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Contents

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

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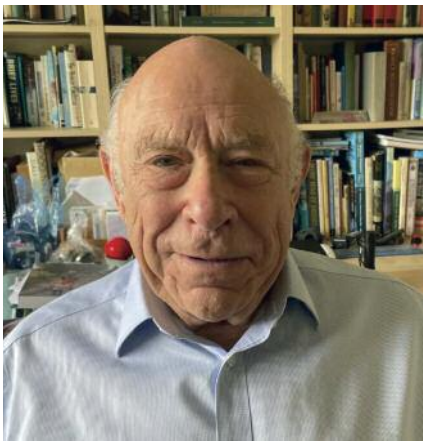
Editorial

Welcome to CACR51 which starts with another chapter from Bill Whyte's *Cleanroom Testing and Monitoring* book: *Classification of air cleanliness by particle concentration according to ISO 14644-1*. Classification of cleanrooms is right at the heart of our technology and a cleanroom must be classified according to particle concentration for it to be recognised as a cleanroom. The chapter also explains the assessment of cleanliness of cleanrooms with macroparticles, i.e. particles greater than 5µm in size. A full attribution to Bill Whyte and the CTCB-I is given at the start of the article.

The second main feature, by Bengt Ljungquist and Berit Reinmüller, explains the derivation of the simplified expression for the d_{50} value used in the European standard EN17141:2020 – *Cleanrooms and associated controlled environments - Biocontamination control for the evaluation of the monitoring efficiency of impaction air samplers*. The d_{50} value (cut-off size) is the aerodynamic particle diameter above which 50% of particles are removed from the airstream and



impacted, and is a useful measure of the performance of impaction air samplers.

The third main feature by Tim Sandle reports on the results of tests to assess the microbial recovery of several swab formats and materials. The results for the swabs tested are conclusive and point to the importance of swab specification for meaningful testing with swabs.

The fourth article is by Jason Kelly and is about Pharma 4.0™, the adoption by the pharmaceutical industry of Industry 4, the fourth industrial revolution. Pharma 4.0™ is orchestrated by ISPE (International Society for Pharmaceutical Engineering) and seeks to take forward such advances as 'The Internet of Things' (IoT), cloud computing, Artificial Intelligence (AI), Machine Learning (ML) and Smart Factories. The important take-away from this article is that when you buy new equipment, you must ensure that where, appropriate, its data output is in real time, and is as comprehensive as necessary to integrate into a Pharma 4.0™ environment.

The final article is based on a blog by Toni Horsfield which is based in turn on a webinar by Gordon Farquharson on EU GMP Annex 15: Qualification and Validation. The article contains useful information including the table giving a schedule of recommended cleanroom tests from the National Annex of the British edition of ISO 14644-2:2015 – BS EN ISO 14644-2:2015. This National Annex is obviously not in other editions of this standard.

I hope you enjoy this issue.

John Neiger

Classification of air cleanliness by particle concentration according to ISO 14644-1

W. Whyte

This article is the fifth of a short series of extracts from Bill Whyte's new book *Cleanroom Testing and Monitoring*. Chapter 12, *Classification of air cleanliness by particle concentration according to ISO 14644-1*, 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 previous chapter, Chapter 11, *Airborne particle counting with an LSAPC*, was published in CACR49. 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

Introduction

Classifying a cleanroom or clean zone by its airborne particle concentration is carried out according to the method described in ISO 14644-1: 2015 [ref 7]. It requires the measurement of the concentration of particle in the size range between 0.1µm and 5µm throughout a cleanroom or clean zone. This method is described in this chapter. However, in some cleanrooms, contamination problems can be mainly caused by particles larger than 5µm. These particles are known as 'macroparticles' and how the cleanroom cleanliness can be assessed for this size of particle is described towards the end of this chapter.

12.1 Occupancy states in cleanroom

The classification of a cleanroom or cleanzone can be carried out in three occupancy states which are likely to give different airborne concentrations of particles and an ISO class. These occupancy states are defined in ISO 14664-1: 2015 as follows:

- *As built:* condition where the cleanroom or clean zone is complete with all services connected and functioning but with no equipment, furniture, materials or personnel present,
- *At-rest:* condition where the cleanroom or clean zone is complete with equipment installed and operating in a manner agreed upon, but with no personnel present,
- *Operational:* agreed condition where the cleanroom or clean zone is functioning in the specified manner, with the equipment operating and with the specified number of personnel present.

Cleanroom classification is carried out in the 'as built' state when the cleanroom is newly constructed. It should also be carried out if there has been a change to the structure of the cleanroom, or its ventilation system. Before the classification is carried out, the cleanroom and its ventilation system should be shown to provide the correct performance specification by measurement of (a) the air volume supply and extract rates, and air velocities, (b) the integrity of its high efficiency air filter systems (c) the pressure differentials and airflow between cleanrooms and adjacent areas, and (d) the airflow patterns within cleanrooms.

Once the cleanroom has been shown to conform to the 'as built' classification, the installation of machinery and equipment is carried out. When this is completed and everything is found to be operating satisfactorily, the cleanroom can be classified in the 'at rest' state. When this classification is shown to be satisfactory, the task of preparing the cleanroom for manufacturing can proceed.

When the cleanroom is complete and ready for operation, the cleanroom should be tested and classified in the 'operational' state in order to show that the correct class of airborne cleanliness will be achieved during actual operations. Normal operational activities may then start.

The classification of cleanrooms and clean zones should be carried out over their lifetime, to ensure they continue to function correctly, and this can be either in the 'at rest' or 'operational' state. They are often classified in the 'at rest' state when the cleanroom is closed for maintenance, rather than the 'operational' state where testing may cause a disruption and contamination of product.

ISO 14644-1:2015 states that 'at-rest' or 'operational' cleanliness classification may be performed periodically and the time interval should be based on a risk assessment of the application, but is typically on an annual basis. ISO 14644-2: 2015 [ref 8] confirms that the classification should be undertaken annually but suggests that this frequency can be extended based on risk assessment, the extent of the monitoring, and data that are consistently in compliance with acceptance limits or levels defined in the monitoring plan.

It should be noted that according to the definitions given in ISO 14644-1 and reproduced above, no personnel should be present during classification in both the 'as built' and 'at rest' states. However, testing personnel are often present, as well as personnel who audit the tests. Airborne particles will be dispersed by these people and this will increase the airborne particle count. Therefore, the number of people in the cleanroom during airborne particle measurements should be minimised. Activating the particle counter from outside the cleanroom in a room free of personnel is an approach that should be considered. Another option is to set a time delay in the LSAPC, which allows personnel to leave the cleanroom and delay sampling until contamination from personnel has dropped to an insignificant level; this will occur when the concentration has dropped to a low and constant level.

Although no personnel should be present during the classification in the 'as built' and 'at rest' occupancy states, the situation is reversed in the 'operational' state. It is then best to ensure that the maximum number of personnel that might be found during actual operations are present during testing, and that machinery and equipment is functioning. This approach will demonstrate that the cleanroom's ventilation system can provide the required cleanliness classification during the greatest challenge from dispersion of airborne contamination.

12.2 Method of classifying a cleanroom or clean zone

To classify a cleanroom according to the method given in ISO 14644-1: 2015, it is necessary to determine (a) the required number and position of sampling locations, (b) the minimum air sampling volumes, and (c) the minimum sampling time. When the concentration of particles does not exceed the acceptance criteria for a specified ISO Class, the cleanroom can be classified accordingly.

Determination of number of sampling locations for classifying a cleanroom

To classify a cleanroom, it is necessary to gather sufficient air samples to have confidence that the airborne particle concentration in the whole of the cleanroom is below the maximum limit set by ISO 14644-1: 2015. The required number of sampling locations is related to the cleanroom's floor area, and the larger the floor area the more locations that must be sampled. ISO 14644-1:2015 gives a table, which is reproduced here as **Table 12.1**, for obtaining the minimum number of locations that should be sampled. However, when the area of the cleanroom or clean zone is greater than 1000m^2, the table is not used and the minimum number of locations (N_L) is calculated by the following formula:

Equation 12.1

$$N_L = 27 \times \left[\frac{A}{1000}\right]$$

Where N_L is the minimum number of sampling locations to be evaluated, which is rounded up to the next whole number, and A is the area of the cleanroom in m^2.

Division of cleanroom into sampling sections

After the number of sampling locations has been determined, the next step is to divide the cleanroom or clean zone, into sections. The number of sections should be the same as the number of sampling locations given in **Table 12.1**. It is written in the Introduction of ISO 14644-1: 2015 that these sections should be of 'near equal area'. The division of the cleanroom into sections is relatively easy if the floor area is a simple square or rectangle, but more difficult if the floor area is asymmetrical, or an uneven number of sampling locations is specified. However, ISO 14644-1 suggests that additional sampling sections can be added to help in the subdivision.

Position of sampling location in each sampling section

When the floor area of a cleanroom, or clean zone, has been divided up into the appropriate number of 'equal' sections, a sampling location must be selected in each section. The following information is given in ISO 14644-1: 2015:

1) A sampling location should be chosen that is 'representative of the characteristics of the section'. This suggests that locations with unusually high, or unusually low, particle concentrations should be avoided. However, contrary to what is written in ISO 14644-1: 2015, it is often considered that it is best to demonstrate the capability of the ventilation system to control the worst situation, and to sample at locations where the highest particle concentrations are likely to be found. This should be decided, according to the circumstances in the cleanroom being tested.
2) In non-UDAF cleanrooms, sampling locations may not be representative of the area being sampled if they are located directly beneath non-diffused supply air inlets. If the air supply inlet has no diffuser, the supply air will provide a cleaner area directly below the inlet that may not be representative of the airborne conditions in that section of the cleanroom. These sampling positions should, therefore, be avoided.
3) If there are additional locations that are considered critical, sampling can be carried out at more locations than given in **Table 12.1**,
4) The sampling probe should be positioned in the plane of the work activity, or at another specified point. This allows the probe to be placed at any height, but samples are normally taken at working height.

Airborne sampling volume and sampling time

The lower the airborne concentration of particles expected in the cleanroom or clean zone, the more air should be sampled. ISO 14644-1: 2015 requires

Table 12.1 Sample locations related to cleanroom area

Area of cleanroom (m^2) less than, or equal to	Minimum number of sampling locations to be tested (N_L)
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
64	12
68	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
636	26
1000	27
>1 000	See Equation 12.1 in this chapter

Note 1 – If the floor area falls between two values in the table, the greater of the two should be selected.
Note 2 – In the case of unidirectional airflow, the area may be considered as the cross section of the moving air perpendicular to the direction of the airflow. In all other cases, the area may be considered as the horizontal plan area of the cleanroom or clean zone (floor area).

the volume sampled to be large enough to detect a minimum of 20 particles of the largest particle size being counted, when the concentration is at the class limit being considered.

The following equation should be used to calculate the minimum volume for each air sample:

Equation 12.2

$$V_S = \frac{20}{C} \times 1000$$

where,

V_S is the minimum single sample volume per location, expressed in litres,

C is the class limit (number of particles/m³) for the largest considered particle size specified for the relevant class,

20 is the defined number of particles that could be counted if the particle concentration were at the class limit.

The air volume sampled must be at least two litres, and the minimum sample time must be at least one minute.

ISO 14644-1:2015 allows the particle concentration at each location to be measured by a single sample, or an average of several samples.

Sampling more than one particle size

ISO 14644-1:2015 allows the classification of a cleanroom to be carried out at one, or more, particle sizes. However, if more than one particle size is chosen, then each larger size of particle must be at least 1.5 times the next smaller particle size.

Acceptance criteria

ISO 14644-1:2015 considers that a cleanroom has met the required cleanliness classification criteria if no single count, or average of counts at a single location, exceeds the class limits. These class limits have been previously given in **Table 4.1** in Chapter 4, and they are reproduced here in **Table 12.2**. **Table 12.2** has been simplified by the removal of the additional notes given in the original table. **Table 4.1** should be consulted for this extra information. If an out-of-specification count is obtained during testing, then ISO 14644-1: 2015 requires that an investigation shall be undertaken. The result of the investigation and remedial action shall be noted in the test report as follows:

1. If the count is caused by an identified abnormal occurrence, the count can be discarded and noted on the test report, and a new sample taken.
2. If the cause is a technical failure of cleanroom or equipment, then the cause should be identified, remedial action taken, and retesting performed of the failed sampling location, the immediate surrounding locations, and any other locations affected. The choice shall be clearly documented and justified.

Designation of cleanrooms

ISO 14644-1: 2015 requires that the class of a cleanroom to be designated in the following manner: 'ISO Class N', along with information on its occupancy state and the cumulative particle size(s) that are measured. For example, an ISO Class 4 cleanroom that has passed the classification in the 'at rest' condition at particle sizes of both ≥0.2µm and ≥0.5µm is designated as follows.

ISO Class 4; at rest; ≥0.2µm, ≥0.5µm

12.3 Cleanrooms with low airborne particle concentrations

Some cleanrooms can be over 1000m² in floor area and, therefore, require a large number of sampling points to carry out a cleanliness classification. In addition, low concentrations of airborne particles are often specified in some cleanrooms and, therefore, a large sampling volume is required at each location. For example, if an ISO Class 2 room has to be certified at 0.3µm, the minimum air volume at each location is 2000 litres. A long testing programme will result, where the tester is likely to be under pressure to complete the certification of the cleanroom so that manufacturing operations can quickly start.

In cleanrooms that require long sampling times, it may be found that as the sampling proceeds, the particle counts are consistently well below the class limit and the expected outcome of the sampling is that the particle concentration will be well below the class limit. In this situation, a statistical method described in ISO 14644-1: 2015 and known as 'sequential sampling' can be used to ascertain if sampling can stop before the full sampling time. Employing this method can substantially reduce the overall sampling time in large cleanrooms with low concentrations of airborne particles. The method is not discussed here but described in Annex D of ISO 14644-1:2015 and in Annex C of this book.

To assist in reducing the time required to classify a cleanroom, an LSAPC with a large sampling rate can be used. The sampling rate of a typical LSAPC is 28.8L/min (1ft³/m) but airborne particle samplers that sample at 50L/min or 100L/min are the best choice in this situation.

12.4 Worked example of ISO 14644-1:2015 test method

To show the application of the ISO 14644-1:2015 method, the following example is used:

The cleanroom to be tested has a 4m × 5m floor area. It is a UDAF room with a complete ceiling of high efficiency filters. It is required to comply with ISO Class 4 in the 'at rest' condition at a

Table 12.2 ISO Classes of air cleanliness by particle concentration

ISO Class number (N)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes shown below					
	0.1µm	0.2µm	0.3µm	0.5µm	1µm	5µm
1	10	-	-	-	-	-
2	100	24	10	-	-	-
3	1 000	237	102	35	-	-
4	10 000	2 370	1 020	352	83	-
5	100 000	23 700	10 200	3 520	832	-
6	1 000 000	237 000	102 000	35 200	8 320	293
7	-	-	-	352 000	83 200	2 930
8	-	-	-	3 520 000	832 000	29 300
9	-	-	-	35 200 000	8 320 000	293 000

particle size of 0.3µm. The airborne particle concentrations should, therefore, be less than 1020/m³.

The required calculations are as follows.

Sampling locations

The area of the cleanroom floor is 4m × 5m = 20m². The ISO 14644-1: 2015 table of sample locations related to area of cleanroom (**Table 12.1** in this document) shows that for a floor area above 10m², and less than 24m², the minimum number of sampling locations is six.

As the area of the cleanroom is 20m², and the minimum number of locations is six, each sampling floor area should be no larger than 3.33m². Dividing the cleanroom of 4m x 5m into six equal floor areas can be achieved if the 4m side is divided into two lengths of 2m, and the 5m side is divided into three lengths of 1.67m. This division is shown in **Figure 12.1**.

Having divided the floor area into six equal sections, it is necessary to decide where each sampling point should be located. After considering the ISO 14644-1 requirement that sampling should be carried out at points 'representative of the characteristics of the section', the sampling points are located in the middle of each of the six rectangular sections.

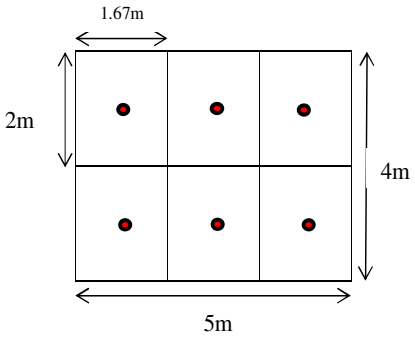


Figure 12.1: Division of a 4m x 5m cleanroom into six equal sections ● = sampling points

Minimum air sampling volume

The minimum air volume for each sample can be calculated by use of the previously discussed Equation 12.2, which is as follows:

$$\text{Minimum sampling volume} = \frac{20}{\text{class limit for given particle size}} \times 1000$$

As the class limit for a particle size of 0.3µm in an ISO Class 4 room is 1020 particles/m³, then,

$$\text{Minimum sampling volume} = \frac{20}{1020} \times 1000 = 19.6 \text{ litres}$$

Using an LSAPC with a sampling rate of 28.3L/min (1ft³/min), a 42 second sample should be sufficient for each location. However, ISO 14644-1 requires a minimum sample time of 1 minute, and therefore a 1 minute sample is taken.

Sampling results and designation of cleanroom

Air is sampled at working height at the six locations for one minute in the 'at rest' state, and the results are given in **Table 12.3**. If the counts obtained from the particle counter are expressed as particles/ft³ then they must be converted to particles/m³. The results given in the table are single air samples taken at each location. If several samples are taken at each location, the average at each location should be used.

Table 12.3 Particle counts in the cleanroom during classification

Sampling Location	Number of particles ≥ 0.3 m /m³
1	280
2	300
3	220
4	160
5	140
6	220

All of the results shown in **Table 12.3** are well below the class limit for an ISO Class 4 room, which is 1020 particles/m3 for particles ≥0.3µm, and the ISO acceptance criteria are satisfied. The cleanroom can, therefore, be designated as follows:

ISO Class 4; at rest; ≥0.3µm

12.5 Assessment of cleanliness of a cleanroom with macroparticles

In some cleanrooms, the critical size of particle that causes contamination problems can be larger than 5µm. This size of particle is known as a 'macroparticle' and a method is given in ISO 14644-1: 2015 on how to report the airborne concentration of macroparticles using the following 'M descriptor' format, which is as follows:

ISO M (a; b);c

Where,

a is the maximum permitted concentration of macroparticles /m³ of air,

b is the equivalent diameter (or diameters) associated with the specified method for measuring macroparticles, expressed in µm,

c is the specified measuring method.

For example, if macroparticles of a size ≥10µm are measured by a time-of-flight instrument, and their concentration is found to be 35/m³, the M descriptor would be as follows:

ISO M (35; ≥10µm); time-of-flight instrument

There are several methods that can be used to measure the concentration of macroparticles in the air and these are described in Annex H:

12.6 Sampling and monitoring nanoparticles

Nanoparticles are particles smaller than 100nm (<0.1µm), there being 1000nm in one micrometre. A nanoparticle is below the size measured by an LSAPC, and the instrument normally used to measure nanoparticles is a condensation particle counter (CPC). This instrument is described in Annex G.

Nanoparticles can be important contaminants in some types of cleanroom, such as those used for semiconductor production, and their concentration may need to be monitored at critical locations during manufacturing. However, this type of particle is mainly generated during the manufacturing process and it is logical to monitor their concentration only during manufacturing.

There is no method of classifying a cleanroom by its nanoparticle concentration but a method of monitoring the concentration of nanoparticles is given in ISO 14644-12 (2018) [ref 28]. Information about monitoring nanoparticles is discussed in Annex G in this book.

References

Note: The reference numbers are those used at the end of the *Cleanroom Testing and Monitoring* book from which this Chapter is taken.

7. ISO 14644-1:2015 – Part 1: Classification of air cleanliness by particle concentration. International Organization for Standardization, Geneva, Switzerland.
8. ISO 14644-2:2015 – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration. International Organization for Standardization, Geneva, Switzerland.
28. ISO 14644-12:2018 – Part 12: Specification for monitoring of air cleanliness by nanoscale particle concentration. International Organization for Standardization, Geneva, Switzerland.Abstract

Dr William (Bill) White is an Honorary Research Fellow at the University of Glasow and has the useful dual qualifications of a BSc in microbiology and a DSc in mechanical engineering. There is a full biographical note in CACR50 on page 9.

The d_{50} cut-off size of microbiological impaction air samplers: derivation of simplified expressions

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Abstract

Microbiological impaction methods used for active monitoring of air in controlled areas should be able to measure concentrations of biocontamination by collecting airborne particles of a certain equivalent particle size. The difference in results between microbiological impaction samplers depends on the physical parameters of the samplers. The d_{50} value (cut-off size) is a valuable tool in evaluating the monitoring efficiency of impaction air samplers.

Simplified mathematical expressions of the d_{50} value for impaction air samplers with circular or slit nozzles have been used in international standards such as EN17141:2000 and this paper explains their derivation.

Introduction

The physical sampling efficiency of microbiological impaction air samplers is based on the physical characteristics of the sampling device, such as airflow, orifice shape, and orifice size. The d_{50} value (cut-off size) describes the aerodynamic or equivalent particle diameter above which 50% of the particles are removed from the airstream and impacted.

The d_{50} value is a valuable tool in the understanding of the efficiency of microbiological air samplers. Simplified expressions for the d_{50} value have been used in discussions of international microbiological standards, notably EN 17141:2020. To avoid misunderstandings/errors the mathematical background of the simplified expressions of d_{50} is described in the following.

Mathematical treatment

The classical derivation of the d_{50} value uses the Stokes number and can be calculated as follows (from Nevalainen *et al* (1993) and Hinds (1999)):

Equation 1

$$d_{50} = \sqrt{\frac{9\eta W \cdot Stk_{50}}{\rho U C}}$$

Where η = Viscosity of air *(Pa·s)*
W = Characteristic size of the air inlet *(m)*, (diameter for circular nozzle, width for rectangular nozzle)
Stk_{50} = Stokes number that gives 50% collection efficiency (non-dimensional)
ρ = Particle density (kg/m³)
U = Impact velocity (m/s)
C = Cunningham slip correction factor used for particles smaller than 1µm (non-dimensional)

Impact collection data are usually given in terms of an aerodynamic d_{50} (i.e. using aerodynamically calculated particle sizes). For particle sizes under consideration here, i.e. particles ≥ 1.0 µm (Whyte *et al* (2007), a Cunningham slip correction factor of 1 is chosen. For smaller particles and more accurate estimations, see Hinds (1999). With accurate correction factors for particles with diameters of 1µm and 0.5µm, reductions in d_{50} values of 7% and 13% respectively will occur. The Stk_{50} number is often chosen as 0.24-0.25 for inlet circular nozzles and 0.50-0.59 for inlet slit nozzles with a rectangular shape, see Nevalainen *et al* (1993) and Hinds (1999).

Equation 1 can be simplified by using constant values for air viscosity, particle density, and correction factor; see for example Meier and Zingre (2000), Ljungqvist and Reinmüller (2008), Romano (2011), and European standard EN 17141:2020.

The constant values used are:

Air viscosity, η:*1.8* • 10^{-5} Pa· , (at 20°C, 1 bar)
Particle density, ρ: 1000 kg/m³, (=1g/cm³, unit density)
Cunningham slip correction factor: 1

With the above given values **Equation 1** becomes:

Equation 2

$$d_{50} = \sqrt{\frac{162W \cdot Stk_{50}}{U}}$$

Where d_{50} = cut-off size (µm)
W = Characteristic size (mm)
U = impact velocity (m/s)

With the Stk_{50} values for circular and slit nozzles given by Nevalainen *et al* (1993) and Hinds (1999) (**Equations 3-6**) can be calculated.

According to Nevalainen *et al* (1993):
Stk_{50} = 0.25 for circular nozzle
Stk_{50} = 0.50 for slit nozzle

According to Hinds (1999):
Stk_{50} = 0.24 for circular nozzle
Stk_{50} = 0.59 for slit nozzle

The characteristic size, *W*, in **Equation 2** for a circular nozzle is the diameter, *d*, and for a slit nozzle is the width, *s* (slit width).

Thus, the expressions become:

Circular nozzle:

Equation 3

$$Stk_{50} = 0.25 \text{ gives } d_{50} = \sqrt{\frac{40.5 \cdot W}{U}} = \sqrt{\frac{40.5 \cdot d}{U}}$$

Equation 4

$$Stk_{50} = 0.24 \text{ gives } d_{50} = \sqrt{\frac{38.9 \cdot W}{U}} = \sqrt{\frac{38.9 \cdot d}{U}}$$

Rectangular nozzle:

Equation 5

$$Stk_{50} = 0.50 \text{ gives } d_{50} = \sqrt{\frac{81 \cdot W}{U}} = \sqrt{\frac{81 \cdot s}{U}}$$

Equation 6

$$Stk_{50} = 0.59 \text{ gives } d_{50} = \sqrt{\frac{95.6 \cdot W}{U}} = \sqrt{\frac{95.6 \cdot s}{U}}$$

In **Equations 3** to **6** d_{50} is in µm, *W*, *d* and *s* are in mm, and *U* is in m/s.

Nevalainen *et al* (1993) suggest that the hydraulic diameter of the inlet nozzle (D_h) can replace the characteristic size (*W*) together with Stk_{50} = 0.25.

Equation 7 gives hydraulic diameter D_h.

Equation 7

$$D_h = \frac{4A}{P}$$

Where A = Cross-sectional area of the flow (m^2)
P = Perimeter "wetted" by the flow (*m*)

Therefore, for a circular opening, the hydraulic diameter is the hole diameter.

For a rectangular slit opening (length much larger than the width), the equivalent hydraulic diameter is normally taken as being approximately twice the slit width, see Nevalainen *et al* (1993).

Once thus simplified, the approximate expression for d_{50} (µm) as a function of the hydraulic diameter, valid for both circular holes and rectangular slits can be shown as:

Equation 8

$$d_{50} = \sqrt{\frac{40 \cdot D_h}{U}}$$

Where D_h = Hydraulic diameter of the inlet nozzle (mm)
U = Impact velocity (m/s)

Equation 8 will yield the following expressions for a circular nozzle and for a rectangular nozzle:

Circular nozzle:

Equation 9

$$d_{50} = \sqrt{\frac{40 \cdot d}{U}}$$

Rectangular nozzle (long slit):

Equation 10

$$d_{50} = \sqrt{\frac{80 \cdot s}{U}} = \sqrt{\frac{40 \cdot 2 \cdot s}{U}}$$

Where d_{50} = cut-off size (µm)
d = diameter for a circular nozzle (mm)
s = slit width for a long rectangular slit nozzle (mm)
U = Impact velocity (m/s)

Some examples

To demonstrate the effect that the D_h in the simplified expression (**Equation 8**) has on the value of the d_{50} value, examples of a microbial air sampler are considered with rectangular slits that are respectively 0.5mm, 1mm, and 2mm wide and 20mm long, and an air velocity through the slit of 20m/s. There are three solutions of the simplified expression:

- Slit width = 0.5mm and hydraulic diameter = approx. 1mm

d_{50} for slit width 0.5mm $= \sqrt{\frac{40\times1}{20}} = 1.4\mu m$

- Slit width =1mm and hydraulic diameter = approx. 2mm

d_{50} for slit width 1mm $= \sqrt{\frac{40\times2}{20}} = 2\mu m$

- Slit width =2mm and hydraulic diameter = approx. 4mm

d_{50} for slit width 2mm $= \sqrt{\frac{40\times4}{20}} = 2.8\mu m$

The examples show that the equivalent hydraulic diameters – twice the slit width in the approximate formula – give the correct d_{50} levels compared to those calculated from **Equation 1**.

Summary

The **Equation 8** gives d_{50} values in the same range as **Equations 3-6**. The errors of d_{50} values for circular nozzles with **Equation 9** compared to **Equations 3** and **4** are about 1%, while the errors for rectangular nozzle estimated with **Equation 10** compared to **Equations 5** and **6** are less than 1% and 9%, respectively. These errors are due to the assumptions made for Stk_{50}. If more accurate values are required **Equation 1** should be used.

The advantage of performing calculations with **Equation 8, Equation 9**, and **Equation 10** is that the method is fast and easy to use and, as a first approximation, gives reliable results of d_{50} values.

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In 2006 She was appointed "Outstanding PDA Scientist" in Contamination Control by the Parenteral Drug Association (PDA) and, in 2008, awarded honorary membership. She has been an honorary member of R3 Nordic since 2007 and of PHSS since 2011.

Selection of microbiological swabs for cleanroom monitoring: design considerations

Tim Sandle

Abstract

The range of sampling methods for the environmental monitoring of cleanrooms has included swabbing for several decades. It has long been accepted that the use of swabs leads to a relatively low recovery of microorganisms from surfaces. However, the recovery from swabs can be improved by selecting flocked swabs over plain swabs and with fine tuning the method, including the testing of the swab recovery fluid. This article presents data showing the superiority of flocked swabs and considers how different surface materials affect microbial recovery.

Introduction

Swabs are commonly included as part of an environmental monitoring programme to assess the number of microorganisms on a surface within a cleanroom environment[1]. In many sampling regimes, swabs are regarded as a secondary method for surface monitoring since they are theoretically less efficient at surface recovery than contact plates[2,3]. Hence, the use of swabs is normally reserved for surfaces where a contact plate cannot be used (such as curved or irregular surfaces).

In selecting a suitable swab there are different choices for the cleanroom manager and microbiologist to make. These include the material used to form the swab tip and the method of creating the tip (with an important distinction arising between so-called 'plain' and 'flocked' swabs). The sampling technique also needs to be well-described and consistently practiced, especially applying pressure and rotating the swab tip across an area of no more than 25sq cm; conventionally the swab should be rolled between the fingers and thumb to rotate it across the surface whilst swabbing in three directions: horizontal, then vertical then diagonal. (The swab needs to be rotated during swabbing to ensure that the entire surface of the swab is used)[4]. A further choice is with the testing method for obtaining the estimate of microbial numbers: a) releasing the swab tip into growth medium (something suitable only for EU GMP Grade A surface monitoring since the obtained result can only be expressed quantitatively); agitating so that any held microorganisms are released into a suspending medium and testing the medium by membrane filtration; or b) a direct streaking of the swab onto a solid agar plate[5].

Swab tip material

The material used for the swab tip is an important determinant of recovery efficacy[6], such as whether it is made from nylon, rayon, calcium alginate, cotton or an alternative material like a cellulose viscose sponge material[7]. The material difference appears to influence absorbance capacity. Swabs are most commonly manufactured from polyester or nylon. (Cotton swabs, perhaps still featuring high in public consciousness when the word 'swab' is used, are rarely used in cleanrooms today)[8]. To support the tip, the applicator is important in terms of its tensile strength as so not to break during the swabbing activity.

Swab tip design

With the design of the swab tip, different studies have demonstrated that a flocked swab tip provides a superior recovery to a plain swab tip[9,10]. With flocked swabs, the tip of the applicator is coated with short fibres, arranged in a perpendicular fashion. The perpendicular arrangement (flocking) is formed when the fibres are sprayed onto the tip of the swab, while the tip is held in an electrostatic field. Recovery is superior because capillary action between the fibre strands facilitates strong hydraulic uptake of a liquid sample, including any microorganisms present. In addition, a tip that is pre-moistened is superior at recovering organisms from a surface compared with a dry swab.

Example study

To illustrate the differences in recoveries between plain and flocked swabs, a study was undertaken at the author's facility to determine which type of swab produced the highest recovery of a selection of microorganisms from two common cleanroom surface materials: 316 L stainless steel and polyvinyl chloride. A comparison was made between plain tipped swabs and flocked tipped swabs.

The plain tip swabs are supplied in irradiated triple wrapped packs of 10 swabs. Each swab is individually wrapped supplied dry with an accompanying tube container with a liquid amies* recovery medium to moisten the swab prior to sampling and to protect the swab sample after sampling. The flocked swabs are supplied sterile single wrapped dry with an accompanying tube container with a liquid amies recovery medium to moisten the swab prior to sampling and to protect the swab sample after sampling. Swabs are available with a range of different fluids, including some containing disinfectant neutralisers. For this study, to enable a direct comparison between the flocked and woven head swabs, a flocked swab with liquid amies medium was used to eliminate any distortion is results due to medium use with the swab and not the swab head.

To illustrate the differences in recoveries between plain and flocked swabs, a study was undertaken at the author's facility to determine which type of swab produced the highest recovery of a selection of microorganisms from two common cleanroom surface materials: 316 L stainless steel and polyvinyl chloride.

* Amies liquid medium is a nonnutritive balanced salt solution containing inorganic phosphates to provide buffering capability, sodium chloride, potassium chloride, calcium chloride and magnesium chloride to provide essential ions that help maintain osmotic balance.

For the evaluation of the results, a criterion of ≥50% was set. This was based on the method validation criterion for testing non-sterile products in the Ph. Eur. (2.6.12) and the USP (<61>). In these pharmacopoeial chapters the spread plate, pour plate and other microbial recovery methods are described.

The microorganisms chosen for the evaluation study represent a range of different types (Gram-positive rods, yeast, Gram-negative rods, Gram-positive coccus and a filamentous fungus).

Staphylococcus aureus	(ATCC 6538)
Bacillus subtilis	(ATCC 6633)
Pseudomonas aeruginosa	(ATCC 9027)
Candida albicans	(ATCC 10231)
Aspergillus brasiliensis	(ATCC 16404)

The information in parenthesis is the American Typed Culture Collection reference number. In addition to the above typed cultures, two common environmental isolates were selected:

Micrococcus luteus
(Source: Environmental monitoring swab)
Staphylococcus epidermidis
(Source: Operator exit suit contact plate)

An appropriate number of surfaces with marked areas of 25sq cm were prepared and sterilised (autoclaved) prior to being used for each test. The surfaces were 'new' (that is, not subjected to any damage or roughening).

With this method, an aliquot of less than 100cfu of each microorganism for testing was applied to each test surface in triplicate and allowed to dry before the test was progressed. Each inoculated surface was swabbed with a separate swab for each microorganism tested, ensuring that each 25sq cm surface was sampled completely. The swabs were then plated out onto 9cm TSA. The plates were incubated at 30°C–35°C for 24–48 hours and the number of colonies counted.

Positive controls for each test microorganism were prepared by directly inoculating a swab tip with less than 100cfu of each microorganism and then plating each swab on to a 9cm TSA plate. This was performed in duplicate for each test microorganism. The plates were incubated at 30°C–35°C for 24–48 hours and the number of colonies counted. In addition, duplicate spread plates were prepared with less than 100cfu for each test microorganism to determine the inoculum level.

The results from the surface testing performed using the above spread plate methodology are summarised in **Tables 1** and **2** opposite.

The percentage recovery for all of the tests was calculated using the following formula:

$$\frac{Test\ swab\ recovery}{Control\ swab\ recovery} \times 100$$

The *test swab recovery* is the average of all the mean swab recoveries from the two surfaces tested.

The *control swab recovery* is the average of the mean swab recoveries from the positive control swabs.

Self-contained surface environmental monitoring swab systems are suitable for testing Grade A environments where EU GMP Annex 1 expectation is for 'no growth'.

The results obtained from the plain and flocked swab comparison when tested using the swab spread plate method demonstrated that the flocked swabs gave a better recovery when comparing the surface results with the swab positive results: 56% and 37.5% mean recoveries, respectively. There were variances, however, between different surfaces (stainless steel and PVC) and between organisms (something which matches the results of earlier studies)[11]. With surface material, recovery was higher from PVC compared with stainless steel (with the best recovery being from PVC using the flocked swab, at 60%). With organisms, the most challenging organism to recovery was the yeast-like fungus *Candida albicans*, followed by the environmentally isolated *Staphylococcus*. These results demonstrate the variables that affect the way that different microorganisms bind to different surfaces, through different physicochemical interactions.

Self-contained swabs for Grade A environments

Standard swabs are not protected whilst being transferred from the testing site to the culture medium. Self-contained swabs, where the tip is released into a broth medium without re-exposing the swab to the external environment, carries an advantage for monitoring Grade A environments. This is because the risk of cross-contamination from the environment within which the self-contained swab is subsequently handled or from the person processing the swab is greatly reduced.

Such systems provide a qualitative microbial presence/absence testing of dry, difficult to sample surfaces. The swabs are presented as individually wrapped pre-moistened swabs within a housing tube that encloses a reservoir of soyabean casein digest medium (equivalent to tryptone soya broth [TSB]) containing appropriate disinfectant neutralisers (such as lecithin and Tween 80).

The tips of the swabs are typically manufactured from a low abrasion material of knitted polyester and the swabs should be supplied in bags impermeable to hydrogen peroxide vapour (given that this is the most common means of decontaminating the critical zone) and sterilised by gamma irradiation. Once the swab is sampled and replaced into the housing tube, the reservoir housing can be snapped to release the TSB into the tube containing the swab. The self-contained TSB-swab can be incubated as a unit, thereby eliminating the need to plate out the swab onto agar. This significantly reduces the potential risk of cross-contamination (a false positive), which is of particular importance given the regulatory expectation of zero contamination.

The use of these swabs would apply to those parts of an aseptic processing environment that are critical in terms of batch release decisions and where the presence or absence of microorganisms is significant. These areas would include bowls for filling needles and stoppers, as well as isolators used for sterility testing.

Conclusion

This article has looked at some of the variables in terms of swab selection and design that need to be considered. These have been identified as the material used to create the swab tip and, more criticality, the way the tip is produced either in terms of being 'plain' or 'flocked'. To illustrate the differences in recovery, an example study has been provided whereby both designs of swabs were evaluated against two different surfaces using a range of suitable microorganisms. The study demonstrated that the flocked swabs gave the greatest recovery of microorganisms. As to why this is the case, it is most likely that although plain swabs can remove microorganisms from the surface with similar efficiency

Table 1 Results for plain swabs

Micro-organism	Inoculum (cfu/plate)		Swab +ve control (cfu/swab)			Stainless steel surface swab recovery			Vinyl surface swab recovery		
	Counts/ plate		Counts/ plate		Mean	Counts/ plate	Mean	% recovery	Counts/ plate	Mean	% recovery
S. aureus	55	38	45	40	43	10 17 10	12	**28**	11 11 10	11	**21**
B. subtilis	42	53	41	71	56	17 12 9	13	**23**	14 29 25	23	**41**
Ps. aeruginosa	41	47	20	19	20	12 6 3	7	**35**	5 5 3	4	**20**
C. albicans	49	54	18	17	18	4 3 2	3	**16**	0 1 0	1	**6**
A. brasiliensis	32	27	31	31	31	3 3 5	4	**13**	10 3 4	6	**19**
M. luteus	97	86	76	59	68	63 88 56	49	**72**	50 52 41	48	**71**
Staph. epidermidis	21	27	19	10	15	0 3 1	1	**7**	1 1 4	2	**13**
Average of means					36		13			14	
Overall % recovery	37.5%										

Table 2 Results for flocked swab

Micro-organism	Inoculum (cfu/plate)		Swab +ve control (cfu/swab)			Stainless steel surface swab recovery			Vinyl surface swab recovery		
	Counts/ plate		Counts/ plate		Mean	Counts/ plate	Mean	% recovery	Counts/ plate	Mean	% recovery
S. aureus	47	50	30	23	27	20 12 19	17	**63**	25 7 11	14	**52**
B. subtilis	50	39	46	32	39	11 12 18	14	**36**	17 16 14	16	**41**
Ps. aeruginosa	50	54	36	24	30	8 13 10	10	**33**	19 17 14	17	**57**
C. albicans	53	45	29	27	28	11 10 7	9	**32**	5 5 5	5	**18**
A. brasiliensis	43	39	24	16	20	7 14 10	10	**50**	10 13 8	10	**50**
M. luteus	51	36	26	36	31	20 30 28	26	**84**	24 56 30	37	**119**
Staph. epidermidis	21	27	21	12	17	10 13 14	12	**71**	16 13 13	14	**82**
Average of means					27		14			16	
Overall % recovery	56%										

Many of the points made in this article are illustrative; the important point being that the selection of swabs for cleanroom sampling needs to be thought out and justified, supported with applicable laboratory qualification data.

to flocked swabs there are difficulties with the release viable microorganisms (absorbance is presented as a key variable in differentiating between different swab efficiencies).

- As well as direct surface recovery there are other aspects of swab use that require examination, including:
- Suitability of the holding or recovery fluid. To demonstrate that the recovery from the swabs is valid, users of swabs should perform a recovery study to show that the recovery fluid is not toxic to microorganisms.
- Optimisation of the likelihood of recovery. The fluid should be mixed before testing. Greater consistency can be achieved using a laboratory vortex mixer. Assessing the period required for vortex mixing the fluid is important.
- Hold time prior to testing. This should be evaluated and a maximum time period set.
- Pre-test storage temperature. This should be defined (typically 2-8°C) to prevent excessive microbial growth.
- Other types of surfaces common to cleanrooms. These should be evaluated as appropriate.
- Aging facilities. Assessment of surfaces at different states of simulated damage or 'roughness' should be carried out[6].
- Consideration of possible other microorganisms for adding to the test panel. This depends on the types of microorganism recovered from the facility's environmental monitoring programme.
- Consideration of the time that a microorganism is in contact with the surface in question. There are not only differences between species of microorganism in this respect, but also with the amount of time that has elapsed after deposition on a surface (especially when physicochemical interactions become stronger and in cases when a biofilm community develops)[13].

A further determinant with the test method is with inter-individual differences in sampling technique, i.e. variations between people[14]. In this article, only one test method was examined (the relatively common streak plate method). However, there are alternative methods, such as membrane filtration of the fluid that has been used to moisten the swab and to preserve the swab prior to testing.

In drawing together swab design considerations, the article has also considered the use of self-contained swabs, where the sampled swab tip is incubated in broth within the overall swab system. The advantage of this method is the reduction in the number of processing steps which lowers the possibility of cross-contamination occurring during processing.

This is necessary for optimising microbial recovery from surfaces and for formulating a defensible regulatory position.

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Pharma 4.0™ and how it impacts EU GMP Annex 1 CCS (Contamination Control Strategy)

Jason Kelly

Abstract

Pharma 4.0™ represents a transformative shift in the pharmaceutical manufacturing landscape, particularly in the context of aseptic processing of sterile products. It is driven by the integration of advanced digital technologies to enhance efficiency, compliance, and quality in drug manufacturing. The latest revision of the EU GMP Annex 1 emphasizes a stringent Contamination Control Strategy (CCS) and incorporates Quality Risk Management (QRM) principles, highlighting a shift towards risk-based approaches and real-time environmental monitoring. This paper explores how Pharma 4.0™ facilitates a robust CCS by leveraging real-time data collection, digital maturity, and data integrity within pharmaceutical operations. Enhanced use of digitally enabled tools such as particle counters and air samplers, and advanced data analytics enables better decision-making, ensures compliance with regulatory standards, and supports continuous manufacturing. By fostering an interconnected pharmaceutical environment, Pharma 4.0™ not only aims to safeguard product quality and patient safety but also propels the industry towards a future where digital integration ensures seamless operation and superior product integrity.

What is Pharma 4.0™?

The term 'Fourth Industrial Revolution' was first used in around 2015 and quickly led to the catchphrase 'Industry 4'. Very roughly, the first industrial revolution comprised the replacement of manpower and horsepower by steam power. The second industrial revolution started with the arrival of electricity, production lines and telegraphic communication. The third industrial revolution is the digital revolution which occurred as computers were developed and became more widely used. And the fourth industrial revolution recognizes the interconnectivity of everything as characterised by 'The Internet of Things' (IoT), cloud computing, Artificial Intelligence (AI), Machine Learning (ML) and Smart Factories.

Pharma 4.0™[1] is the pharmaceutical industry's response to Industry 4, orchestrated by ISPE (International Society for Pharmaceutical Engineering). Pharma 4.0™ is seen as an evolution of ICH 10: *Pharmaceutical quality system – Scientific guideline* and ISPE have set up a Pharma 4.0™ Community of Practice (CoP) where, under a structured leadership and with working groups, ISPE members can share their experiences of implementing Pharma 4.0™ principles in their organizations.

Pharma 4.0™ is tailored to meet the pharmaceutical industry's unique challenges and strict regulatory environment. It's about leveraging digital advancements to boost drug manufacturing efficiency and quality, ensuring compliance, data integrity, faster decision making, a robust quality system and fostering innovation. Whether you're an expert in aseptic manufacturing or a Quality Manager superhero, Pharma 4.0™ signifies a shift towards a more interconnected and data-centric pharmaceutical landscape. Pharma 4.0™ is promising to reshape our approach to sterile medicine production with enhanced Environmental Monitoring (EM) and data integrity of aseptic processing of sterile pharmaceutical products.

Pharmaceutical Aseptic Processing is the art of performing a specific process within an ultra-clean environment to ensure that the sterile product, in this case an injectable liquid medicinal product, is transported from bulk sterile containers and filled into vials, or syringes without loss of sterility. Environmental Monitoring of that process is critical for product safety and integrity. **Figure 1** shows a view inside a sterile filling operation.

The latest revision of EU GMP Annex 1 is a testament to the evolving landscape of aseptic processing. It brings forth stringent requirements for Environmental Monitoring, aiming to safeguard the manufacturing of sterile products. EU GMP Annex 1[2] is a regulatory guideline for the manufacture of sterile medicinal products, ensuring their quality and safety. The key focus of the document is to provide a framework for establishing a robust contamination control strategy (CCS). This strategy is critical for sterile pharmaceutical manufacturing, where the risk of microbial and particulate contamination must be minimized to protect the patient's health.

A Contamination Control Strategy (CCS) is an organised approach to maintaining a clean environment throughout the manufacturing process. It encompasses all aspects of production that could affect the sterility of the final product. This includes the design and maintenance of cleanrooms, the handling of materials, personnel hygiene and gowning, equipment sterilization, environmental monitoring, and process validation.

Figure 1: Sterile filling operation.

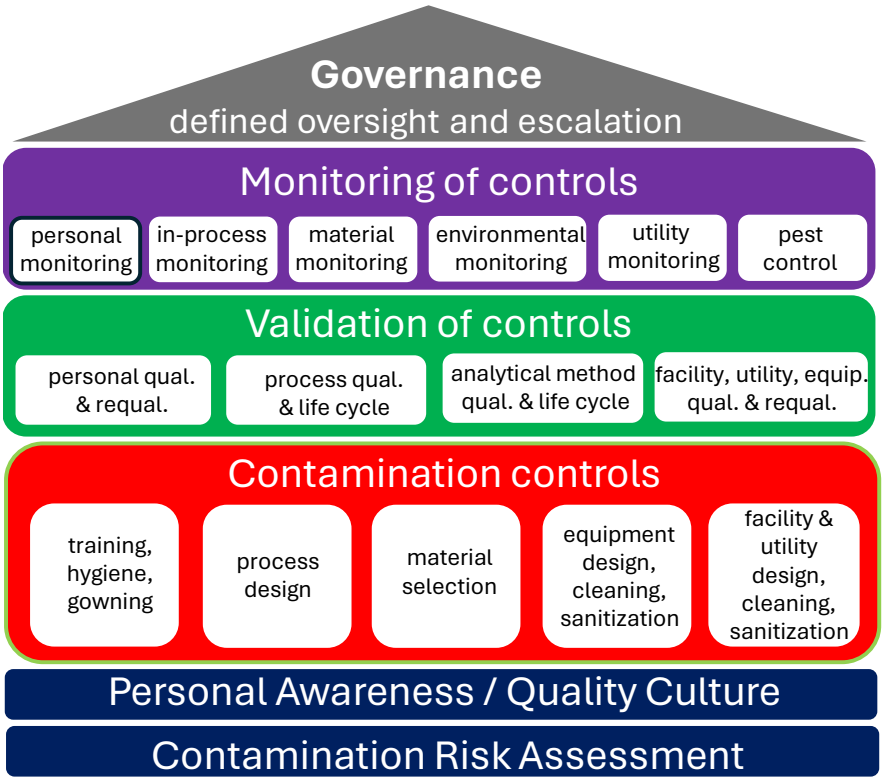

Figure 2: Principles of a Contamination Control Strategy.

The latest revision of EU GMP Annex 1, released in 2022, places a greater emphasis on risk-based approaches to contamination control. It integrates Quality Risk Management (QRM) principles into the CCS, ensuring that decisions regarding contamination risks are made with a thorough understanding of their potential impact.

In the context of Pharma 4.0™ digital data becomes increasingly important for the CCS. The use of digital technologies such as real-time environmental monitoring with particle counters and air samplers, and advanced data analytics tools, allows for the collection and analysis of vast amounts of data. This data can be used to make informed decisions quickly, improve the quality of the products, and ensure compliance with regulatory standards. **Figure 2** shows all the aspects that come into consideration in a CCS.

Digital data also supports data integrity and governance within the CCS. It ensures that all data related to contamination control is accurate, complete, and reliable throughout its lifecycle. This is essential for both regulatory compliance and ensuring the effectiveness of the CCS. With digital data, companies can adopt more efficient, automated, and error-resistant processes, reducing the risk of contamination and enhancing overall product quality. This speeds up the production and product release process.

Pharma 4.0™ pushes for digital maturity. In order to enable seamless data integrity and faster and more informed decisions to be made the pharmaceutical facility must have digital maturity built into their IT frameworks. **Figure 3**. Expands on digital maturity for Resources, Information Systems, Organization and Processes, and culture in Pharma 4.0™.

Pharma 4.0™ is redefining the industry by digitalizing data and processes, linking information, fostering transparency, and enhancing adaptability. This interconnectedness leads to swifter decision-making, better control, and superior product quality. It's a holistic approach that binds technology with the processes and people, revolutionising the production landscape.

At the heart of Pharma 4.0™ lies the principle of Holistic Control Strategy Lifecycle Management, underpinned by 'Data Integrity by Design'. Achieving this requires an organization's 'Digital Maturity' within the Industry 4.0 framework. A critical component of this new era is continuous manufacturing, which depends on a constant stream of data from environmental monitoring systems, ensuring digital regulatory compliance and traceability.

Key aspects of Pharma 4.0™ include:

Digitalization of Operations: Implementing digital tools and solutions across the manufacturing process, from research and development to packaging and distribution.

Data Integration and Analytics: Leveraging big data and advanced analytics to gain insights that drive better decision-making and predictive maintenance. This is where data integrity and real time data merge – is your vendor up to the challenge?

Smart Manufacturing: Using smart devices and IoT to monitor and control the manufacturing environment, ensuring product quality and operational efficiency. Does your vendor have Smart EM Devices that enable smart manufacturing which flags up bad data?

Artificial Intelligence and Machine Learning: Applying AI and ML to improve process control, forecast demand, and personalize medicine. Is your Vendor capable of providing such enhanced Analytical EM tools?

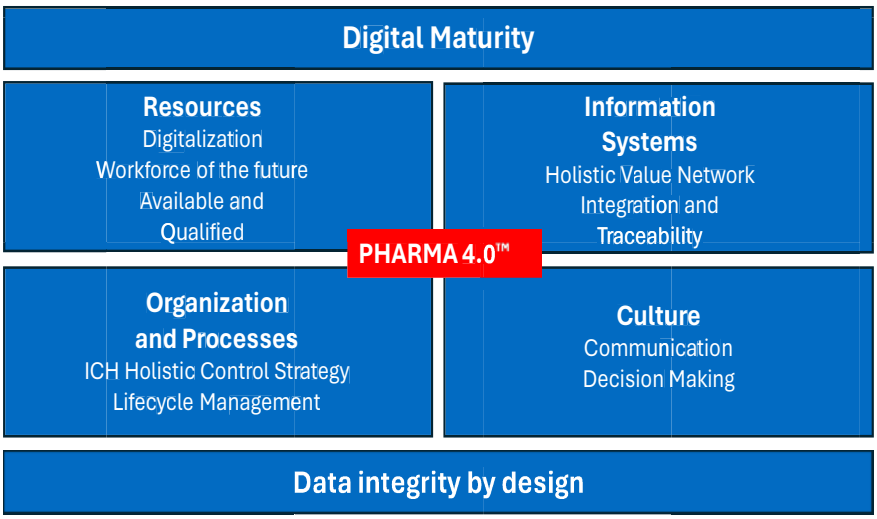

Figure 3: Pharma 4.0™ digital maturity.

Advanced Robotics and Automation: Enhancing precision and efficiency while reducing the risk of contamination by employing robotics in production lines.

Continuous Manufacturing: Shifting from batch to continuous production processes to increase flexibility and efficiency. You are going to need continuous EM data sources to enable more efficient and compliant decisions to be made in a continuous manufacturing environment.

Regulatory Compliance: Ensuring that digital transformation aligns with global regulatory standards, including data integrity and traceability requirements. Does your EM equipment and software enable this?

Supply Chain Optimization: Streamlining the supply chain through digital technologies for better traceability and responsiveness. Remote vendor audits can speed up this process.

Personalized Medicine: Utilizing digital tools to cater to individual patient needs, leading to more personalized and effective treatments. We are going to see demand increase as more patients opt for personalized medicine.

In the world of Annex 1, digital data is king. The heart of Annex 1 compliance lies in digital data. Real-time monitoring through advanced devices like smarter digitally advanced particle counters and air samplers connected to automated monitoring Systems provides a data-driven foundation for Environmental Monitoring, ensuring that we meet the stringent Annex 1 regulations.

In the world of aseptic manufacturing, maintainability is critical. Digitization is not just about adopting new technologies; it's about building sustainable compliance. With enhanced digital technology in Environmental Monitoring, we create a contamination control strategy that's not just effective today but is resilient for the challenges of tomorrow and beyond.

Figure 4: Operator reviewing real time Environmental Data.

It's all about the data and the integration of sensors and digitally enhanced processes throughout the pharmaceutical facility. Today's Pharmaceutical Sterile Manufacturing facilities need to embrace Pharma 4.0™ and get to a level of digital maturity, so the data collection process and the analysis of the data run like a well-oiled machine. AI technology can assist in identifying, in real time, trends and facility issues that impact product sterility and safety.

At the heart of Pharma 4.0™ lies data integrity and governance. It's about ensuring the accuracy, completeness, and reliability of data throughout its lifecycle. This is what allows us to make decisions with confidence. How do you know that the data lifecycle from the collection setup to the digital transfer has maintained integrity? I would say look at the technology EM monitoring vendors provide and see how they manage data integrity in their technology. For example, how does their particle counter handle BAD Data? Does their technology even have the ability to sense BAD Data at the sensor level? Data integrity and governance are the cornerstones of Pharma 4.0™, and this is embedded in the Contamination Control Strategy. It's all about the data and the integrity of that data. **Figures 4, 5** and **6** are simply statements that illustrate and reinforce the message of this paper.

Figure 5: Example of particle counter data Integrity in operation red flagging bad data.

Real time decision making for batch release

Pharma 4.0™, with the innovation of Quality by Design (QbD), is reshaping pharmaceutical sterile manufacturing. It's a strategy that doesn't just solve problems during the manufacturing process – it prevents them. By integrating a Pharma 4.0™ and QbD approach, we ensure that our clean spaces aren't just controlled, they're intelligently managed. QbD is a proactive approach to pharmaceutical manufacturing. Engage with your EM vendors and build Quality into your EM systems together. EM Data can be seamlessly integrated into Data Lake systems where data from multiple facility locations are all centralized. AI, as mentioned previously, can be used to scan all the facilities' data, pinpoint emerging trends and pick up catastrophic events before they impact on the product.

With QbD built into your EM systems, real-time Environmental Monitoring will revolutionise batch release processes. It enables us to respond immediately to data records, streamline product release, and enhance market readiness while upholding the highest quality standards. Continuous Manufacturing

Figure 6: Operator inspecting vials of sterile injectable product.

will need robust environment monitoring systems with reliable data to enable batch releases to be quicker with confidence and these monitoring systems, whether portable or fixed, need to integrate and have reliable connectivity to the main CCS database.

So where is all this digital advancement leading us? We are heading into a continuous manufacturing process that is fully automated, moving the mobile particle generators (i.e. people) outside the cleanroom where we can manage the process in real time and verify the data in real time leading to a seamless approval process which underpins continuous manufacturing.

Conclusion

The integration of Pharma 4.0™ into aseptic manufacturing paves the way for a future where efficiency, safety, and compliance are not just goals but guarantees. It's a future we're not just predicting; we're actively creating it.

References

1. Pharma 4.0™: https://ispe.org/initiatives/pharma-4.0
2. EU GMP Annex 1:2022: https://www.gmp-compliance.org/files/guidemgr/20220825_gmp-an1_en_0.Abstract

Jason Kelly is Director of Applications at Lighthouse Worldwide Solutions, based in Oregon, USA. He has over 28 years' experience in providing Environmental and Particle Monitoring Solutions to the Cleanroom Industry and specializes in Pharmaceutical, Medical Device, Life Science, Semiconductor, Aerospace and Military Cleanroom applications. Jason presents worldwide on current cGMP and Environmental Monitoring Systems from risk management, system design, GAMP protocols, system installation, validation, customer training and system service support and has many technical webinars and papers available online in relation to Environmental Monitoring in Cleanrooms. Jason is also on the technical committee of IEST in the USA and presents at IEST seminars and conducts training classes in Cleanroom Technology/Certification and Monitoring Solutions. He is also on the PDA Ireland and Irish Cleanroom Society committees. Email: jasonk@golighthouse.com

Understanding the route to compliance with EU GMP Annex 15: Qualification and Validation

Toni Horsfield

Abstract

This short article, which is based on a Webinar by Gordon Farquharson and a blog by the author, introduces the principles of qualification and validation as described in EU GMP Annex 15. The key requirement is for the Validation Master Plan to be a living document with a robust change-control protocol. Two flow diagrams illustrate the workflow through the validation stages of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) and a list is given of recommended tests for cleanrooms and clean zones.

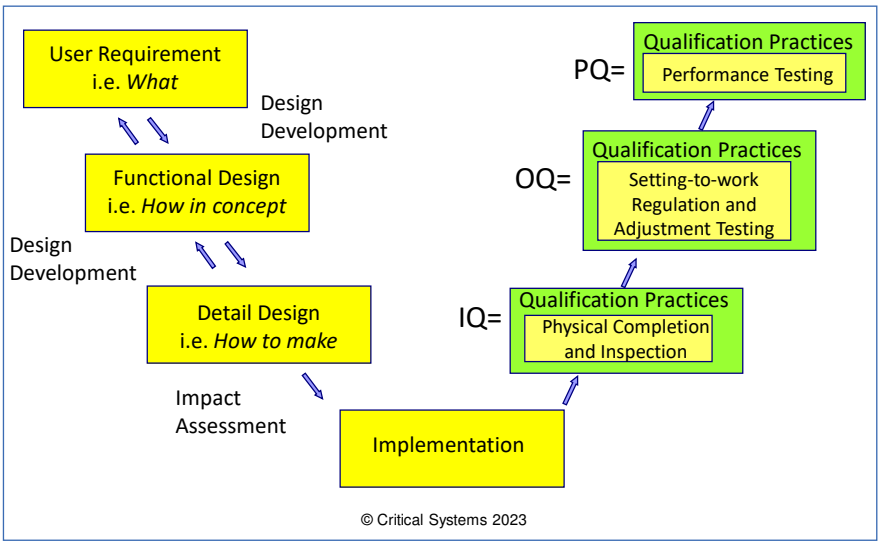

Figure 1: Classic "V" Model – courtesy of Gordon Farquharson, Critical Systems Limited.

Introduction

For those setting out on the validation journey there may seem to be a dizzying number of standards without a roadmap from which to navigate. This article aims to shed a light on the direction to take and on the role of Annex 15[1].

Who needs Annex 15?

The EU GMP principle outline for Annex 15 reads:

This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to EudraLex, Volume 4, Part II.

It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process.

Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed.

In summary you are aiming to validate the manufacture of your medicinal products in qualified facilities (cleanrooms) on qualified equipment (isolators).

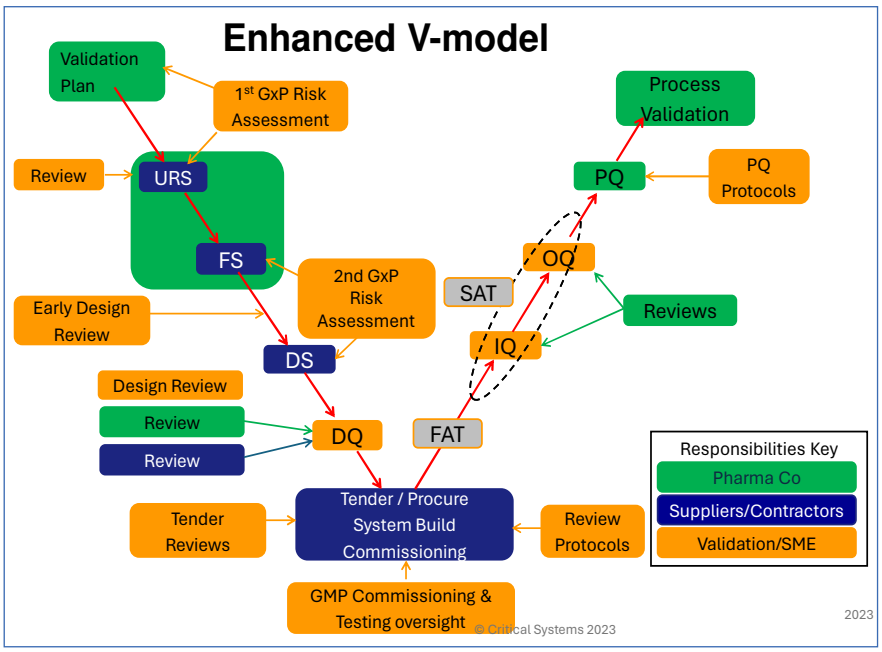

Figure 2: Enhanced "V" Model, commissioning integrated, courtesy of Gordon Farquharson, Critical Systems Limited (SME is Subject Matter Expert).

What is involved in validating the manufacture of a medicinal product?

Firstly, download the free copy of Annex 15 (a link is provided in References). It contains a wealth of information. As an overview, Annex 15 talks about a Validation Master Plan, a VMP which is made up of the following documents.

1. User Requirement Specification (URS)
2. Design Qualification (DQ)
3. Installation Qualification (IQ)
4. Operational Qualification (OQ)
5. Performance Qualification (PQ)
6. Computerized Systems Validation (CSV)
7. Process Validation (PV)
8. Cleaning Validation (CV)

The two graphics, shown here as **Figure 1** and **Figure 2**, depict the expected workflow and suggest how this would look when a quality risk management approach is applied.

A key point to note for those new

Table 1: Table NA.1 from BS EN ISO 14644-2:2015

Test parameter/Performance attribute	Maximum time interval between tests
Airborne particle concentrations ≤ ISO Class 5	6 months
Airborne particle concentrations > ISO Class 5	12 months
Pressure differentials	Continuously monitored by frequent manual observation or by automated instrumentation
Installed filter leak test in unidirectional airflow and cleanliness classes ≤ ISO Class 5	6 months
Installed filter leak test in non-unidirectional airflow and cleanliness classes > ISO Class 5	12 months
Airflow velocities in unidirectional airflow	6 months
Airflow volume supply in non-unidirectional airflow	12 months
Containment leak (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Airflow visualization (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Recovery time in non-unidirectional airflow (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Particle deposition rates (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Segregation tests (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
a) Temperature b) Humidity c) Electrostatic and ion generator	As required, and in agreement with the cleanroom user

to Annex 15 and best validation and qualification practice is that this should not be a tick-box exercise that needs to be completed, filed away, and never kept up to date or looked at again. Annex 15 requires the VMP to be a living document with a robust change-control protocol.

The current version of Annex 15 was published in 2015 but for those familiar with the old Annex 15 it is worth noting that retrospective validation is no longer considered an acceptable approach. The 2015 revision introduces the requirement for on-going or continuous verification, which goes beyond just three batch tests.

For aseptically processed Sterile Products we undertake Aseptic Process Simulation (APS) [used to be called media fills].

How do you qualify a facility or cleanroom?

The ISO 14644 series form the global standard for cleanroom and contamination-controlled environment compliance. There are 20 parts to this standard which demonstrates the breadth of this field, but we would recommend that you initially purchase parts 1, 2, 3, 4 and 7 which provide the foundations to qualification.

In addition to the ISO 14644 set of standards, which are generic, EU GMP in Annex 1 provides specific requirements for the manufacture of medicinal products. This is available as a free download – see References.

There will be a number of tests that will need to be performed regularly to satisfy qualification requirements set out in your VMP. The list of tests may vary slightly for different applications but to help, the BS (UK) version of EN ISO 14644-2:2015 has a National Annex titled *'Guidance on maximum time intervals for periodic testing of cleanrooms and clean zones* with a table, Table NA.1 – Recommended schedule for testing cleanrooms and clean zones – shown here as **Table 1**.

The diagram shown in **Figure 3**, lists the tests that may be required and suggests the order in which they should be performed. These qualification tests should not be confused with facility monitoring as described in ISO 14644-2:2015 and EU GMP Annex 1.

The person employed to do these tests should be 'suitably qualified'. The Cleanroom Testing and Certification Board International (CTCB-I) run internationally accredited courses aimed at cleanroom certifiers and other certified professionals working within cleanrooms and clean air devices. Passing these courses should satisfy the EU GMP requirement of 'suitably qualified'.

Summary

There is a lot of information and process specific detail that must be contained within a VMP but to keep the document focused it might be helpful to keep in mind that the aim is to validate the

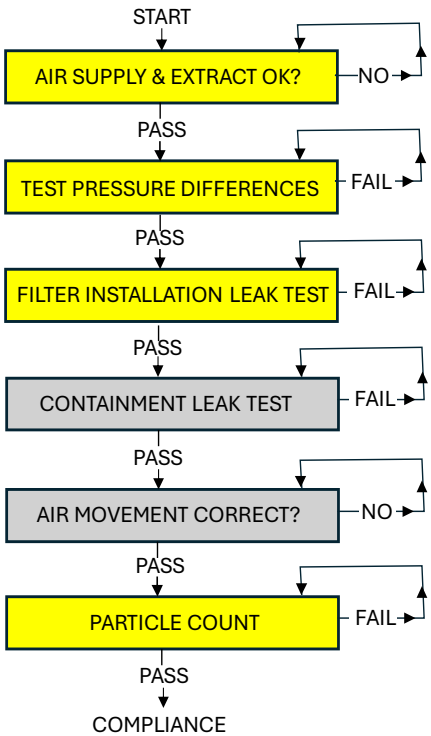

Figure 3: Suggested order for cleanroom tests, courtesy of Tim Triggs, Consultant at Air Techniques International.

manufacture of the medicinal products in qualified facilities (cleanrooms) on qualified equipment (isolators).

References

1. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Annex 15: Qualification and Validation. European Commission, Brussels, 2015. Free download at https://health.ec.europa.eu/system/files/2016-11/2015-10_annex15_0.pdf
2. ISO 14644-1:2015 – Part 1: Classification of air cleanliness by particle concentration. International Organization for Standardization, Geneva, Switzerland
3. ISO 14644-2:2015 – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration. International Organization for Standardization, Geneva, Switzerland
4. ISO 14644-3:2019 – Part 3: Test methods. International Organization for Standardization, Geneva, Switzerland
5. ISO 14644-4:2019 – Part 4: Design, construction and start-up. International Organization for Standardization, Geneva, Switzerland
6. ISO 14644-7:2004 (under review) – Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments). International Organization for Standardization, Geneva, Switzerland
7. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Annex 1. European Commission, Brussels, 2022. Free download at https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf
8. BS EN ISO 14644-2:2015 – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration. British Standards Institution, London, UK.

Acknowledgement

This article is based on a blog for CCN which was in turn based on a webinar delivered to CCN members by Gordon Farquharson. For more information about the CCN and the learning opportunities it offers please visit https://www.theccnetwork.org

Toni Horsfield is Founder and Managing Director of ISO Cleanroom having previously run Clean Environments before its sale in 2021. She has been designing cleanrooms since coming into the industry through the vacuum science sector in 2009. In 2023, Toni was appointed to the CCN committee. She has a long-standing passion for knowledge and is keen to help further develop the cleanroom sector through the CCN's education program.

Andy Cowan appointed President, Particle Measuring Systems (PMS)

Andy Cowan has been appointed President at PMS, taking over from Mark Fleiner, President Spectris Scientific and Malvern Panalytical, who acted as Interim President from July 2023.

Andy returns to familiar territory, as he was VP for Finance and Business Development between 2016 and 2018. His career includes several successful roles within Spectris PLC, the parent company of PMS.

Immediately prior to the present appointment, he was President of Servomex, a sibling company to PMS, where, under, his leadership, the company achieved record sales, improved on-time delivery, met profit expectations and won awards for Continuous Improvement, Health & Wellbeing, and Sustainability.

"I am excited to be returning to PMS and to Colorado. The company has great opportunities to grow and positively impact clean manufacturing while also being a great place to work," said Andy.

"I have worked with Andy for many years and the combination of his industry experience and business leadership made him the easy choice for this position," said Mark Fleiner.

For more information please visit https://www.pmeasuring.com/

Contec helps you get a handle on contamination

Contec has launched a range of carbon fibre mop handles for use with their range of cleanroom mop head frames. The Quick Connect Carbon Fibre handles are extremely lightweight, ***up to 60% lighter*** than the equivalent stainless steel handle. This means the handles are very easy touse and helps to minimise operator fatigue.

The handles are all telescopic with easy-to-use latches. The smallest handle, with hanging loop is ideal for isolators and minienvironments. Four additional handles range from a standard 1m telescopic handle to a 1.7m handle which extends to 8m for high ceilings.

Suitable for sterilisation and fully autoclavable at 121˚C QuickConnect carbon fibre mop handles are ideal for all cleanroom environments. Please get in touch to request a trial, infoeu@contecinc.com or visit https://emea.contecinc.com/

Remote Particle Counter: IsoAir® Pro from Particle Measuring Systems (PMS)

With much of our industry focussed on the latest EU GMP Annex 1 and on cleanroom monitoring, one of the products that features frequently in the current programme of PMS Webinars is the IsoAir ® Pro remote particle counter. In fact there are two basic models: the IsoAir® Pro Plus and the IsoAir® Pro E, the main differences being that the Pro E model has an internal flow path that is resistant to vaporized hydrogen peroxide (VHP) and uses Power over Ethernet (PoE). Both models are available in a number of configurations to suit different applications.

The features that are common to all models are the internal blowers eliminating the need for an external vacuum, quick release mounting brackets which store essential sensor data such as the IP address at the point of measurement and data outputs that can be incorporated into the PMS FacilityPro® Monitoring Systems or other software. Both are "plug-n-play" with no complex re-programming required.

For more information please visit: https://www.pmeasuring.com/product/remote-particle-counter-isoair-pro/

Guide from Cherwell: Four considerations when buying an Active Air Sampler

Cherwell, cleanroom microbiology solutions expert, has published a helpful guide: Four Considerations When Buying an Active Air Sampler. Active air samplers are an essential component of fully compliant environmental monitoring programmes. They are used widely in areas of different grades.

Various active air samplers are available, so it's important to be fully informed when making a purchasing decision. Armed with the necessary information, you'll be able to obtain the system best-suited to your unique facilities and production processes.

The guide will assist you in choosing the best air sampler for your premises and requirements, ensuring that compliance, efficiency and consistency are met with confidence.

Cherwell has been distributing the SAS range of air samplers for over 40 years so fully understands that no two cleanrooms are the same and, therefore, offers bespoke solutions.

The SAS Super 180 Air Sampler

For more information visit: https://www.cherwell-labs.co.uk/en/downloads

Advancements in HEPA filter leak testing by ATI

"The iProbe Plus Scanning Probe, as shown on the front cover of this journal, brings important and exciting advancements to filter leak testing," according to Gautam Patel, Global Product Manager for ATI. "Our customers want data integrity and traceability to enhance quality control, and we have delivered that with, in addition, new conveniences and time-saving benefits for users. Best of all, the iProbe Plus is compatible with existing ATI 2i aerosol photometers, making it a straightforward 'plug-and-play' upgrade with minimal investment."

Tim Triggs, ATI Consultant shared his thoughts "It's a smart upgrade for your 2i Photometer, which gives immediate data capture and reporting functionality - all you buy is the iProbe Plus!." To ensure the HEPA filter is tested in line with the 14644-3 standard, the tester must scan at the appropriate rate of 5cm per second. By having the time elapsed clearly stated on the screen, the tester knows exactly how long each scan takes. The iProbe Plus also automatically logs the highest leakage values and documents them as part of the reporting options."

Our EMEA Service Manager, Rory Hulley commented, "One feature my team loves is the firmware update – it's so quick and easy for the user, taking less than a minute to complete. This means we can distribute firmware updates with new features without the customer needing to send their iProbe Plus into a service centre."

For more information www.ATItest.com/products/2i-iprobe-plus/ or contact salesuk@ATItest.com. Or pop into our office for a coffee and demonstration.

Busy time for the Contamination Control Network (CCN)

April saw CCN hosting a CTCB-I Testing course with delegates not just from across the UK, but also from Denmark, Lithuania, Singapore, Malaysia and Thailand. In the same month CCN hosted two CTCB-I Certification courses in Advanced Cleanroom Technology, one in the Manchester area and one in Hertfordshire, again with delegates from the UK and abroad.

Dates have been published for more courses in 2024 – see Training courses on page 29 in this issue – and provisional dates announced for 2025 – see the CCN advert on page 30. Please go to https://www.theccnetwork.org/pages/events to book places on these popular courses.

CCN aims to develop more course topics, for which it encourages new trainers, and contamination control experts are invited to join the CCN committee and support its ambitious plans. If you wish to discuss any of this, please contact chair@theccnet.org.

CCN is a not-for-profit group society with a no-fee membership. To join please visit www.theccnetwork.org

Pharminox Isolation Ltd to concentrate on high quality isolator consumables

After a very successful ten years in the industry, the directors of Pharminox Isolation Ltd have moved into semi-retirement, and the consultancy section of the business has now been closed down. However, the company will continue to supply isolator sleeves and telescopic safe-change cuffs for the foreseeable future. These are items that Pharminox has steadily produced for some twenty years, with both large and small pharmaceutical companies amongst a catalogue of clients in the UK, in Europe, and across the world. E-mail pharminox@pharminox-isolation.com to receive a copy of the Pharminox Cuff and Sleeve brochure.

Come to ISCC 2024 in Milan in October

ISCC 2024, the 26th edition of the International Symposium of Contamination Control, the biennial symposium of ICCCS, International Confederation of Contamination Control Societies, will be hosted by ASCCA, the Italian Society of Contamination Control, in Milan, Italy from 15-18 October 2024.

The theme of the symposium will be "Connecting the dots… of contamination control."

ISCC2024 will bring together leading technology providers, end users, academic scientists, and international regulators to network, share insights and provide an outlook on the evolving landscape and future of cleanroom technology and related applications in biotech, pharmaceuticals, healthcare, aerospace, electronics, semiconductor, automotive and, last but not least (being in Italy), the preservation of the artistic heritage.

The symposium agenda will showcase recent innovations and trends, and directly discuss practical challenges and solutions, from a technical, logistical, and regulatory standpoint.

Attendees will have the opportunity to engage with industry leaders, regulators, and peers through networking events like workshops, tutorials and site visits.

In the same period, ASCCA will host ISO TC 209 delegates from 23 member countries, who have been working continuously on developing the ISO 14644 family of cleanroom standards since 1993.

On behalf of ASCCA and the whole organization team, we look forward to meeting you in Milan in October 2024… and do not forget to make time to discover the wonders of Italy!
Please visit https://iscc2024.com/

Welcome to Cleanzone 2024

Cleanroom and cleanliness technology, hygiene and contamination control will meet at Cleanzone in Frankfurt am Main on 25-26 September 2024. Hot topics, solutions for cleanroom production and optimisation of cleanroom technology are the focus of the international trade fair and conference programme. Cleanzone covers the entire process chain - from planning and set-up, measuring technology, consumables, infeed and outfeed, logistics and packaging to services, media and, of course, the most important networks in cleanroom technology.
For more information on Cleanzone see
https://cleanzone.messefrankfurt.com/frankfurt/en.html

Life-lines

Quotations of Desmond Tutu

When the missionaries came to Africa they had the Bible and we had the land. They said 'Let us pray.' We closed our eyes. When we opened them we had the Bible and they had the land.

Hope is being able to see that there is light despite all of the darkness.

If you are neutral in situations of injustice, you have chosen the side of the oppressor. If an elephant has its foot on the tail of a mouse and you say that you are neutral, the mouse will not appreciate your neutrality.

God is not upset that Gandhi was not a Christian, because God is not a Christian! All of God's children and their different faiths help us to realize the immensity of God.

The price of freedom is eternal vigilance.

Without forgiveness, there's no future.

Peace comes when you talk to the guy you most hate. And that's where the courage of a leader comes, because when you sit down with your enemy, you as a leader must already have very considerable confidence from your own constituency.

Exclusion is never the way forward on our shared paths to freedom and justice.

Before Nelson Mandela was arrested in 1962, he was an angry, relatively young man. He founded the ANC's military wing. When he was released, he surprised everyone because he was talking about reconciliation and forgiveness and not about revenge.

How could you have a soccer team if all were goalkeepers? How would it be an orchestra if all were French horns?

A person is a person because he recognizes others as persons.

Events

2024	Event	Location
May 22-23	Cleanroom Technology Conference	Birmingham, UK
June 10-14	Achema	Frankfurt, Germany
September 11	PHSS Annual Conference 2024	Oxford, UK
September 25-26	Cleanzone	Frankfurt, Germany
October 8-10	A3P International Congress	Biarritz, France
October 15-18	ISCC 2024 International Symposium on Contamination Control	Milan, Italy
October 22-23	R3Nordic Symposium 2024	Oslo, Norway
November 18-21	EDUCON 2024	Schaumburg, Illinois
2025	**Event**	**Location**
May 5-8	ESTECH 2025	Orlando, Florida

Training Courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2024	**Event**	**Location**
June 11	Stop Contamination in Your Operations with Reusable and Disposable Garments	Schaumburg, Illinois and virtual
June 12	The Unseen Contaminant: Taking Charge of Electrostatic Contamination	Schaumburg, Illinois and virtual
June 13	Contamination Busters: Get the Dirt Out of the Cleanroom	Schaumburg, Illinois and virtual
July 30	Contamination Fallout in the Cleanroom: Monitoring Airborne Molecular Contamination (AMC) and Surface Molecular Contamination (SMC) to Minimize Impact	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		
2024	**Event**	**Location**
July 10	CTCB-I Introduction to Cleanroom Technologys	Online
August 21	CTCB-I Advanced Cleanroom Technology	Letchworth, UK
November 5-7	CTCB-I Cleanroom Testing - Professionals and Associates (Course and Exam)	Online
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:		
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
SCC	United Kingdom	www.societyforcontaminationcontrol.org
*CTCB-I Certification: Cleanroom Testing and Certification Board International Certification, see CTCB-1 website: www.ctcb-i.net/index.php		

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To learn more about the range, request a sample or talk to one of our experts, visit emea.contecinc.com/annex-1-compliant-cleaning

SCAN ME

Clean counts most