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Filter leak testing with an LSAPC

Optimizing VHP cycle development with Enzyme Indicators

Bringing it home – The final stages of a project

EU GMP and Annex 1: The new version

The Data Quality Concept

ATI Air Techniques INTERNATIONAL

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

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Editorial

Welcome to CACR48. Apologies for the delayed publication due to temporary indisposition now resolved. This issue contains several articles that should be of interest. Bill Whyte and CTCB-I have very kindly given permission to publish another extract from Bill's recent book, Cleanroom Testing and Monitoring, this time the Annex on filter leak testing with an LSAPC (light scattering airborne particle counter). Hopefully the clear and detailed explanations will encourage readers to buy the book. Enzyme indicators (EIs), on account of their instant response as compared with biological indicators (BIs), will surely have a place in the validation of biodecontamination processes and the paper from Stephen Dawson and Miriam Guest of AstraZeneca describes how EIs were used at AstraZeneca to optimize gassing cycle development. Andrew Watson, in the next of his unknown knowns series, examines the ingredients that ensure a successful conclusion to a project. It might sound obvious, but these include access to cleanroom experience and genuine expertise from conception to conclusion. Cherwell Laboratories have very kindly allowed us to reproduce their take on the 2022 EU GMP Annex 1. Speaking for myself, I was delighted to see that the authors of the new Annex 1 have defined and adopted the term 'first air' to describe desirable airflow arrangements for aseptic work. This term is not popular in all circles and does not feature in cleanroom standards, but it has always appealed to me. In unidirectional airflow systems it helps to define the placement of work zones and operators in relation to the filtered air supply, and in non-unidirectional airflow systems it helps to determine the positioning of filtered air supply points and air extract points in relation to the work. On a visit to Malaysia many years ago I heard 'first air' referred to as 'Virgin Air'! Finally, Particle Measuring Systems have very kindly allowed me to publish their White Paper on the Data Quality Concept.

I hope you enjoy this issue and find it useful!

John Neiger

Filter leak testing with an LSAPC

W. Whyte

This article is the third of a short series of extracts from Bill Whyte's new book *Cleanroom Testing and Monitoring*. Annex D, Filter leak testing 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. High efficiency filters are normally tested by the photometer method given in ISO 14644-3: 2019 and described in Chapter 8 of the book (as reproduced in CACR47). The LSAPC method, also given in ISO 14644-3: 2019 can be difficult to understand. Partly because of this, and partly because of the additional steps that are required, the method is not used, or is used incorrectly. Annex D was written with the object of giving a clearer and shorter explanation, to make the method less difficult to use.

Editor

Annex D: Filter leak testing with an LSAPC

High efficiency filters are tested during manufacturing to ensure that they have the correct overall particle removal efficiency and contain no leaks that are considered excessive for the class of filter being manufactured. This is carried out according to the methods given in ISO 29463 [Ref 1] or EN 1822 [Ref 2] and these methods have been discussed in Chapter 3. After testing, the filters are dispatched to the cleanroom for installation.

To verify that no leaks have occurred during transportation, or installation, the high efficiency filters are tested. This test is carried out by releasing test particles in the air approaching the filter and scanning the cleanroom side of the filter's media, frame, gasket, and housing to locate any leaks that might allow unfiltered air to enter the cleanroom. High efficiency filter installations are also tested in the same way over their lifetime to ensure that no leaks develop.

Leaks in high efficiency air filter installations can be found by a photometer using the method described in Chapter 8. The filter system is challenged with a test aerosol generated from one of the liquids described in Chapter 8. The filters are tested with the ventilation system running and liquid test particles can deposit onto filters and air supply ducts, and 'outgas' into the cleanroom for some time after production starts. This may cause contamination problems in semiconductor and similar types of manufacturing. To avoid this problem, inert particles, such as polystyrene latex spheres (PLSs) are used to challenge the filter, and leaks are found by a light-scattering airborne particle counter (LSAPC), in place of a photometer. However, the LSAPC method can also be used with the same test aerosols as used with the photometer, if contamination is not a problem.

D.1 Overview of the LSAPC method of locating filter system leaks

The LSAPC method for locating leaks in high efficiency filter systems is described in ISO 14644-3: 2019. It was first described by Bruce McDonald [ref 38]. His method was adopted into the IEST Recommended Practice 34 [ref 6] and was progressively modified to be used in ISO 14644-3: 2005 and then in ISO 14644-3: 2019 [ref 9].

The LSAPC method is carried out in two stages. In the first stage, the filter system is scanned with a probe connected to an LSAPC to seek and locate potential leaks. In the second stage, potential leaks are further investigated by holding the probe stationary over the leak; the number of particles coming from the potential leak is counted over a specified time and, if the number is greater than a predetermined number, it is classed as an actual leak.

Stage 1 – Scanning the filter:
To find a potential leak in a filter installation by the LSAPC method, a known concentration of test particles is introduced into the air approaching the filter, and the filter face is scanned by a probe attached to an LSAPC (see **Figure D1**). The scanning method is the same as used in the photometer method explained in Chapter 8 and that chapter should be consulted for information. Potential leaks are detected by LSAPCs if the particle count exceeds a number that is discussed later in this chapter.

Figure D1: A probe scanning over a filter face to locate a leak

Stage 2 – Stationary measurement: The second stage of the test method is used to confirm that a potential leak found by scanning is an actual leak. This requires the probe to be kept stationary over the potential leak for a specified time. If the particle count is greater than a number that is calculated by a method discussed later in this annex, the leak is confirmed as an actual leak.

To find a leak in a filter installation, the following variables must be considered.

a. The air volume sampling rate of the LSAPC,
b. The dimensions of the sampling probe,
c. The scanning velocity of the probe over the filter face,
d. The particle penetration of a filter which, when exceeded, is considered a leak,
e. The type of aerosol test challenge,
f. The number of test particles measured by an LSAPC that indicate a leak.

D.2 Values of variables needed for calculations

Information about the variables listed above, and their values used in calculations, are now discussed.

(a) Air volume sampling rate of the LASPC *(Q_{VS})*

A typical air volume sampling rate of an LSAPC is 28.3 L/min (0.000472m^3/s), and this is the standard rate suggested by ISO 14644-3: 2019. It is also suggested that the LSAPC should count particles ≥0.3µm.

(b) Probe dimension *(D_P)*

The probe used to scan a filter and to carry out stationary measurements should have the correct dimensions to ensure that the air sample will closely reflect the particle concentration coming from the leak. A good sample is obtained if the air velocity into the probe is the same as the air velocity passing outside the probe i.e. the face velocity of the filter. This type of sampling is known as iso-kinetic sampling and is discussed in more detail in Annex G. In practical situations, it is unlikely that these two velocities will exactly match, and ISO 14644-3: 2019 allows the intake velocity of the probe to be within +/- 20% of the filter face velocity.

ISO 14644-3: 2019 recommends two standard sizes of probe. These are as follows:

Rectangular probe: This probe is often called a 'fish tail' probe and is the type shown in **Figure D1**. It has an inlet opening of 8cm x 1cm and its dimension in the direction of scanning *(D_P)* is 1cm. The surface area of the intake is 8cm^2 (0.0008m^2) and the probe's intake velocity, when used with a LASPC that samples 28.3 L/min (0.000472m^3/s), can be calculated as follows:

$$\text{Intake velocity of probe (m/s)} = \frac{\text{sampling rate (m}^3\text{/s)}}{\text{intake area (m}^2\text{)}} =$$

$$\frac{0.000472(\text{m}^3\text{/s})}{0.0008(\text{m}^2)} = 0.59\ \text{m/s}$$

This rectangular type of probe will, therefore, provide the best sampling conditions when the face velocity of the filter is 0.59 m/s. However, a variation in velocity of +/- 20% is acceptable and it can, therefore, be used with a range of velocities of between 0.47m/s and 0.71m/s.

Circular probe: This probe has a diameter of 3.6cm. However, the nominal dimension in the direction of the scan *(D_P)* is not the same as its diameter but, as calculated in ISO 14644-3: 2019, it is 2.54cm. For a sampling rate of 28.3L/min (0.000472m^3/s), the inlet velocity of the probe is 0.46m/s and the range of velocities that it can accommodate is between 0.37m/s and 0.55m/s.

A large proportion of high efficiency filters are manufactured to operate with a face velocity of 0.45m/s and the two standard probes are satisfactory. However, some high efficiency filters are manufactured to operate at higher face velocities and, therefore, to obtain the correct isokinetic conditions for filters with a face velocity greater that 1m/s, a probe with a smaller intake and higher air velocity should be used.

(c) The scanning rate of the probe *(S_R)*

The filter installation should be scanned with a probe held approximately 3cm from the filter face and using overlapping passes. It is necessary to scan over the filter installation at the correct velocity. If it is scanned too fast, a leak may be missed and, therefore, the correct scanning rate should not be exceeded. If the probe moves too slowly over an insignificant leak, additional particles may be sampled and a leak thought to exist. However, in the latter case, the erroneous leak will not be confirmed when stationary measurement is carried out, although this will be an unnecessary waste of time.

ISO 14644-3; 2019 recommends a standard scanning rate (S_R) of 5cm/s for the 1cm x 8cm rectangular probe and 12cm/s for the 3.6cm diameter circular probe. However, it is not always possible to achieve the correct concentration of particle challenge that matches these scanning rates, and it may be necessary to adopt a different scanning rate.

(d) What particle penetration of a filter is considered a filter leak *(P_L)*?

The photometer method of testing leaks in filters has been discussed in Chapter 8 of this book, and the chapter reports what ISO 14644-3: 2019 considers a leak. The same information applies to a leak test carried out with an LSAPC.

It is considered in ISO 14644-3: 2019 that a leak exists for most types of filters if there is a location in the filter installation where the penetration *(P_L)* is more than 0.01% of the particle challenge. However, if the overall removal efficiency of the filter is between ≥99.95% and <99.995% (as it is for an EN H13 filter or an ISO 35H filter), there is considered to be a leak when the penetration is greater than 0.1%. When the overall removal efficiency of a filter is less than 99.95%, the penetration that is considered a leak should be agreed between customer and supplier.

(e) What type of aerosol test challenge should be used?

The photometer method of filter leak detection uses a test challenge of aerosols generated from liquids discussed in Chapter 8. However, the particles in the aerosols can deposit on surfaces, and then 'outgas' into the supply air during manufacturing, and cause contamination. Aerosols of solid inert particles are used to overcome this problem. In a cleanroom, which is not sensitive to this type of contamination, the same type of aerosol can be used with the LSAPC method as for photometer method.

In some cleanrooms, such as those used in semiconductor manufacturing, solid inert test particles are specified for leak testing and are, typically, Polystyrene Latex Spheres (PLSs). These are shown in **Figure D2** and **Figure D3**. They are available as suspensions of

homogeneous spherical particles of various sizes, but 0.3µm particles are used for filter leak testing. The suspensions are diluted in clean water, nebulized by a generator such as a Laskin nozzle, and introduced into the air approaching the filter system.

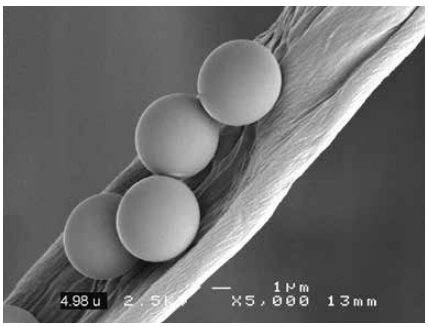

Figure D2: Electron microscope image of PLS test particles deposited on a fibre

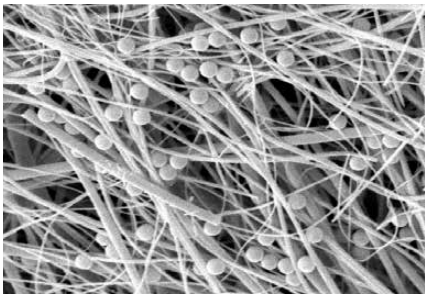

Figure D3: PLS deposited on filter media

(f) How many particles need to be counted by the LSAPC during scanning to indicate a leak?

When scanning a filter, the number of airborne particles that have to be registered by an LSAPC to indicate a potential leak has to be selected. This count is known in ISO 14644-3: 2019 as the 'acceptable' count, and given the symbol N_A. This number should be kept low, or the calculation of the concentration of the challenge aerosol can result in a concentration that is high and difficult to achieve.

In a situation where the undamaged filter is known to remove all the challenge particles and the LSAPC does not record spurious counts in particle-free air, the acceptable count can be taken as zero and any count greater than zero used to indicate a potential leak.

If the LSAPC gives an occasional spurious count from particle-free air, or an occasional particle passes through undamaged filter media, then an acceptable count of 1 may be the best choice to indicate a potential leak. In this situation, any count of 2, or greater, is considered a leak. However, if the background count is higher, a higher count will be required to indicate a potential leak.

When measuring airborne particles coming from a leak, it will be found that the counts have a natural variation around an average value, and this variation conforms reasonably well to the Poisson statistical distribution. When a filter is scanned, an occasional low count may be encountered that is unlikely to be lower than the 95% lower confidence limit (LCL) of the distribution. The 95% LCL count is considered in ISO 14644-3: 2019 to be the 'acceptable count' and given the symbol 'N_A'.

The average count (N_P) of the count distribution is considered in ISO 14644-3: 2019 to characterise the designated leak, and is the value used in the calculation of the required challenge concentration or, if required, the scanning rate. In a Poisson statistical distribution, the average count of the distribution (N_P) can be calculated from knowledge of the acceptable count (95% LCL) and use of *Equation D1*.

Equation D1

$$N_P = (N_A + 2) + 2\sqrt{1 + N_A}$$

Average values of the count distribution (N_P) that correspond to N_A are given in **Table D1**. It should be noted that the values N_A of 0 and 1, which are the preferred values, have corresponding values of N_P of 4 and 5.8, respectively, and these are the values that are used in the calculations. However, if higher values of N_A are encountered because of high background counts, the corresponding values of N_P that can be used in the calculations can be obtained from **Table D1**.

D.3 Summary of standard values

Information in the previous section gives the standard values of the variables that ISO 14644-3: 2019 suggests for use with the LSAPC method of leak testing. These are summarised as follows:

a. Q_{VS} is the sampling rate of an LSAPC of 28.3L/min (0.000472m^3/s).

b. D_P is the dimension of the probe's intake in the direction of the scan. A standard rectangular probe has a rectangular inlet of 1cm x 8cm, and the dimension in the direction of the scan (D_P) is 1cm. A standard circular probe has a diameter of 3.6cm, and the dimension in the direction of scan (D_P) is 2.54cm.

c. S_R is the scanning velocity of 5cm/s that is used for a 8cm x 1cm rectangular probe, and 12cm/s is required for a 3.6cm circular probe.

d. P_L is the proportion of particles that passes through the filter and, when exceeded, is considered a leak. A proportion of 0.0001 (0.01%) is used as the standard value but exceptions are applied to low efficiency filters.

e. N_A is the acceptable number of particles that is considered to show a potential leak when a filter installation is scanned, and the preferred values are 0 or 1. The corresponding average values of N_P that are used to calculate

Table D1. Average values (N_P) of the Poisson distribution

Acceptable particle count from a leak (N_A) – 95% LCL	Average count of distribution (N_P)
0	4.0
1	5.8
2	7.5
3	9.0
4	10.5
5	11.9
6	13.3
7	14.7
8	16.0
9	17.3
10	18.6

the particle challenge, or scanning rate, are 4 and 5.8, respectively.

Although it is best to use the standard values in the list, non-standard values may be required when locating leaks. The calculations carried out with standard and non-standard values in the two stages of the LSAPC test method are now discussed.

D.4 Stage 1: Calculation of particle challenge concentration or scanning velocity

A common approach to locating leaks in filter installations by means of an LSAPC is to start by calculating the concentration of test particles needed to challenge the filter installation. This should, preferably, be carried out using the standard values given in the previous section but it may be necessary to modify one, or more, of the standard values.

When setting up the required particle concentration it may not be possible to achieve the correct airborne particle concentration. In this situation, the standard scanning velocity of 5cm/s may have to be modified to correspond with the concentration that can be achieved. How the particle challenge concentration and scanning velocity are calculated is now described.

Calculation of test challenge concentration:

The variables needed to calculate the test challenge concentration have been previously discussed and shown in Figure D4.

The concentration of airborne particles used to challenge a filter is calculated as follows:

Equation D2

$$C_C = \frac{N_P \times S_R}{Q_{VS} \times D_P \times P_L}$$

Where,

C_C = concentration of airborne particles ≥0.3µm used to challenge the filter (number/m³);

N_P = average count of particles that characterise a leak.

S_R = scanning rate of the probe over the filter surface (cm/s);

Q_{VS} = air sampling rate of the LSAPC (m³/s);

D_P = probe dimension in direction of scanning (cm);

P_L = penetration of the challenge particles ≥0.3µm through the filter that is considered a leak. This is given as a proportion e.g. 0.0001, and not a percentage (0.01%).

It should be noted that centimetres are used in both the numerator and denominator of the equation for dimensions associated with the probe.

If the standard values listed in the previous section are used, including a P_L value of 0.0001 and a D_P value of 1cm, the following result is obtained.

$$C_C = \frac{N_P \times S_R}{Q_{VS} \times D_P \times P_L} = \frac{N_P \times 5}{0.000472 \times 1 \times 0.0001} = N_P \times 105{,}932{,}203/m^3$$

If this result is rounded up, the following equation may be useful during testing,

$$C_C = N_P \times 106{,}000{,}000/m^3$$

The above calculation uses recommended standard values, but should any variation from the standard values be required, *Equation D2* can be used to calculate the corrected concentration. In these non-standard situations, a spreadsheet is useful, or an LSAPC with suitable computational abilities.

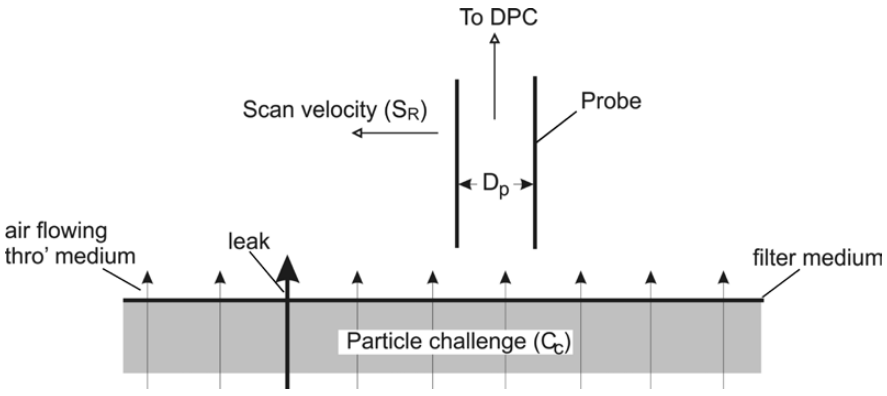

Figure D4: Diagram of probe scanning over a filter surface

If the recommended standard values of N_P are entered into the *Equation D2*, the rounded values of the challenge concentrations are shown in **Table D2**.

It can be seen from the results in **Table D2** that the required particle challenge concentrations are high, and it may be necessary to use a diluter to avoid coincidence losses in the LSAPC. Coincidence losses and diluters are discussed in Chapter 10.

Table D2. Particle challenge concentration required for standard values of N_P

N_A	N_P	Challenge test concentration/m³
0	4	424,000,000
1	5.8	614,000,000

Calculation of scanning velocity

The method described in the previous section is used to set the particle challenge concentration for the standard values suggested by ISO 14644-3: 2019. However, it may be found that it is difficult, if not impossible, to establish the required particle concentration. It may, therefore, be necessary to employ a different challenge concentration and modify the scanning velocity. The modified scanning velocity can be calculated by use of *Equation D3*.

Equation D3

$$S_C(\text{cm/s}) = \frac{C_C \times P_L \times Q_{VS} \times D_P}{N_P}$$

Where, D_P is 1cm for the fish tail probe, and 2.54cm for the circular probe.

Again, a spreadsheet, or an LSAPC with suitable computational abilities, is useful to carry out the calculation.

D.5 Stage 2: Confirmation of a leak by stationary measurement

It has been previously explained that the method of determining leaks is divided into two stages, namely:

Stage 1: The filter system is scanned to locate potential leaks, and,

Stage 2: The potential leaks are confirmed as actual leaks by stationary measurement.

The presence of an actual leak is confirmed by holding the probe over the potential leak (**Figure D5**) and obtaining, in a specified time, a particle count that is greater than the count calculated for the circumstances of the testing. It is suggested in ISO 14644-3:2019 that the

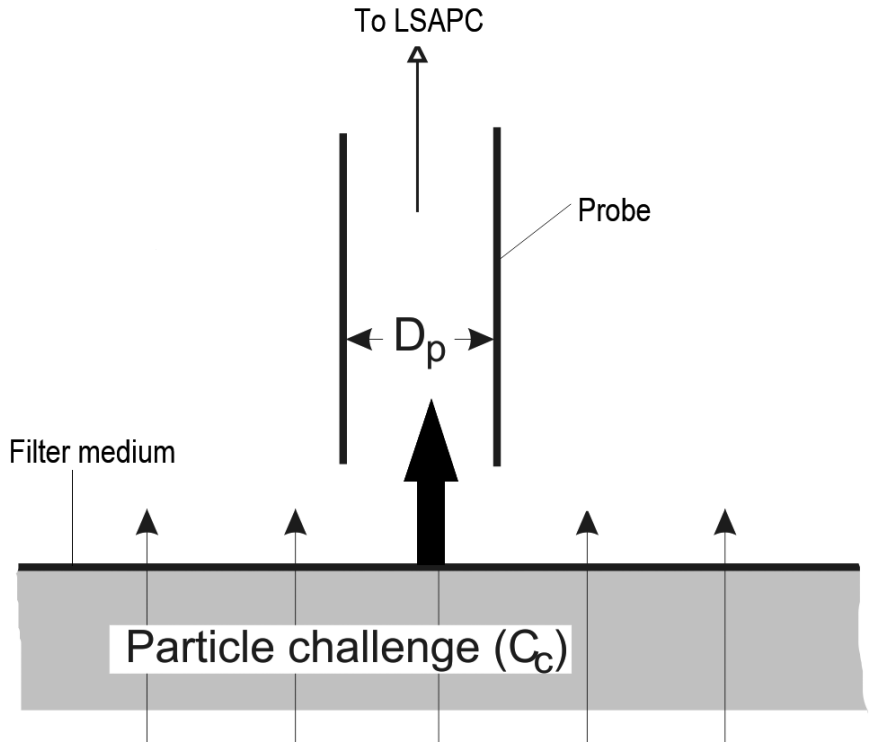

Figure D5: Diagram showing a probe stationary over a filter surface

standard time the probe is held over the leak *(T_R)* should be 10 seconds.

The number of particles needed to confirm that a potential leak (found by scanning) is an actual leak is calculated in two steps. Firstly, the average number of particles that will characterise the leak *(N_{PR})* is calculated by *Equation D4.*

Equation D4

$$N_{PR} = C_C \times P_L \times Q_{VS} \times T_R$$

Where,
C_C = concentration of airborne particles ≥0.3µm used to challenge the filter (number/m³);
P_L = penetration of the challenge particles through the filter that is considered a leak. This is given as a proportion e.g. 0.0001, and not a percentage (0.01%).
Q_{VS} = air volume sampling rate of the LSAPC (m³/s);
T_R = residence time the probe should be held over a potential leak (10s).

The counts obtained from a leak will vary over time, and it can be assumed that they are distributed in a way that can be predicted by the Poisson statistical distribution. The value of N_{PR} is considered to be the average value of the count from the leak, and the minimum count that might be encountered during the stationary measurement is known as the 'acceptable count' *(N_{AR})*. N_{AR} is the minimum count that confirms a leak and is given by the 95% lower confidence limit (LCL). Assuming a Poisson distribution, it can be calculated as follows.

Equation D5

$$N_{AR} = N_{PR} - 2\sqrt{N_{PR}}$$

If, for example, N_{PR} had been calculated by *Equation D4* to be 100, the 95% lower confidence limit, which is the acceptable count *(N_{AR})*, is calculated by *Equation D5* and is found to be 80. If the count measured during a residence time of 10s is greater than 80, the presence of an actual leak is confirmed.

D.6 Practical example of how to find a leak in a filter installation

An example is considered of a high efficiency filter that has to be leak tested by the LSAPC method and is an EN 1822 Type H14 (ISO 45H), with an overall removal efficiency of ≥99.995%. To locate leaks, the following steps should be carried out.

Step 1: Before starting the test, it is necessary to establish the following requirements:

a. The filter to be tested is supplied with the correct air supply volume and, therefore, has the correct filter face velocity.

b. The choice of test aerosol. If it is the same as used in the photometer method, then Chapter 8 should be consulted for relevant information. If inert solid particles are required, Section D2 of this annex should be consulted.

c. The following standard values are chosen for the LSAPC and its probe:

- The sampling rate *(Q_{VS})* of the LSAPC is 28.3 l/min i.e. 0.000472m³/s.
- A 'fish tail' probe is selected with an intake of 8cm × 1cm, and the dimension in the direction of scanning *(D_P)* is 1cm.
- The scanning rate of the probe *(S_R)* is 5cm/s.

Step 2: The 'acceptable' number of particles *(N_A)* that indicates a potential leak when scanning has to be decided. To ensure the required aerosol challenge concentration is not excessive, the acceptable count would preferably be either 0 or 1. It is known from a preliminary scan of the filter that an occasional particle is counted. Therefore, the acceptable count that is chosen is 1. A potential leak will therefore be indicated by a count of 2, or greater.

Step 3: Knowing the acceptable count *(N_A)* is 1, the N_P value is obtained, which is the value used in the calculations. This is obtained from **Table D1** and is 5.8.

Step 4: The penetration of a filter by the challenge particles *(P_L)* that is considered to be a leak is required. For the type of filter being tested, the leak should be greater than a proportion of 0.0001 (0.01%).

Step 5: The particle challenge concentration required for the scanning test can now be calculated by use of *Equation D2.*

$$C_C = \frac{N_P \times S_R}{Q_{VS} \times D_P \times P_L} = \frac{5.8 \times 5}{.0.000472 \times 1 \times 0.001} =$$

$$6.1 \times 10^8/m^3$$

It should be noted that this is the same value as given in **Table D2**.

Inspection of the literature of the manufacturer of the LSAPC shows that this particle concentration is greater than the particle counter's coincidence level of 1 x 10⁷/m³. Therefore, a diluter should be used to obtain an accurate measure of the challenge concentration. Diluters are discussed in Chapter 10.

Step 6: The test aerosol is introduced before the filter to obtain a constant concentration that is very close to 6.1 x $10^8/m^3$. The location where it is introduced should be chosen to assist in the mixing of the aerosol, and to obtain an even concentration across the back of the filter. The evenness of the challenge concentration should be confirmed, as should the consistency of concentration over the time of testing.

Step 7: The filter gasket, frame, and filter media should be scanned at a rate of 5cm/s. The method of scanning has been discussed in Chapter 8, and this method should be applied.

Step 8: The value of the acceptable leak that has been chosen is 1 and, therefore, the number of particles that must be registered by the LSAPC to show a potential leak is 2, or greater. If this occurs, then the exact location of the leak should be determined. This can be found by turning the fish tail probe though 90 degrees and scanning back and forwards over the location to exactly locate the leak. A small piece of masking tape can then be used to mark where the leak is located.

Step 9: To confirm that a potential leak found by scanning is an actual leak, a stationary test must be carried out. This is carried out by holding the same probe over the potential leak for a standard time of 10 seconds. The average number of particles that characterise a leak *(N_{PR})* and must be exceeded in 10s is calculated by *Equation D4*, and is as follows:

$$N_{PR} = C_C \times P_L \times Q_{VS} \times T_R = 6.1 \times 10^8 * 0.0001 * 0.00047 * 10 = 287$$

$$N_{PR} = C_C \times P_L \times Q_{VS} \times T_R = 6.1 \times 10^8 * 0.001 * 10 = 287$$

However, the counts of airborne particles coming through the leak will vary and, to take this variation into account, *Equation D5* is used to calculate the lowest acceptable count *(N_{AR})* that confirms a leak.

$$N_{AR} = N_{PR} - 2\sqrt{N_{PR}} = 287 - 2\sqrt{287} = 287 - 34 = 253$$

The actual result obtained during the test by counting the particles for 10s was 285. This count was higher that the lowest acceptable count of 253 and the leak confirmed as an actual leak. It should be noted that it may be unnecessary to sample for the full 10s, but only as long as it is necessary to show that the lowest acceptable count *(N_{AR})* has been exceeded.

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Acknowledgement

The images in **Figures D2** and **D3** were obtained from Duke Scientific, a division of Thermo Fisher Scientific.

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.

***CTCB-I (Cleanroom Testing and Certification Board – International)** is an association which promotes, prepares and accredits internationally recognised educational courses for people who design, construct, test, monitor, operate and work in cleanrooms. Only societies set up for the education and promotion of contamination control techniques in cleanrooms can apply for membership of the CTCB-I. They must run or wish to run CTCB-I courses. Current members of the CTCB-I are Contamination Control Network (CCN), Cleanroom Technologies Society of Turkey (TTD), Irish Cleanroom Society (ICS), Cleanrooms and Contamination Control Association for Denmark, Finland, Norway and Sweden (R3 Nordic) and Netherlands CC Society (VCCN). The CTCB-I is run by a Board of Delegates comprising delegates nominated by each member society and the current chairman is Tim Triggs of CCN. The Board of Delegates monitors the written and practical content of the cleanroom courses and the standard of examinations to ensure the maintenance of a common and high standard across the courses, and evaluates the course structure and teaching material from each new submission from a cleanroom society. The aim of the CTCB-I is to help foster the development of cleanroom practitioners in its member societies so that they practice to a very high standard. For further information please visit http://www.ctcb-i.net

How AstraZeneca optimised Vapor Phase Hydrogen Peroxide gassing cycle development with Enzyme Indicators

Stephen Dawson, Miriam Guest

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Abstract

Vaporised hydrogen peroxide is used within the pharmaceutical industry as a surface decontamination tool, in both cleanrooms for the production of pharmaceutical products and in the quality control testing laboratories for the testing of such products. Efficacious decontamination is demonstrated in routine requalification traditionally using biological indicators. In this article, an approach to the application of data from enzyme indicators to cycle development is outlined. The case study highlights the ability to optimise an established cycle and provide a quantitative safety margin, providing robust assurance of process efficacy.

Introduction

Vaporized hydrogen peroxide (vH_2O_2) is widely used as a surface decontamination tool in the pharmaceutical industry. Vaporized hydrogen peroxide is safe to use, has good material compatibility and low toxicity, and is active at ambient temperatures; it is scientifically proven to have broad, non-specific, and rapid microbial activity. Within the pharmaceutical industry, it is extensively used to support aseptic manufacturing and sterility testing environments as well as a tool for decontamination of cleanrooms.[1] Standard procedures include the preparation of the location to be decontaminated prior to a decontamination cycle being performed. As with any GMP procedure, the process must be understood, verified, and validated.

Demonstration of efficacious decontamination is a critical aspect of aseptic processing and sterility testing. This process currently takes a large data set and the use of biological indicators (BIs). Enzyme indicators provide a mechanism to further understand the process and therefore enhance cycle robustness and sterility assurance. By adopting enzyme indicators in the cycle development phases, greater understanding of efficacy of the gassing process can be achieved by providing quantitative results in a faster time frame. This can lead to efficiency benefits through cycle design being performed with data driven decisions and by demonstrating a substantial margin quantitatively (rather than a simple pass/fail criteria).

The application of vH_2O_2 is widely adopted and recognized in the both the European[2] and United States[3] pharmacopoeias for sterilizing primary packaging, equipment, and some pharmaceuticals. Different gases may be used including ethylene oxide, and the typical process involves exposure to the agent within a leak-proof chamber. In the case of production RABs (restrictive access barrier systems) and isolators, equipment to be sterilized is cleaned prior to the application of the gas cycle. It is essential to monitor any cycle for temperature, humidity, and gas concentration in routine use (as well as throughout cycle optimization and validation).

Cycle efficacy, in line with sterilization techniques, is an assessment of the lethality of the cycle; traditionally, biological indicators are used to demonstrate this. There is an expectation that they are placed at locations where decontamination conditions are most difficult to achieve.

Understanding decontamination and sterilization cycles is a responsibility that industry should take seriously. With the development of overkill cycles, establishing worst-case conditions can be challenging, with biological indicators providing a binary answer on cycle efficacy. Enzyme indicators can provide a quantifiable result, which enables safety margins to be built into cycle design based on data.

Learnings from our Enzyme Indicator study

A sterility testing isolator with well-established decontamination cycles was

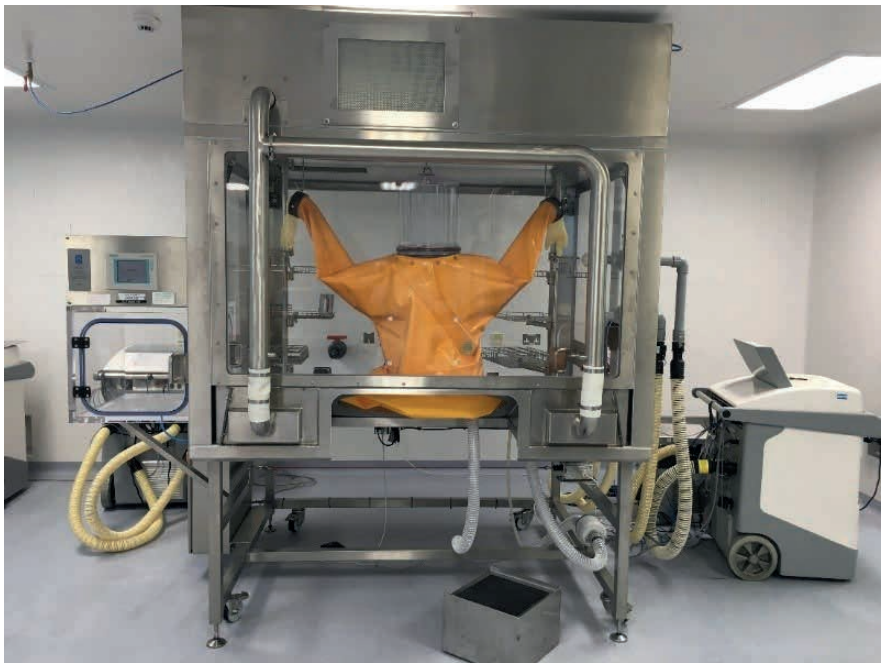

Figure 1 – Sterility testing isolator with "half-suit" and vH_2O_2 gas generator attached

used to perform a study to assess the application of enzyme indicators to cycle optimization (see Figure 1). Vaporized hydrogen peroxide (vH_2O_2) is used to decontaminate surfaces within isolators prior to use. The validation and cycle development of vH_2O_2 bio-decontamination processes is routinely undertaken by using BIs consisting of *Geobacillus stearothermophilus* spores carried on a vehicle such as a stainless-steel disc. BIs can be deactivated/killed by vH_2O_2 if the decontamination cycle conditions are appropriate and repeatable deactivation of BIs under defined parameters allows a validated cycle to be determined. However, BIs have limitations in that they are prone to false positives, only give a qualitative positive or negative result, and they require seven days' incubation to provide a result. Thermostable adenylate kinase (tAK) as an enzyme indicator (EI) takes an enzyme-based approach as a process indicator[4] alternative to the bacterial spore-based BIs. The enzyme tAK has been shown to be inactivated by vH_2O_2, and a rapid 1-minute test has been developed using a luciferin-luciferase based assay for the immediate quantification of oxidized tAK values, determined by measuring ATP (adenosine triphosphate) produced by residual active tAK enzyme remaining after vH_2O_2 dosing. EI inactivation by vH_2O_2 is dose- and time-dependent, and when exposed to vH_2O_2 alongside BIs, the EI activity from RLU (relative light unit) obtained can be compared with the BI inactivation to establish a quantitative estimate of achieved log reduction (ALR) in RLU values rather than the qualitative growth/no growth outcome of a BI.

Learnings from our Enzyme Indicator vs Biological Indicator correlation study

A correlation study was performed, with the aims of the study as follows:

- To enable further understanding of the performance of EIs.
- To establish if EIs are a feasible technology to adopt within AstraZeneca.
- To gain more understanding of the vH_2O_2 gassing cycle used by AstraZeneca to sanitize the sterility test isolator by correlating the BI inactivation with EI enzyme activity.

In the study, EIs were placed in triplicate alongside single BIs in 13 predetermined locations taken from the isolator's annual gassing cycle revalidation protocol. Eight vH_2O_2 gassing cycles were performed, after which the EIs were analyzed using a luciferin-luciferase assay and the BIs incubated in tryptone soya broth (TSB) at 55°C to 65°C for seven days prior to recording if the TSB was turbid (indicating a positive result) or not.

Cycles one through three used the validated sterility test gassing cycle parameters as follows:
Gassing (3 g/min) – **15** minutes
Gassing dwell (1 g/min) – **25** minutes
Aeration – **420** minutes

The long gassing and gassing dwell phases, which use a combined 70 g H_2O_2, result in an extended aeration phase of 420 minutes to break down H_2O_2 into $H_2O + O_2$ to leave a safe level of H_2O_2 = <1.0 ppm.

During the gassing cycle it was noticed that there was a large amount of condensation on the isolator surfaces, which indicates too much vH_2O_2 is being used. It is not always the case that more vH_2O_2 produces a better "kill," so the gassing cycle should be developed to only use as much vH_2O_2 as necessary, plus an added safety margin. However, it can take an extended period of time to optimize a gassing cycle using only BIs; therefore, cycles often use much greater amounts of vH_2O_2 than necessary in order to validate a repeatable cycle within a short time period.

Using EIs alongside BIs and analyzing the EIs immediately after the gassing cycles had completed meant data was instantly available regarding the "log reduction" and an accurate prediction of whether the BIs would be inactivated could be made. This allowed modifications to the length of gassing to be made prior to each gassing cycle, and within eight cycles, the amount of H_2O_2 used was able to be reduced by 39.5 g without adversely affecting the cycle efficacy. The gassing phase was reduced from **15** minutes to **10** minutes and the gassing dwell phase from **25** minutes to **1** minute. Due to the reduction in H_2O_2 the aeration time was also reduced by approximately **180** minutes.

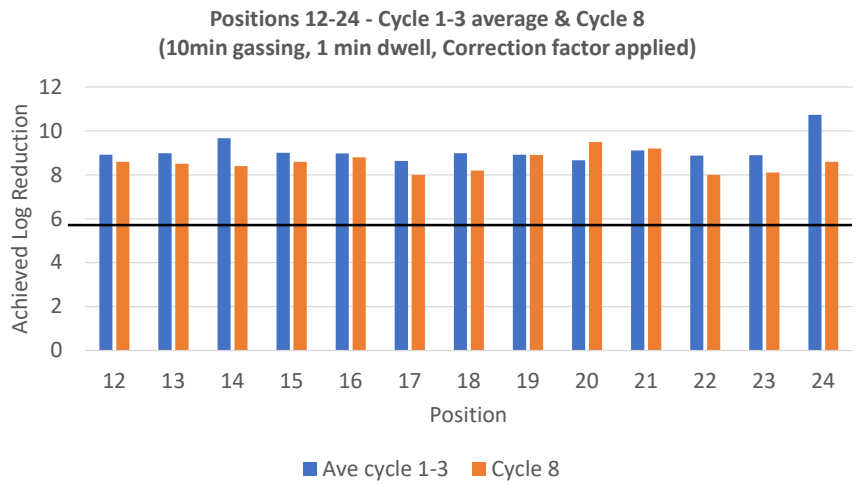

Figure 2 – Average achieved log reduction for positions 12-24 from validated cycles one through three compared with achieved log reduction for positions 12-24 for cycle eight (reduction in gassing to 10 minutes and 1 minute gassing dwell).

Conclusion

The gassing cycle was able to be effectively optimized and the aeration cycle length greatly reduced due to the quantitative data gained about the cycle from using enzyme indicators rather than only biological indicators. BIs were used alongside EIs to ensure cycle effectiveness was not compromised and still met regulatory expectations. EIs are an exciting tool that allows gassing cycle effectiveness to be accurately determined and could be used to ensure a satisfactory cycle has been completed prior to manufacturing taking place.

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He is currently studying for a Business Analysis qualification with the International Institute of Business Analysis (IIBA).

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Over recent years, she has designed and developed AstraZeneca's "21st Century Microbiology Strategy" to innovate, industrialise and implement technology solutions to drive efficiencies and process robustness benefits with the AZ global network.

Miriam is an active committee member of the Pharmaceutical Microbiology Interest Group (Pharmig).

Outside of work, she keeps active by being a taxi-driver for her 2 teenage daughters, walking her two dogs, tries to squeeze in gym visits and playing soccer.

Unknown knowns: Bringing it home – The final stages of a project

Andrew Watson

Abstract

Cleanrooms are not built everyday. Often the people building them, and those having them built, are in virgin territory. The final stages of completing a project are where reality sets in and the success of the project can be in jeopardy. Whilst there is a lot written on this topic, those with previous experience are the ones to unlock the unknown knowns. In this article, the author, who has to be frank seen some things in his time, attempts to provide common sense and advice on how to plan for and approach the final stages of a project.

Introduction

The requirements of how to commission, certify and qualify a cleanroom are very well defined. If a highly technical project is similarly well defined to these requirements from the outset, with a competent construction team and well informed and engaged client, the process of handover from constructor to customer should be straight-forward. However, as anyone with the experience of even just a few cleanroom projects well knows, this is rarely the case.

Many pages have been written, many, many PowerPoint presentations given and many, many, many hours of advice have been delivered by consultants such as myself all in hope of a successful conclusion to an important project. Yet all too often, projects fail to meet their potential, or worse, fail to be completed at all. This area is truly the motherlode of unknown knowns.

The fact is, in many parts of the world, a construction business dedicated to cleanrooms or other highly technical projects can be difficult to maintain without a reasonable turnover of projects. Many projects are being designed and built by companies with little to no experience. The information is out there, but it needs the time, effort and intellectual curiosity to obtain it. I find that people prefer to be told what to do, rather than find it out for themselves, which is fine if you can find the right person. This is discussed in more detail later.

It is not practical in an article such as this to describe everything that needs to be known to deliver a successful cleanroom or containment project (or both together). Anyway, other people have already done this, notably Bill Whyte,[1] and standards have already been written, notably ISO 14644-4,[2] therefore I'm going to use this article to deliver some key points to consider.

What does finished look like?

This is a question that is rarely asked at the beginning of a project and is often fought over at the end. The list below describes a perfect end to a project:

1. Interior finishes are smooth and uniform. The areas are well lit and no defects of design or workmanship catch the eye.
2. All aspects of the finalised design specification have been met, or a mutually agreed compromise has been reached.
3. The commissioning (and qualification) work has been completed and is sufficient to show that the facility is operating in a controlled, stable and well-understood manner. The facility is ready to be put to its intended use when the production equipment has been installed.
4. All the necessary documentation has been delivered, reviewed and approved.
5. The production equipment has been installed and is operating with minimal changes to the as-built commissioned facility.
6. Everyone has been paid.
7. Everyone is still talking to each other and everyone has got together for a nice lunch a few months after the completion of the project.

Compromises in point 2 should never impact the requirements of point 3. The integrity of the objective of point 3 should be held sacred. However, I see many facilities that limp along post completion and only function through the use of alarm-mute buttons.

Specifications – from the beginning, thinking about the end

The initial specification, often called the User Requirements Specification or URS, should not only detail the facility design, but how that design will be confirmed as being to specification. In other words, commissioning should be considered from the outset.

The initial specification should be broad, not too ambitious and have the right level of detail. Key details, such as cleanroom classification, containment level and key performance metrics should be spelt out. Fitting and finish requirements should allow for interpretation and innovation, without being too specific.

As the project progresses, with every step of the design development, design review and tender process, the commissioning needs to be kept front of mind. Commissioning sequences and responsibilities need to be considered taking into account the stages when each section of a project is finished, or when a specific contractor has completed his work and can leave the site. It needs to be determined what is being handled by the main contractor, and what might be handled by the client or owner.

Have someone on your side

Whether you are a contractor or a client, if this is your first project or it has been a while since your last one, engaging an expert can be a very good idea in order to tap into those 'unknown knowns'. Choosing the right person should take into account:

- Their connections. This should extend from the regulators to the actual people who do the work. Their connections to other experts are particularly important.
- Their ability to find solutions, resolve conflicts and learn new things.

- Their availability and responsiveness.
- Their ability to calm a room in a crisis or escalate a minor issue so it is given the necessary attention.

Very often, after a few fruitful weeks with experts, there is a tendency for project team to think 'we get this', and disengage, only to bring them back at the end of the project either to demonstrate what a great job they've done, or because its all gone to the dogs. Your expert does not need to be in your back pocket, but the project should have a structure whereby the expert can dip in and out, keep abreast and leap in if they see something untoward.

Getting the right finishes

Appropriate finishes are always difficult to define. It is surprising what people will accept, particularly after installation. The best way to avoid disputes in this area is to set up a finishes room in the early stages of the project. This can be a room with all of the details and samples of the fixtures and fittings either loose or installed on boards. It can be a completely separate room, or a small room within the facility that is fully completed at an early stage of the project.

This early-stage room can be difficult to coordinate and will increase your budget – getting all the trades in early to do what is probably half a day's work can be expensive in time and money – but it will give you the best result in the end because you will have a template that everyone can refer to during the project. In addition, fittings that looked great in the brochure may not appeal when fixed to your wall. Much better to find this out when you have purchased two fittings rather than two hundred.

Contingencies

Consider the following scenario. The budget was tight, as was the program. Commissioning was starting and I was discussing the program with the HVAC contractor. I asked about the HEPA filters in a couple of rooms that were slightly smaller than the others. "Discontinued stock, got them cheap" he said. "Great!", I said, as I watched one of his staff walk past with one of the HEPA filters, supply side down, balanced on his hard hat. "Hope they pass the integrity test." Six to eight weeks later, after a bin full of HEPA boxes and HEPA filters with small top-of-hard-hat indentations was removed from the site, the ceiling penetrations were enlarged (with only a few over-cuts), and the new HEPA boxes and filters were installed and integrity tested. Only one HEPA failed, but that was replaced on the same day from the local suppliers' stock.

Contingencies extend beyond making sure you have back-ups in case things fail. Commissioning a facility at the same time as all the local factories shut down for maintenance means that you need to have a special relationship with your testing team, and that you have booked and secured the team well in advance.

In addition, optimism has no place in commissioning planning. If you ask a contractor that performs pressure tests for containment laboratories 'how many days to perform a pressure test?', they would probably reply 'anywhere between one day and one hundred'. Similarly for room balancing, particularly if the guy programming the Building Management System had a 'brilliant idea' but forgot to tell anyone about it.

The key to successful project management, particularly when your commissioning program includes activities such as pressure testing and or balancing, is not to know how to do everything, but to know the people who can fill in the gaps in your knowledge.

Proper commissioning

If you combine an inexperienced builder with an inexperienced client, the prospect of commissioning might seem to them like a walk in the park. Well defined, plenty of standards to refer to, and a trained professional to come in and do the tests. The reality is not so simple:

- There are three states of occupancy according to ISO 14644-1[3]
  - As-built – where it is just the building and the HVAC
  - At-rest – as above but with equipment installed and either functioning or not functioning, but with no product or materials or personnel present
  - In operation – as above but with personnel and materials

  The as-built test is rarely used. However it is a useful tool if the main contractor is handing over an empty shell and the client is installing the equipment. As the equipment will contribute its own level of contamination, if this exceeds the at-rest limit, it is hardly the fault of the contractor that built the cleanroom. However, it might be the fault of the designer who has not provided adequately for the amount of contamination generated.

  Similarly, the particles generated by staff and materials during an in operation test, means that it is very difficult to pin a failure on the people that built the cleanroom.

  Finally, although an airborne particle count is the cornerstone of cleanroom classification, it is quite easy to pass if you know what you're doing. Particularly an at-rest test.
- Fraud in certification does occur, and as very few people bother to scrutinise the reports, it can proliferate. Fraud itself is not necessarily nefarious. It can occur through a simple favour to wave something through or it can be in the form of a threat from an under-pressure builder but most often, it is through the application of Hanlon's Razor.[i]

  The key is to get the raw data and have someone experienced to review the reports. Of course, using a trusted testing company is also key. My own experience is that even when I review the best of the best, there are always one or two things I pick up.
- A recovery test, or a series of recovery tests provides a much more robust demonstration of the quality of a cleanroom installation. If observed, it is very difficult trick up a positive result. However, it does need a degree of knowledge and skill. Locations need to be carefully chosen as well.
- A key error I pick up when reading commissioning reports is when a single reading is presented for room pressure, temperature and or

i. Hanlon's razor states "never attribute to malice that which is adequately explained by stupidity.

humidity. One of the biggest problems I find when I'm called in to troubleshoot a problematic facility is stability. Most settings for pressure, temperature and humidity have a specified range, therefore a trend over a suitable period should be presented to demonstrate that the facility is operating within the specified range.

Conclusions

I've seen people age ten years over a six week commissioning process. Commissioning needs to be considered from the very start of a project. This needs experience, diligence, and a second, third and sometimes fourth set of eyes. Following the written word is not enough. The real knowledge is out there in the people that have gone through the process before. This is, perhaps the real secret to a successful conclusion of a project. Seek out the experience at the start, learn from those that have come before you and, when all is done, gather everyone together and share your experience, perhaps over a nice lunch.

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3. 14644-1:2015. *Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration*

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EU GMP and Annex 1: The new version

A paper prepared by Cherwell Laboratories Ltd

Abstract

This paper sets out to highlight some of the principal differences between the new 2022 Annex 1 and the 2008 version. The new Annex places emphasis on a rationale for preventing contamination, the use of a quality risk management (QRM) approach, the development of a facility-wide contamination control strategy (CCS) and the deployment of a continuous monitoring approach for Grade A and B areas. Tables are used to illustrate the change in word-count for key words, grade level details for microbial contamination and grade descriptions, sample frequencies for viable air monitoring, aseptic preparation and vapourised hydrogen peroxide (VHP). Some of these are extracts from the old and new Annexes.

Introduction

The new version of Annex 1, published on 22 August 2022, has been expanded considerably and now contains a strong focus on risk management and having a contamination control strategy (CCS).

The new document is 59 pages long and requires manufacturers to have clear rationale for preventing contamination of finished products by micro-organism, particulate or pyrogen. This should be achieved by developing, validating and reviewing a holistic, facility wide strategy to prevent contamination.

The deadline for the revised Annex 1 to come into operation, is 25 August 2023, except for point 8.123 relating to lyophilizers which is postponed until 25 August 2024

Good Manufacturing Practice (GMP)

First published in 1971, the latest iteration is the third revision and is one of the many key annexes of Good Manufacturing Practice (GMP). The regulatory bodies, for example in the UK the Medicines and Healthcare products Regulatory Agency (MHRA), issue manufacturing licences to pharmaceutical manufacturers in response to an application for a UK marketing authorisation for a product.

A licence can only be granted after detailed evidence has been collected to demonstrate compliance to GMP. It is worth noting that GMP is the minimum requirement for medicines manufacture and within the UK there are over 700 GMP licenced organisations. General information on the process of application and inspection is available on the UK governments website.

Key messages in new Annex 1

Annex 1 was last revised in 2008, so an update was much overdue. The new version has some key areas of focus, namely:

Use of quality risk management (QRM) approach.

Developing a holistic, facility-wide contamination control strategy (CCS).

Deploying a continuous monitoring approach for grade A environmental monitoring.

The term 'Risk assessment' is mentioned 20 times in the new Annex 1, demonstrating a key message. The term is more easily associated with health and safety, but broadly speaking a risk assessment consists of the identification of hazards, the analysis and evaluation of the risk and its potential impact on a process, an individual or a business. If that impact is likely and could be significant, then preventative measures need to be considered and deployed.

Resources to aid in building robust risk assessments are available, for example, European Medicines Agency guideline ICH Q9 Quality risk management.

Changes to previous version

The first obvious change is in the number of pages, the outgoing Annex 1 had 16 pages only, the new version has increased in size to 59 pages. There is also a marked difference in the repetition of key words within the new version, for example, the word 'monitoring' is mentioned five times more frequently in the 2022 Annex 1.

As mentioned above there are some key focuses within the new version. Whilst both Annex 1 documents, and GMP in general, talk about minimising the risk of microbial, particulate and pyrogen contamination in a finished product, the new version emphasises the importance of considering facility, personnel, processes and monitoring. This is supported by the use of terms such as quality risk management and pharmaceutical quality systems to manage the process of identifying and controlling risks. The new version clearly provides a broader directive on risks throughout a facility and process, for example consideration around the increased use of RABs, isolators and blow fill seal technology. All of these factors form the basis for the holistic facility wide approach and the creation of a contamination control strategy (CCS).

A more obvious change in the new Annex is the revision to Grade A limits for biocontamination. Previously the limits for active samples stated an average of less than one cfu per cubic metre, this was of course open to some interpretation. The new Annex 1 is clear, the limit is zero, meaning any event represents a breach and will need a full investigation. Manufacturers will need to recognise that this could lead to an increase in resource within QA and/or QC Microbiology to carry out the in-house investigations and document the findings.

The outgoing version of Annex 1 was last revised in 2008, so an update was much overdue. The 2022 version has expanded considerably in length. Tables 1-6 represents a comparison between the two versions, highlighting some key areas of focus. While this is not a comprehensive account of every single update, we hope you find it useful.

Annex 1 – 2022 Some comparisons

Table 1: Word page number comparison

2008 Annex 1	2022 Annex 1
16 pages	59 pages

Table 2: Change of emphasis – Keyword comparison chart

The 2022 version of Annex 1 has been expanded considerably and now contains a strong focus on risk management and on having a contamination control strategy. There is a marked difference in the repetition of key words within the 2022 version.		
Word	**2008 Annex 1 count**	**2022 Annex 1 count**
Contamination	35	137
Monitoring	26	127
Risk	20	124
Environment	25	96
Microbial	12	97
CCS	0	51
Organism	13	43
Viable	4	23
Risk Assessment	0	20
Continuous	1	17

Table 3a: Grade level detail – Microbial contamination – 2008 Annex 1

2008 Annex 1				
19. Recommended limits for microbiological monitoring of clean areas during operation:				
Recommended limits for microbial contamination (a)				
Grade	**Air sample cfu/m³**	**Settle plates (diameter 90 mm) cfu/4 hours (b)**	**Contact plates (diameter 55 mm) cfu/plate**	**Glove print 5 fingers cfu/glove**
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	30	-
Notes (a) These are average values. (b) Individual settle plates may be exposed for less than 4 hours. 20. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.				

Table 3b: Grade level detail – Microbial contamination – 2022 Annex 1

2022 Annex 1				
9.30 Action limits for viable particle contamination are shown in Table 6				
Table 6: Maximum action limits for viable particle contamination				
Grade	**Air sample cfu/m³**	**Settle plates (diameter 90 mm) CFU/4 hours (a)**	**Contact plates (diameter 55 mm) CFU/plate (b)**	**Glove print 5 fingers CFU/glove**
A		No growth (c)		
B	10	5	5	5
C	100	50	25	-
D	200	100	30	-
(a) - Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used). - For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM. - Individual settle plates may be exposed for less than 4 hours. (b) Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function. (c) It should be noted that for grade A, any growth should result in an investigation.				

Table 3c: Grade level detail – Grade descriptions – 2022 Annex 1

2022 Annex 1
The 2022 revision of Annex 1 includes a greater level of detail describing requirements and guidance on operations in Grade A – D facilities.
4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.
4.4 For the manufacture of sterile products, there are four grades of cleanroom/zone. *Grade A:* The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design. *Grade B:* For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Air pressure differences should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used (see paragraph 4.20). *Grade C and D:* These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation/filling of terminally sterilised products. (See section 8 for the specific details on terminal sterilisation activities)

Table 4: Grade B Sample Frequency – 2022 Annex 1

2022 Annex 1
9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided.

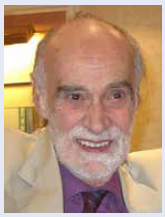
Table 5: Aseptic Preparation – 2022 Annex 1

2022 Annex 1
8.7 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.
8.8 Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilisation), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres should be minimized in cleanrooms

Table 6: Vapourised Hydrogen Peroxide (VHP) – 2022 Annex 1

2022 Annex 1
4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator. i. For isolators The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms. ii. For RABS The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly include all areas of the interior surfaces and ensure a suitable environment for aseptic processing.
4.36 Where fumigation or vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide) of cleanrooms and associated surfaces are used, the effectiveness of any fumigation agent and dispersion system should be understood and validated.
10.8. Any process (e.g. Vaporized Hydrogen Peroxide, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the sample.

Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.



The late Lawrence Whittard – Founder of Cherwell Laboratories

Cherwell Laboratories was founded by Lawrence Whittard in 1971 as a veterinary diagnostic laboratory. Lawrence was an entrepreneur with an eye for an opportunity thus Cherwell evolved and became a distributor for a range of laboratory equipment. A focus on microbiology, and particularly within the pharma sector, set the foundations for the business. Today, Cherwell is a specialist supplier of 'cleanroom microbiology solutions' with products for environmental monitoring and process validation for healthcare, pharmaceutical and industrial applications. From our site in Bicester, we manufacture Redipor® Prepared Media, our own range of microbiological media products which has been developed to meet the specific needs of our customers. We also supply SAS® and ImpactAir® microbial air samplers and monitors, as well as a range of EM accessories.

Cherwell focuses on supplying high quality and tailored products supported by excellent customer service. This ethos is fundamental to our business values and helped us achieve ISO9001:2015 accreditation for: 'the manufacture and supply of microbiological media. Supply, service and calibration of viable air sampling equipment. Distribution and sales of laboratory equipment and consumables.'

For further information Cherwell and its products, please visit www.cherwell-labs.co.uk

Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing.

A new challenge for quality experts – the Data Quality Concept

Maurizio Della Pietra

This article is based on a White Paper by Particle Measuring Systems Inc. and is published here with their kind permission.

Abstract

The role of quality systems in pharmaceutical organizations has grown faster than any other function during the last 15 years. During this period, a small group dedicated to traditional Compliance grew and expanded to include Quality Experts in areas such as validation, product release, operations, sterility assurance, and other specialized functions. Creating a deeper quality connection between manufacturing and engineering has always been the aim of that growth. Little by little, quality became fundamental to every step of the pharmaceutical manufacturing process: changing from a silo[i] concept to a more fluid one. Now, a new challenge is approaching. The fourth industrial revolution (Pharma 4.0™)[ii] is the beginning of the "Smart Facility" era, where digitalization and automation will combine to reach very complex applications and life cycles. In this brand-new framework, Quality Experts will face the challenge of rethinking their roles and redesigning the Quality Systems of their pharmaceutical companies to be based on the concepts of Data Quality.

Keywords: Data Quality; Holistic; Digital Maturity; Data Maturity; EVO[iii]2; Pharma 4.0™

The ICH Idea of Pharma

Since 1990, the International Council for Harmonization (ICH) has aimed to achieve a unique response worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. Between 2005 and 2008, with the publication of the Q9 and Q10 guidelines, the council explained what the quality systems should be and how they should work to assure the highest possible quality drug product.

During these years, we can affirm that most of the pharmaceutical firms in the world designed their quality system to fit the ICH guidelines, enhancing the ICH's role in the pharmaceutical organization. Simultaneously the value and the challenge of the ICH was, fundamentally, to use science and risk-based quality system principles to cover the entire manufacturing product life cycle.

The New Keywords

The ICH Q9 and Q10 were the real revolutions for what we can call the blockbuster era of pharmaceuticals, or "Pharma 2.0". This era was characterized by the mass production of homogeneous products for extended periods of time. The main characteristics of these Pharma 2.0 organizations was that they were controlled by a hierarchical culture based on the experience of the decision-makers, and they were organized in silos. After the ICH guidelines, Quality organizations broke down this mentality,

The fourth industrial revolution (Pharma 4.0™) is the beginning of the "Smart Facility" era, where digitalization and automation will combine to reach very complex applications and life cycles.

making the function of Quality departments so pervasive that they could be perceived as fluid. The key person in this newly less structured organization was the Quality Expert. Acting as a Subject Matter Expert, they had to correlate information from the field with their own experience in Quality matters to make decisions based on science.

Now, the game is changing quickly. The already rapid progression of traditional pharmaceuticals into biotech and genetics has been accelerated by the COVID-19 crisis, market changes, and technical advances. These are the engines that are driving the

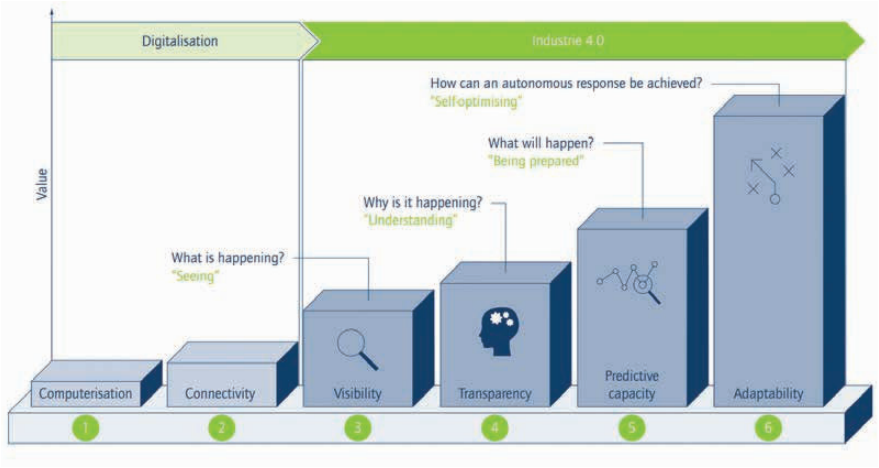


Figure 1: Acatech digital maturity stages (Source : FIR e. V. at RWTH Aachen University)

i. Although the historical definition of a silo is a container (traditionally used on farms for storing grain or cattle food), the word also has a more abstract meaning today. It is often employed as a metaphor for groups of people (e.g., a team is a 'container' of colleagues) who work independently from other groups.

ii. Pharma 4.0™ is a trademark of ISPE

iii. Empowered Value-driven Organizations

pharmaceutical world to a new industrial revolution: or, as titled by ISPE, Pharma 4.0™.

As with every new era, some keywords are fundamental to understanding the critical differences from the past. For the fourth industrial revolution, Digital Maturity, Automation, and Holistic are the most vital terms to understand.

From Digital Maturity to Data Quality Concept

One of the strongest pieces of evidence of the fourth industrial revolution in Pharma is the emergence of Smart Facilities. After years spent developing this concept on paper, these tech enabled sites are becoming real. Briefly, a facility is "Smart" if all the Acatech digital maturity stages[iv] shown diagrammatically in Figure 1. are fulfilled:

- Stage 1: Computerization.
- Stage 2: Connectivity.
- Stage 3: Visibility.
- Stage 4: Transparency.
- Stage 5: Predictive Capacity.
- Stage 6: Adaptability.

Fulfilling Stage 1 means moving from a "paper-based" to a "data-based" operation, while guaranteeing Connectivity (Stage 2) means moving from isolated devices to system integration with data that can be shared among the services.

The first step into the Pharma 4.0 revolution is the Visibility stage (Stage 3), which is the capacity to see what happens in real-time through data coming from the sensors in the digital chain built in the previous stage. It is evident that most of the pharmaceutical industry is at this stage. This is the stage where key performance indicators (KPIs) are collected and available online. However, as mentioned before, it still relies on Quality Experts to make decisions partly on experience and partly on a scientific basis using historical data analysis performed offline.

The digital shadow of the processes created in the first three stages is completed by the "Automation" provided by the last three stages. Transparency (Stage 4) is defined by the capacity to identify and interpret interactions in the digital shadow when they happen in order to find the true root causes (deductive capacity). Furthermore, Predictive Capacity (Stage 5) is fundamental for automated decision making. In Stage 4, the systems start to analyze the trends, projecting the digital shadow into the future to implement appropriate countermeasures in good time. The last step is Adaptability, which is the automated capability to adapt processes to corrected outcomes without manual intervention and despite changing input and circumstances.

Not all pharmaceutical companies need to fulfill all these stages. For example, firms that manufacture large consumer products may not have the intrinsic necessity for climbing the digital maturity stages. On the other hand, having this holistic approach will be the only way to sustain business for the high technology products, advanced therapies, and high value-added products. Additionally, it is important to note that an organization can fulfill all five of the Acatech Digital Maturity stages by simply having the capacity to carry them out; however, it is the role of the Quality Experts and system owners to convert that capacity into existence.

"Holistic" means, in fact, the complete view of something, including all influences and all possible contexts. Holism in science is an approach to research that emphasizes the study of complex systems. Systems are approached as coherent wholes, whose component parts are best understood in context and in relation to one another and to the whole.

We can call this approach for making decisions in pharmaceutical production "Data Quality." This refers to the long data journey through the digital maturity stages, and its ultimate purpose of transforming the data collected into informed decisions (CAPA).

The New Challenge

What will happen to the Quality Expert as imagined by the ICH? Systems will advance to be able to correct, predict, and adapt existing processes in an automated way, and, in a short time, they will replace the methods for

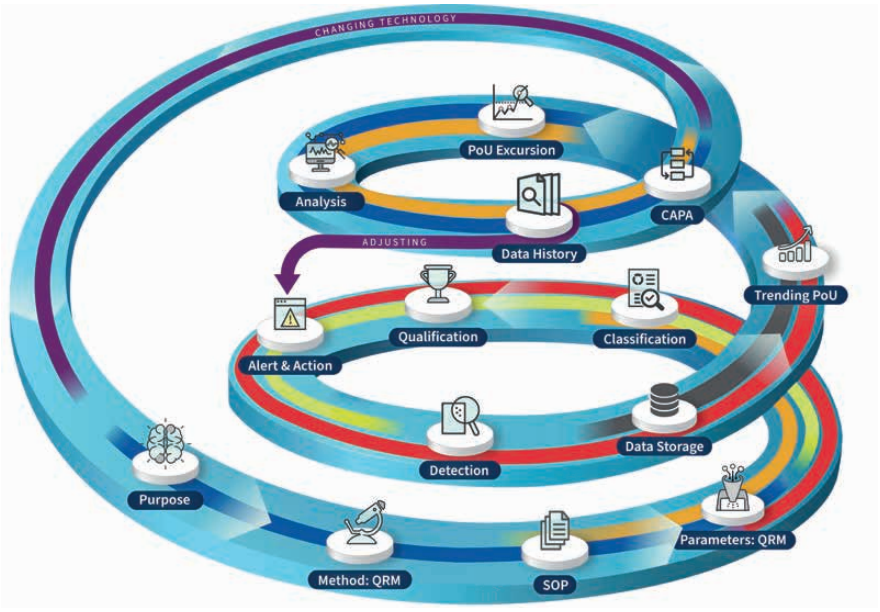


Figure 2: Data quality spiral

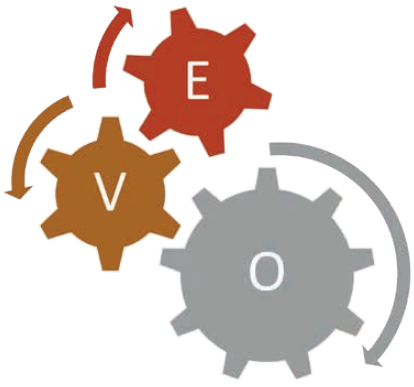


Figure 3: Empowered value-driven organisation (EVO)

iv. Acatech – National Academy of Science and Engineering, funded by the Federal Government of Germany and the Länder, is the voice of the technological sciences at home and abroad. Acatech provides advice on strategic engineering and technology policy issues to policymakers and the public.

decision making we are using right now. Can we say that Data Quality itself is enough to assure the quality of pharmaceutical products?

As in every industrial revolution, technical advancement is not enough to change an era; cultural progress must be present with the same strength.

Cultural changes can be top-down processes when upper management forces change or a bottom-up process when a widespread movement causes a revolution. In both cases, it is evidence of the presence of a siloed organization that needs to evolve. In Pharma 4.0, after the digitalization and automation process, a company will no longer need an organization that is structured with levels and departments. For the first time ever in the industry, we are experiencing both top-down and bottom-up cultural changes together. Employees of every level must become multi-skilled in a fluid, process-oriented lean organization.

This is also true for the Quality Unit and its experts. Because the process of sharing Quality information is faster and more accurate than before, there will not be time to ask for advice and authorization. The understanding of Quality Concepts should be one of the skills of new experts, along with process, manufacturing, and statistical knowledge. The Quality department of Pharma 4.0 will be an Empowered Value-driven Organization (EVO) where each expert is empowered with information from Data Quality that allows them to make decisions without a decision hierarchy. The Automation stages (Transparency, Predictive capacity, Adaptability) guarantee that these decisions will be made to reach the expected objectives of increasing system reliability, improving product quality, and reducing the documentation needed.

In fact, recent market studies indicate that automation is destined to replace most of the "predictable work," but, on the other hand, it will increase the demand for experts who can manage the decision phase of all that is "unpredictable." The magnitude to the necessary increase in the workforce of new experts is impressive. We are talking of global growth of 150% with several hundred million people globally that will have to evolve their skills alongside the rise of this new industrial revolution.

Conclusions

In the age of the fourth industrial revolution, Data Quality is the foundation on which pharmaceutical companies must build up their production. This will occur through a deep connection between all the different stages of manufacturing, which are currently losing their defined outlines. On one hand, digitalization and automation will replace the types of work that we can define as "predictable." On the other hand, the massive amount of data created that is the basis for decision-making requires multi-skilled experts for interpretation. Advanced skills in statistics, process engineering, contamination, and microbiology are just some examples of the portfolio of knowledge that will be needed.

Moreover, the role of these new Quality Experts will become more fundamental than in the past. The fluid organization created by the Data Quality concept will change traditional departments into EVO's, where fundamental decisions will come from the Quality Experts without any decision hierarchy.

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Particle Measuring Systems (PMS) specializes in viable and nonviable particle counters and particle counting solutions that measure and monitor contamination levels in clean and controlled environments. Since 1972, our knowledgeable and experienced team has been developing innovative technologies to advance the cleanroom monitoring industry. Led by our technology which provides accurate and reliable results and information for our clients, Particle Measuring Systems is one of the world's leading environmental control companies and manufacturers for particle counting instruments, and molecular and microbial monitoring.

It's time to take control of Annex 1

Annex 1 of the European GMP Guidelines for Medicinal Products was updated in August 2022. The document has been significantly revised to align to Quality Risk Management, the Pharmaceutical Quality System, and to embrace the development of new technologies within the Life Sciences industry. The introduction of a requirement for a Contamination Control Strategy brings cleaning, disinfection and decontamination practices to the forefront. Working with Ecolab, you can build your roadmap to compliance with the Annex 1 requirements for contamination control. Our global team of technical experts can support you with product selection, regime design, manual and automated solutions, and validation planning and execution. Learn more by attending our Annex 1 Masterclass webinar series – register at www.ecolablifesciences.com/annex1

Senior staff changes at ATI UK

Rory McLellan

Tim Triggs

ATI welcomes Rory McLellan as its new EMEA Director. Rory will manage the team selling and supporting the ATI range which includes filter leak testing equipment, automated filter testers, Lighthouse particle counters and Lighthouse Environmental Monitoring Systems. He takes over from Tim Triggs who will continue working as a consultant for ATI. Tim will focus his efforts on delivering the ATI range of training courses covering HEPA filter testing, cleanroom classification, airflow measurement and biological safety cabinet testing. The ATI team wish them both every success in their new roles.

Further details of ATI's range of products can be found at www.atitest.com or for any questions on products or training courses, please e-mail salesuk@atitest.com or call +44 (0)1462 676446.

Training at Air Techniques International (ATI)

On July 21-22, Tim Triggs conducted internal staff training at ATI USA headquarters in Owings Mills, MD. The training comprised cleanroom and clean air device testing and included HEPA filter testing, airflow measurement, and particle counting to international standards. New employees and experienced personnel participated and benefitted from the sessions. "It was great to travel to America again and see everyone in person. ATI has grown over the last two years, so it was perfect for helping about twenty new staff learn more about our industry, products, and applications," said Triggs.

In the UK, external training is held at ATI's Letchworth facility for anyone with a role in engineering, testing, quality, validation, operations, management, or inspections of clean air facilities and equipment. Typical courses include theory, practical demos, Q&A, and testing. Candidates may select one of twenty days each year to gain knowledge in HEPA filter testing, airflow measurement, cleanroom classifications, or biosafety cabinet testing. New course material will be added in 2023, so book your place early. A few spaces are available for November 2022. Contact salesuk@atitest.com for availability and pricing.

Connect with ATI and Tim Triggs on LinkedIn for the latest information. View the full training calendar and course descriptions at: https://www.atitest.com/event_type/training-events/.

Validair launches in Ireland and appoints Conor Murray as BioTrak specialist

Connor Murray

Validair has established new infrastructure in Ireland and launched its technical sales and support services across the country. Validair Monitoring Ireland Ltd (VMIL) has its headquarters in Dublin and is the TSI Channel Partner. Through this partnership, the company now supplies the entire range of TSI AeroTrak® airborne particle counters, Facility Monitoring Software (OPC UA Client/Server) and the unique TSI BioTrak® Real-Time Viable Particle Counter to new and existing customers in Ireland.

VMIL has enlisted the specialist technical expertise of Conor Murray, who takes exclusive responsibility for the BioTrak in Ireland. Murray is the Irish SME (subject matter expert) on ISO/TC209 and past Convenor of EN 17141 on Microbiological Contamination Control. He is also a BioTrak enthusiast, seeing the instrument as a game changer in pharmaceutical aseptic manufacture as part of ARMM in support of Pharma 4.0 PAT and real-time release testing. The BioTrak's capabilities meet the new EU GMP Annex 1 update requirements for continuous monitoring during Grade A manufacturing.

For more information about VMIL, go to https://validair.ie/

To request a demonstration of the BioTrak, please email enquiries@validair.ie

The BioTrak Real-Time Viable Particle Counter

Another hands-free mopping system is added to Contec's range

Designed to simplify the cleanroom mopping process, Contec's Hands Free Mop Head Saturation System allows mop heads to be presaturated prior to being passed into the controlled environment. The system allows mop heads to be installed AND removed "hands-free" reducing the risk of cross contamination and speeding up the cleaning and disinfection process.

Designed for use with Contec's QuickTask flat mop system, the new trolley with a choice of polypropylene and stainless steel buckets, allows up to 20 flat mops to be presaturated at any one time. A stainless steel, "A" frame insert allows the mop heads to be loaded onto the mop frame hands-free, and maybe more importantly the integral mop removal tool allows the dirty mop to be removed hands-free, falling freely straight into a waste bag.

For more information or to request a trial, please email infoeu@contecinc.com

Cherwell launches educational video hub

Cherwell Laboratories has launched a new online video training library sharing educational content for individuals in the pharmaceutical and healthcare industries. Cherwell's Delivering Knowledge platform offers best practice information delivered by experts in monitoring of controlled environments, aseptic processes and sterility.

The new educational video hub has been developed by Cherwell as a conduit for vital knowledge transfer and therefore a useful learning aid. Each subject focus is delivered by an expert in that area, offering consistent, accurate and compliant answers.

The latest videos available include discussions on: environmental monitoring and microorganism morphology; the future of pharmaceutical environmental monitoring; and use of needle free infusion bags for cytotoxics at Torbay and South Devon NHS Foundation Trust.

Cherwell are keen to hear from and interview experts in their field, to share their knowledge with the Cherwell community and support the effective management of controlled environments and processes.

For more information, please visit www.cherwell-labs.co.uk/delivering-knowledge.

EECO2 and Cambridge Pharma presentation at Cleanroom Technology Conference

Keith Beattie of EECO2 (L) and David Mitchell of Cambridge Pharma (R)

At this year's Cleanroom Tech Conference, EECO2's Keith Beattie teamed up with Cambridge Pharma's David Mitchell to present "Implementing Dynamic Cleanroom Control to Create GMP Compliant & Energy Efficient Cleanrooms". Calling upon the real-world experience of implementing dynamic cleanroom control in a commercial facility, the talk tackled the challenge of qualifying a facility with adaptive demand-based control of the HVAC system, as well as providing an insight into the energy-saving figures when implementing a dynamic cleanroom control system.

The two-day conference also provided a great opportunity to connect and network with many industry experts in cleanroom technology and practices, as well as attend countless other great talks, including "Annex 1 and its Impact on Innovation and New Technology Adoption" and "Cleanroom Personnel, Effective Garments and Considerations for Energy Savings".

For more information please e-mail info@eeco2.com or visit www.eeco2.com

Particle Measuring Systems announces corporate HQ relocation

Particle Measuring Systems (PMS) is relocating its global manufacturing and commercial headquarters to the Boulder Technology Center in Niwot, Colorado, USA. The new facility is over twice the size of the current HQ at 124,000 square feet (11,500 square meters) and, when fully open in early 2024, will optimize workflow and operational efficiencies across all PMS's core business functions.

"This is a unique opportunity for us to design a space that accommodates all our needs while creating a positive customer and employee experience. It demonstrates a significant capital investment by our parent company, Spectris." said John Mitchell, President of Particle Measuring Systems. John continued, "The vision for our new PMS HQ is to create an engaging, inclusive, and welcoming workplace with employees and customers in mind."

This year PMS celebrates the 50th Anniversary of its founding. Since 1972, PMS has grown into a solutions and thought leader for contamination monitoring and control for clean manufacturing facilities. They are the industry leader in monitoring sensitivity. PMS delivers not only contamination instruments, but also expert consultants, data management software, and training and education to their customers around the globe.

For more information visit www.pmeasuring.com

Environmental control and particle counting – PMS gives answers to FAQs

At Particle Measuring Systems, we receive many questions regarding suitable or best practices in environmental control and particle counting compliance and applications. Our industry experts summarize and answer your most frequent questions as application notes or blogs and these can be found on the Particle Measuring Systems website by typing FAQ in the search field. If you're wondering about something, there are certainly others in the industry asking the same questions.

Here are two examples

Question: Can you speak to the requirements for monitoring Class D clean areas for viable and non viable particulate? The regulations don't make it black and white.

Answer: The regulations surrounding viable and non viable monitoring of Class D clean areas point toward appropriate actions being established on a site-by-site, risk-based assessment … to read more go to www.pmeasuring.com/blog/faqs-class-d-clean-area-viable-and-non-viable-monitoring-requirements/

Question: What is the need of taking a nonviable particle count after a power shut down for an hour? Our Class C area is stabilizing within 30 minutes after the shut down.

Answer: There are several reasons for deploying your Nonviable Environmental Monitoring Program following a power outage, but primarily it is to ensure that the HVAC has been restored and is now operating optimally … to read more go to www.pmeasuring.com/blog/faqs-non-viable-particle-recovery-verification-after-a-power-outage

We are happy to share our experts' knowledge with everyone. If you can't find your question and answer in the FAQs, please write to info@pmeasuring.com.

Events

2022	Event	Location
November 14-17	IEST EDUCON	Schaumburg, Illinois
November 23-24	Cleanzone	Frankfurt, Germany
2023	**Event**	**Location**
May 8-11	IEST ESTECH 2023	Minneapolis/ St Paul, Minnesota

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2022	**Event**	**Location**
February 7	The Foundations of Contamination Control using Essential Cleanroom Standards ISO 14644-1 and ISO 14644-2	Schaumburg, Illinois/Virtual
February 8	Basic Information and Implementation of the New ISO 14644-3:2019 Test Methods	Schaumburg, Illinois/Virtual
February 9	Universal Cleanroom Operations Guidelines with ISO 14644-5	Schaumburg, Illinois/Virtual
For a complete list of courses, please see www.iest.org/Training-Certs/IEST-Contamination-Control-Learning-Path		

CCN (Contamination Control Network) www.theccnetwork.org		
2023	**Event**	**Location**
March 21-23	CTCB-I Cleanroom Testing Course	Letchworth, UK
May 16-18	CTCB-I Cleanroom Testing Course	Letchworth, UK
July 14	CTCB-I Cleanroom Technology	To be confirmed
November 7-9	CTCB-I Cleanroom Testing Course	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:		
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

Peace quotes

It is madness for sheep to talk peace with a wolf.
Thomas Fuller

Those who are at war with others are not at peace with themselves.
William Hazlitt

Democracy must learn to defend itself.
Mikhail Gorbachev

Peace is not absence of conflict, it is the ability to handle conflict by peaceful means.
Ronald Reagan

Peace is a journey of a thousand miles and it must be taken one step at a time.
Lyndon B. Johnson

Peace and justice are two sides of the same coin.
Dwight D. Eisenhower

If you want to make peace with your enemy, you have to work with your enemy. Then he becomes your partner.
Nelson Mandela

Peace cannot be kept by force; it can only be achieved by understanding.
Albert Einstein

An eye for an eye only ends up making the whole world blind.
Mahatma Gandhi

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