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Enhance your knowledge of contamination control

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Picture: 2i Digital Aerosol Photometer and iProbe from ATI for installed filter system leakage tests

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

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Editorial

Welcome to CACR49 which starts with a chapter from Bill Whyte's *Cleanroom Testing and Monitoring* book: *Airborne particle counting with an LSAPC*. Bill Whyte and CTCB-I, who own the copyright for the book, a copy of which goes to every delegate on the CTCB-I Cleanroom Testing courses, have very kindly given CACR permission to reproduce these extracts. Koos Agricola is back again writing about the recent particle deposition standard ISO 14644-17 in which he played such a large part. It is blindingly obvious that particles only become harmful when they deposit on surfaces. For this reason I am sure that this standard, which applies to larger particles, will gain in importance as its value is recognised. The next article, by Mark Hallworth of Particle Measuring Systems homes in on the environmental monitoring aspect of GMP compliance, especially with respect to the manufacture of Advanced Therapeutic Medicinal Products (ATMPs). Tim Sandle of the UK Bio Products Laboratory writes about the control of viruses in cleanrooms. His article describes the various types of viruses and gives guidance on the selection of disinfectants as many common disinfectants are only suitable for bacterial or fungal contamination. A transatlantic trio of authors, Tim Coles, Rick Nieskes and James Agalloco, all with extensive experience of validation of isolators and biodecontamination, present compelling arguments on the way forward. An important new member of the ISO 14644 series of standards is about to 'hit the bookstands' or rather the ordering pages of ISO and national standards bodies: ISO TR 14644-21 *Airborne particle sampling techniques*. This document will be particularly useful for everyone implementing the latest revision of EU GMP Annex1 which is due to come into force in August. A short preview has been prepared by John Hargreaves and Andrew Watson, Convenor and Secretary respectively of the ISO Working Group responsible. Finally, Bill Whyte has just published the third edition of his comprehensive book *Cleanroom Technology*. It is over 12 years since the second edition so there has been much to update and should be on the bookshelf of every cleanroom practitioner. It is reviewed here by your editor.

So there is much to read – I hope you enjoy it.

John Neiger

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Airborne particle counting with an LSAPC

W. Whyte

This article is the fourth of a short series of extracts from Bill Whyte's new book *Cleanroom Testing and Monitoring*. Chapter 11, Airborne particle counting with an LSAPC, is reproduced here with the kind permission of the author, Bill Whyte, the publisher, Euromed Communications, and the owner of the copyright, the Cleanroom Testing and Certification Board – International (CTCB-I). The objective in publishing these extracts is to give readers a flavour of the content and depth of the book which is recommended as a comprehensive textbook and an essential reference for cleanroom managers, cleanroom test engineers, cleanroom service engineers, cleanroom designers and specifiers and anybody who is concerned with cleanrooms.
Editor

11.0 Introduction

It is necessary to demonstrate in cleanrooms that the concentration of airborne particles does not exceed that which is acceptable. Chapter 4 gives the table of the maximum airborne particle concentrations for different cleanliness classes of cleanrooms and cleanzones according to ISO 14644-1: 2015 [ref 7]. To ensure that a cleanroom complies with the specified ISO class, it is tested by the method given in ISO 14644-1 which will be explained in the next Chapter 12. It is also necessary to monitor the cleanroom over its lifetime to ensure that the specified airborne particle concentration is not exceeded. This chapter discusses airborne particle counters that are used to carry out these tasks.

Airborne particle counters are referred to in ISO 14644-1: 2015 as 'light scattering airborne particle counters' (LSAPCs). This name distinguishes them from aerosol photometers used to detect leaks of particles in high efficiency air filter installations and are discussed in Chapter 8. An LSAPC sizes and counts the number of individual particles in air, whereas photometers measure the total concentration of particles in air. A typical LSAPC with an isokinetic intake and Wi-Fi aerial is shown in Figure 11.1.

11.1 How does an LSAPC work?

Figure 11.2 shows the main components of an LSAPC. A sample of cleanroom air is drawn into the instrument and passes through the sensing zone. Also passing through the sensing zone is a beam of light, which comes from a laser diode or a helium-neon laser. Single particles passing through the beam will scatter light. This light is collected and directed by an optical system to a photodiode where it is converted into an electrical pulse. The height of the pulse enables the size of particle to be obtained and, by counting the number of pulses, the number of particles is ascertained. Knowing the sampling rate of the LASPC, the concentrations of different sizes of airborne particles are obtained.

The size of a particle is obtained by an LSAPC from the amount of light scattered by the particle. Therefore, it is not its physical size that is measured but its 'equivalent optical size', which is the diameter of a spherical particle that scatters the same amount of light as the particle being measured. The equivalent optical size that is measured by the LSAPC is obtained by calibrating the instrument with standard mono-dispersed particles of polystyrene latex, which are spherical and readily scatter light. Therefore, the correlation between the actual physical dimensions of a particle and its equivalent optical size depends on the substance of which it is composed and its shape.

The range of particle sizes required in the classification of a cleanroom, according to ISO 14644-1: 2015 is between ≥0.1µm and ≥5µm and these sizes can be counted by an LSAPC. However, an LSAPC that only measures particles down to 0.3µm or 0.5µm may be suitable for testing in many types of cleanrooms. LSAPCs are available with airflow sampling rates of 2.8L/min (0.1

Figure 11.1 A typical LSAPC

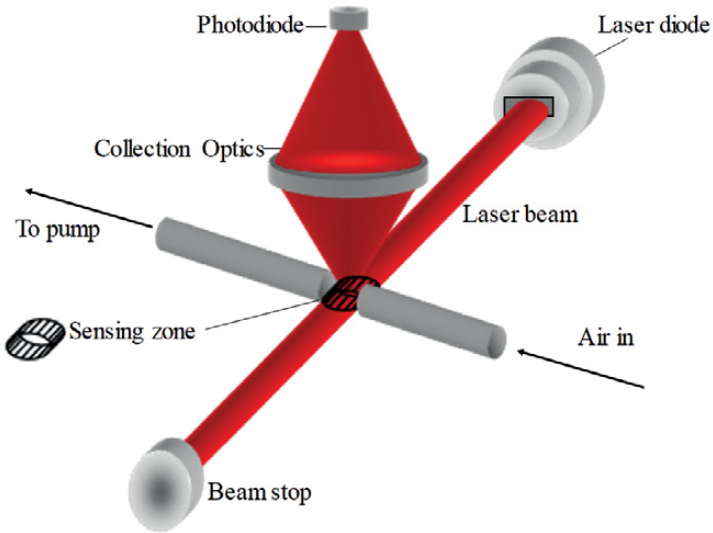


Figure 11.2 Particle detection method used in an LSAPC with the light path shown in red

ft³/min), 28.3L/min (1 ft³/min), 50L/min and 100L/min.

LSAPCs must be regularly serviced and calibrated. The calibration should conform to ISO 21501-4: 2018 [ref 26]. However, ISO 14644-1: 2015 points out that some particle counters cannot be calibrated by use of all of the tests and, if this is the case, this information should be recorded in the test report.

11.2 Cumulative and differential counts

An LSAPC is normally used to count particles that are equal to, or greater than (≥), a specified size of particle. This is known as a 'cumulative' count, and it is this count that is required by the ISO cleanroom standards. However, LSAPCs can also measure 'differential counts', which are counts between given particle sizes, e.g. between ≥0.5µm and ≥1.0µm. Care must be taken to ensure that differential counts are not mistakenly measured when testing cleanrooms.

An example that explains the difference between differential and cumulative counts is given in Table 11.1. Shown in column 1 are the differential size ranges and in column 2 are their particle counts. In column 3 are the cumulative size ranges that correspond to the smallest differential size in each row, and include all particle sizes equal to, and above those sizes. Finally, in column 4, are the cumulative particle counts, which are obtained from an LSAPC, but can also be obtained by adding together all the differential particle counts in column 2 up to the particle size in question.

11.3 Coincidence loss

If the concentration of airborne particles is too high, inaccurate counts may be obtained from an LSAPC because of 'coincidence' losses. These losses can be caused by two or more particles in the light beam being 'seen' by the LSAPC as one large particle. It is also possible that small particles can be hidden behind large ones. ISO 21501- 4: 2018 suggests that the maximum particle concentration that should be sampled is one where the coincidence loss is less than 10% of the total count. This will typically occur in concentrations above 10^6/m³ to 10^7/m³ but the actual value should be obtained from the manufacturer's literature.

11.4 Diluting an air sample

When high particle concentrations are encountered that cause coincidence loss in an LSAPC, it may be necessary to dilute the airborne particles before they are counted by an LSAPC. If tests are being carried out to (a) measure the decay of particles to obtain the recovery rate, (b) challenge a high efficiency filter installation with particles to measure leaks using an LSAPC, or (c) establish the penetration of particles into clean air devices by the segregation test method, it may be necessary to measure airborne concentrations that are higher than the concentration where coincidence losses occur. Should this be the case, a 'diluter' can be used to remove particles from a portion of the air that is sampled, and thereby reduce the high concentration of airborne particles to a level that can be accurately measured.

Figure 11.3 shows how a diluter works. The air entering the diluter is split into two alternative paths. The minor part of the sampled air passes through a small diameter tube that restricts the airflow without affecting the concentration of particles. The greater part of the sampled air passes though the larger diameter side arm and through a high efficiency air filter that removes all of these particles. The two flows are united and this results in the actual air sample that has passed through the small tube being diluted with particle-free air from the side arm. A variety of diluters are available that give dilution ratios of between about 10: and 1000:1. It is also possible to combine two diluters in series to dilute the particle concentration.

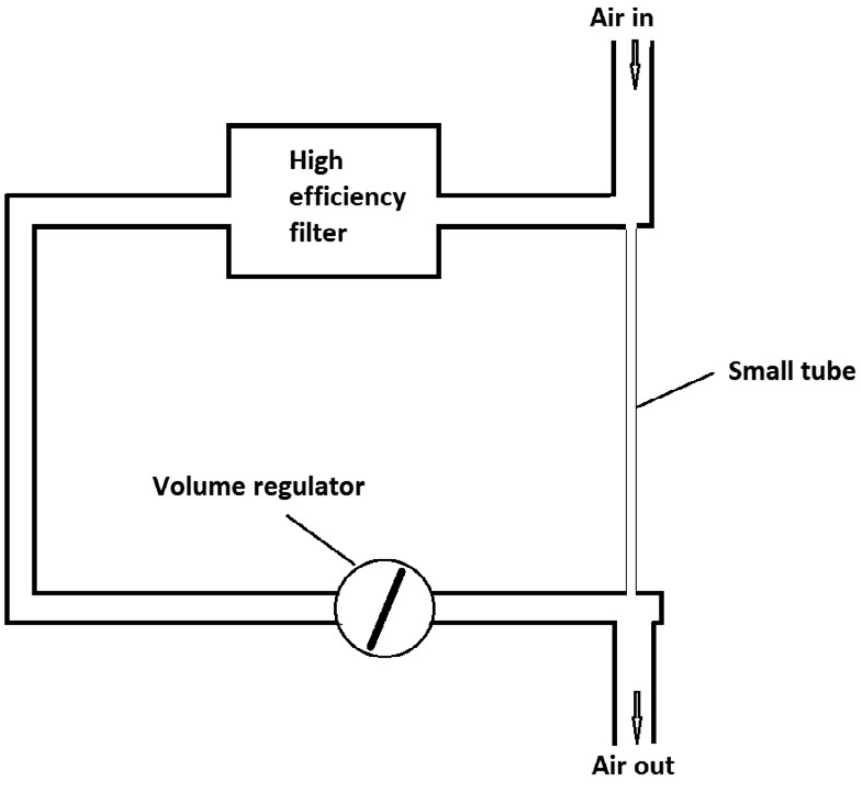


Figure 11.3 Particle diluter

Table 11.1. Differential and cumulative counts from an LSAPC

Differential particle size range	Differential particle count/m³	Cumulative particle size range	Cumulative particle count/m³
≥0.3µm to ≥0.5µm	12,053	≥ 0.3µm	16,276
≥0.5µm to ≥1µm	3,105	≥ 0.5µm	4,223
≥1µm to ≥5µm	1108	≥ 1µm	1118
≥5µm	10	≥5µm	10

11.5 Particle losses during air sampling

When cleanroom air is sampled by an LSAPC, it is necessary to ensure that the LSAPC accurately sizes and counts all of the airborne particles, and none are lost or added. To do this, the following information should be considered. Further information is given in Annex G.

Wall losses in the sampling tube: If the air sampling location is some distance away from the LSAPC, a sampling tube is required to transport the airborne particles to the LSAPC. However, as particles flow along the tube they may deposit onto the inner wall. This loss is mainly caused by larger sizes of particles, which are deposited by gravitational settling. Because of this problem, it is best not to use a sampling tube but, if it must be used, it should be as short as possible. ASTM F50-12 (2015) [ref 27] recommends that sampling tubes should be no longer than 3 metres, and ISO 14644-1: 2015 suggests that for sampling particles ≥1µm, the tube length should not be longer than 1 metre. There can also be particle losses at the bends of a tube owing to the particles being thrown by their inertia onto the inner tube wall, and it is suggested in ASTM F50-12 (2015) that the radius of curvature of the tube should be greater than 15cm.

Particle losses in a sampling tube owing to electrostatic attraction: If the sampling tube possesses an electrostatic charge, then particles can be attracted to the tube's inner wall and deposited. To minimise this loss, the tubing should be a good electrical conductor, such as Bev-A-Line tubing, or tubing made from polyurethane with a conductive additive.

Other sampling tube considerations: The tube to the particle counter should not be knocked or moved during sampling, or particles deposited in the tube may be dislodged. This is especially important if a low concentration of particles is being measured. In addition, the sampling tube should be sealed when not in use, to protect it against particle contamination. Similarly, when not in use the inlet into the LSAPC should be capped to protect it from contamination.

Orientation of sampling probe: To ensure good sampling, the sampling probe should be correctly orientated to the airflow direction. When sampling in unidirectional airflow, the probe inlet should face directly into the unidirectional airflow. In the mixed airflow found in non-UDAF systems, the intake of the tube or probe should face upwards.

Isokinetic sampling: When sampling in unidirectional airflow, isokinetic sampling is required to give the true concentration of the airborne particles. This is unnecessary for small particles around the size of 0.3µm and 0.5µm, as these will not leave the airstream and are not lost by impaction onto intake surfaces. However, if larger macroparticles are sampled, isokinetic sampling is required. Isokinetic and anisokinetic sampling are illustrated in Figure 11.4. It should be noted that, as discussed in the previous paragraph, the sampling probe should be orientated so that the unidirectional air flows parallel to it.

Figure 11.4 (a) shows the situation where the velocity of the air into the probe is the same as the air passing it. This is known as isokinetic sampling. When isokinetic sampling is used, the air flows smoothly into the probe and particles are neither lost nor gained. In Figure 11.4 (b), the air velocity into the probe is greater than outside it and the airflow is anisokinetic. As shown in the figure, particles with sufficient size and inertia will not flow with the air but are thrown outside of the probe and not sampled. The air sample will therefore have a lower concentration of large particles than the actual concentration in the air being sampled. Shown in Figure 11.4 (c) is a probe in which the air velocity into the probe is less than that outside it. The streamlines of the expected airflow are shown. As the air turns away from the probe, particles with sufficient inertia will be thrown into the probe and the air sample will have a higher concentration of large particles than the actual concentration in the air being sampled.

It is usually impossible to provide isokinetic sampling in non-UDAF cleanroom as the air flows in a variety of directions and at different velocities, but to obtain the best sample, the probe should face upwards. However, an isokinetic probe may be used to provide a sharp entrance at the air intake and reduce particle deposition caused by a blunt intake.

If attention is paid to the information given in this chapter, an accurate count

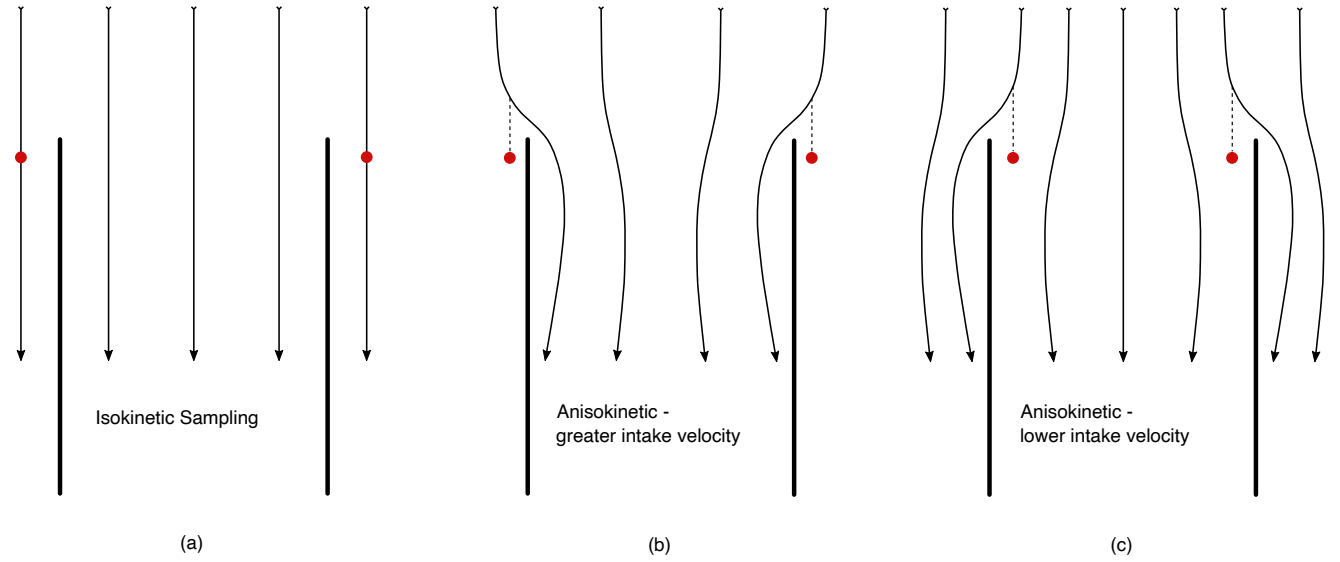


Figure 11.4 Isokinetic and anisokinetic sampling

of the specified sizes of particles in sampled air should be obtained. This ensures that the cleanliness classification of a cleanroom or clean zone will be correct. The classification method given in ISO 14644-1: 2015 will be discussed in the next Chapter 12.

Acknowledgements

The LSAPC shown in Figure 11.1 is reproduced by permission of Particle Measuring Systems. Bob Latimer kindly drew Figure 11.2.

References (numbered as at the end of the book)

[7] ISO 14644-1:2015 – Part 1: Classification of air cleanliness by particle concentration. International Organization for Standardization, Geneva, Switzerland.

[26] ISO 21501-4:2018. Determination of particle size distribution – Single particle light interaction methods – Part 4: Light scattering airborne particle counter for clean spaces. International Organization for Standardization, Geneva, Switzerland.

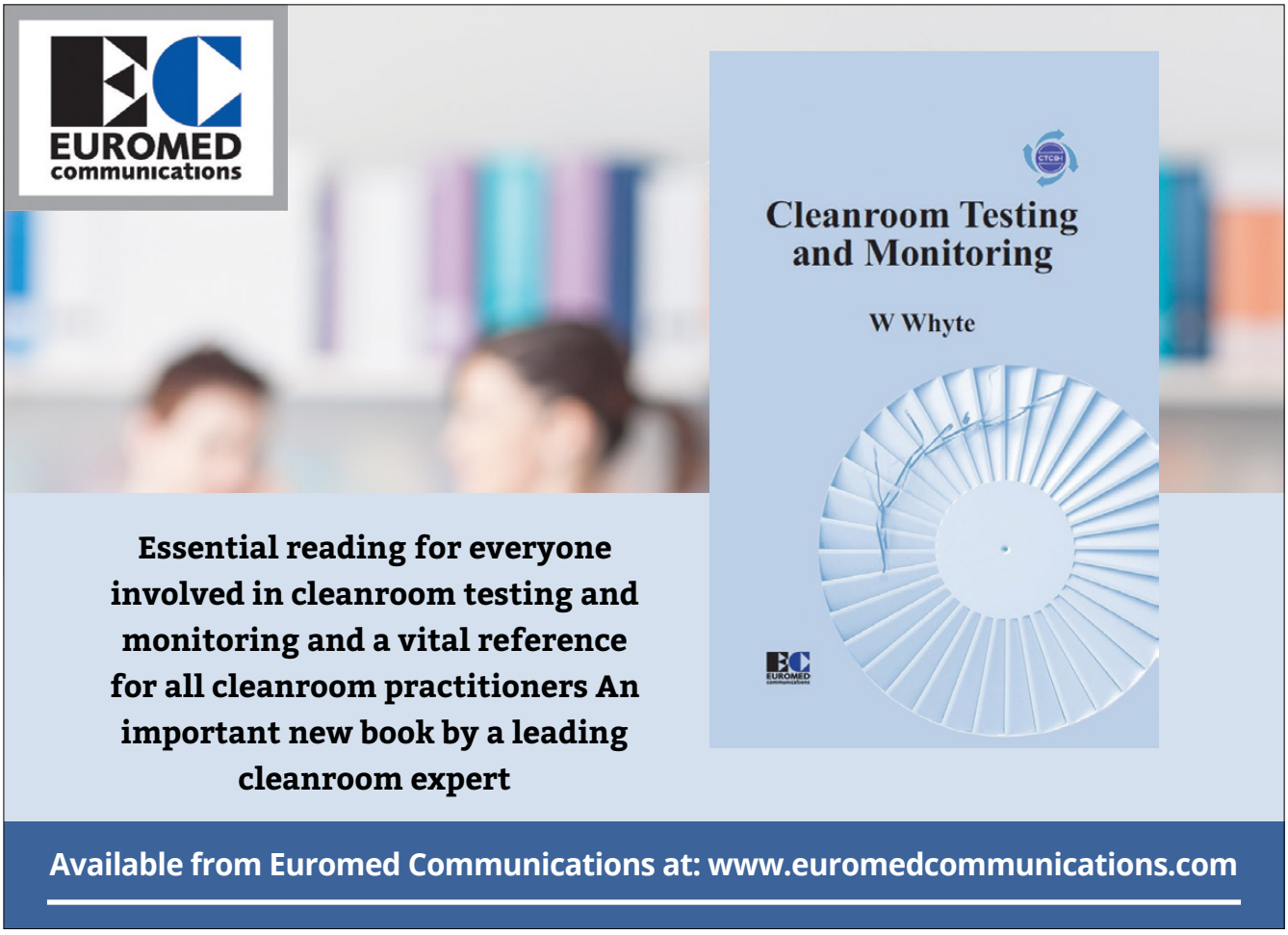
[27] ASTM F50-12 (2015). Standard practice for continuous sizing and counting of airborne particles in dust-controlled areas and cleanrooms using instruments capable of detecting single sub-micrometer and larger particles. ASTM International, West Conshohocken, PA, USA.

Dr William (Bill) Whyte is an Honorary Research Fellow at Glasgow University and has the useful dual qualifications of a BSc in microbiology and a DSc in mechanical engineering. He has been involved in the design, testing, and operation, of cleanrooms and hospital operating rooms for over 50 years.

Bill Whyte has published over 140 journal articles on the design of cleanrooms and operating theatres, and the control of the transmission of contamination within them. He has written two books titled 'Cleanroom Technology – Fundamentals of Design, Testing and Operation' and 'Advances in Cleanroom Technology', and edited the book 'Cleanroom Design'.

He was founder and former chair of both the Scottish Society of Contamination Control and the Cleanroom Testing and Certification Board – International. He is a member of BSI and ISO working groups that are writing, or have written, cleanroom standards. He has extensive experience as an industrial consultant and presenter of educational courses about cleanrooms.

He has received the following awards for his work in Cleanroom Technology: Fellowship of the IEST, Honorary Life Member of S2C2, James R Mildon Award from the IEST, Michael S Korczyneski Grant from the PDA, Parenteral Society Annual Award, and Special Commendation Award from the British Standards Institution.



Particle deposition rate application ISO standard to control contamination by macro- and visible particles

Koos Agricola

Abstract

Starting in 1999, ISO TC209 has published a series of standards on cleanrooms and associated controlled environments. Since the publication of the first standard, 16 further standards have been developed and published. With respect to particles the focus has been on airborne particles up to 5 micrometers (µm). In many applications larger particles, which have been termed macroparticles, and even visible particles, need to be controlled. ISO 14644-17 *'Particle deposition rate applications'* provides guidance on the control of these particles. This paper gives background information and a personal view on the application of this recent standard.

Macroparticles and visible particles that are not removed by airflow will deposit on surfaces. The removal efficiency of visible particles is especially low.

Introduction ISO 14644 standards

Cleanrooms are classified by the particle concentration in air measured by a light scattering airborne particle counter. The considered concentration is the cumulative number of particles of a given size larger than or equal to the equivalent optical diameter within the particle size range between 0.1 and 5 micrometers (µm). The procedure and classification levels are described in ISO 14644-1 [1]. Additionally, macroparticles (> 5 µm) that can be counted in an air sample can be added outside the classification table. These are defined by what are known as the M-descriptors. Macroparticles that cannot be counted in an air sample are excluded, because they easily get trapped and their concentration is relatively low.

In contamination control often the control of macroparticles and even visible particles is important since they can have extreme adverse consequences on products, processes and human health. These particles cannot be removed effectively by airflow. They can be detected by their deposition rate. Macroparticles include microbe carrying particles (MCPs), and the likelihood of MCPs increases with particle size. The particle deposition rate also gives direct information on the likelihood of surface contamination.

In 2021 ISO TC209 published a new standard, ISO 14644-17, on the applications of particle deposition rate [2]. The standard is especially useful for cleanrooms with personnel. Industries that can use particle deposition rate as a control parameter are for example: aerospace, optics, electronics, automotive, healthcare, medical devices and life sciences.

Importance of the control of macroparticles and visible particles

Personnel in a cleanroom shed and distribute many particles including microbe carrying particles (MCPs). These particles include particles in the range 0.1 µm – 5.0 µm (against which cleanrooms are classified), macroparticles (> 5 µm) and visible particles (> 25 µm). Goods that come into the cleanroom can also carry many macroparticles which can become airborne by local turbulent airflow. Cleanroom ventilation is capable of removing airborne particles as long as the particles do not deposit on surfaces. In non-unidirectional airflow, the removal efficiency or ventilation effectiveness depends on the airflow rate in the cleanroom and the positioning of the supply air and exhaust points [3]. Macroparticles and visible particles that are not removed by airflow will deposit on surfaces. The removal efficiency of visible particles is especially low. Therefore it is important to limit the introduction of airborne and surface macroparticles into the cleanroom and to remove these particles by frequent cleanroom cleaning. In Figure 1 a sample calculation of the particle removal efficiency is shown for a 3 meter high cleanroom for two air change rates (ACR), 20 and 40 air changes per hour. Particles that are not removed by airflow will deposit onto surfaces. Increasing the air change rate will improve the removal of visible particles, but this needs a lot of energy and therefore it will be better to prevent introduction and generation of these particles by better entry procedures and frequent removal of surface particles by cleaning.

Deposition of macroparticles can lead to immediate product rejects or

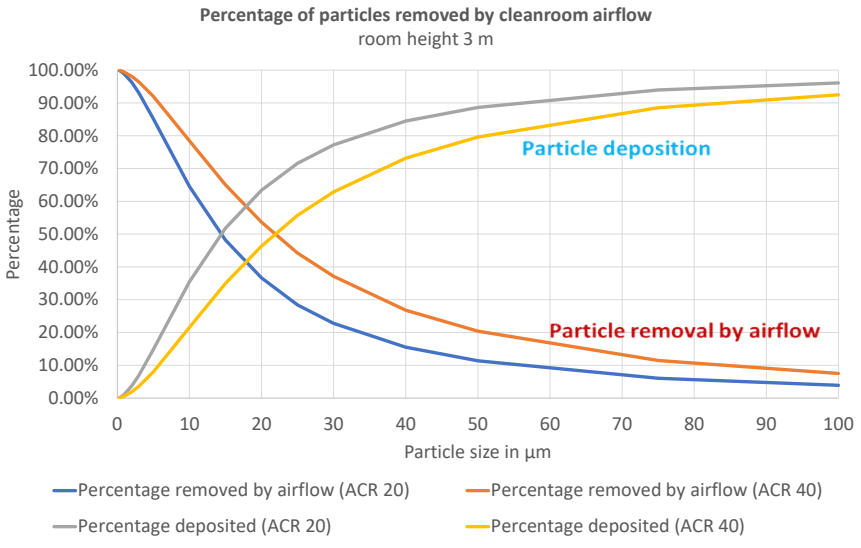


Figure 1. Removal of particles up to 100 µm by cleanroom air flow and consequent particle deposition

health problems. However often a single macroparticle that causes a problem is hard to detect. Then smaller particles are blamed because of lack of knowledge regarding macroparticles.

Nowadays several types of particle deposition instruments are available to collect data on particle deposition rate and the size distribution of the particles. By monitoring the effect of actions to reduce the particle deposition rate, lessons can be learned about effective measures to limit particle deposition.

The new ISO standard 14644-17 provides guidance on setting limits and potential means to establish control and monitoring to demonstrate control [2].

Particle deposition rate

Particle deposition rate is the product of the airborne concentration (number/m^3) times the participation deposition velocity (m/h) and depends on particle size. For small particles the concentration is relatively high and the deposition velocity is relatively low, and for large particles the concentration is low and the deposition velocity is high.

Particle deposition can be monitored by determining the change of surface cleanliness (number/m^2) over time (h).

Particle deposition rate is expressed in number of particles ≥ D µm per m^2 per hour (number/(m^2·h)). Particle size D is measured under a microscope and usually the diameter of the smallest circumferential circle is taken as the particle size. This is larger than the equivalent optical diameter unless the particle is perfectly spherical.

The symbol used for particle deposition rate is R_D. The particle deposition rate R_D can be used to calculate the expected contamination during exposure.

$$N_D = R_D \cdot a \cdot t$$

Where,

N_D = the number of particles ≥ D µm deposited onto the considered vulnerable surface,

R_D = the particle deposition rate for particles ≥ D µm expressed as number of particles per m^2·h,

a = the considered vulnerable surface area in m^2,

t = the time of exposure in hours.

It is normal to consider particle deposition during the operational state of occupancy, since there is no particle deposition during the at rest state of occupancy. Sometimes the number of particles deposited onto the considered surface is called particle fall out.

In general, for most particle sizes, the particle deposition rate R_D is proportional to the reciprocal of the particle size D. The particle deposition rate level L is expressed in the equivalent number of particles ≥ 10 µm per m^2·h.

$$L = R_D \cdot D/10$$

When the particle deposition rate level is known the particle deposition rate for the particle size of interest can be calculated by:

$$R_D = 10 \cdot L / D$$

The particle deposition rate level can be expressed in multiples of 10: L = 10, 100, 1000, etc. For some particle sizes the R_D that is calculated from the particle deposition rate level L, can be higher than measured.

In some applications, like for example optics, it is not the number of particles that is important, but the obscuration or area coverage. The area coverage caused by particle deposition is the sum of the cross-sectional area of the deposited particles A. The relation to the observed surface area a is the obscuration factor O:

$$O = A/a$$

The increase of the obscuration factor during exposure is the obscuration rate F:

$$F = O/t$$

The obscuration rate can be applied in a similar way to the particle deposition rate in order to determine the expected surface contamination in term of area coverage:

$$A = F \cdot a \cdot t$$

Measurement methods

The principles of the measurement of the particle deposition rate are described in ISO 14644-3:2019 [4]. The measurement is performed using a witness plate. The change of surface cleanliness during operational exposure is measured microscopically. This principle is also used in real time particle deposition rate monitors with a test surface [5,6]. The change of surface cleanliness of the test surface during the sample time is determined. Alternative particle detection methods applied to a witness or test plate can be found in [7,8,9].

The surface cleanliness of a witness or test plate before and after exposure is measured as a differential distribution of surface particles in a number of particle size bins. This distribution is recalculated into a cumulative distribution. The change of surface cleanliness can be expressed in the same manner as described in ISO 14644-9:2012 as the cumulative number of particles ≥ D µm per m^2 [10].

To determine the particle deposition rate of interest R_D the exposure time of interest should be known. This is normally the time of exposure during operation so as to determine the likelihood of contamination during operation.

The result of a particle deposition measurement is a cumulative distribution R_D per m^2 per hour. The particle deposition rate level L is the maximum product between R_D and the considered D.

If the measurements are in real time, the R_D data can be plotted against time. This will demonstrate the moments of high and low particle deposition.

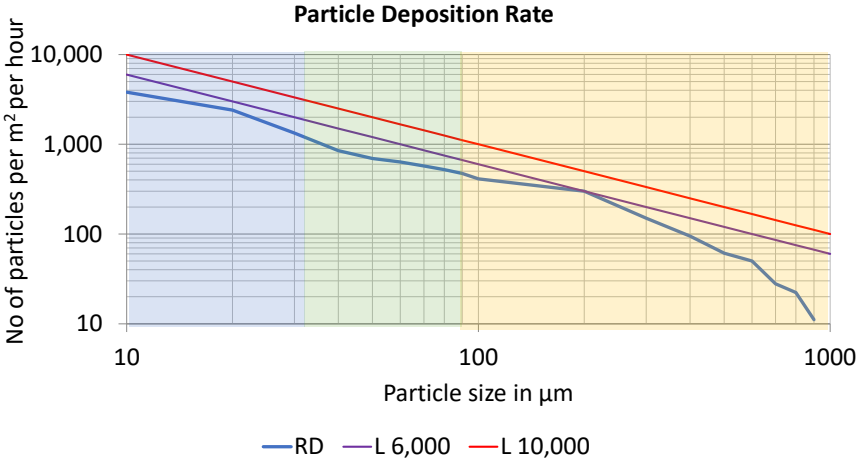


Figure 2. Cumulative particle deposition rate distribution log R_D – log D with particle deposition rate level lines

R_D can be plotted in a $\log_{10} R_D$ - $\log_{10} D$ diagram. The value of the tangent with directional coefficient -1 to this graph at D = 10 µm shows the particle deposition rate level L.

$\log_{10} R_D = -\log_{10} D + \log_{10} 10 + \log_{10} L$

Figure 2 shows an example. The tangent gives L = 6,000. The upper multiple of 10 is L = 10,000.

Some information on contamination risk of macroparticles , microbe carrying particles and visible particles can be found in references [11] and [12].

From practical experience it can be found that the cumulative graph can be divided into three sections as shown in Figure 2. In the example, the first section, starting with particles > 5 µm, shows the impact of the cleanroom ventilation. This section goes up to around 30 µm which is the largest particle for which the removal efficiency is 75 % or more and is also the approximate size at which particles become visible. The middle section, of particles between 30 µm and 100 µm, is mainly influenced by personnel and their discipline. For particles > 100 µm, the deposition rate is mainly influenced by the cleaning program. Overall, the level is usually determined by the number of personnel. In Figure 2 the actual particle deposition rate level is determined by particles (probably fibres) > 200 µm. Deposition of particles increases the number of surface particles. External forces like footsteps and turbulent airflow can cause particles to re-enter the air and deposit elsewhere. The particle deposition rate can be reduced by improvement of cleaning at the monitored location.

Setting limits

A risk assessment can provide the data necessary to set limits. Some information on contamination risk of macroparticles, microbe carrying particles and visible particles can be found in references [11] and [12].

Where the critical particle size and the minimum acceptable surface cleanliness of a product or process surface is known, the particle deposition rate limit for the critical location on the exposed critical surface can be determined by dividing the acceptable cumulative number of critical particles N_D onto the product by the critical surface area a in m² and by the operational time of exposure t in hours:

$$R_D = \frac{N_D}{a \cdot t}$$

The associated particle deposition rate level is then:

$$L = \frac{R_D \cdot D}{10} = \frac{N_D \cdot D}{10 \cdot a \cdot t}$$

The lower the acceptable number of particles, and the larger the vulnerable area and time of exposure, the lower the particle deposition rate level should be.

Establishing control

To establish proper control a clean controlled environment must be established. This should be a separated room in which the introduction of airborne particles is limited, airborne particles can be removed by clean airflow and surface particles removed by effective cleaning.

ISO 14644-17 uses the work of Hamberg to find a relation between particle deposition rate for particles ≥ 5 µm per m²·h, R5, and air cleanliness level for particles ≥ 5 µm per m³, C_5, at the critical location [13]. This is the resulting equation:

$$C_5 = \frac{R_5^{1.294}}{295}$$

This can also be recalculated using particle deposition rate level L:

$$C_5 = \frac{L^{1.294}}{120}$$

The required cleanroom air cleanliness for particles ≥ 5 µm in the operational state of occupancy should be better than the calculated local air cleanliness for particles ≥ 5 µm C_5. Guidance on design and construction is given in ISO 14644-4 [14].

Where a cleanroom requires control of macro-particles and visible particles, the necessary facilities and procedures should be considered at the design stage. These should include entry and exit facilities and procedures for personnel and material, garment change procedures and cleaning procedures. ISO 14644-5 provides guidance on operational procedures [15]. ISO 14644-14 provides guidance on the suitability of equipment to be used in the cleanroom in terms of emissions of macro-particles [16]).

Demonstrating control

ISO 14644-2 provides guidance on how to select locations for monitoring, method and frequency [17]. During operation the particle deposition rate can be monitored to demonstrate that the particle deposition rate or particle deposition rate level are within the set limit. Alert and action levels can be applied as limit values. In case the particle deposition rate exceeds a limit value, measures should be taken to reduce the particle deposition rate. Realtime data help to find the cause of particle deposition events so working procedures can be improved. The cumulative particle size distribution provides information that can be used to decrease the particle deposition level. The first step is usually the improvement of local cleaning, room cleaning, cleaning off incoming goods, then attention should be given to garment choice and changing procedure.

Example

A simplified example is taken from a case of the assembly of an inkjet printhead for production printing applications [18]. The critical particle size is 25 µm. The critical product area is 10 cm². The exposure time is 2.5 hours. The maximum number of critical particles that is acceptable on the critical surface is 4 particles ≥ 25 µm.

Therefore, the final cleanliness should be better than 4 x 25 / 10 = 10 particles ≥ 1 µm per cm², which is equal to ISO SCP 5 for particles ≥ 25 µm.

The initial surface cleanliness is 4 particles ≥ 1 µm per cm² (ISO SCP 4.6).

Then the acceptable increase is 6 particles ≥ 1 µm per cm², 60,000 particles ≥ 1 µm per m² or 6,000 particles ≥ 10 µm per m².

The acceptable particle deposition rate level L is 6,000/2.5 = 2,400 particles ≥ 10 µm per m²·h.

This means the air cleanliness levels for particles ≥ 5 µm at the critical location C5 = 2,4001,294 /120 = 198 particles ≥ 5 µm per m³. The means that the operational air cleanliness class for particles ≥ 5 µm during operation should be about ISO 5.5 (≤ 93 particles ≥ 5 µm per m³). In order to achieve control of visible particles full occlusive cleanroom clothing and daily cleaning was required and proved to be sufficient.

If the exposure time were reduced from 2.5 to 1.5 hours the requirements would be less strict and the acceptable particle deposition rate level L would be 6,000/1.5 = 4,000 particles ≥ 10 µm per m^2·h.

In this case, $C_5 = 4{,}000^{1{,}294}$ /120 = 382 particles ≥ 5 µm per m^3, which means that the operational air cleanliness class for particles ≥ 5 µm during operation should be about ISO 6 (≤293 particles ≥ 5 µm per m^3) plus proper control of visible particles.

Conclusion

In cleanroom technology the focus has always been on the control of airborne particles up to 5 µm. There are many applications that are threatened by macro particles or even visible particles. The new standard ISO 14644-17 provides guidance on the control of macro particle contamination. New measurement instruments make it possible to monitor the established control and to find measures to keep the particle deposition rate within required limits.

References

1. ISO 14644-1:2015 Cleanroom and associated controlled environments: *Classification of air cleanliness by airborne particle concentration*
2. ISO 14644-17:2021 Cleanroom and associated controlled environments: *Particle deposition rate applications*
3. Whyte W and Agricola K, *Comparison of the loss of macroparticles and MCPs in cleanrooms by surface deposition and mechanical ventilation*. Clean Air and Containment Review. 2018, Issue 35, pp 4-10. http://eprints.gla.ac.uk/167850/1/167850.pdf
4. ISO 14644-3:2019 Cleanroom and associated controlled environments: *Measurement methods*
5. Agricola K, *Realtime particle deposition monitoring*. Journal of the IEST 2016, 59(1) pp4-8
6. Agricola K, *Realtime obscuration monitoring*. SPIE Proceedings. 2016, 9953: Systems Contamination: Prediction, Control, and Performance. Doi:10.1117/12.2237260
7. Tovena-Pecault I, Godefroy P, Escoubas L. *Qualification testing of an innovative system for monitoring particle contamination fall out*. Sensors and Actuators: A. Physical. 2017, 253, pp181-187
8. Holland A, Shaylor A, Holland K, Colebrook D, Boada IL and Rampini R, *The PFO 1000 Monitor: A Real-Time, In-Situ, Automated Instrument For Monitoring Particulate Fall-Out In Clean Environments*, ISCC 2018 Proceedings pp568-576 published by VCCN
9. Jong A de, Oostrom S, Donck J van der, Zwan B van der, Speet B, *Fast Particle Cleanliness Monitoring Of High Tech Product Surfaces*, ISCC 2018 Proceedings pp212-219 published by VCCN
10. ISO 14644-9:2022 Cleanroom and associated controlled environments: *Assessment of surface cleanliness for particle concentration*
11. Whyte W, Agricola K and Derks M, *Airborne particle deposition in cleanrooms Calculation of product contamination and required cleanroom class*. Clean Air and Containment Review. 2016, Issue 26, pp4-10.
12. Ashtekar D, *Strategies for the Control of Visible Particles in Sterile Devices*. Journal of the IEST 64- 1 © 2021
13. Hamberg O, Particle fallout predictions for clean rooms. The Journal of Environmental Sciences. 1982, 25, pp.15-20
14. ISO 14644-4:2022 Cleanroom and associated controlled environments: *Design, construction and start up*
15. ISO 14644-5:2004 Cleanroom and associated controlled environments: *Operations*
16. ISO 14644-14:2016 Cleanroom and associated controlled environments: *Assessment of suitability for use of equipment by particle concentration*
17. ISO 14644-2:2015 Cleanroom and associated controlled environments: *Monitoring to provide evidence of cleanroom performance related to air cleanliness by airborne particle concentration*
18. Agricola K, *Contamination control applied to inkjet printhead*, ISCC 2018 Proceedings pp371-382 published by VCCN

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He has written various papers on the determination of requirements of cleanrooms, operational procedures and monitoring of surface contamination.

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Environmental Monitoring in Advanced Therapeutic Medicinal Products (ATMP) facilities

Mark Hallworth

Abstract

With the increase of Advanced Therapeutic Medicinal Products (ATMPs), therapy development, and available marketed products, the modern manufacturing process must meet relevant regulatory requirements. ATMPs are pharmaceutical products or drugs; ATMPs require the cellular product to be modified, not simply transplanted. Where more complex cell therapy manufacturing is required or cells are used in the treatment of a different organ, the processes must adhere to different regulatory agency approvals to ensure they are manufactured in facilities that pose low risk (or acceptably low risk) to the patient. The FDA and EMA are responsible for ensuring the safety, efficacy, and compliance with Good Manufacturing Practices for manufacture.

The primary importance of environmental monitoring for ATMP facilities is therefore to demonstrate the highest degree of control over the aseptic manufacturing environment and the potential for cross contamination between batches / manipulations

These GMP requirements include environmental monitoring in critical areas and take into consideration the special requirements that ATMP production requires. The use of standard environmental monitoring technologies can be adapted to suit ATMP production, and where possible, implementing new technologies can reinforce the contamination control strategy for the overall risk management of production environments and workflows.

Overview of Process

Preparation of typical ATMP products differs from traditional biopharma product manufacturing as it is produced from cells initially obtained from the recipient patient. The cells are collected, modified per therapy type, and returned to the donor patient. As the process and product are unique to an individual patient, ATMP batch volumes are small scale and do not use certain sterilization steps that might damage the finished cellular product. Because of this, the process flow must be aseptic to prevent contaminant risk and, importantly, to prevent cross contamination between batches. Gene therapy is slightly different in that cells taken from a patient may be modified to suit a wider population of potential patients, and although batch sizes may be larger than individual cell therapy batches, they are still small scale relative to classic pharmaceutical drug manufacturing.

These small batches are predominantly manually manipulated through the stages of the process and, the potential for risk to the aseptic environment is more pronounced. A switch to isolator glove boxes reduces the exposure of external contamination but makes some manipulations more difficult; robotics is being investigated to move the whole process to a 'single box' manufacturing format, as scales increase.

Environmental Monitoring

The primary importance of environmental monitoring for ATMP facilities is therefore to demonstrate the highest degree of control over

- The aseptic manufacturing environment
- The potential for cross contamination between batches / manipulations

There are two primary processes, Open processing and Closed processing.

Where open system manufacturing is performed, the processes must be maintained under Grade A (ISO5), with unidirectional airflow, and within a Grade B (ISO7) room environment. These environments pose the greatest risk of contamination from the ambient environment as operators (the primary source of contamination) are near the processing performed; operators reach into the process to perform routine functions.

Closed processing isolates the room environment from the processing environment, and access to perform manipulations is executed via glove ports fixed within the isolator. Isolators also offer an opportunity to automate CIP/SIP processing.

Environmental Monitoring to Demonstrate Aseptic Control

Looking to regulatory guidance on how best to perform monitoring in aseptic manufacturing, the EU GMP Annex 1 (recently updated and released in August 2022) has information for the demonstration of control over the aseptic environment, specifically the Grade A critical areas – see Figure 1. The environment needs to be rigorously monitored to ensure that there is full and constant awareness of current conditions, including the detection of periodic events which could be catastrophic if gone unnoticed. Constant monitoring creates a continuous flow of information, resulting in a large quantity of data which can be analyzed for trends.

Therefore, the manufacturing facility should have a comprehensive environmental monitoring program, which includes monitoring for non-viable airborne particles, viable airborne particulates, surface viable contamination, and personnel, in the aseptic areas. These procedures should address frequencies and locations for the monitoring sample points, warning and alarm limits for each area, and corrective actions which need to be undertaken if any of the areas show a deviation from expected results. Actions taken when limits are exceeded should include an investigation into the source of the problem, the potential impact on the product, and any measures required to prevent a recurrence.

A Contamination Control Strategy (CCS) will include the environmental monitoring program and should be implemented across the facility. The CCS should define critical control points as part of a risk assessment and assess the effectiveness of the controls and monitoring measures used to manage risks associated with contamination.

Monitoring should be performed using suitable techniques that meet the needs of the Risk Assessment. The Grade A areas should be monitored continuously (for particles ≥0.5 and ≥5 µm) and with a suitable sample flow rate (at least 28.3 LPM / 1 CFM) so that all interventions, transient events, and system deterioration are captured. The system should frequently correlate each individual sample result with alert levels and action limits.

This should be done at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded.

Grade	Maximum limits for total particle ≥ 0.5 $\mu m/m^2$		Maximum limits for total particle ≥ 5 $\mu m/m^2$	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined[(a)]	29 300	Not predetermined[(a)]

(a) For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and on routine data, where applicable.

Note 1: The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period defined during qualification (guidance value of less than 20 minutes) in an unmanned state, after the completion of operations.

Note 2: The occasional indication of macro particle counts, especially ≥ 5 µm, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration system, equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation.

Figure 1: Maximum permitted total particle concentrations for monitoring from EU GMP Annex 1:2022 (Table 5)

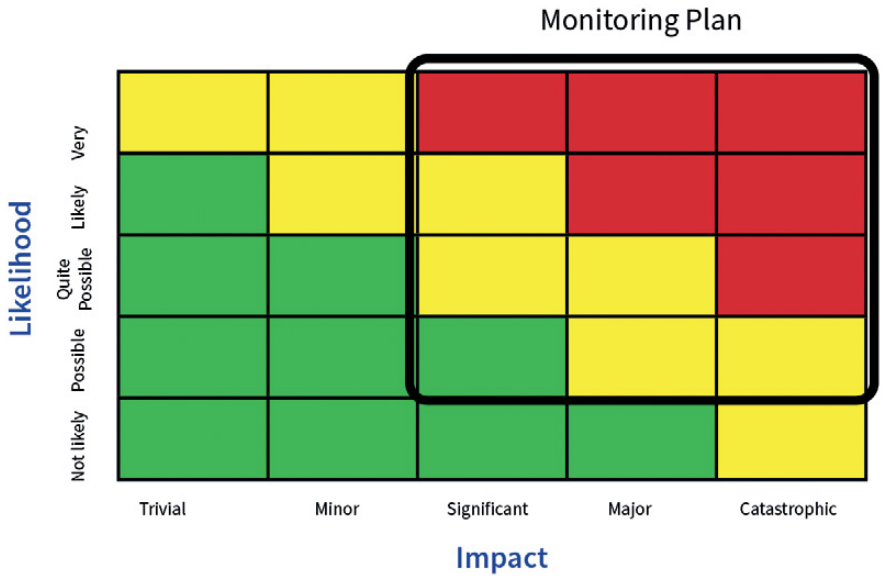

Figure 2: Risk assessment to determine monitoring plan

Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

The requirement for continuous monitoring within Grade A areas is satisfied by using point of use dedicated sensors; these are connected to a central monitoring software application that can send alarm outputs to operators within the cleanroom or messages to relevant groups. These alert and alarm excursions are also permanently recorded in the audit trail of the system.

Risk Assessment – Part 1

One aspect of the system is the location of the sample points; these should be determined following a documented Environmental Monitoring Risk Assessment (EMRA) – see Figure 2 – and should include the following information:

- Sampling locations
- Frequency of monitoring
- Monitoring method used and
- Incubation conditions (e.g., time, temperature(s), aerobic and/or anaerobic conditions).

The risk assessment is based on inputs from the different groups within the facility.

Instrumentation used in constructing an integrated solution and, as shown in Figure 3, will typically include:

Particle Counting – The need for continuous data requires a dedicated sensor at each location that samples continuously during the set-up and production phases of manufacturing. Sample points will be mounted within the hood or isolator line and connected to the sensor via a short length of sample tubing (no more than 2 m, ideally shorter). The location and orientation of the probe are dependent on the findings of the risk assessment.

Microbial Sampling – Where a risk has identified the need for total particle counting, there is an associated requirement for microbial sampling.

Active Air Sampling – Only the sample head is placed within the environment, ensuring that any sample is not exhausted locally within the critical space. The sampling is quantitative and can run continuously for up to 4 hours. Start and stop controls are performed via the software interface.

Static/Passive Air Sampling – Here, a plate is placed in the local environment for a period of up to 4 hours and is an additional valuable data point in the overall understanding of the microbial risk. The active nature of impaction sampling can damage certain microbiology, and although this technique does not need to be part of routine monitoring, it should form an aspect of qualification studies and the EMPQ (Environmental Monitoring Performance Qualification).

Rapid Automated Microbial Monitoring (RMM) – The use of autofluorescence microbial instrumentation, capable of differentiating inert and biological particles in real-time, adds a new determinant in how the environment is demonstrated as being in control. In conjunction with total particle and active and passive air sampling, it adds value in making fast decisions relative to lost control of an area.

Demonstration of asepsis and sterility is not guaranteed by a single piece of evidence alone, this is the introduction to the environmental monitoring chapter in EU GMP Annex 1.

9 Environmental and Process Monitoring

9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particle contamination.

It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS [Aseptic Process Simulation]) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. *When considered*

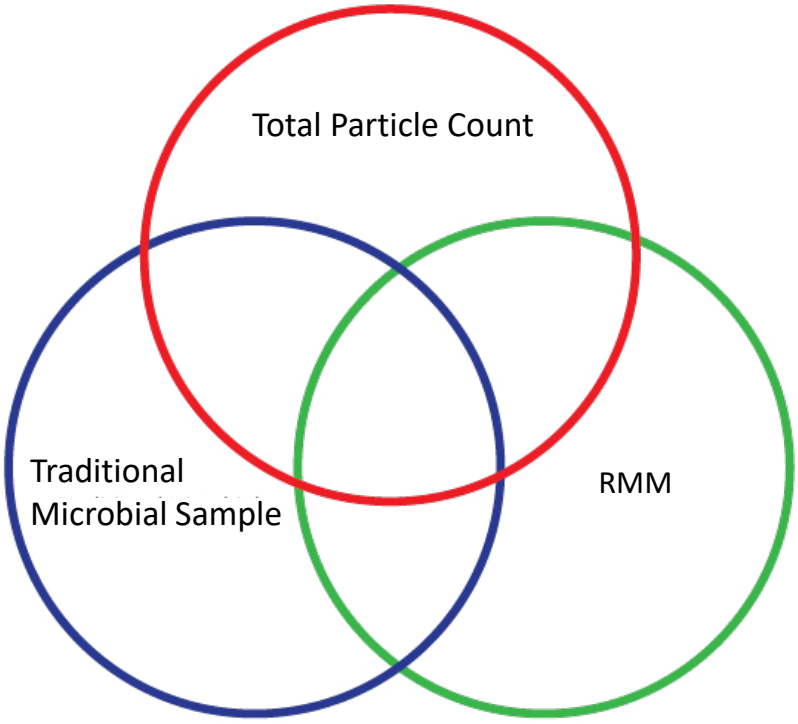

Figure 4: Venn diagram to illustrate the overlap of particle and microbial data

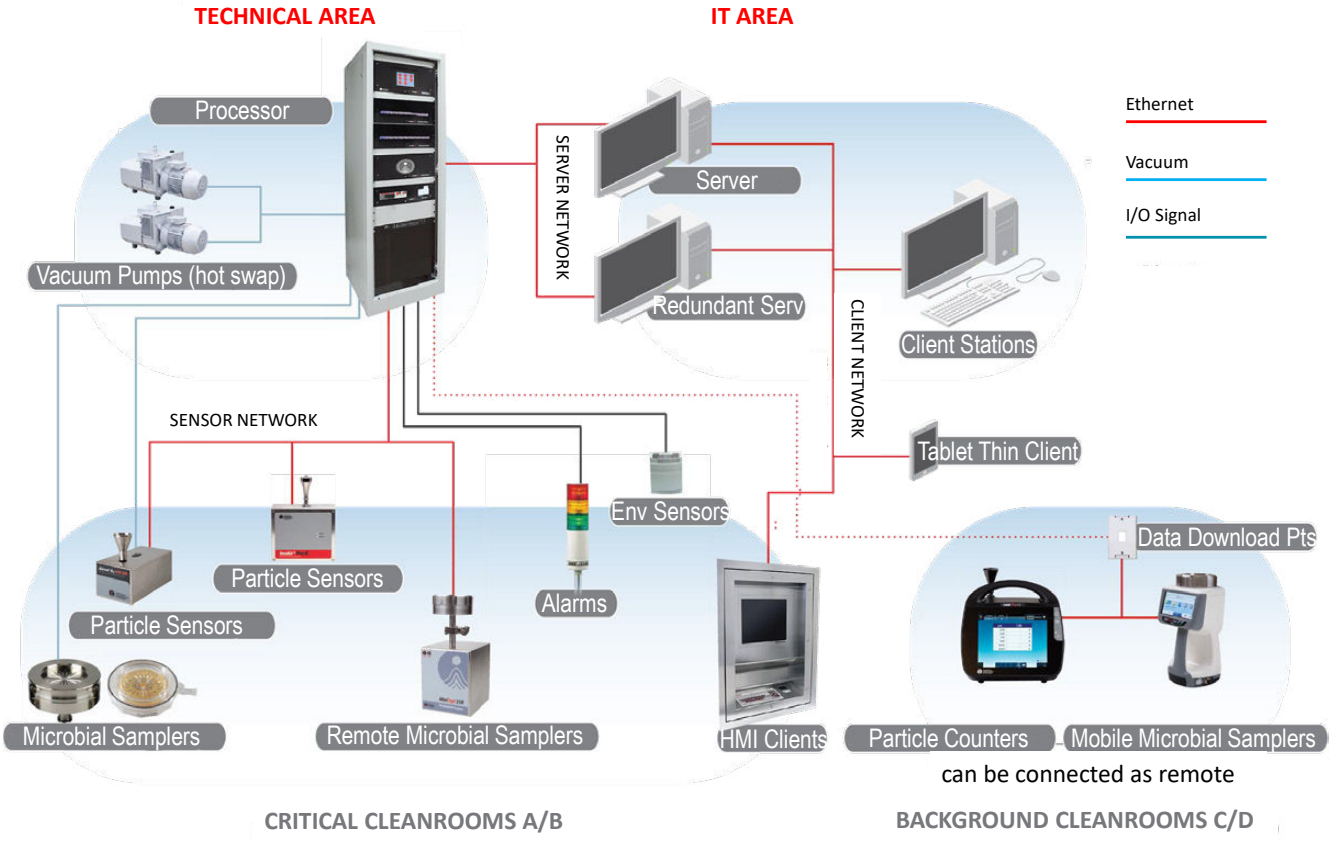

Figure 3: Schematic of theoretical Facility Monitoring System configuration

together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.

It is an accumulation of data and information that leads to a complete understanding of the effectiveness of the environmental controls put in place. The overlap of particle and microbial data as illustrated by the Venn diagram in Figure 4 has been the established approach for demonstration of environmental control for over 20 years. Ideally no ≥ 5 µm should exist. Where such particles are found, they may either be a potential for carrying microbiological agents or they may be clusters of microbiological entities capable of sustaining viability in the dry air associated with cleanroom environments. This can be verified by traditional microbiology and RMM. If microbial agents are present on the particles, they may be potentially harmful.

A continuous monitoring system will use tags in the data to isolate each batch record without the need to stop monitoring.

Environmental Monitoring to demonstrate cross contamination control

The resilience of a program to demonstrate cross-batch contamination, or intra-batch contamination, relies on the type of processing performed.

Many facilities use individual rooms per batch; a single cleanroom is dedicated to one product batch for its processing stages and filling. Each room features a central bio-safety hood within a Grade B background. Operators within each space are responsible for maintaining the preparation, gowning, cleaning, and environmental monitoring required. The sample point location(s) may need to reflect the different activities within the hood / room, and flexibility in design of the monitoring system is required. Once a process has been completed, the room can be prepared for the next batch of product. The environmental monitoring performed at the beginning and end of each batch demonstrates separation and the effectiveness of the cleaning and sanitization protocols. A continuous monitoring system will use tags in the data to isolate each batch record without the need to stop monitoring. This allows for easy transitions between phases of the process; separate recipes associated with each phase can assign appropriate alert and action limits prescribed for those activities.

In cleanroom operations where a production line process is established

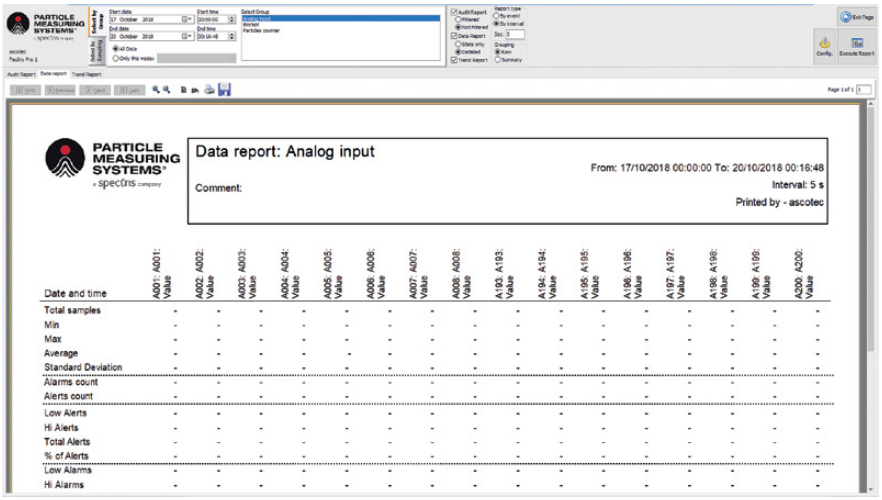

Figure 6: Screenshot of a report from the Report Generator

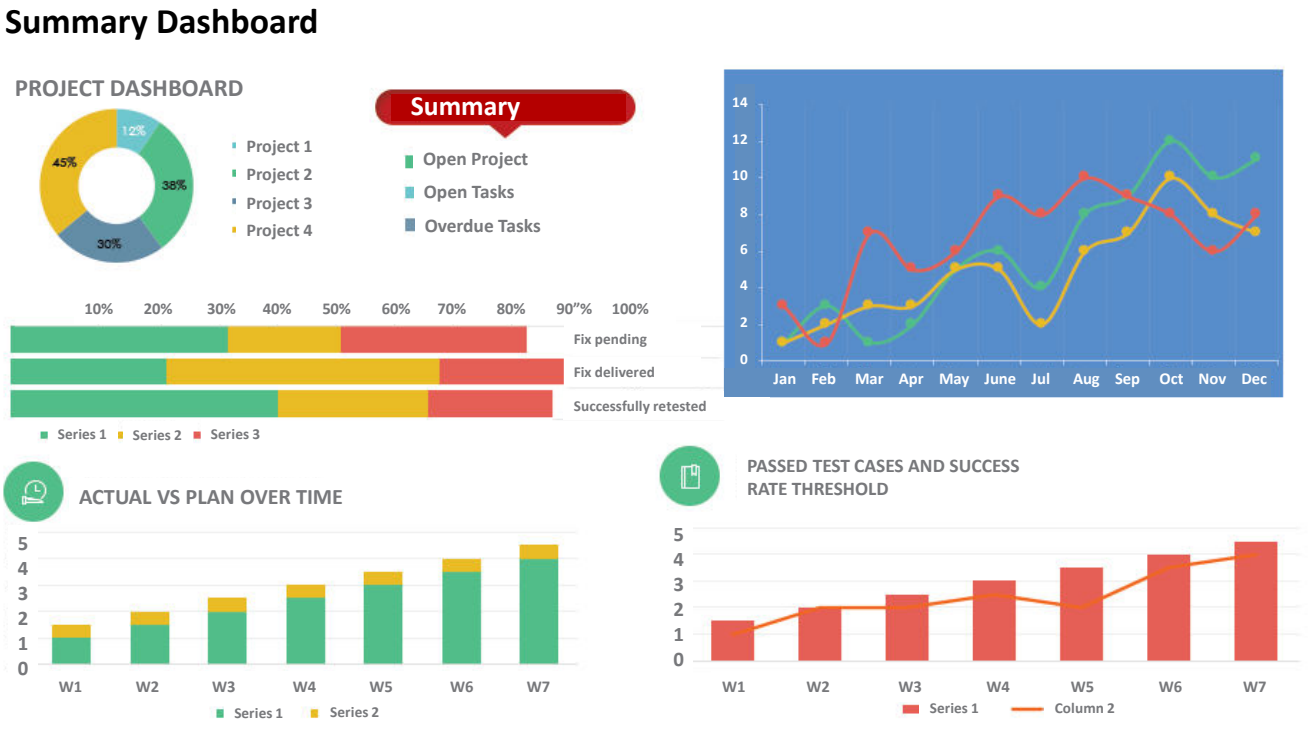

Figure 5: Data and status information display

(i.e., where one product manipulation is performed at a single stage and then moved forward along the process for subsequent steps), the location of the environmental sample probe can be better aligned with the process. Each step can be monitored continuously, and during the 'at rest' phases between batches, unique data identifiers can be added via bar codes. A final report showing the progress and rest phases can be generated at the end of processing. Where processing occurs within different modules of an isolator, it is possible to sanitize between batches, where required. Alternatively, sanitization and surface monitoring can be performed to demonstrate compliance. For QbD (Quality by Design) operations, the process can be validated and tags in the data can show that specific functions for intra-batches occurred and the system is not as reliant on finished product testing as previously may have been established.

There is a third hybrid operation where functions can be grouped into those being performed in lower grade zones and those that must be performed under unidirectional airflow. The tracking of data in these applications becomes a key for reporting. Batch identification tags within the data (bar codes, RFID, etc.) allow for easier reporting of the finished product. Intra-batch isolation becomes focused on critical risk activities, and monitoring is continuous throughout.

Environmental Data Reporting

Data and Status Information Displays – As the data being collected is now multivariate, a central reporting tool is applied; the data from various environmental components, along with the tagging of product through production, allows for a visualization of the facility layout with dashboards for current data and status information for each batch relative to the room and stage it is currently at.

Data, status, and sampling information can also be viewed for each dedicated area on a single screen as shown on Figure 5.

Report Generator – The software requires a data report generator capable of providing reports for all recorded data as human readable: audit trails (events), data/statistical summaries, and trend charts. The system should be capable of retrieving data historically (as defined in the site User Requirement Specification) for the associated system. Using filters for data, time, location, and batch, data should be readily accessed and, where required, exported, or printed to support the release of product. A typical report from the system is shown at Figure 6.

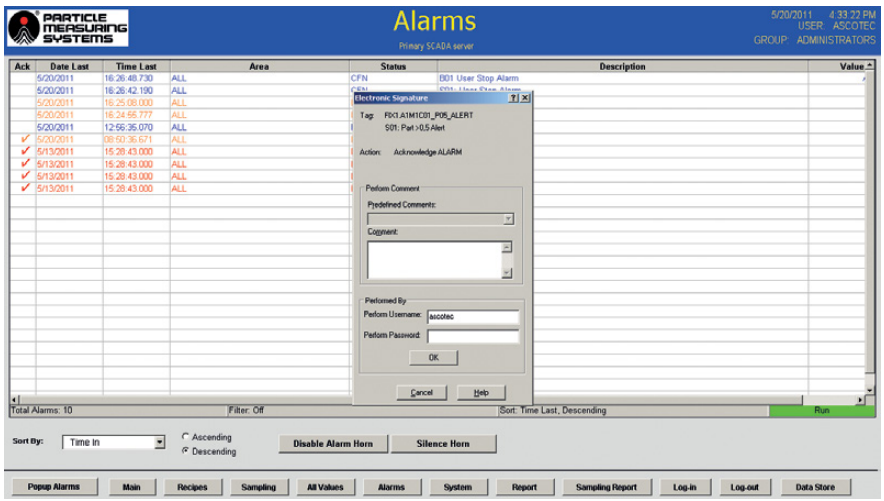

Figure 7: Screenshot of an alarm display

Alarms – The establishment of appropriate alarms based on the product and process steps can be tracked and reported via the dashboard interface. The display provides an alarm acknowledgment function; date, time, area, description, and other information for alarms; and the capability to sort alarms by different criteria.

Alarms based on trends should include a review of the process to determine any increasing excursions from action limits or alert levels. The identification of consecutive or frequent excursions from alert levels may identify a common cause. For microbial limits, it is important to consider not only the quantity of CFU detected but also any change in qualitative information, such as type and the predominance of specific organisms. A screenshot of an alarm display is shown at Figure 7.

Risk Assessment – Part 2

The information gathered in processing environmental data should feed back into the production activities. Operations should be reviewed when certain functions create an environmental concern: elevation of baseline values increasing towards alert or actionable thresholds. The review should be a gap analysis between the initial risk assessment and either a review of the control point and any associated changes for improvement or enhanced / additional monitoring to ensure coverage of potential functions that may cause future defects.

Summary

A continuous monitoring system for environmental parameters (including total particle, traditional microbiology, rapid microbiology, air velocity, temperature, humidity, air exchange rates, etc.) will establish the required demonstration of maintenance of the cleanroom. The association of the data to the batch will also allow for demonstration that intra-batch separation is established and maintained, and records of sanitization can be added to complete the batch record. All the data can be visualized on a central dashboard allowing for fast, accurate analysis.

Mark Hallworth is the Life Sciences Regional Manager for Particle Measuring Systems. He has lectured for pharmaceutical societies throughout Europe, Asia, and the US on nonviable particle and facility monitoring and the implications of validating those systems.

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Control of viruses within cleanrooms: A review of disinfectant agents

Tim Sandle

Abstract

This paper identifies the risks of contamination by viruses in the manufacture of biopharmaceutical products in cleanrooms. Different types of viruses are described with non-enclosed viruses being more resistant to disinfectants. Care should be taken as many common disinfectants are only suitable for bacterial or fungal contamination. A table gives guidance on the selection of appropriate disinfectant types to deal with viral contamination.

Introduction

Viruses pose a risk to the manufacture of many types of biological products and control of viruses is an important consideration for manufacturers of biopharmaceutical products. Viruses are of particular concern since they are generally more difficult to detect than other microbial contaminants. At risk biopharmaceutical products include:

- Products produced from *in vitro* culture of cells lines of animal or human origin;
- Products produced from *in vivo* culture of cell lines;
- Products produced from organs or tissues of human origin;
- Products produced from blood or other human fluids.

Viral contamination can affect raw materials, cell culture processes, bioreactor contamination and downstream processing. It is for these reasons that pharmaceutical organizations need to practice viral safety and incorporate virus clearance into the manufacturing process.

While the broad focus of virological control is with the purity of cell cultures and the deployment of techniques to remove or inactivate viruses within the bulk pharmaceutical product (such as heat, pH adjustment, use of a solvent-detergent or nanofiltration), an additional important area is disinfection. The application of a biocide for controlled environments used for the manufacture of biopharmaceutical products is an essential part of contamination control, especially to address adventitious and endogenous viral contaminants during purification of the product.

Many types of viruses pose contamination risks to biopharmaceuticals during processing and the majority of these will be located on cleanroom surfaces. Outside of a host cell, viruses cannot replicate. However, they can survive on surfaces as viral particles (virions) (1). Most literature for pharmaceutical manufacturing focuses on disinfectants used to address bacterial or fungal contamination. This articles looks at the selection and factors for success relating to disinfectants for the control of viruses.

Contamination concerns and regulatory requirements

Viral safety is necessary either to preserve the intended properties of the product (such as the maintenance of cell lines) or to protect the patient from harm. Complete viral safety, as defined by absolute freedom from extraneous viral agents, is not easy to achieve and some would argue that it is an impossible task due to the range of viruses. Nonetheless, the responsibility of manufacturers is to ensure that an identified range of pathogenic viruses and any residual pathogenicity is not present in the drug product.

The greatest risks in the processing stages are:

- Contamination in incoming materials and excipients, including animal-derived additives such as bovine serum albumin.
    - Many incidents of viral contamination stem from using poorly characterized materials.
- Contamination of cell lines.
- Contamination in purification and formulation reagents.
- Presence of impurities leading to viral stability in the process.
- Failure of controls within a viral secure area.
- Accidental contamination of a production system.
- Incomplete inactivation of live viruses used in biopharmaceutical production.
- Infected donor when the source material is human plasma. This is an additional complication with blood and plasma products.

These risks can become elevated if:

- Changes in critical process parameters that alter the safety profile take place;
- Virus detection systems fail to detect low levels of viruses.
    - Weaknesses with current molecular methods include limited assay sensitivity (enhanced by the low volume of sample volumes assayed); limitations with detection methods; and the unavailability of permissive cell lines to detect viral variants.
- Data errors occur, for example, with the extrapolation of viral inactivation data.
- Cleanrooms are poorly maintained, including air filtration and inadequate cleaning and disinfection practices.
- New and emerging viral risks are present.

The primary regulation for viral safety is ICH 5A "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (2). In addition, there has been increased regulatory scrutiny of incidents relating to adventitious viruses in manufacturing processes.

Different types of viruses and responses to disinfectants

Viruses are composed of DNA (such as herpes viruses) or RNA (such as hepatitis viruses) encapsulated by a protein coat. Viruses can be enclosed

in an envelope made of proteins (capsid), carbohydrates, and lipids (enveloped) or alternatively they are non-enveloped. An example of an enveloped virus is herpes. Enveloped viruses can be subdivided based on the proportion of lipophilic particles, where an example of low lipid content is vaccina, and of high lipid content is flaviviruses. Of the enveloped viruses, larger viruses are generally more sensitive to disinfectants (3). An example of a non-enveloped virus is parvovirus. This distinction is important since, generally, non-enveloped viruses are the most difficult to inactivate. The reason for this is because it is easier for a disinfectant to interfere with the envelope by breaking the lipids that form the envelope structure. The lipid envelope is the mechanism such viruses use to infect the host cell, and hence chemicals that interfere with the envelope reduce virus infectivity. In contrast, non-enveloped viruses have a protein coat and inactivation using a disinfectant requires penetration and denaturation of the viral capsid or replicative proteins (4). Therefore, the viruses most resistant to disinfectants are small, non-enveloped viruses.

Cleanrooms and viral control

In cleanrooms, viral control is achieved through air systems, cleaning and disinfection and with segregation and personnel controls. With the latter, facilities should operate 'viral secure areas' with dedicated spaces, personnel and clothing requirements, especially for stages of manufacturing that occur post-viral inactivation or removal. These tend to be closed processes.

The extent of the risk of any viral airborne transmission will depend on whether viruses enter the area intended to be excluded and then in part on the concentration of viral genetic material and viral particles (virions) contained within the cleanroom air. As with microbial contamination, the primary process to create 'cleanliness' is by passing air through a HEPA filter. While standard cleanroom HEPA filters are only certified in relation to their ability to remove particles from the air of a size of ≥0.3 µm to a given efficiency rating, HEPA filters are capable of removing particles of a smaller size. To support this, some HEPA filter manufacturers have undertaken testing in relation to virus removal (although different types of viruses and different viral challenges will have been used in the absence of any standardization). The reason why HEPA filters can capture smaller particles (and most likely a large number of viral particles) is due to one of the mechanisms of particle capture: diffusion. This was demonstrated in one study where silver particles – at 5 nanometers (challenge particles smaller than most viruses) – were shown to be captured with a 99.99% efficiency using a cleanroom grade HEPA filter. This was evaluated using an Ultrafine Condensation Particle Counter. The functionality of HEPA filters can potentially be enhanced through viral inactivation measures like ionisation technologies or germicidal ultraviolet light.

The other area of control is through disinfection.

Cleanroom disinfectants for virus control

Within the cleanroom context, the term 'disinfectant' is more commonly reserved for the elimination of a microbial population on an inanimate object, such as the range of surface materials used for cleanroom fabric and equipment. These are commonly selected and assessed for their abilities to kill or inhibit the growth of vegetative bacteria and fungi (and, as a special class of agents, against bacterial and fungal spores). It may also be that the selected disinfectant for a cleanroom is capable of addressing a specific viral concern. In this context, a viricidal disinfectant is different to an "antiviral" compound which inhibits virus replication in host cells (5). Acceptable viricidal disinfection is typically expressed as a reduction of a virus titre by greater than 99.9%, under experimental conditions. A non-pathogenic bacteriophage or other model virus such as adenovirus or murine norovirus is typically used. Designing efficacy tests is not straightforward and specialist laboratories are required to prepare test suspensions (by infecting monolayers of cell lines), and to evaluate

Table 1: Disinfectant efficacy against enveloped and non-enveloped viruses

Disinfectant	Enveloped virus	Non-enveloped virus
Bases	+	+/-
Acids	+	+/-
Peracetic acid	+	+
Hydrogen peroxide	+	+/-
Formaldehyde	+	+
Glyoxal	+	+/-
Glutaraldehyde	+	+
Phenolic compounds	+/-	-
Quaternary ammonium compounds	+	-
Amphoteric agents	+	-
Ethanol	+	+/-
Iso-propyl alcohol	+	-
Butanol	+	-
Iodine and iodine compounds	+	+/-
Chlorine and chlorine compounds (such as chlorine dioxide) (5,000 ppm or above is generally classified as viricidal)	+	+
Other oxidising agents (oxygen bearing compounds)	+	+

Key:

+	Effective at inactivating viruses
-	Not effective at inactivating viruses
+/-	Variable effect

test data for titre reductions using end point dilution techniques.

To assess which disinfectants are effective for the inactivation of viruses within cleanrooms, it important to understand the differences between virus structures, surfaces interactions, and disinfectant chemical types.

Viral structure and disinfectant types

Enveloped viruses are easier to inactivate using chemical disinfectants compared with non-enveloped ('naked') viruses. This is the case across several classes of agent with disinfection properties (6-9), according to Table 1 which has been drawn up from different studies using manufacturer's recommended concentrations and levels of activity where applicable (such as free chlorine).

Inactivation refers to actions that destroy viruses or alter their surface structures to prevent them from infecting potential host cells. With 'variable effect' this relates to inconsistent data from laboratory studies and in relation to factors like surface age. In each case, the surface is taken to be 'clean'.

From the table, the most efficacious agents against non-enveloped viruses are strong oxidising agents (10). Of these agents, peracetic acid and chlorine dioxide are shown by studies to be the most effective (a relatively high concentration of hydrogen peroxide is required to equal the viricidal effect of chlorine, for example; and peracetic acid is a more potent oxidiser). These agents are not without variation since chlorine based disinfectants lose efficacy as the pH increases and peroxides are far more greatly affected by the presence of soiling on a surface (hence very clean surfaces are required in order for disinfectant activity to be optimal).

From the personnel hygiene perspective, alcohols – as would be used as hand sanitisers – are not particularly effective against non-enveloped viruses like norovirus due to their lipophilic nature (11). Methanol displays some efficacy against non-enveloped viruses with no lyophilic nature but it is not used due to toxicity to humans, and butanol displays some efficacy to non-enveloped viruses with a slight lipophilic nature; however, butanol is unsuitable as a disinfectant due to its odour (12). This leaves the cleanroom manager with a choice of ethanol, n-propanol, or iso-propanol as choices, and none of these offer a complete control solution. It is of interested that one of the most widely used cleanroom disinfectants - quaternary ammonium compounds – demonstrate weak viricidal properties.

Factors influencing viral survival on surfaces

The survival or viruses on surfaces is variable. Depending on the type of surface and ambient conditions, viruses can persist for as little as 5 minutes to greater than 28 days (13).

In terms of factors influencing the efficacy of viricidal disinfectant, viruses that become dried onto surfaces are generally more challenging to inactivate than viruses suspended on surfaces (such as in the form of droplets) or in air or liquids (this excludes consideration of viruses in association with people, such as on the skin or contained within the mucous membranes). It follows that viruses dried onto surfaces where soiling is present are more challenging still, since many types of soiling provide clumping protection to viruses (preventing penetration or interaction with the disinfectant to reduce the potency of the active ingredient) and also to stabilise the virus (14, 15). This is a further reason why cleaning prior to disinfection is beneficial (16). While the primary purpose of cleaning using a detergent is to remove or disassociate soil, the act of cleaning also helps to hydrate dry matter, including viral particles, thereby increasing disinfection success (17).

Application techniques are also of importance. As with disinfection aimed at addressing bacterial contamination, the spray-wipe-spray method of surface disinfection (or the use of pre-saturated wipes) using the conventional cleanroom "one site, one direction, one use" wiping method is superior to simply spraying a surface with the disinfecting agent (18). Physical activity aids disassociation from surfaces and distributes the disinfectant more evenly ensuring contact with viruses.

Factors influencing disinfectant efficacy

The key factors that influence the efficacy of disinfectants against viruses include the contact time, concentration of disinfection agent, and the type of virus (19). These come together in the Chick-Watson law (20):

$$Log_{10}\frac{N}{N_o} = -kCT$$

Where:

N_o is the original microbial population
N is the final microbial population
C is the disinfectant concentration
T is the contact time.
k is the inactivation rate constant (which will be specific to the microorganism).

This law indicates that a decrease in disinfectant concentration leads to an increase in contact time and vice versa. The law is affected by external factors such as temperature (where the rate of reaction tends to slow as the temperature is lowered) and humidity. pH can also be influential on disinfectant efficacy.

Alternatives to surface disinfectants

An alternative approach to surface disinfection is with the incorporation of silver (or silver salt such as silver dihydrogen citrate) into surfaces. While viral inactivation times are longer (30 to 60 minutes to achieve 4-log reductions in challenge titres) the viricidal effect is continuous unlike the periodic use and short-term activity of liquid disinfectants (21). A variant is with the incorporation of silver nanoparticles, although the toxicity of these in relation to human and animal health remains an area undergoing review. In theory, silver nanoparticles have some ideal properties for inclusion into surface materials due to their polydispersity. A further alternative, at a more experimental stage, is surfaces containing photoactive metal nanocrystals which require visible light stimulation for viral inactivation. These may have a more likely application within a clinical setting than in a standard cleanroom.

Conclusion

Viral contamination is a potential safety threat common to all animal and human-derived biologics and it follows that ensuring virological safety is challenging. Contamination of the production system can occur, and the processes of viral removal are complex and require regular assessment. A further challenge arises with creating viral secure areas and three of the components of particular relevance to cleanrooms are: strict personnel

gowning, HEPA filtration, and disinfection application. These protective measures are supported by material controls and segregation.

This article has focused on disinfection and disinfectant selection for cleanroom use to support process controls and has been undertaken because less attention has been paid to the viricidal potential of commonly used disinfectants compared with bactericidal action, despite many disinfectants being poor viricides. This review has established that careful selection is required in terms of disinfectant where virus inactivation is required, not least due to the relative resistance of some viruses (particularly small, non-enveloped viruses) to many disinfectants. Furthermore, there are several factors that influence disinfectant efficacy under non-ideal conditions, such as the presence of microbial or animal cell debris, various types of soil (such as protein residues), and aerosolised droplets on a surface.

The use of disinfectants should be undertaken as part of a wider quality risk assessment, in conjunction with other methods for viral control, removal and inactivation.

References

1. Yeargin, T., Buckley, D., Fraser, A., Jiang, X. The survival and inactivation of enteric viruses on soft surfaces: a systematic review of the literature, *Am. J. Infect. Control* 2016, 44: 1365
2. ICH 5A: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Geneva, Switzerland, October 1997
3. McDonnell, G. *Antisepsis, Disinfection, and Sterilization: Types, Action, and Resistance*, American Society for Microbiology Press, Washington, DC. 2007, 45: 1251
4. Nuanualsuwan, S., Cliver, D. Capsid Functions of Inactivated Human Picornaviruses and Feline Calicivirus, *Appl. Environ. Microbiol.* 2003, 69: 350.
5. Inglesby, A. Expert Rev. *Anti-infect.* Ther. 2019, 17, 467
6. Bond, W., Favero, M., Peterson, N. and Ebert, J. Inactivation of hepatitis B virus by intermediate-to-highlevel disinfectant chemicals. *J. Am. Med. Assoc.* 1983, 18:535-538
7. Mbithi, J., Springthorpe, V., Sattar, S, Chemical disinfection of hepatitis A virus on environmental surfaces, *Applied and Environmental Microbiology*, 56 (11): 3601-3604
8. Chen, L., Lee, W., Ma, Y. et al. The efficacy of different sanitizers against MS2 bacteriophage introduced onto plastic or stainless steel surfaces, *Current Research in Food Science*, 2022, 5: 175-181
9. Tagaino, R., Washio, J., Otani, H. et al. Bifacial biological effects of ethanol: acetaldehyde production by oral Streptococcus species and the antibacterial effects of ethanol against these bacteria, *Journal of Oral Microbiology*, 2021, 13: 1
10. Mulder, R., Sher, M. Comparison of Aerosolized Hydrogen Peroxide Fogging with a Conventional Disinfection Product for a Dental Surgery, *The Journal of Contemporary Dental Practice*, 2020, 21 (12): 1307-1311
11. Hans, M., Lugani, Y., Chandel, A. et al. Production of first- and second-generation ethanol for use in≈alcohol-based hand sanitizers and disinfectants in India, *Biomass Conversion and Biorefinery*, 2021, 10.1007/s13399-021-01553-3
12. Jang, M., Yang, H., Shin, G. Determination of Methanol in Commercialized Alcohol-based Hand Sanitizing and Other Similar Products using Headspace GC-MS, *Current Analytical Chemistry*, 2022, 18 (7): 774-780
13. Kampf, G., Todt, D., Pfaender, S. Broad-spectrum antiviral agents: a crucial pandemic tool, Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents *J. Hosp. Infect*. 2020, 104, 246
14. Springthorpe, V., Sattar, S. Chemical disinfection of virus-contaminated surfaces *Crit. Rev. Environ. Control* 1990, 20: 169
15. Terpstra, F., van den Blink, A., Bos, L. Resistance of surface-dried virus to common disinfection procedures, *Journal of Hospital Infection*, 2007, 66, 4: 332-338
16. Santhakumar, K., Viswanath, V. Novel Methods for Efficacy Testing of Disinfectants – Part I, *Tenside Surfactants Detergents*, 2019, 56, 1: 14-24
17. Suman, R., Javaid, M., Haleem, A. Sustainability of Coronavirus on different surfaces, *Journal of Clinical and Experimental Hepatology*, 2020, 10.1016/j.jceh.2020.04.020
18. Song, X., Vossebein, L, Zille, A. Efficacy of disinfectant-impregnated wipes used for surface disinfection in hospitals: a review, *Antimicrobial Resistance & Infection Control*, 2019, 81 (1): 10.1186/s13756-019-0595-2
19. McDonnell, G., Russell, A. Antiseptics and disinfectants: activity, action, and resistance *Clin. Microbiol. Rev.* 1999, 12, 147
20. H., An investigation of the laws of disinfection *J. Hyg.* 1908, 8, 92
21. Buckley, D., Dharmasena, M., Fraser, A. et al. Efficacy of silver dihydrogen citrate and steam vapor against a human norovirus surrogate, feline calicivirus, in suspension, on glass, and on carpet *Appl. Environ. Microbiol.* 2018, 84, e00233

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Where did it all go so wrong? An account of the turbulent history of Vapour Phase Hydrogen Peroxide (VPHP) bio-decontamination

Tim Coles, Rick Nieskes and James Agalloco

Abstract

This paper considers the current industry status of the vapour phase hydrogen peroxide (VPHP) bio-decontamination process, and its supposed fragility in relation to sterilisation. Some brief historical notes are followed by consideration of appropriate challenges. It is argued that with good understanding, monitoring, and controlling of the principal VPHP cycle parameters, together with certain changes to the BIs themselves, then bio-decontamination by VPHP can be considered to be a sterilisation process.

Introduction

The three authors of this paper have all developed careers in the technology of pharmaceutical isolators. Between them, they have amassed around 100 man-years of experience in the industry. It would be fair to say that the authors are widely published, and well-respected in their specialisations. The view ultimately expressed by the authors in this discussion paper may be at some variance with current regulatory views. The authors make no apology for their stance.

The Nub of the Matter

In 2019, the UK Medicines and Healthcare Regulatory Authority (MHRA) issued a document in which was stated, inter-alia, that the process of bio-decontamination using vapour phase hydrogen peroxide (VPHP) was "fragile". With the process well-established, particularly for pharmaceutical isolators, this caused considerable consternation in the industry, to the extent that there was discussion of abandoning VPHP altogether. It is the contention of the authors that the VPHP process, when correctly applied, is in fact a robust process, and is highly desirable in that it leaves virtually no residues other than water and oxygen. It is the failure to understand how the VPHP process works, combined with some commercial pressure, that has driven the technology off course.

Some History

Pharmaceutical isolators effectively originated with the amalgamation of research animal isolators and some nuclear glovebox technology. The French company La Calhène (now Getinge La Calhène) was a pioneer here offering, amongst other isolator-related items, a basic gassing system named "Sterivap" for the bio-decontamination of their isolators. This device used peracetic acid as the active agent. Meanwhile, the US company Baxter was developing vapour phase hydrogen peroxide (VPHP) as an alternative to ethylene oxide as a sterilising agent.

The US company AMSCO subsequently purchased the VPHP patent from Baxter, introducing it as a means to bio-decontaminate isolators, with the added advantage of innocuous breakdown products. They took on a number Baxter people before proceeding to market a generator. Eventually, the American company Steris bought out AMSCO, and their VHP 1000 machine became, for a time, the benchmark of vapour phase hydrogen peroxide bio-decontamination.

With the apparent success of the new generation of VPHP generators, some isolator manufacturers placed emphasis on regarding a VPHP "sterilised" isolator as being equivalent to using terminal sterilisation. Indeed, the word "sterilisation" was used at times in their literature. The second phase of gassing cycles was termed the "Sterilisation Phase". The regulatory agencies were, perhaps not surprisingly, sceptical. The aseptic guidance produced by the FDA in 2004 voiced some of these concerns.

At the time, there were suggestions that you could put an isolator in a totally unclassified warehouse: a splendidly naïve assumption that only served to increase the doubts of the regulators, concerning isolators in general and gas phase "sterilisation" in particular.

A further issue developed with deciding the most appropriate biological indicator (BI) to be used for validation of the new technology. Whilst the majority have agreed that spores of *Geobacillus stearothermophilus* represent a robust challenge to the VPHP process, there was a choice between naked inoculated carriers and Tyvek® enclosed carriers. The latter are perhaps rather easier to handle, and there is now a convention that validation of the VPHP process requires log 6 reduction of *G. stearothermophilus* spores in Tyvek® envelopes.

A significant point in the current debate is that some parties have emphasised from the outset that no condensation should be present in any form during the developed cycle. More recently, other researchers have shown that the VPHP process actually requires condensation to be effective; this condensate being a very thin layer of high concentration hydrogen peroxide. The apparent dispute between using a "dry" process and a "wet" process only served to fuel regulatory suspicion of hydrogen peroxide as a "sterilising" agent.

In the light of these developments and discussions, scepticism and uncertainty from regulatory agencies has been growing for some time now, especially with the apparently casual acceptance of "rogue" BIs. The incidence of "rogue" BIs has seemed to be getting worse, and this whole debacle reached a boiling point when Andrew Hopkins of the MHRA issued his "fragility" blog in 2019.

Sterilisation or Bio-Decontamination and the Dreaded "Rogue" BI

A rogue BI has been described as one showing positive growth following a VPHP bio-decontamination cycle which had hitherto appeared robust. It has been suggested that the rate of rogue BIs, to be found amongst a population of BIs, might be between 0.5% and 5%.

The consequent industry acceptance of rogue BIs then led to protocols which allowed a certain number of positive BIs following, most typically, PQ and re-validation VPHP cycles.

The principal tactic here has been to use triplicate BIs at each test site. Because it can be shown mathematically that log 6 has been achieved provided that two out of three BIs at a site are negative, the logic was that a certain number of positives were permissible, under a certain set of rules. PQ protocols would for example, permit one positive BI at one site during three back-to-back PQ cycles.

These rogue BIs were accounted for by the apparent difficulty of producing an even monolayer of spores on a carrier. It was suggested that spores might clump together, or that residual cell debris might protect some spores from the effects of the VPHP cycle. Some electron micrographs were produced to illustrate the issue of spore protection.

However, perhaps a more fundamental question should be raised before delving too deeply into the issue of rogue BIs. That question is simply:

Is the VPHP process a sterilisation process, or not?

If the answer to that question is that the VPHP process is not a sterilisation process, then there will be, by definition, occasional instances of growth positives. The authors have suggested that such growths might be termed "Statistically Inevitable Growth Positives" or SIGS. Perhaps SIGS and rogues are one and the same thing?

If on the other hand, the VPHP process is to be regarded as a sterilisation process, then we must anticipate no SIGS or rogues. The authors feel that, provided the bullet points laid out in Section 6 below are fully addressed, then there will indeed be no rogues, and we can reasonably accept the VPHP process as a sterilisation process. Such acceptance would then render VPHP suitable for indirect product contact items such as the stopper feed bowls on vial filling machines. And there would be no need for triplicate BIs in the PQ and subsequent re-validation cycles.

Realistic Challenges

All of this has to be set against a background which has evolved to dictate a requirement for the demonstration of log 6 reduction of resistant spores, on a stainless-steel carrier, inside a Tyvek® envelope, in order to validate a VPHP cycle. The authors are of the opinion that this requirement stemmed not so much from any science-based logic, but from the fact that this is probably about the most difficult challenge which could reasonably be applied.

In practice of course, the real micro-flora present on the surfaces of a properly cleaned isolator is limited to something around a dozen Colony-Forming Units (CFUs) per 25 square centimetres. Furthermore, these will be mostly vegetative organisms as opposed to resistant spores. Compare this to the standard BI which concentrates some two or three million spores in an area of roughly 0.2 square centimetres, equivalent to about four hundred million spores in 25 square centimetres. Overall, the demand for log 6 reduction represents, in purely numerical terms, an overkill of 108, or one hundred million-fold.

Add to this the fact that the BI uses resistant spores, and that these are further placed in an envelope which inevitably places a moisture barrier to the VPHP process, and the only reasonable conclusion is that the currently conventional test method is technically unsupportable. It can be argued that the current debate about the VPHP process and its so-called fragility is, in truth, an artifact of the illogical challenges applied.

Quo Vadis?

What then, is a reasoned and practical way forward? There are some steps which might be taken:

a. Remove the Tyvek® envelope. The actual challenge lies openly on the surfaces of the isolator, not behind a gas-permeable barrier. Thus, an inoculated carrier, such as a stainless-steel ribbon strip, far better represents the real challenge. The Tyvek® envelope makes the handling of BIs easier, but does nothing to give a realistic challenge to the VPHP process as such.

b. Reduce the challenge from log 6 to log 4. This still represents a huge overkill in terms of the actual microbiological challenge on the surfaces of the isolator, but it is perhaps a supportable figure.

c. Optimise the VPHP process. This means understanding, monitoring, and controlling the principal VPHP cycle parameters:

- VPHP-laden air-flow rate
- Thorough, turbulent, VPHP / air distribution
- Appropriate and consistent humidity at the start of VPHP injection
- Appropriate and consistent temperature at the start of VPHP injection
- Peroxide solution flow rate
- Peroxide vapour concentration

Conclusion

It is the opinion of the authors that the VPHP process is not "fragile". The debate over the seeming unreliability of the process stems from:

a. Unrealistic challenges.

b. Failure to understand the VPHP process.

If these issues are addressed through reasoned discussion and better understanding, then the VPHP process can be applied with confidence.

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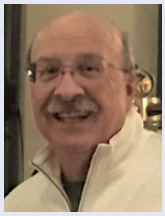

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Jim is a past President of the Parenteral Drug Association and served as an Officer or Director from 1982 to 1993. He is a past member of USP's Microbiology Expert Committee. He has authored or co-authored more than 60 book chapters, over 160 papers and has lectured extensively on process validation, aseptic processing, sterilization, and isolation technology, domestically and internationally.

Rick Nieskes BScMicr, is the founder, in 1994, and chief consultant of Ardien Consulting Services (ACS). ACS provides customized biodecontamination and isolator validation and engineering support services to the pharmaceutical industry. ACS has successfully validated over 150 isolators for production, sterility testing, and containment-based applications at well over 50 different pharmaceutical and medical device companies throughout the world. Prior to founding ACS, Rick worked as a Sterility Testing Biological Quality Assurance Microbiologist at Abbott Laboratories and as a VHP® Sterilization Systems Engineer at AMSCO International (now known as the STERIS® Corporation). Rick holds a BS degree in Bacteriology from the University of Wisconsin – Madison.

ISO Technical Report* 14644-21 is set to join the ISO 14644 family

John Hargreaves and Andrew Watson

A new ISO document in the ISO 14644 series of standards has been prepared by Working Group 15 (WG15) of TC 209, the ISO Technical Committee for cleanrooms. The document, which has been submitted to ISO in Geneva for editorial review, including a committee internal ballot starting in June, will be ISO TR 14644-21: *Cleanrooms and associated controlled environments – Airborne particle sampling techniques*.

The document addresses observed issues of misuse and misunderstanding of key sections of ISO 14644 Part 1, the ISO standard on cleanroom classification, and ISO 14644 Part 2, the ISO standard on cleanroom monitoring. These issues became readily apparent in the requirements for airborne particle sampling included in the revision of EU GMP Annex 1, for production of Sterile Medicinal Products, within the EU, and the corresponding PIC/S GMP regulations. The latest version of Annex 1 has corrected a number of technical and scientific misapprehensions, highlighted during the draft enquiries and dialogue.

Some issues do remain in Annex 1, which will come into force in August 2023, but it will be possible to answer these in large part by justification in the Contamination Control Strategy (CCS) documents that users will have to produce.

A prime use of the new ISO TR21 will be to inform users of the broader scientific consensus regarding airborne particle sampling for classification and monitoring, on which the ISO 14644 standards have been built. The document will also suggest avenues of investigation to enable users to test and evaluate the causes and extent of particle loss in sampling lines, and to decide appropriate technical responses.

ISO is expected to publish TR21 during the summer, in line with the implementation of the new Annex 1. WG15 experts are now preparing communication on the issues conveyed.

John Hargreaves and Andrew Watson are Convenor and Secretary of ISO TC 209 WG15.

* An ISO Technical Report (TR) is an informative document, not a normative document. It contains information of a different kind from that of a standard or technical specification. A TR may include data obtained from a survey, for example, or information on the perceived "state of the art". In the case of ISO TR 14644-21, the document supports the requirements and information regarding airborne particle counting enshrined in Parts 1 and 2 of ISO 14644.

Further information on the types of ISO document, their nature and scope, can be found on https://www.iso.org/deliverables-all.html

Cleanroom Technology by William Whyte

Reviewed by John Neiger

This is the third edition of Bill Whyte's *Cleanroom Technology*, which has been comprehensibly revised and expanded in many areas. The first edition was published in 2001 and the second in 2010. Therefore, with the pace of change in cleanroom technology and in cleanroom standards, this new edition is seriously needed and most welcome. One only has to look at the ISO 14644 series of cleanroom standards to see how much is new. In 2010 there were only 10 Parts published (including the two Parts of ISO 14698 *Biocontamination control* which also belong in the series). Since then, five of the 10 have been comprehensively revised, four are currently under periodic review with substantial revisions contemplated, and one, Part 6 *Vocabulary*, has been withdrawn. In addition, eight entirely new Parts have been published, including one on energy efficiency and one on particle deposition, with two more under development.

This third edition of Cleanroom Technology has 25 Chapters compared to 22 previously. Existing chapters have been updated to a greater or lesser degree and one or two have been split. For example, Chapter 12 *Air Movement Control: Containment, Visualisation and Recovery* in the second edition has developed into Chapters 11 *Air Movement between and within Cleanrooms* and 12 *Recovery Performance and Ventilation Effectiveness*. This reflects the attention given to Recovery and Ventilation Effectiveness in the latest Parts 3 and 4 and the new Part 16 of ISO 14644.

One completely new and rather important chapter is Chapter 16 *Particle Deposition Rate (PDR)*. It is well known that particles smaller than 5 µm are largely removed in the airflow, whereas particles larger than 5 µm are deposited by gravity onto cleanroom surfaces and, by various forces, onto the walls of particle counter sampling tubes resulting in airborne particle counts for such particles being understated. ISO 14644 Part 17 *Particle deposition rate applications* applies and it doesn't take much reflection to recognise the importance of Particle Deposition.

Bill is well known to most cleanroom practitioners. In my review of his excellent *Cleanroom Testing and Monitoring* book, I wrote "Bill has been around the cleanroom world since the late 1960s and is internationally respected, not least for his broad, soundly based and well-reasoned contributions to standards work. He has also made a massive contribution to the fountain of knowledge of cleanroom technology by way of lectures, training courses, learned papers (over 140) and books such as this. His research is carried out with other experts who often provide the test equipment and the facilities where the work can be carried out. Quite often he is behind work reported by others. He is clearly an avid reader of all publications concerned with cleanrooms, be they standards, guidelines, articles or books and has an encyclopaedic knowledge of these. He has been involved in testing since the year dot!" There is nothing I can add to that.

This third edition of *Cleanroom Technology* is, as one expects from Bill, comprehensive, well-structured and well written. It is illustrated with good diagrams and photographs, many of which are in full colour. Each chapter has a useful bibliography comprising mainly of the ISO standards and relevant published papers by the author. The book would have benefitted from an index but the Contents page is specific enough on what is covered in each chapter.

I strongly recommend this third edition of *Cleanroom Technology* to everybody who wants to learn about cleanrooms or update their knowledge, be they cleanroom specifiers, designers, testers, service engineers, managers and, of course, users.

Cleanroom Technology is available from Amazon and can be found via this link: https://www.amazon.co.uk/Cleanroom-Technology-Fundamentals-Testing-Operation/dp/B0BVT7GC2Z

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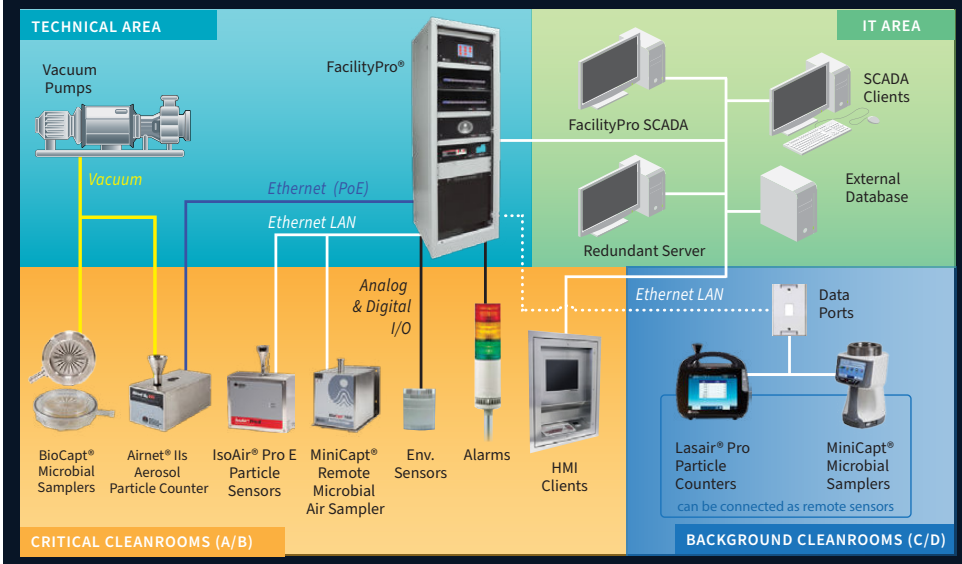

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Nanoparticle counter for the most critical fab spaces from PMS

The NanoAir™ 10 Condensation Particle Counter (CPC) is a revolutionary new product from Particle Measuring Systems (PMS). It provides the sensitivity of a CPC with the ease of use and functionality of a traditional cleanroom particle counter. Designed to monitor ultra-clean environments, it delivers 10 nm detection sensitivity at a sample flow rate of 2.8 L/min (0.1 CFM).

The NanoAir 10's size is 83% smaller than competitive products making it practical to use anywhere in ultra-clean environments, including inside semiconductor process tools and equipment front-end modules (EFEM). The innovative patent-pending working fluid handling system design is robust and efficient, enabling 24/7, 365 days continuous operation without the need for maintenance or user intervention of any kind between the annually required working fluid refill and calibration. Thereby, reducing sampling and data collection interruptions and tool downtime.

A 10-port manifold companion product (ParticleSeeker™) supports applications that require multiple sample locations to be monitored in sequential or programmed sequences.

Additionally, the NanoAir is high-pressure gas compatible with the HPD-III from PMS, and data can be viewed, analyzed, and reported using PMS Facility Net facility monitoring software or transmitted directly to third-party SCADA systems or process tool inputs.

For further information please see www.pmeasuring.com/product/nanoair-aerosol-particle-counter-2/, www.pmeasuring.com/product/particleseeker-multiport-aerosol-sampler/ and www.pmeasuring.com/product/facility-net-monitoring-software/

Biosafe from CHTS – The CL3/HG3 emergency recovery plan that allows you to pick and choose only the services you need

Stuck paying for elements of a disaster recovery plan that you'll never use? Free yourself from a 'one size fits all' contract by choosing Crowthorne Group's Biosafe scheme. You'll benefit from a team of specialists in cleanrooms, containment laboratories/environments, clean air equipment and fumigation services, who'll provide impartial testing, advice if necessary, and certification.

Our **Emergency Recovery** scheme is specifically for customers with a CL3/HG3 facility, offering a range of servicing and decontamination response solutions. These range from efficacy studies and validation of fumigation plans to sealability integrity tests. Further options including HEPA filter testing, safety cabinet servicing, KI Discus testing, deep cleaning, or a full fumigation.

The biggest benefit? Flexibility! You choose only the items you require. For complete peace of mind, contact us to discuss your requirements!

www.crowthornehitec.co.uk

Cherwell launches BAMS portable Biofluorescent Particle Counter

Cherwell, specialists in cleanroom microbiology solutions, has partnered with MicronView Limited of Texas to introduce a new portable Biofluorescent Particle Counter (BFPC) to the UK and Ireland. The BioAerosol Monitoring System (BAMS), manufactured by MicronView, enables the rapid real-time monitoring of airborne microbes. The value of BAMS is in continuous monitoring, real-time feedback, and trending in sterile medicinal product manufacturing environments detailed in the 2022 Annex 1 revision. The certified ISO particle detector uses laser induced fluorescence to detect Active Fluorescent Units (AFU) and count viable microbes without need for culturing. Lightweight at just 5.8 Kg with a large touchscreen useable with latex gloves, BAMS delivers real-time results in critical areas for up to 6 hours while on battery power. The introduction of the BAMS rapid microbial monitoring (RMM) system means Cherwell now offers a complete environmental monitoring (EM) portfolio to meet all cleanroom microbiology needs.

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

Particle Measuring Systems on track to meet Net Zero goals

As part of our goal to make the world cleaner, healthier, and more productive, Particle Measuring Systems (PMS) is committed to Net Zero Carbon and Net Zero Waste to Landfill.

Our goals, validated by the Science Based Targets Initiative (SBTI), are to reach Net Zero in Scope 1 and 2 by 2030 and Scope 3 by 2040; we are on track, thanks to large Scope 1 and Scope 2 progress in 2022 and an aggressive Scope 3 plan for 2023.

In 2022, PMS saw huge gains in our Roadmap to Net Zero. By the end of 2022, we reduced our Scope 1 and Scope 2 Emissions by 56%. This milestone was achieved by implementing LED lights, timed heating, employee training and involvement, motion lighting, 100% sustainable energy use, and initial rollouts of electric/hybrid vehicles for our fleets.

For our Net Zero Waste to Landfill Program, we have established projects globally to eliminate waste and reuse or recycle material where possible. We switched to digital operations manuals, eliminated waste as much as possible, and added robust recycling and composting to all offices.

We also started a program to switch to sustainable packaging (recycled and curbside recyclable materials). In January 2022, we kicked this off by eliminating 95% of our polyurethane and replacing it with a paper-based protective packaging material. We also made some changes to the plastic we use and how we use it, reducing 50% of our plastic packaging. We are currently tackling our use of polyethylene; the expectation is that all our highest-volume products and all our new products will be free of polyethylene packaging before the end of 2023.

We recently completed a third-party audit of our progress and are very pleased to announce that we are on track to meet our Net Zero goals. However, there is still a lot of urgent progress to be made over the next few years.

With huge progress in our Scope 1 and 2 (direct emissions), 2023 will see more focus on our Scope 3 (indirect) emissions. Our goal is to remove 3600 tons of carbon from our waste stream in 2023. Our Scope 1 and 2 initiatives for 2023 include having 40% of our fleet be Electric Vehicles (EVs) and continuing to identify and implement improved energy efficiencies in our buildings. Our Scope 3 initiatives will focus on the end-of-life procedure for our products, the shipping of products, and the start of working with our vendors (starting with EcoVadis participation) and distributors.

"We are working hard at sustainability and Net Zero because it is the right thing to do and now is the time to do it," said John Mitchell, President of Particle Measuring Systems. He continued, "Our parent company, Spectris, prioritizes sustainability and continually challenges us to do more and do it faster."

For more information about the company and its Net Zero initiative please visit www.pmeasuring.com

Update: Particle Measuring Systems awarded EcoVadis silver medal

Particle Measuring Systems (PMS), a global leader in contamination monitoring solutions, is pleased to announce that it has been awarded a Silver EcoVadis Medal for its progress towards sustainability. The EcoVadis rating is a comprehensive assessment of a company's environmental, social, and governance (ESG) practices, and PMS received a score of 61/100, placing the company among the top 25 percent of companies assessed by EcoVadis.

EcoVadis, has acknowledged PMS for its strong ethical business practices, renewable energy progress, and responsible waste reduction. Over the past few years, PMS has converted all of its sites to 100% renewable energy and are always looking for opportunities to improve their ESG. The Ecovadis assessment provided them with many recommendations that they will be prioritizing and implementing over the next years.

Southern Group Laboratory offers a Pre-poured Burkholderia Cepacia Selective Agar (BCSA) in 90mm plate format

Our selective growth medium is designed to meet the formulation requirements listed in USP <60> to recover B. cepacia and BCC.

SGL BCSA pre-poured media contains numerous nutritional components, energy sources supporting BCC growth, and a mixture of antibiotics designed to prevent the growth of non-fermenters not belonging to the BCC and typical environmental isolates such as Pseudomonas and Staphylococcus species.

This allows for easier detection of BCC in test samples containing background contaminants.

Using our pre-poured BCSA you are able to meet the USP formulation criteria, quicker and better isolation of BCC, increased selectivity, and fewer false positives leading to consistent media every time.

We supply a wide range of pre-poured media for use in pharmaceutical, cosmetic, clinical and veterinary applications. These include standard media as well as bespoke media products tailored to customer-specific formulations.

For more information, visit www.sglab.com

Events

2023	Event	Location
June 13-14	PHSS Sterile product manufacturing conference and Aseptic Processing workshop	Sutton Coldfield, UK
October 10-12	A3P International Congress	Biarritz, France
November 13-16	IEST EDUCON 2023	Schaumberg, Illinois

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2023	**Event**	**Location**
June 20	The Unseen Contaminant: Taking Charge of Electrostatic Contamination	Schaumburg, Illinois or Virtual
June 21	Contamination Busters: Get the Dirt Out of the Cleanroom	Schaumburg, Illinois or Virtual
June 22	Stop Contamination in Your Operations with Reusable and Disposable Garments	Schaumburg, Illinois or Virtual
For a complete list of courses, please see https://www.iest.org/Training-Certs/IEST-Contamination-Control-Learning-Path		

CCN (Contamination Control Network) www.theccnetwork.org		
2023	**Event**	**Location**
July 14	Course: CTCB-I Cleanroom Technology	TBC
November 7-9	CTCB-I Cleanroom Testing Professionals and Associates (Course and Exam)	Letchworth, UK
For a complete list of courses and webinars, please see https://www.theccnetwork.org/pages/ccn-events-calendar		

Other training courses including CTCB/I* training courses are provided by:		
BCW	Belgium	www.bcw.be/
ICS	Ireland	www.cleanrooms-ireland.ie/training/
R3Nordic	Nordic Countries	www.r3nordic.org/
VCCN	Netherlands	www.vccn.nl/cursusaanbod
TTD	Turkey	www.temizoda.org.tr/en/trainings
*CTCB-I Certification: Cleanroom Testing and Certification Board International Certification, see CTCB-1 website: www.ctcb-i.net/index.php		

Life-lines

Quotations of Russian literary giants

Leo Tolstoy, 1828 – 1910

Everyone thinks of changing the world, but no one thinks of changing himself.

Government is an association of men who do violence to the rest of us.

In all history there is no war which was not hatched by the governments, the governments alone, independent of the interests of the people, to whom war is always pernicious even when successful.

The greater the state, the more wrong and cruel its patriotism, and the greater is the sum of suffering upon which its power is founded.

War is so unjust and ugly that all who wage it must try to stifle the voice of conscience within themselves.

The sole meaning of life is to serve humanity.

The two most powerful warriors are patience and time.

Anton Chekhov, 1860 – 1904

Love, friendship and respect do not unite people as much as a common hatred for something.

Let us learn to appreciate there will be times when the trees will be bare, and look forward to the time when we may pick the fruit.

We shall find peace. We shall hear angels, we shall see the sky sparkling with diamonds.

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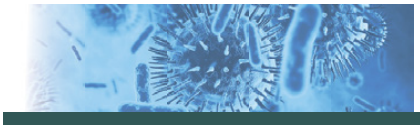

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CCN Membership benefits include:

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- CCN Newsletter,
- Access to events,
- Cleanroom content,
- CACR Quarterly Journal,
- Cleanroom information resources, Networking opportunities
- Special offers and discounts on Cleanroom Books and CTCB-I training courses.

The CCN is proud to host the
CTCB-I Cleanroom Testing courses
The March and May 2023 courses were fully taken up.
The next course will be:
7th – 9th November 2023
Click here to reserve a place

www.theccnetwork.org

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The new Pharmig Training Portal gives your team access to superior online training. A series of detailed videos cover:

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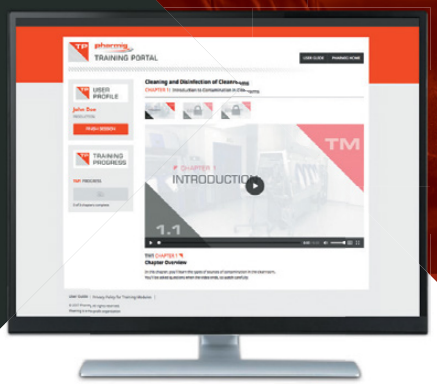
The module is designed for Production Operators, Cleaners, and QA. This online training module can also be used as part of hygiene training for anyone that enters a GMP cleanroom (eg QC, Engineers etc).



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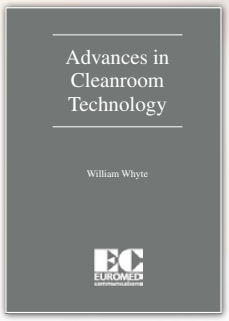
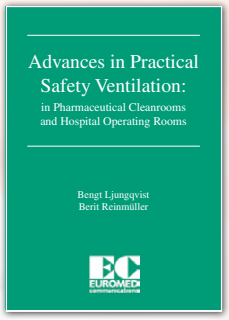


Advances in Cleanroom Technology

By William Whyte

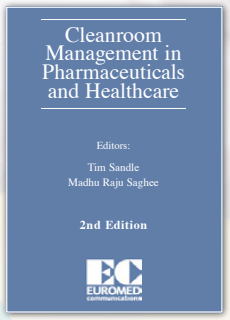
In 34 chapters this book covers surgical operating rooms through to the latest thinking on energy and sustainability in Cleanroom technology.



Advances in Practical Safety Ventilation

Written by Bengt Ljungqvist and Berit Reinmüller

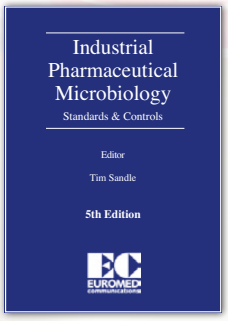
Thirty-six chapters dealing with airborne contamination control in industrial environments and hospital operating rooms.



Cleanroom Management in Pharmaceuticals and Healthcare

Edited by Tim Sandle and Madhu Raju Saghee

An essential resource for all practitioners in cleanroom technology. Includes 23 authors, 26 chapters and over 500 pages of text.



Industrial Pharmaceutical Microbiology: Standards & Controls

Edited by Tim Sandle

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