Outterson, K. Regulating Compounding Pharmacies after NECC. N Engl J Med, 2012, Vol. 367, pp. 1969-1972.

ii. Whyte, W., Green, G. and Whyte, M. Removal of Microbe-Carrying Particles by High Efficiency Air Filters in Cleanrooms. International Journal of Ventilation, 2012, 10 (4), pp. 339-351.

iii. Payne, D. N. Microbial ecology of the production process. In Denyer, S.O. and Baird, R.M. (Eds.) Guide to microbiological control in pharmaceutics. London : Ellis Horwood, 1990, pp. 53-67.

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

v. Sandle, T. Keeping Hands and Surfaces Clean. Arab Medical Hygiene, Issue 3, 2011, pp. 11-17.

vi. Taxis K and Barber N. Ethnographic study of incidence and severity of intravenous drug errors. British Medical Journal, 2003, Vol. 326, p. 684.

vii. Mehmi, M., Marshall, L. J., Lambert, P.A. et al. Evaluation of disinfecting procedures for aseptic transfer in hospital pharmacy departments. PDA journal of pharmaceutical science and technology, 2009, 63 (2), pp. 123-138.

viii. Hiom, S.J. Validation of disinfection techniques in hospital aseptic dispensing units. The Pharmaceutical Journal, 2000, Vol. 265, pp. 277-278.

ix. Whyte, W. and Eaton, T. Microbial risk assessment in pharmaceutical cleanrooms. European Journal of Parenteral and Pharmaceutical Sciences, 2004, 9 (1), pp. 16-23.

x. Sandle, T. and Saghee, M. R. Some considerations for the implementation of disposable technology and single-use systems in biopharmaceuticals. Journal of Commercial Biotechnology, 2011, 17 (4), pp. 319-329.

xi. Sandle, T. Trends in healthcare cleanroom practice: single-use sterile disposable technology. Clean Air and Containment Review, 2013, Issue 16, pp. 18-20.

xii. Sandle, T. Contamination Control Risk Assessment. In Masden, R.E. and Moldenhauer, J. (Eds.) Contamination Control in Healthcare Product Manufacturing. River Grove : DHI / PDA, 2013, Vol. 1, pp. 423-427.

Tim Sandle, PhD, CBiol, MSBiol is Head of Microbiology at the UK Bio Products Laboratory overseeing microbiological contamination control policy and investigation and developing programmes for environmental monitoring, cleanroom classification and batch review. In addition, Tim sits on LBI/30, the BSI Cleanrooms Committee, and the Pharmig committee. He also runs a blog: Pharmaceutical Microbiology.

Containment and Ebola in an outbreak setting

Allan Bennett, Simon Parks and Tom Pottage

Biosafety, Public Health England, Porton Down

Abstract

This article describes the diagnostic laboratories commissioned by PHE in Sierra Leone to support Ebola treatment Centres. Specialised isolators were designed, assembled and tested in the UK before being dismantled and shipped to site for reassembly. The isolators were designed and constructed based on the experience of HPE Porton in containment.

Introduction

Ebola virus is a risk group 4 virus. In the United Kingdom, research carried out on this virus is carried out only in BSL4 containment laboratories. These facilities rely on the highest level of containment including negative pressurisation, HEPA filtration, waste treatment and use of primary containment. These facilities are complex, expensive and take many years of planning, design, construction and commissioning. In September 2015 PHE was tasked by the British Government to provide diagnostic laboratory capability for the three Ebola treatment units to be constructed in Sierra Leone attached to Ebola treatment centres. The option of transplanting BSL4 containment practices from the UK to Africa was impractical due to the required speed of the deployment, the limited facility resources in an outbreak situation and its purely diagnostic function.

Ebola diagnostics

The laboratories to be deployed in Sierra Leone were intended to carry out diagnostic procedures to allow rapid diagnosis of patients with Ebola so treatment could be started, and the identification of those negative for the virus to allow them to be quickly separated from the infected cohort to avoid any cross infections.

Ebola disease is diagnosed using polymerase chain reaction (PCR) assays. RNA is extracted from the virus in a step that should inactivate the virus by lysis before being amplified. Therefore, the only containment required is surrounding sample reception, aliquoting and nucleic acid extraction. In recent deployments this has been undertaken within flexible film isolators with purification and concentration of the RNA occurring outside of the isolator.

European Mobile Laboratory

In the early days of the Ebola outbreak the European Mobile Laboratory (EML) was deployed in Gueckedou in Guinea (http://www.emlab.eu/). The EML is a consortium of European Laboratories, including PHE, funded by the European Commission and led by the Bernard Nocht Institute for Tropical Medicine, Hamburg. The concept of the EML is to have the components for the laboratory stored in boxes suitable for air transport and cross country travel in 4X4 vehicles which could quickly be deployed to rural Africa. Containment for sample handling, virus inactivation and nucleic acid extraction is provided by a collapsible flexible film isolator; samples could then be decontaminated and removed from the isolator and further processing and RNA concentration would occur on the bench. Negative pressure is provided by the use of a battery powered respirator fan. Filtration is provided by two canister type filters. Inlet filters were also used to stop gross contamination from entering the glove box. Decontamination was carried out using high concentration liquid sodium hypochlorite.

PHE deployment Sierra Leone

The design principles behind the EML are centred on rapid deployment, with an expectation of minimal supporting infrastructure with a philosophy of get in fast and get working fast. This approach has been very effective for the EML, but as the extent of the Ebola outbreak became clear the need for a more extensive additional deployment was identified. The UK government therefore approved the construction of three treatment centres in Sierra Leone. These were located in Kerrytown, Port Loko and Makeni, each treatment centre was to have an adjacent laboratory, operated by PHE to provide diagnostic testing and blood chemistry analysis.

Specialised isolators were required for both of these activities and the small systems used by the EML did not allow the sample throughput required to be achieved. The infrastructure in Sierra Leone was of a higher standard than that experienced by the EML allowing for a more flexible approach. Equipment was flown out on a combination of military and chartered aircraft and the treatment centres were situated such that road transportation was feasible for larger vehicles. This allowed for the delivery of larger and more sophisticated isolators for these laboratories

Design of isolators

Manufacturers were contacted to find out whether they were capable of supplying isolators to a tight schedule. Those who were positive were invited to meet with both containment specialists and scientists with experience of field diagnostics mainly from deployment with the EML. A design of isolator was developed to meet safety, ergonomic and practical requirements based on the standard transfer isolators used within PHE Porton facilities. This process was informed by the previous experience of PHE Porton and the equipment currently installed within our high containment facilities. Using a supplier with a proven track record allowed a high level of confidence in the resilience of the final product.

Critical to the design of the new isolator system was the input from those staff returning from deployment to EML in Guinea and Liberia. This allowed the design to be built directly around the PCR work flows and the equipment due to be deployed. In collaboration with the PHE training team, existing isolators were used to carry out laboratory procedures for staff members due to be deployed, and this in use testing allowed further design modifications to be defined, and informed key decisions on the resilience of the overall systems.

The other critical design principle was to keep it simple and flexible; due to limited resources and increased time pressures parts should be easy to repair or replace. So simple fixed speed fan boxes were used, which could be easily swapped out in the event of failure. The same approach was taken for the power back up; off-the-shelf inverters, which could run off car batteries, were chosen as a flexible option. The film canopy material was designed to be easily patched, so repairs could be undertaken, in-situ, if needed.

Some of the basic design principles used are as follows:

- Initially designed to be flat packed onto standard Euro pallets for ease of shipping;
    - Subsequently shipped pre-constructed in two parts
- Modular in design, such that critical items such as fans and filters could easily be replaced
- Independent battery backup for power, running off readily available 12 volt car batteries
- Robust sleeves and gloves, giving high protection, but which could be quickly and safely changed with the isolator still operating
- Manufactured from materials proven to be resistant to high concentrations of liquid disinfectant
- Use of cartridge filters, which are more resistant to transportation and easier to install than panel filters.

Testing and validation of the isolators

Through PHE's long use of containment isolators for working with dangerous pathogens, a range of stringent tests have been developed to ensure the integrity of the systems. The PHE Porton requirements go beyond the basic minimums described in HSE guidance[i] and reflect the methods used for testing Class 3 type safety cabinets on our site, including pressure testing. These tests would normally be undertaken under very controlled conditions, in clean laboratories with pre-filtered air supplies and dedicated HVAC systems. The laboratories in Sierra Leone were purpose built and highly effective, but not to the standards found within the UK, and without ventilation and control systems normally associated with BSL3 or 4 facilities.

Tests Undertaken at Porton	Test Undertaken at installation
Integrity of canopy. Pressure decay test, pressure loss should be <10% at an overpressure of 150Pa. Positive pressure scan test with DOP, all seals fittings and joints.	Integrity of canopy. Soap bubble leak test at +150Pa. Lack of temperature control made pressure hold testing impractical. Dirty/dusty environment make the use of sensitive photometers impractical.
HEPA filter test to <0.003% Penetration DOP.	Visual inspection only.
Measurement of airflow to determine air change rate (>40 ACH) and maintenance of negative pressure (>-40 Pa).	Measurement of negative pressure as indication of flow rate. Confirm correct operation of manometer against calibrated instrument.
Operation of battery backup systems, alarm systems, etc.	Operation of battery backup systems, alarm systems, etc.

In light of this a two phase approach was developed for the test and validation of the isolators; a) the isolator was constructed on the PHE Porton site and a full range of test were undertaken here to confirm the performance of every aspect of each isolator prior to careful packing and shipment, b) this was followed up in Sierra Leone by more limited, but achievable tests during installation undertaken using minimal equipment under field conditions.

An additional benefit of this process was to identify faults before the equipment was shipped overseas. Most faults found were minor, such as pilot holes drilled in the wrong place on a few frames or misaligned connections which were easily fixed in the UK. The limited engineering resources in Sierra Leone would have proved a major obstacle in the replacement of certain elements such as bolts that were supplied too short for the joint. The construction of the isolators in the UK allowed the team to identify areas where additional spares would be needed and these could be packaged and shipped with the isolators to Sierra Leone.

The final part of the work at Porton was to systematically dismantle each isolator, label, pack and bag all the parts, such that they could be matched back to each isolator in country, thus removing as many variables as possible.

Installation of isolators

An experienced containment engineer volunteered to be deployed to Sierra Leone to install and test the isolators. Logistics and communications were two of the most challenging aspects of this project. Deploying staff against hard and tight deadlines, whilst the labs were still being constructed led to delays and then long working days. Then each isolator was quickly assembled, part for part,

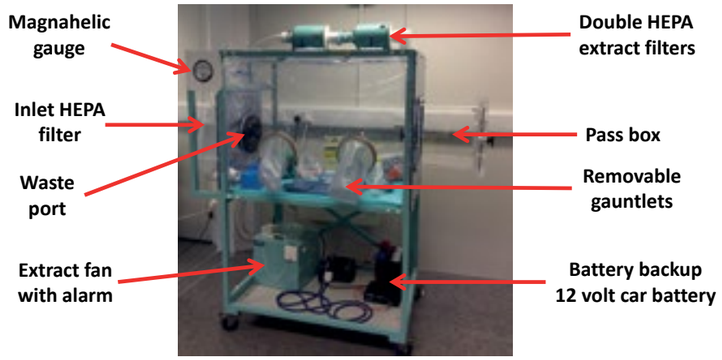


Figure 1: Flexible film isolator constructed and validated at PHE Porton prior to disassembly and shipping to Sierra Leone

knowing that the work at Porton had ensured that every screw and part would fit without fault. Once constructed, the test phase was undertaken and in all cases, it went without major faults, only occasionally interrupted by the varying animal and insect life of Sierra Leone. The isolators were all installed to a tight deadline as part of the dedicated teams setting up new labs which proved to be a rewarding and fulfilling experience.

Discussion

The ability to provide high quality equipment over a very short time period was essential to the operation of the PHE diagnostic laboratories in Sierra Leone, facilitating a very high throughput of samples, whilst maintaining the highest level of safety for the operational staff. The decision to supply two isolators to the Porton based training team also paid huge dividends, allowing the direct training of predeployment staff with the equipment that they would be using in the field. That and the expertise of the training staff ensured that the deployed lab staff fully understood the equipment and had confidence in its performance.

Lessons learned

The isolators sent to Sierra Leone are still being used 10 months after deployment without major problems. One area of concern is the continued use of high concentrations of sodium hypochlorite. Whilst this has been challenging and much of the other laboratory equipment has fared less well, the isolators have performed well. When issues have arisen, the communications between the Sierra Leone laboratories and PHE Porton has been good and problems have been quickly solved by isolator experts in the UK.

The future

The use of flexible film isolators in the diagnosis of high consequence pathogens has been used successfully and safely in the Ebola outbreak response. It provides a future model for the construction of fully sustainable diagnostic laboratories in resource-limited countries.

Figure 2: PHE Laboratory within Sierra Leone just prior to becoming operational

Acknowledgements

Chris Daniels from pfi who provided the majority of the isolators. Martin Hesford from PHE Porton who installed the isolators in Sierra Leone. All the staff of the Sierra Leone laboratories who used them and the PHE team in the UK who procured and dispatched the isolators, and also completed the paper work.

References

i. Health and Safety Executive. Biological agents. The principles, design and operation of Containment Level 4 facilities. 2009. http://www.hse.gov.uk/pubns/web09.pdf

Allan Bennett is the lead scientist of the Biosafety department of PHE Porton Down. He leads a team of 15 research scientists delivering projects in aerobiology, biocontainment, decontamination and water microbiology. He has over 40 peer reviewed scientific publications.

Simon Parks has been working in the Biosafety department of PHE Porton Down for 25 years where he works as a specialist in bio-containment, aerobiology and gaseous decontamination. He has inputs into many PHE projects across the agency, most recently taking a lead role in the installation and validation of new CL4 isolators and the development of aerosol transmission systems.

Tom Pottage has been working in the Biosafety department of PHE Porton Down for 10 years where he worked on a number of gaseous decontamination projects for bodies such as Public Health England, the Department of Health and European Space Agency. At present he is working on the UK Recovery Handbook for Biological Incidents which provides an evidence based approach for dealing with biological contamination in a range of human environments. The Handbook is due to be published in 2015.

EU GMP Annex 1

Tim Eaton

Introduction

Progress with the revision of Annex 1 to the EU GMP guidelines[i] was the focus of interest at the Pharmaceutical and Healthcare Sciences Society (PHSS) and UCL School of Pharmacy joint annual conference. This event was held at the UCL School of Pharmacy, London on 11th September and was extremely well attended as representatives and associates of the pharmaceutical and healthcare industries were eager for early indicators of the changes in the revision of this key document. Such changes may have a significant impact on many aspects of the manufacture of sterile medicinal products. The overview of the revision of Annex 1 was provided by Andrew Hopkins, MHRA Senior Inspector and representative on the review process.

Background and Revision Process

The revision was initiated in response to changes arising from a) new and emerging technologies and b) the adoption of the ICH (International Conference on Harmonization) Q9 (Quality Risk Management)[ii] and Q10 (Pharmaceutical Quality System)[iii] guidelines. Several clarifications of the existing content were also considered to be necessary. The revision has been progressed by EMA (European Medicines Agency) with the help of PIC/S (Pharmaceutical Inspectors Cooperation Scheme), to get worldwide support, and attempts to also understand and address concerns fed back from the industry. The revised timescales points to December 2015 for the updated draft documents relating to a number of sections, with April 2016 the target date for the final drafting.

Updates

It was explained that the basis for the update also relates to the fundamental issue that many manufacturing companies still do not adequately understand the basic principles and requirements associated with product aseptic and sterility assurance and therefore more guidance is required. This has been further compounded by a general loss of technical skills and expertise within the industry and the lack of experience in the new and emerging markets where knowledge continues to be evolved, one of the key learning vehicles being based on deficiency observations.

The scope of the document is to be expanded to include overlap with Annex 2 to the EU GMP guidelines (Manufacture of Biological Active Substances and Medicinal Products for Human Use)[iv] and considerations for the application of (common) standards that could also be applicable to the manufacture of non sterile products. The structure of the document will be adjusted to accommodate the environmental monitoring, both microbiological and non-viable, and Process Simulation Trials in the same section. There will be new sections for Quality Risk Management (QRM) and further guidance on Water for Injection (WFI) that will cover generation of WFI using membrane technology and water systems biofilm issues.

Clarifications regarding the definition of Grade A air supply and environmental monitoring frequencies, with a focus on lower grade areas and the averaging of microbiological limit values, will be added. The current version prescribes that the transfer of partially stoppered freeze dried vials should remain under grade A conditions until the stopper is fully inserted, but the conflicting statement that permits transfer in a sealed tray in a grade B environment will be removed.

Recently published ISO/FDIS 14644 Part 1[v] excludes particles ≥5µm at ISO Class 5 from the classification table for the simple reason that it is not practical to use the specified classification method for such low concentrations due to particle drop-out and lengthy sample times. The concentration of particles ≥5µm can however be measured by methods that do not comply with the specified classification method and it was indicated that that for routine monitoring, particles at both the ≥0.5µm and ≥5µm sizes would remain within the Annex 1 document.

The revision will include inputs on closed systems and the manufacture of small batches, such as those associated with advanced therapy medicinal products (ATMPs), with regard to operators and process simulation trials, with further considerations for RABS and isolator technology. There will also be guidance on sterilising grade filters (for liquid product) pre and post integrity testing.

Summary

The update of Annex 1 has been undertaken as a shared project between PIC/S and EMA. Whilst the new document detail has not yet been seen, a number of additions and changes to the existing content have been progressed and reported. The most significant of these relate to microbial limits for classified areas, clarification of the term 'Grade A air supply' and Grade A continuity for partially stoppered vials, prior to freeze drying. Significantly, the requirement to routinely monitor particles at the ≥5µm size, as well as at ≥0.5µm will remain.

References

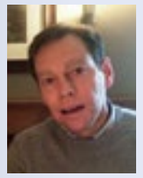
i. Eudralex, The Rules Governing Medicinal Products in the European Union, Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 1. Manufacture of Sterile Medicinal Products, European Commission. Brussels, Belgium. 2008

ii. ICH Harmonised Tripartite Guideline, Quality Risk Management Q9. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2005

iii. ICH Harmonised Tripartite Guideline, Pharmaceutical Quality System Q10. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2008

iv. Eudralex, The Rules Governing Medicinal Products in the European Union, Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 2, Manufacture of Biological active substances and Medicinal Products for Human Use. European Commission. Brussels, Belgium, 2013

v. ISO/FDIS 14644-1 – Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration. ISO. Geneva, Switzerland. 2015



Tim Eaton is a process chemist with over 22 years of experience of steriles manufacture with ICI Pharmaceuticals, Zeneca Pharmaceuticals and AstraZeneca. During this time he has had extensive roles in technical support, production management and specialist activities for aseptically prepared products. He has had responsibilities for the design, construction, start up and validation of multimillion pound aseptic manufacturing facilities and has managed the introduction, technical transfer and scale up activities for a number of sterile products. He has published a number of papers relating to cleanroom activities and has also presented at various industry forums in Europe and the US. In his current role of Sterile Manufacturing Specialist he has responsibilities for the derivation, optimisation and implementation of best practices for aseptically prepared products. He sits on LBI/30, the British Standards Committee for Cleanroom Technology.

Life-lines

Sayings of Yogi Berra, legendary baseball player who died in September 2015 aged 90

I never said most of the things I said.

If the fans don't wanna come out to the ballpark, no one can stop 'em.

The future ain't what it used to be.

You can observe a lot just by watching.

Cut my pie into four pieces, I don't think I could eat eight.

If you come to a fork in the road, take it.

If you don't know where you are going, you might wind up someplace else.

You should always go to other people's funerals; otherwise, they won't come to yours.

Ninety percent of all mental errors are in your head.

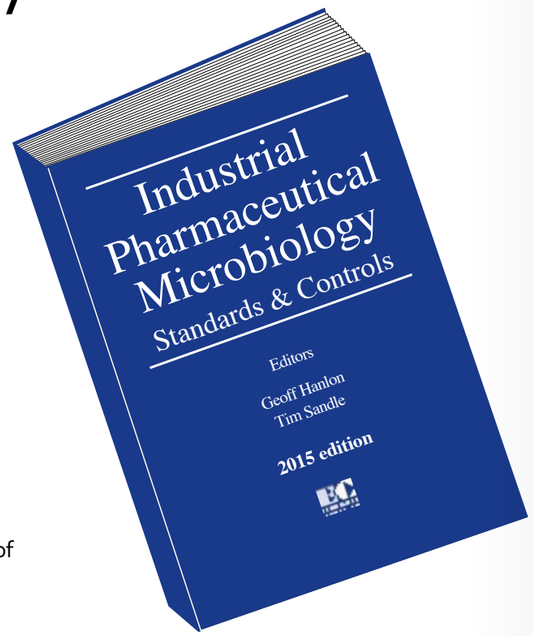
It's like deja-vu, all over again.

Nobody goes there anymore, it's too crowded.

It ain`t over until it`s over.

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.

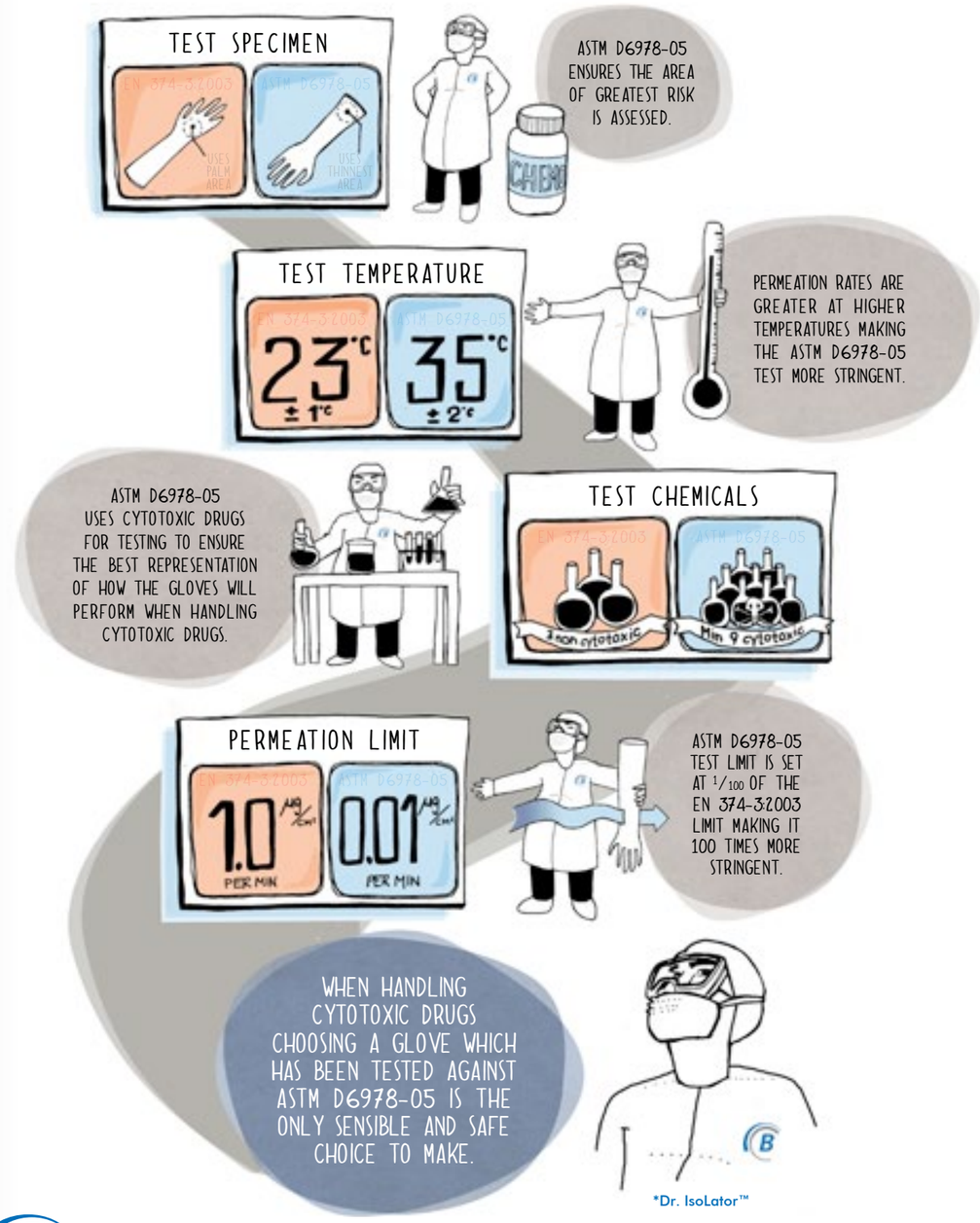
Pharmig

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

You're safe in our hands

Exposure to even tiny doses of cytotoxic drugs can be harmful. That's why all BioClean™ Chemo Safety Wear gloves are tested against ASTM D6978-05 the most stringent standard.

Why is ASTM D6978-05 more stringent than EN 374-3:2003?



BioClean™
pure • product • protection

For more information on the BioClean Chemo Safety Wear range please visit www.bioclean.com/chemo or email info@bioclean.com, please quote ref: CT0056.

*Dr. IsoLator™ represents BioClean's range of Chemo Safety Wear.

Contec ProChlor validated for sporicidal transfer disinfection

The MHRA has requested the use of a sporicide, as part of the transfer disinfection process for items used for aseptic compounding and this is mandatory for Specials Manufacturers. The NHS Micro Protocols Group has concluded that it is necessary for all NHS aseptic units to heed the warnings and apply the MHRA Guidance by including a sporicidal wipe phase into the transfer disinfection process.

Contec ProChlor is a revolutionary sporicide achieving a 100% kill against spores in less than one minute. It is validated for sporicidal transfer disinfection in practice-mimicking conditions, achieving a log 5 kill on syringe paper samples and complete kill on plastic syringe samples, in one minute.

Contec ProChlor is provided as a point-of-use SATWipe system. Each double bag pack contains a canister of dry SATWipes and a 500ml capped bottle of Contec ProChlor for introduction into the canister to saturate the wipes prior to use. For more information or to request a sample please contact Karen Rossington at infoeu@contecinc.com

New isolator half-suit from Pharminox Isolation Ltd

Pharminox Isolation Ltd is pleased to announce the new and improved Pharminox (Px) half-suit for isolators which has been developed with a specialist plastic fabricator in response to feedback from users.

The new suit is very similar to the original Cambridge suit, but incorporates significant advantages.

It retains the double layer ventilation and separate semi-rigid helmet from the design originally registered over 20 years ago, but the inner layer is now a smooth white low-friction PVC making entry and exit very much easier. The neck-ring, in white high-density polyethylene, is smaller and easier to clean and includes specially-formed foam shoulder pads to reduce operator fatigue. With the original three-hook suspension system, which optimises the suit position during gas sanitisation, the Px half-suit is practical and comfortable.

Perhaps the most significant advantage however, is the cost of the new suit. Using new techniques and materials, it has been possible to reduce the cost of the suits. Furthermore, they will now be generally available from stock, with consequently short delivery time.

The Pharminox (Px) half-suit is a direct replacement for the Cambridge suit and can also be fitted to most existing half-suit installations with an 800mm by 500mm oval half-suit plinth. It is supplied with full instructions for fitting and operation, risk assessment, drawings and appropriate certification.

For any more information, or to request a demonstration, contact Dr Helen Hale on 01954 267 359 or email helen@pharminox-isolation.com

DOP Solutions introduces a new cleanroom Airflow Mapper

DOP Solutions Ltd is very excited to introduce the new DOP6000 Airflow Mapper, an ultrasonic water fogger, for Cleanroom airflow visualisation. The growing use of pure water fogging suits many applications in the pharmaceutical and medical industries where surface contamination is a risk.

This new model delivers a high fog output for a very reasonable budget. Functions are easily accessed, and fog output is regulated and delivered using a range of tubes and nozzles.

This high quality DOP Solutions Airflow Mapper is now the most affordable option for airflow visualisation using a method that does not contaminate the Cleanroom.

These are supplied throughout the world by DOP Solutions and their established network of distributors. Hire units also available.

Email sales@dopsolutions.com , +44 (0)1462 676446, or visit www.dopsolutions.com

Edinburgh Molecular Imaging is first customer for Envair Lab's brand new safety cabinet

As one of the first customers of the brand new Envair Lab range, Neil McDonald of Edinburgh Molecular Imaging professed his delight at his new Envair eco safe Basic Plus class II safety cabinet. Delivered from UK stock by our specialist logistic crew and commissioned by one of our fleet of trained service engineers, Envair Lab aims to create as little disruption as possible during the installation of any product.

Envair Lab is proud to be associated with Edinburgh Molecular Imaging due to their development of an Optical Molecular Imaging technology that can help diagnose and monitor of several major diseases. The company's innovative technology revolves around the development of fluorescent imaging reagents that detect harmful processes deep inside the human body, at the bedside, in real time and at molecular resolution.

We are very much looking forward to working with Neil and his team in the future.

For more information, please visit http://envairlab.co.uk/product/life-science/ e-mail info@envairlab.co.uk or call +44 (0) 3333 706 560.

Clean Room Construction completes flagship projects in record-breaking year

Demand continues to grow for quality cleanroom and containment solutions resulting in another record-breaking year for design and build specialist Clean Room Construction (CRC).

CRC has recently completed numerous flagship projects including cleanrooms for the £61m National Graphene Institute (NGI) at The University of Manchester and state-of-the-art laboratories for the Cell Therapy Catapult at Guy's Hospital.

CRC has also delivered a cleanroom facility for the Technology & Innovation Centre at the University of Strathclyde, which was opened by The Queen in the summer, and completed cleanrooms for space satellite testing for RAL Space in Oxfordshire and for high performance imaging projects at e2V in Essex.

Steve Lawton, CRC's Managing Director, said: "CRC is very proud to have worked on so many prestigious projects. Clients investing huge amounts of money in world class facilities value our unrivalled experience and expertise."

For more information about CRC, visit www.crc-ltd.co.uk

Mission accomplished: Cleanrooms built by CRC for RAL Space will accommodate the UK's largest thermal vacuum calibration facility (Photo: Science Technology Facilities Council)

CHTS helps CL3 lab managers meet increasing demands for evidence of fumigation efficacy

It is a fundamental requirement that containment level 3 laboratories can be effectively fumigated in the event of an emergency without entering the room. Therefore external inspectors/ auditors are frequently demanding evidence of fumigation efficacy in order to meet compliance or insurance requirements.

Fumigation efficacy studies are integral to validating a new facility, but what about existing laboratories that have never had an efficacy study carried out? Results from a number of studies have shown that fumigation has a limited effect in many facilities, frequently due to low temperatures from the building structure or humidity caused by air conditioning units.

Carrying out an efficacy study will confirm whether your laboratory can be effectively fumigated without the need to wait for results back from the incubation of BIs. Do you have evidence of the fumigation efficacy of your lab? Now is the time to review how effective your fumigation protocols are.

To learn more about how Crowthorne Hi-Tec Services can help, please contact Angela Simms on +44 (0)1252 372333 or sales@chts.co.uk

Cleanroom Guangzhou Exhibition 2015 Post-Show Report

With the growing market in China for cleanroom products, components and installations, Cleanroom Guangzhou 2015 took place at exactly the right moment to display the latest cleanroom products and technology.

Strong support of the Guangdong Association of Cleanroom Technology attracted about 250 stands and more than 100 established companies.

The products shown, including weighing booths, air showers, laminar flow hoods, transfer hatches, coloured steel sandwich panels etc. received great attention. Visitors were interested in product specific details such as air speed and energy consumption, and many good discussions took place in a harmonious business atmosphere.

During the exhibition and conference, the Organizing Committee also arranged China (Guangzhou) Cleanroom Technology Development Forum 2015 with about 80 professionals in attendance.

The total number of visitors during the three days was more than 3,600 and therefore this exhibition is probably the largest cleanroom show in Asia.

The next exhibition will be held in area B of China Import and Export Fair Complex during September 20 – 22, 2016. We look forward to your visit.

See www.clcte.com

Ecolab helps reduce exposure to cytotoxic drugs

Baglan, UK, 28 September 2015 Following the recent implementation of a reference value of 0.1ng/cm^2 for pharmaceutical cleanrooms in Germany, Switzerland, Austria and Poland dealing with cytotoxic drugs, Ecolab Contamination Control requested a study to be carried out on the safe removal and destruction of cytotoxic drugs on surfaces, testing its own disinfectants and their performance.

Independent work performed by the Institute of Energy and Environmental Technology (IUTA) recommends a combined procedure. Firstly, the surface is wiped with a Klerwipe Polyester Dry Wipe that has been sprayed with Klercide Sporicidal Active Chlorine spray. Then, following a contact time of 5 minutes, the surface is wiped again with a Klerwipe 70/30 IPA impregnated wipe. This combination is proven to have optimum efficacy in the removal of a full range of cytotoxic compounds from surfaces, eliminating up to 99.9 per cent of them.*

James Tucker, marketing director at Ecolab Contamination Control says: 'Uniquely, when the products are used in combination they denature and then remove the cytotoxic residues, making disposal safer and ensuring contamination control right along the waste removal journey.'

*For further information on the test work carried out please e-mail Ecolab Contamination Control at infocc@ecolab.com to request technical report TR1502R. The trial was conducted using Ecolab's Klercide and Klerwipe products. This data is not transferable to similar products.

Validair launch EasySense wireless sensors for use with ViGIE 2.0 software.

Validair ViGIE 2.0 provides a modern approach to monitoring and critical alarm notification for controlled environment applications. Primarily intended to take full advantage of the benefits of the low impact and flexibility of wireless systems, Validair ViGIE provides a robust and secure platform for connection to wireless sensors and transmitters from any leading manufacturer. Validair have added EasySense sensors to the packaged system they can provide.

Sensors are currently available for temperature and relative humidity monitoring, with the option for probes to be added for water detection and CO_2 levels. A magnetic contact probe can be used to provide open/closed feedback for doors and cabinets.

There is no limit to the number of users, departments or sensors which can be used with the system. ViGIE sensors transmit real-time data to the software. All the monitored variables are incorporated into the software allowing simple and effective data evaluation and reporting.

For more information on VIGIE monitoring visit www.validair.com or contact Dave Sears on 07825 130791 or email dave-sears@validair.com

EasySense gateway, sensor and probe

Events

Dates	Event	Organiser
2015		
October 27-28	Cleanzone, Frankfurt, Germany	Messe Frankfurt
October 19	Welsh QP Forum Conference, Brecon, UK	PHSS
November 4-5	Lab Innovations 2015, NEC, Birmingham, UK	EasyFairs
November 9-12	2015 IEST Fall Conference, Chicago, USA	IEST
November 17-19	A3P Congress, Biarritz, France	A3P
November 25-26	Pharmigs 23rd Annual Conference, UK	pharmig
2016		
January 20-21	Pharmaceutical Microbiology, London, UK	SMi
April 19-22	European Biosafety Association (EBSA) 19th Annual Meeting, Lille, France	EBSA
April 21-23	Cleanroom Technology, Maintenance and Equipment Exhibition, Istanbul, Turkey	antexpo
May 2-5	ESTECH '16, Glendale, Arizona	IEST
September 20-22	Cleanroom Guangzhou Exhibition 2016, Guangzhou, China	Guangzhou Grandeur International Exhibition Group

Training courses

IEST (Institute of Environmental Sciences and Technology)		
2015	**Event**	**Location**
November 9	Understanding the Changes to ISO 14644- and ISO 14644-2	IEST Fall Conference. Chicago, Illinois
November 10	Application of ISO 14644-3	IEST Fall Conference. Chicago, Illinois
November 11	Risk Assessments for Cleanrooms and Controlled Environments	IEST Fall Conference. Chicago, Illinois
November 12	Universal Cleanroom Operations Guidelines with ISO 14644-5	IEST Fall Conference. Chicago, Illinois

ICS (Irish Cleanroom Society)		
2015	**Event**	**Location**
November 3-5	CTCB-I Testing and Certification	Dublin, Ireland
November 26	CTCB-I Cleanroom Technology	Letchworth, UK

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

ACT (Academy for Cleanroom Testing)		
2015	**Event**	**Location**
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

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).

Recognising the Risk of Cytotoxic Exposure Among Operators

How a rigorous disinfection and waste management regime - coupled with products which actively destroy cytotoxics - is shown to reduce this risk

There are risks arising from the handling and administration of cytotoxic drugs (Antineoplastics) especially the safe transfer, manufacturing and preparation, waste handling and spill management of these drugs.

Occupational exposure to cytotoxics is a serious issue within the pharmaceutical and compounding industry and is likely to occur when control measures are inadequate.

> **Using disinfectants that vigorously denature and destroy the active chemicals in cytotoxics helps to ensure safe removal**

Those most likely to be at risk include operators, pharmacists and laboratory staff. The types of activities which put them at risk are drug preparation and cleaning up residues and spills.

One of the challenges posed by cytotoxics is that despite being removed from surfaces and equipment they can continue to pose a risk directly as waste. The right procedures and products must be implemented to ensure contamination is kept to an absolute minimum. Under COSHH[1] there needs to be comprehensive assessments of the risks arising from handling cytotoxic drugs at every stage of use and disposal.

Control and monitoring of the effects of exposure has been studied in detail with a range of biological endpoints including, DNA damage, HPRT mutations and thioether excretion, among others, highlighting the seriousness of this issue.

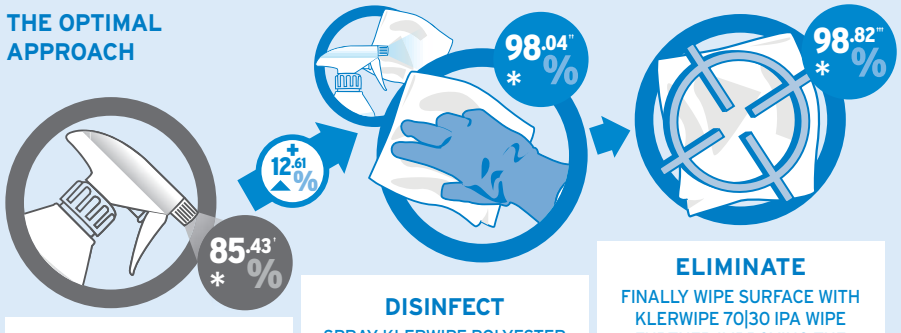
Analytical methods are also now being employed to measure the level of environmental contamination in the workplace. Numerous studies have been published on environmental wipe sampling for these drugs as the issue becomes more widely known.

Similarly, the data collection and actions to identify and remedy exposure levels of cytotoxic drugs is definitely on the increase. Two key agencies responsible for conducting research and making recommendations, the National Institute for Occupational Safety and Health (NIOSH) and the German Institution for Statutory Accident Insurance and Prevention in the Health and Welfare Services (BGW) have taken steps to raise awareness on the subject.

NIOSH have published an alert: *Preventing Occupational Exposure to Antineoplastics* and BGW an authoritative study in Germany: *Monitoring-Effect for Wipe Sampling in Pharmacies (MEWIP)*. In these, cytotoxic drugs were found on 61% of all wipes used in three sampling positions within pharmaceutical cleanrooms: worktop, floor and fridge. Contamination levels of over 70%, 60% and 50% respectively were observed which in turn has led to the implementation of a reference value of 0.1ng/cm^2 for pharmaceutical cleanrooms in Germany dealing with cytotoxic drugs.

Ecolab has developed a range of products that are scientifically proven to reduce the risks associated with cytotoxics. Uniquely, they both remove and denature the cytotoxic residues, when used in combination as described below, making disposal safer and ensuring contamination control right along the waste removal journey.

THE OPTIMAL APPROACH



SPRAYING ALONE

WITH KLERCIDE SPORICIDAL ACTIVE CHLORINE

† Removes on average 85.43% of a wide spectrum of cytotoxics from stainless steel surfaces

DISINFECT

SPRAY KLERWIPE POLYESTER DRY WIPE WITH KLERCIDE SPORICIDAL ACTIVE CHLORINE AND WIPE THE SURFACE

†† Wiping as well as spraying improves the removal rate vs spraying only to 98.04% on average

ELIMINATE

FINALLY WIPE SURFACE WITH KLERWIPE 70|30 IPA WIPE FURTHER IMPROVING THE REMOVAL RATE, REDUCING SURFACE RESIDUES AND ENHANCING MATERIAL COMPATIBILITY

††† This results in a further improvement to 98.82% removal on average

The elimination of cytotoxic drugs on surfaces, should be a major priority for the industry. One definite way to achieve this is through the controlled use of products manufactured in a cleanroom environment, with a proven and tested capability in the removal and destruction of cytotoxics.

The Institute of Energy and Environmental Technology (IUTA) recommends a combined procedure of spraying a Klerwipe polyester dry wipe with Klercide Sporicidal Active Chlorine spray, then wiping the affected surface. Following a recommended contact time of 5 minutes, the surface should then be wiped with Klerwipe 70/30 IPA impregnated wipes. This combination is proven to have optimum efficacy in the removal of cytotoxic compounds from surfaces, eliminating up to 99.9% of them.

For further information on the test work carried out, please contact us for technical report TR1502R.

N.B. The trial was conducted using Ecolab's Klercide and Klerwipe products, data is not transferable to similar products.

> **Ecolab has developed a range of products that are scientifically proven to reduce the risks associated with cytotoxics**

Klercide Sporicidal Active Chlorine Spray, Klerwipe polyester dry wipes, and Klerwipe 70|30 IPA wipes.

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

(1) COSHH - Health & Safety Executive. Control of substances hazardous to health regulations (2013).
(2) MEWIP - Monitoring-Effect Study of Wipe Sampling in Pharmacies. Institution for Statutory Accident Insurance and Prevention in the Health and Welfare Services - BGW.

ECOLAB®