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Clean Air and Containment Review

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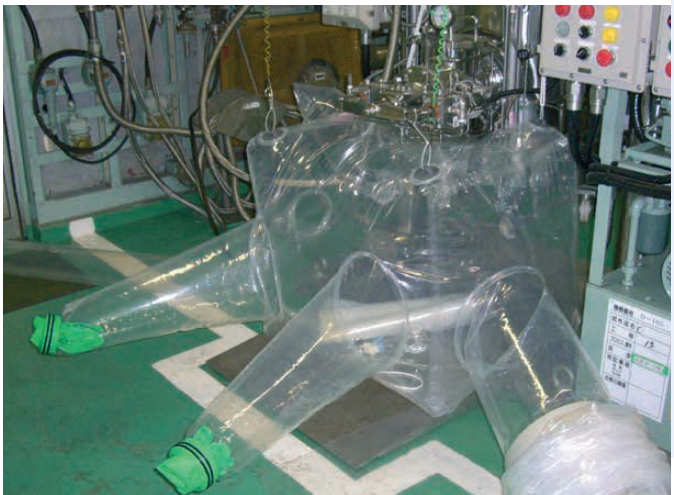

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Picture: Envair + ONFAB are specialist containment engineers

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

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Contents

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Editorial

Welcome to CACR41!

Three of the articles in this issue challenge conventional thinking. The first is another article in Andrew Watson's 'known unknown' series. This time the topic is monitoring and Andrew speculates on whether monitoring points are chosen for "convenience rather than to provide any real insight into what is actually happening in the cleanroom". He questions how alert and action levels are set and interpreted, and then goes on to suggest that engineers should find the time to measure the effect of the cleanroom operating outside specification, for example with the airflow turned down, or with more than the usual number of staff, or with reduced gowning, in order to gain useful data on the boundaries of the cleanroom's capabilities.

In CACR40, Tim Coles wrote an overview of isolator standards in which he highlighted the areas in which existing standards might perhaps be deficient. When this article was seen by two well-known isolator experts in the USA, James Akers and Rick Nieskes, they responded to Tim directly and informally by e-mail. In this issue, CACR publishes substantial extracts from these e-mails with their kind permission. Jim's theme is that cleanroom technology does not necessarily apply to isolators. Rick makes a number of practical suggestions and questions whether a log 6 kill is overkill.

These two articles come under the heading of 'Discussion' as that is what they are. From time to time CACR carries controversial articles – intentionally. They are published to stimulate discussion or debate and on this occasion Tim's article in CACR40 has stimulated two interesting responses.

This issue has a second article by Sanna Lehtinen of Vaisala on the adaptation of RH (relative humidity) sensors to measure hydrogen peroxide vapour concentration and the practical application of these sensors. May I divert for a moment? Readers may notice that I am not consistent in my use of English (UK) or English (US) spellings. This is what I do. If an article comes to me using the English (US) spelling that is how I publish it. If it comes using the English (UK) spelling, then that is how it appears. It was the word 'vapour' that stimulated this comment. In her article, Sanna uses 'vapor' whereas in this Editorial I use 'vapour'. See also Life-lines on page 27 where George Bernard Shaw has something to say on the subject. I have a similar approach to references. I don't prescribe what referencing system authors should use, rather I encourage them to use whatever system they are comfortable with. Hopefully that makes for more fluency in how they write.

In February, the EMA (European Medicines Agency) published a new draft of EU GMP Annex 1, designated as version 12, for targeted consultation by a number of representative bodies. Here Tim Sandle gives his initial reaction to the new draft starting on page 14.

Finally, two UK technical experts who serve on ISO TC 209 Working Groups, Dick Gibbons and Richard Roberts, give updates on some of the lesser known Parts of ISO 14644 with which they have been involved, Dick as Convener and Robert as Technical Expert.

I hope you enjoy CACR41 … and if you have any comments about any of the articles, please write to me or to the authors.

John Neiger

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Cleanrooms – known unknowns: 2. Cleanroom monitoring

Andrew Watson

Abstract

Following the previous discussion on source strength, this article explores the known unknowns associated with cleanroom monitoring. The shortcomings with current practices aredescribed as well as 'enhanced' testing inside and outside the normal performance boundaries of your cleanroom. This will lead to a better understanding of how your cleanroom behaves, giving you the opportunity to improve your facility and better respond to challenges.

Monitoring is generally limited to the critical location. If measuring the "background' of a critical location, this is generally a remote, single point.

Deliberate deviations from standard settings to help you understand your cleanroom better

Recapping the previous article (see CACR 40-2019), there are difficulties in determining a source strength value that can realistically be applied to a cleanroom for the determination of an appropriate air supply rate. Particularly if you take larger particles into account. In the absence of relevant scientific data, the only other method available is to monitor and generate relevant data yourself.

This article is going to focus on the challenges of gathering monitoring data and work through some of the shortcomings that are encountered when interpreting it. In addition, it will look at what improvements this data may allow in improving the efficiency of your facility, such as temporary or permanent fan setback. Finally, it will discuss the known unknowns that may arise throughout the evaluation of particle concentration data and other environmental parameters.

There are many challenges when it comes to monitoring a cleanroom, whether it is real-time monitoring of a critical space, regular cleanroom certification, or an investigational effort. These include:

- The location(s) to monitor
- The activities to occur during monitoring
- Specific and broad characteristics of the cleanroom
- Sample sizes, particle sizes, sampling rates

For critical locations, particularly those that utilise unidirectional flow, there is significant guidance available and specific characteristics such as air velocities, airflow patterns and recovery rates can be readily determined. By the nature of unidirectional flow, the characteristics should be uniform.

However, for non-unidirectional cleanrooms in general, the characteristics vary widely, and characterisation is significantly more difficult. Through ISO 14644 Part 1 we find a method of characterising a cleanroom in terms of particle concentration; the test most of us perform at least annually. With this come the following caveats:

- Applying the number of locations recommended in Table 1 of Appendix A, only provides "at least 95% confidence that at least 90% of the cleanroom or clean zone area does not exceed the class limits". ISO 14644-1 : 2015, clause A.4.1
- The quality and relevance of the data is only as good as the protocols employed performing the tests
- It is essentially measuring the cleanroom's characteristics at a point in time, and by its nature, is performed to prove compliance rather than investigate performance.

Regular or semi-regular monitoring provides us with a broader picture, but in contrast to the above, only a single point over a longer term, rather than multiple points over a short term. Again, the location of a monitoring point is generally chosen to minimise inconvenience, rather than provide any real insight into what is actually happening in the cleanroom.

ISO 14644 Part 2 provides some further guidance on monitoring, particularly around the setting of alert and alert limits. These are a perfect example of cleanroom known unknowns, particularly when it comes to particle concentrations. Many sites set these limits; few sites set them correctly, or respond correctly to occasions when these limits are exceeded. So why is this such a challenge? A few points:

- Monitoring is generally limited to the critical location. If measuring the "background' of a critical location, this is generally a remote, single point.
- Counts tend to be a series of spikes, rather than a longer term trend of rising and falling values
- Samples are generally small (28, 50 or 100L), taken every minute.
- Often, by the time a spike is reported by a particle counter, the incident has concluded, and the threat has passed.
- If a spike occurs across two samples, the actual reported value is significantly less, but cumulatively it is accurate.

The consequences of exceeding a limit are also laced with considerable uncertainty:

- Particle size – is an excursion of particles ≥0.5µm more serious than those ≥5.0µm?
- Are we concerned with 1 minute data normalised to a 1m^3 sample, or only data accumulated up to a 1m^3 sample? Are 1,000 particles over 1 minute worse than 3,400 particles over 35 minutes?
- Surely all particle excursions are not equal? Do we zone our limits

according to their proximity to a critical area? Does each excursion require the same response?

This uncertainty makes the selection of a particular air supply rate even more difficult, as the lower the supply rate, the greater the spike, technically, and the longer the recovery.

In order to obtain the necessary information to make better and more informed decisions regarding our facility, we are going to need to be broader and braver in the data we seek. We need to push the boundary of the activities we perform, while measuring cleanroom data, in order to find the boundary of our cleanroom's capabilities. It is an opportunity for cleanroom engineers to exercise their curiosity.

These activities need to occur outside of regular working hours, obviously, and do not necessarily need to be recorded as official data that is part of the facility's permanent record. Examples include:

- Turning down (or up) your airflow rate
- Exceeding the usual number of staff in a particular area
- Simulating some unusual staff movements from time to time, such as quickly moving to an area to perform an emergency intervention (well characterised for Grade A, not so for Grade B)
- Opening packaging
- Certain cleaning operations
- Reduced gowning

There are of course other cleanroom environmental parameters you may wish to explore. For aseptic cleanrooms there is often an obsession with low humidity to reduce the proliferation of bioburden. In reality it is more about having the dew point of your air lower than the lowest surface temperature in your cleanroom. Mapping the surface temperature in your cleanroom will give you vital information of areas where surface moisture can occur. It will also allow you to reassess your alert and action limits.

There is probably a range of modifications that could be performed with temperature and pressure, although these might be just as easily calculated. Stability of pressure regimes is frequently a problem, and it may pay to play with some of the parameters such as door leakage that may provide additional stability.

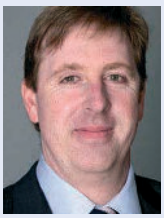
The incident you lost three night's sleep over might be nothing at all. Of course, you may uncover things that will impact your sleep going forward.

Of course, all these activities require some common-sense warnings:

- If you are adjusting flows, make sure you have someone qualified and with the right equipment to put them back the way they were
- Airflow pattern changes can affect the stability of air barriers in BSCs and clean air devices
- Beware of bad data. Ensure instruments are calibrated and the limitations of your devices are known (particularly for devices that measure velocity and for particle counters where coincidence error might occur)
- When making sense of data, don't forget about particle deposition
- If you make a change, don't forget the implications.
- To those in the quality department and potentially the cleanroom owner, this may seem to be a pretty controversial thing to do. A sensible approach with clear boundaries and objectives will hopefully gain you the permission of quality, whereas a targeted and planned approach will gain you the permission of the owner. Doing things "just to see what happens" might not cut it.

The results will probably be surprising. Certain activities might have a significant impact, others not so much. The incident you lost three night's sleep over might be nothing at all. Of course, you may uncover things that will impact your sleep going forward.

The benefits will be more than a better understanding of your cleanroom. Staff will be able to work more confidently and respond more effectively when things go awry. The quality department will find that investigations will be simpler and be closed off more conclusively. You may find that your own curiosity becomes contagious, and spreads to other departments and perhaps to other sites. Discussing and sharing data will drive further knowledge and improvements. You will thus acquire greater knowledge of your known unknowns.



Andrew Watson is a Director of CBE, Centre for Biopharmaceutical Excellence, Australia. He is a Bachelor of Engineering (Chemical and has 25 years' experience in the design, construction, commissioning/validation and operation of a wide range high tech facilities, including pharmaceutical manufacturing, high containment, industrial cleanroom, hospital pharmacy and specialist research facilities. This experience extends to facility layout, building fabric design, construction, and HVAC, utility and purified water specification. His project management experience encompasses all aspects of FDA, EU, TGA, PIC/S and associated regulations, local and international standards and general quality practices. He has performed gap analyses on many pharmaceutical manufacturing facilities and sterile/cytotoxic dispensing suites to assess aspects of compliance, safety, design and rectification. Andrew is a past president of ISPE (Australasia) and is active in establishing ISO standards. He is Independent Chair of ME-060 (Cleanroom Standards) for Standards Australia and a committee member for ISO TC-209 – (ISO 14644 and 14698 suite of standards).

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Understanding critical measurement parameters in vaporized hydrogen peroxide bio-decontamination

Sanna Lehtinen

Abstract

This article discusses the importance of the relationships between temperature and relative humidity in vaporized hydrogen peroxide applications and introduces a new parameter: relative saturation. Relative humidity (RH) is a critical parameter in H_2O_2 vapor applications whether with a dry or wet method of bio-decontamination. Relative humidity is, of course, relative to temperature, so that is the second important parameter. The higher the temperature, the more H_2O_2 ppm can be added to the air mixture before condensation occurs. However, the addition of hydrogen peroxide vapor to the air mixture also has a great impact on the point at which condensation occurs.

Relative saturation is a new measured parameter that indicates the point at which the combined water vapor and hydrogen peroxide vapor will start to condense. When the air mixture contains vaporized H_2O_2, relative humidity can never reach 100%, making it nearly impossible to know exactly when condensation will occur. The greater the temperature, the greater the allowable relative humidity. On the other hand, the higher the H_2O_2 concentration, the lower is maximum achievable RH. It is proposed that relative saturation is a critical parameter in bio-decontamination processes because it accurately represents the point at which condensation can be expected to occur.

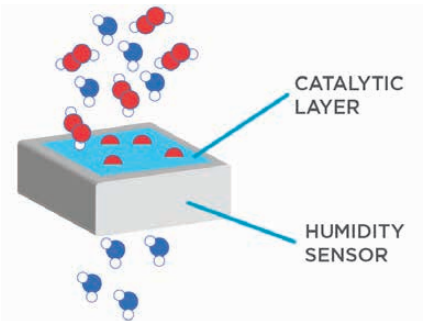

Figure 1: Diagrammatic representation of a humidity sensor with a catalytic layer

Introduction

Because vaporized hydrogen peroxide leaves no residue and is efficient for bio-decontamination in room temperature, it is used widely in applications such as isolators, transfer hatches and in different facilities that require reliable decontamination.

The relationships between temperature, relative humidity and relative saturation

Effective killing of microorganisms can be achieved with different humidity and H_2O_2 ppm levels. Some manufacturers of bio-decontamination chambers or isolators prefer subvisible condensation, whereas others prefer dry bio-decontamination processes where humidity is maintained far from condensation. However, dripping condensation should be avoided due to potentially negative effects on aeration time, materials and uniform decontamination efficiency. Therefore, it's crucial to measure humidity during vaporized hydrogen peroxide bio-decontamination cycles. However, water (H_2O) and hydrogen peroxide (H_2O_2) have a very similar molecular structure. Therefore they both affect the humidity of the air.

Relative humidity by its definition indicates the humidity of the air caused only by water vapor. Therefore, humidity sensors used in vaporized hydrogen peroxide applications typically use a catalytic layer over a normal humidity sensor. The catalytic layer catalyzes the hydrogen peroxide so that the humidity sensor measures only water vapor as shown diagrammatically in Figure 1. The measured relative humidity indicates the humidity of the air caused only by water vapor. When measuring H_2O_2 in a vapor state, relative saturation

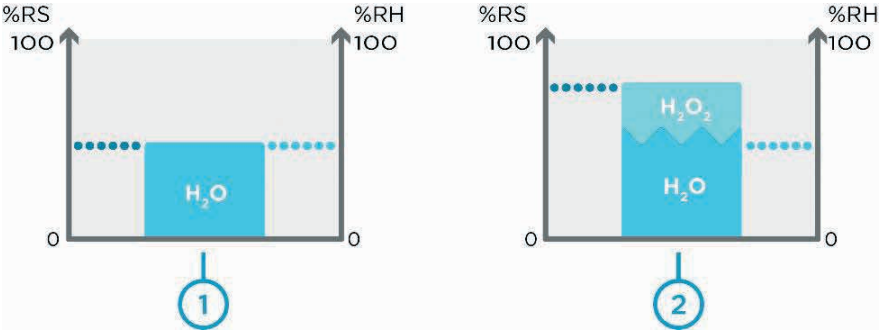

Figure 2: Space 1 without H_2O_2 vapor and space 2 with H_2O_2 Vapor

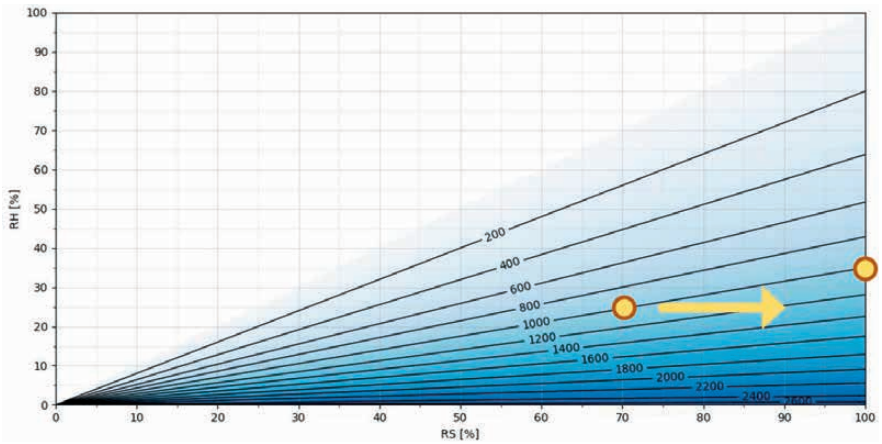

Figure 3: H_2O_2 ppm as a function of RS/RH at T = 25 °C

is the parameter that indicates the amount of humidity in the air caused by both hydrogen peroxide and water vapor. The air mixture starts to condense when the relative saturation reaches 100 %RS. Relative saturation is the only parameter that indicates when the air mixture with the water vapor and hydrogen peroxide vapor starts to condense. Therefore, it is essential to follow the relative saturation value during the bio-decontamination process.

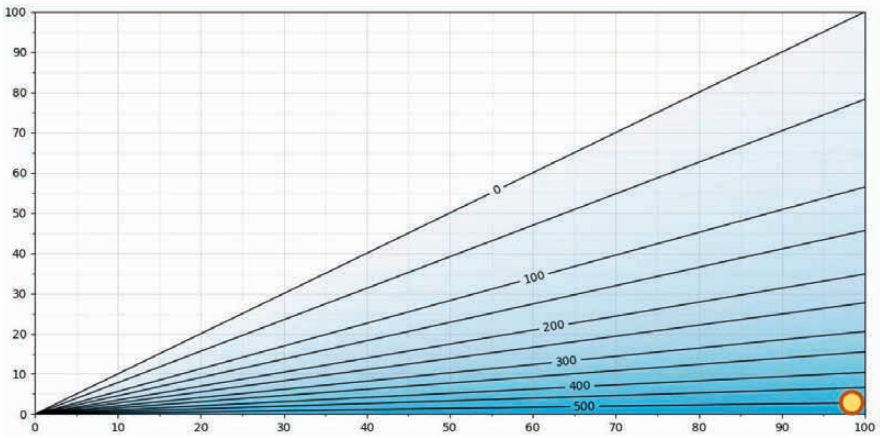

Figure 4: H_2O_2 ppm as a function of RS/RH at T = 5 °C

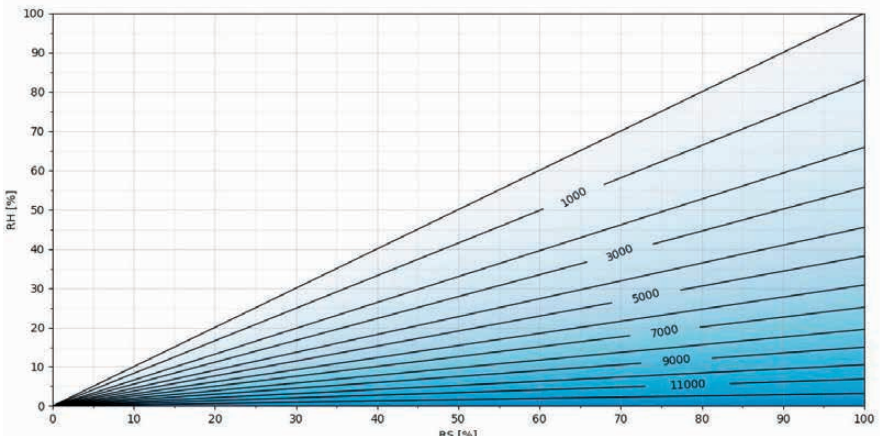

Figure 5: H_2O_2 ppm as a function of RS/RH at T = 50 °C

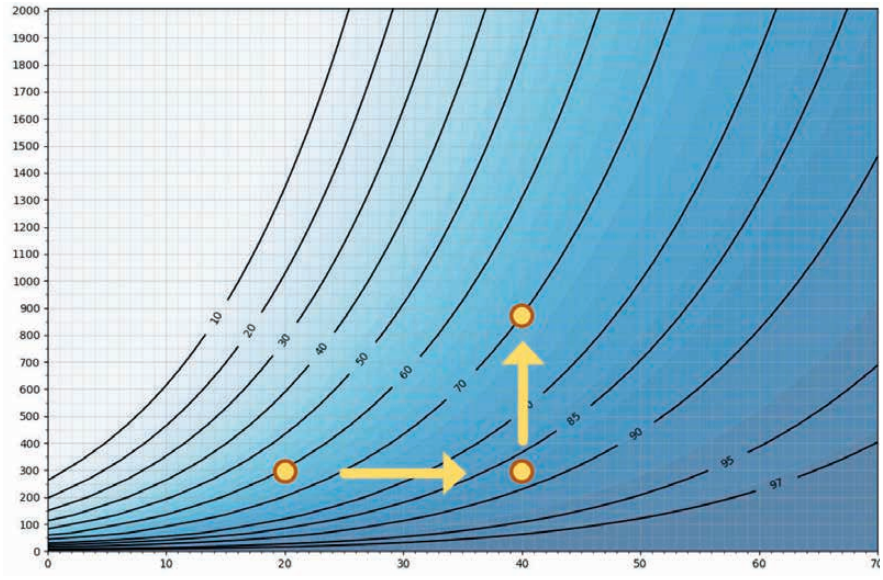

Figure 6: The x axis = temperature, y axis = ppm concentration

Rule: The higher the H_2O_2 ppm, the lower the maximum achievable RH and the greater the difference between RH and RS.

Figure 2 shows two different spaces: space 1 without H_2O_2 vapor and space 2 with H_2O_2 vapor. When H_2O_2 vapor is not present, relative saturation equals relative humidity. This can be seen in space 1. Within space 2, we have the same volume of air with H_2O_2 vapor introduced. Now, relative saturation is higher than relative humidity.

Figure 3 shows you H_2O_2 ppm as a function of relative saturation and relative humidity at 25 °C. Relative saturation is on the x axis and relative humidity is on the y axis. Darker shading shows higher ppm of H_2O_2. As you can see, the more hydrogen peroxide in the air mixture, the greater the difference between relative saturation and relative humidity values. For example, at 25 °C and 1000 ppm hydrogen peroxide, the humidity level 25%RH is equivalent to 70%RS. When this gas mixture with 1000 ppm hydrogen peroxide starts to condense (relative saturation being 100%), relative humidity is 35%.

Temperature affects how much hydrogen peroxide can be in the air before condensation (relative saturation equals 100 %RS). Thus, the graph on Figure 3 changes when temperature changes.

Figure 4 shows same graph at 5 °C. The maximum H_2O_2 ppm level at 5 °C is slightly above 500 ppm. As an example, at 5 °C, 500 ppm hydrogen peroxide and Relative Saturation 100 %RS, the relative humidity is approximately 2 %RH. As the relative saturation is 100 %RS, the air mixture will condense. The difference between %RS and %RH at this temperature is enormous: 100 %RS vs. 2 %RH. Measuring %RH in this particular case is of no real value.

The higher the temperature, the more H_2O_2 ppm can be added to the air mixture before condensation, as seen in Figures 5 and 6. In Figure 5, at a temperature of 50 degrees Celsius, an H_2O_2 concentration of >12000 ppm can be achieved.

Each point in Figure 6 represents a condensation point, I.E. relative saturation is 100 %RS. Temperature is on the x axis and H_2O_2 ppm is on the y axis. The curves show the maximum relative humidity. As an example, at 20 °C and 300 ppm hydrogen peroxide, 60%RH is equivalent to 100%RS. If we increase air temperature to 40 °C with an H_2O_2 concentration at 300 ppm, relative humidity will be 87% and

relative saturation will be 100%. Condensation occurs at a relative humidity of <100% because of the relationship between air temperature and H_2O_2 concentration. Therefore the higher the temperature, the higher the maximum RH%. If we increase the hydrogen peroxide level from 300 ppm to 900 ppm at 40 °C, then the maximum achievable relative humidity decreases from 87 %RH to 70 %RH. The higher the ppm concentration, the lower the maximum %RH.

These figures illustrate why it is insufficient to look only at relative humidity in bio-decontamination processes that use vaporized hydrogen peroxide. Air that is infused with H_2O_2 will condense at <100% relative humidity, depending on the temperature of the air and the concentration of hydrogen peroxide. When the air mixture contains vaporized H_2O_2, relative humidity can never reach 100% making it nearly impossible to accurately estimate when condensation will occur. The greater the temperature, the greater the allowable relative humidity. On the other hand, the higher the H_2O_2 concentration, the lower is maximum achievable RH.

When performing bio-decontamination with vaporized hydrogen peroxide, relative saturation is the only parameter that accurately represents the true saturation level; that is, the point at which you can expect condensation to occur.

To learn more, please visit: www.vaisala.com/biodecontamination or contact Vaisala at www.vaisala.com.

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Assessing microbiological risks in cleanrooms following pharmaceutical facility shut-downs

Tim Sandle

Abstract

Well-designed cleanrooms when operating as intended are invariably in a state of control. There are, however, circumstances that can impact this state of control. Cleanrooms are subject to a greater level of particulate and microbiological risk when they undergo maintenance or where there is a facility shutdown. Such risks are potentially greater with aging facilities. This article considers the controls required to minimise the risks to cleanrooms during shutdowns, including a particular focus on aseptic processing areas, and examines the level of testing required to bring a facility back into use, including the application of sporicidal disinfectants and risk-based environmental monitoring.

Introduction

Once commissioned, well-maintained cleanrooms within the pharmaceutical sector will operate effectively, with the main risk variables being the activities of people and the transfer of equipment and consumables into and out of each area. However, an element of risk is introduced when pharmaceutical facilities undergo shut-down for repairs and maintenance, either to equipment housed within the cleanroom or to the cleanroom itself. Shut-downs can be for planned preventative maintenance, emergency maintenance, for modifications to room design or for the installation of new items of equipment.[1] Shut-down activities can relate to an individual cleanroom or to a suite of rooms or to an entire facility. It is not uncommon for pharmaceutical sites to undergo an annual shut-down to enable modifications to be completed, calibrations to be carried out or new or replacement equipment to be installed.

Regular maintenance is essential in order to ensure that all equipment and processes continue to operate in their validated state and within their defined critical operating parameters. Preventive maintenance includes activities such as pre-planned inspections, lubrication, intensive non-routine cleaning, adjustments, or verification of the proper operation of equipment and utilities. It can also include restoring/upgrading the condition of the facility.[2] As well as maintenance, shut-downs also allow for room modifications to be made. Each activity can present a microbial risk, such as when building works lead to dust generation, when surfaces are exposed, when water is used or when unsanitary items are introduced into the cleanroom. Microbial risks also arise when air handling units are deactivated, resulting in increases to particle levels and the inability of a room to 'clean-up' through operating with adequate ventilation.[3]

This article considers some of the microbiological risk factors as cleanrooms undergo works and are then reinstated.

Risk assessment

All cleanroom modifications during shut-down periods should be covered by a risk assessment. The use of a proactive risk assessment is in keeping with regulatory expectations, as set out in document ICH Q9 *Quality Risk Management*.[4] The level of risk will vary with the extent of the work, with like-for-like replacements of small items being the lowest risk. Beyond this, risks will differ. A new item of equipment presents a validation risk, in that the qualification may not be successful, whereas a major modification to a cleanroom, such as knocking a wall down to make a room bigger, will create dust, presenting a major particulate and microbiological risk.

All risk factors should be assessed. In the context of this article this may include assessing whether there is a risk of dust generation or a microbiological risk from cutting into a water system. Risk assessments should be documented, use pre-agreed criteria, and be written with the involvement of a multi-disciplinary team.

Modifications to facilities

In order to provide an overall level of control, modifications to facilities should be undertaken using clean construction protocols.[5] Such protocols outline the scope of works and stand as an agreement between the contractor and the test facility.

Elements of a protocol include:

- Assigning a project manager to manage the works.
- Setting up a process for issuing permits to work.
- Defining personnel and staffing levels.
- Ensuring the training of contractors is undertaken according to company procedures.
- Ensuring there is a secure access system in place for the control of personnel in and out of the facility.
- Agreeing the clothing standard required for contractors (such as full cleanroom gowns or clean suits).
- Maintaining a personnel database.
- Ensuring protocol related signage is in place.
- Establishing control of materials.
- Agreeing temporary routes for material entry and gown rooms.
- Monitoring material and gown entry procedures.
- Agreeing the level of environmental monitoring, including particle counts, temperature and humidity and maintaining databases.

Where works are being carried out and parts of the operation are continuing, or where there is a need to contain contamination within the affected area so as to minimise dust, a clean zone construction area is often designated through the use of barrier walls (such as those created using plastic sheeting) and positive or negative pressure used to prevent any contamination from entering or from leaving the designated construction area. Particle counters can be employed during each construction process or stage to test for actual particulate levels either in the area undergoing modification or adjacent areas of concern.

Ageing facilities

The risks associated with shut-down activities are arguably greater for older or ageing pharmaceutical facilities. There is no exact definition of ageing facilities (or what are sometimes euphemistically called legacy facilities). A plant, for example, established one hundred years ago to manufacture a simple tablet may, with careful upkeep and an eye on developing regulations, continue to operate perfectly well. In contrast, a biotechnology plant, established ten years ago, may become out-of-date if it cannot adapt to a necessary process change, such as the addition of a viral inactivation step, a change to product formulation or the need to meet a new regulatory recommendation.[6]

There are often commercial and compliance reasons for continuing to maintain or even upgrade older facilities. Significantly, facilities that pre-date more modern practice, such as the application of Quality by Design,[7] face a greater risk of not being able to adapt to future opportunities or threats.[8] These types of facilities may be under greater risk of microbial contamination and hence require more careful management during shut-down and start-up. As an example, poor upkeep, leading to peeling paint or torn lagging, presents opportunities for microbial contamination to occur. Risks are more acute for spore forming organisms, such as *Bacillus* and related genera and fungal spores.[9]

Repairing equipment

Repair or corrective maintenance for an item of equipment includes all actions intended to fix or replace a specific item that is broken or no longer functioning properly. In such instances, it is extremely important that precautions be taken so that product quality is not compromised. When repairing equipment, the following issues should be considered:

- Was any part of the last batch processed, or of earlier batches, directly affected by the breakdown or failure, e.g. overheating, intermittent operation, incorrect temperature readouts, failure to clean or disinfect leading to microbial bioburden, etc.? What evidence supports this?
- Was the repair carried out in a manner that ensured that there was no microbial contamination? What evidence supports this?
- Has the processing system been restored to acceptable operating conditions? What types of microbial and chemical samples will be taken to support this? A particular risk arises when water systems are modified, such as changing valves or where pipework needs to be cut into. To assess the risk of biofilm formation, the section of the water system affected, such as a loop or sub-loop, should be isolated, and bioburden and endotoxin samples taken and assessed prior to that section being reconnected.

Typically, the verification that the modified (or new) item of equipment can be effectively cleaned and disinfected is required. This is undertaken through cleaning validation. For a microbiological assessment this will comprise surface assessment (taking swabs) to assess how many microorganisms remain adhered to the surface material and, in the case of water, final water rinses to ensure that the final water is of the required microbiological quality and meets, for example, the Water-for-Injection standard of not more than 10 CFU/100mL.

Equipment generated particles

Equipment can be a source of particles because of the age of the equipment, or poor maintenance of the equipment, or the general unsuitability of the equipment itself. Sometimes equipment placed in cleanrooms is not of a suitable design. This has been the case despite claims from some manufacturers that the equipment is suitable for use in an area of a given EU GMP grade or ISO class. In the context of this article, the concern is with new items of equipment purchased and installed during the shut-down period.

To assist with the purchasing process, especially the drawing up of a User Requirement Specification (URS) and later assessment, ISO 14644–14 (2016) *Assessment of suitability for use of equipment by airborne particle concentration*[10] can assist with the determination of the suitability of an item of equipment used in pharmaceutical processing, such as a mixing bowl, centrifuge, vessel or Clean-in-Place (CIP) unit. In drawing up an URS, attention needs to be paid to the materials of construction which should be smooth, cleanable, with low particle emissions, suitable for the operating conditions of the cleanroom (i.e. temperature and humidity), resistant to cleaning and disinfection agents and, where required, have low electrostatic properties to avoid particles adhering to the equipment. Equipment should be fitted with suitable seals and use appropriate lubricants.

ISO 14644–14:2016 specifies the methodology that can be used to assess the suitability of equipment in terms of its contribution to airborne particle cleanliness. The level of control required will depend on the class of the cleanroom. ISO 14644–14 covers particle sizes ranging from 0.1µm to 5.0 µm (within the pharmaceutical context particles of ≥0.5 µm and ≥5.0 µm will need to be assessed). The focus of the standard is with undifferentiated particles, which means that biocontamination is not specifically mentioned.

Cleaning and disinfection

Cleaning and disinfection plays a critical role in minimising microbial contamination; therefore the use of detergents (to remove soil) and disinfectants (to kill microorganisms) are a fundamental part of cleanroom operations. It is often good practice to clean and disinfect during the shut-down activities, in addition to deploying measures for the removal or materials and for dust control. Coming out of the shut-down a series of cleaning sessions will be required, since the removal of dirt is essential for later disinfection. Most disinfectants have no cleaning ability and all have poor penetrative capability on the different types of soiling that act as a barrier thus preventing the disinfectant from reaching the microbial cell. When selecting the appropriate disinfectant to use, a sporicidal product should be selected (such as chlorine dioxide, hydrogen peroxide or peracetic acid). This is due to the increased risk of bacterial spores, especially where concrete has been exposed or where panels have been opened, and fungal spores where any part of the facility has been exposed to the external environment.[11]

Care must be undertaken when performing cleaning and disinfection, for example checking that the cleaning

and disinfection sequence does not contaminate already clean surfaces.

Cleanroom recertification

Where a cleanroom has undergone modification, or where HEPA filters have been replaced, or where cleanroom parameters have been adjusted, the cleanroom should be recertified by a suitable contractor. This process will provide data about the particle cleanliness and the ability of the room to deal with a contamination event (in relation to air exchange rates and clean-up times). Such information is of great value when assessing the results of microbial environmental monitoring. The assessment can be helped if earlier data is available that has assessed the time the system takes to recover and operate within specified conditions, especially particle concentrations.

Microbiological environmental monitoring

Microbiological environmental monitoring is a combination of airborne particle counting and viable monitoring (air and surface sampling), where the emphasis upon control is through an assessment of trends. Conducting monitoring to a defined risk-based sampling plan and at a sufficient frequency will provide a benchmark to assess the state of the facility coming out of a shut-down against the situation prior to the start of the shut-down. At the end of the shut-down period, following cleaning and disinfection, cleanrooms should be monitored. The scope of monitoring will depend on the type of works undertaken. The normal set of samples (where locations are typically risk-assessed and orientated towards assessing risk to product) may or may not be suitable depending upon the work undertaken. This is because the focus of the monitoring is to assess the impact of the works on the cleanroom. Ideally monitoring will be carried out both in the unoccupied state (to assess immediate impact of the works and to assess cleaning efficacy) and during operations (to show that the room modifications have not had an adverse impact on the ability of the cleanroom to deal with airborne contamination). Where major works have taken place, such as knocking down of walls, several monitoring sessions in succession may be required in order to give confidence that the cleanroom is in control. It is beneficial to start sampling a few days prior to production start-up.

With the multiple session approach following major works, some organisations will run three or more sampling sessions; others take a more focused approach, to examine cleaning and disinfectant efficacy. This process[12] runs as follows:

1. After an initial clean-up, surfaces are sampled.
2. The cleanroom must then be disinfected and sampled again.
3. The cleanroom should be thoroughly disinfected (second disinfection) and sampled a third time.
4. If the results are unsatisfactory, a third disinfection will be required (and the cleanroom sampled again).

In addition to monitoring the cleanroom where works have taken place, consideration will need to be given to adjacent rooms where no activities have directly taken place. Areas located close by may have been subjected to airflows carrying particles, or contractors may have traversed these other areas to reach the works location. Hence, the scope of environmental monitoring may need to be extended.

The limits assigned should be the standard alert and action levels used for normal operations, given that the objective of reinstatement monitoring is to assess the cleanroom's suitability for normal operations. Where out-of-limits results are recorded, different actions will be required. Such actions will vary depending upon whether the contamination is airborne (which may indicate concern with a cleanroom operational parameter) or surface (which draws attention to an issue with cleaning or disinfection practices). In all cases of out-of-limits results, repeat samples should be taken to assess whether the result was due to an isolated event or if it signals an issue of on-going concern. Typically, three to five repeat sampling sessions are held and it is prudent not just to repeat the location of concern, but all of the samples within the room.

With microbial recovery, as well as assessing numbers of microorganisms recovered data should be reviewed for the recovered microorganisms. The microbiota coming out of the shut-down should be compared with the profile leading up to the shut-down. Where atypical organisms are recovered, such as bacterial or fungal spores, this will most likely signal that residual contamination remains in the area following the maintenance work and further applications of sporicidal disinfectant are required, followed by further monitoring.[13] Some users elect to undertake monitoring during the shut-down, in order to gain some data about spore risks. The appropriateness of this depends on the length of the shut-down relative to the time needed to cultivate, incubate and identify the recovered microorganisms.

The point at which a cleanroom is returned to production use differs according to company policy. Some companies assess particle counts and review overall cleanliness and return cleanrooms for use 'at risk' while viable environmental monitoring samples are incubating. The proviso is often that product will not be released until all viable results have been assessed and deemed to be satisfactory. Other facilities will be more cautious and wait for viable samples to be read following their incubation. The balance between these two approaches may depend upon the extent of the works undertaken and the relative risks. Another deciding factor may be the grade of the cleanroom, with greater caution applied to sterile manufacturing facilities.

Aseptic processing areas

Changes to aseptic processing areas require careful assessment, particularly where there could be an impact on airflow (air direction or air velocity) in relation to EU GMP Grade A / ISO 14644 class 5 environments. This could arise from a factor directly affecting the control of air (such as a replacement HEPA filter or control instrument) or with something that might impede the airflow, such as a modification to machine guarding or the fitting of an additional item within the clean zone, such as a CCTV camera. In such circumstances the airflow requires reassessing by means of an airflow visualisation test, where the objective of the study is to confirm that satisfactory unidirectional airflow has been maintained.[14]

Changes to production equipment and layouts can affect airflow directions, especially in relation to aseptic processing. The addition of more equipment to a working space can cause greater heat generation, placing a greater heat load upon the air conditioning. If environments are not suitably controlled, this can cause personnel to shed higher levels of skin and thus increase the microbial load into the cleanroom. Additionally, as amounts of equipment increase this can make areas more difficult to clean and disinfect simply because operators cannot manoeuvre around the equipment. Poor air circulation also brings with it other risks, such as undetected fungal growth.

With aseptic processing lines, consideration should be given to running media simulation trials. With filling lines, at least three consecutive separate successful runs are necessary for initial line qualification. This is applicable also for revalidation following major changes to the equipment/process/product contact components, or whenever there are doubts about the ability of the aseptic process to exclude contamination. In relation to a shut-down, both of these scenarios could apply: the line may have been modified and hence requires re-validation, or works may have taken place which could impact on the aseptic operation (such as room modifications or changes to room airflow rates). As well as a 'start-up' media fill, some organisations elect to run a 'pre shut-down' media fill (that is a media fill run just prior to the shut-down taking place). The argument in favour of a pre shut-down media fill is that if the post shut-down media fill were to fail (microbial growth recorded in one or more vials) it could be difficult to determine whether the failure was due to a shut-down related modification or due to a pre-existing but, as yet, unidentified weakness with the aseptic process. The pre shut-down media fill also verifies product filled on the line up to the start of the shut-down.

Summary

This article has considered the microbiological risks faced by a pharmaceutical facility implementing a partial or full shut-down, during which time maintenance works or the installation of a new item of equipment takes place. While various measures can be taken to ensure 'clean construction', cleaning and disinfection during the shut-down is necessary and coming out of the shut-down it is essential. Invariably, as highlighted, a triple clean and disinfection sequence is required for each room. Verification of the reinstatement of the facility is through the execution of an environmental monitoring programme (including a short series of repeated sampling sessions to ensure that the area corresponds fully to the set cleanroom classification) and assessment of the data, where not only does the quantity of recovered microorganisms need to be in control but also the types of species, and there needs to be an absence of spore forming organisms.

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Latest draft of EU GMP Annex 1 signals changes for cleanroom management

Tim Sandle

Abstract

EU GMP Annex 1 is currently going through a detailed revision process. In February 2020 a new draft was issued, with the final version expected later this year. The latest revision carries implications for cleanroom design and operations. The draft Annex introduces a new viable count qualification expectation; provides a Grade D particle count 'at rest' limit for the first time; and strengthens personnel controls. This article looks at these changes along with other expectations for cleanrooms and clean air devices.

Introduction

Considerable time has elapsed between the European Medicines Agency (EMA) issuing drafts of Annex 1 to EU GMP. The first draft (without a version number) was released for widespread public comment on 22nd December 2017[1] (designated to replace the current Annex, which was last revised in 2008).[2] This draft was subject to widespread public consultation, which resulted in over 6,000 comments being submitted to the EMA. A new draft, numbered version 12, the first indication of changes made in response to the comments has now been issued (on 18th February 2020).[3] This time around, only specific sections can be commented on and then only by approved professional bodies over the course of three months. The more restricted approach signals that the Annex is close to being locked-down and the finalised version issued.

There are, however, a number of changes made to the February 2020 draft compared with the December 2017 version. This article considers those changes which impact upon cleanrooms, clean air devices, and contamination control.

Aim of the new Annex

The aim of Annex 1 is to set out the minimum standards for the manufacture of sterile products (both aseptically filled and terminally sterilised), which takes place within cleanrooms and barrier devices. There is a major focus within the Annex on the need for a contamination control strategy,[4] purposefully designed for each facility; and for each manufacturer to be using the principles of quality risk management.

While there are several essential points to consider for the contamination control strategy, those that appear to be given the greatest weighting (from this author's reading of the text) are:

- Maintaining the critical processing zone.
- The aseptic assembly of filling equipment.
- Aseptic connections (these should be sterilized by steam-in-place whenever feasible).
- Special focus on aseptic compounding and mixing.
- The risks abound the replenishment of sterile product, containers and closures.
- Concerns around the removal and cooling of items from heat sterilizers.
- Staging and conveying of sterile primary packaging components.
- Aseptic filling, sealing, transfer of open or partially stoppered vials, including interventions.
- Loading and unloading of a lyophilizer.

It is unsurprising that each of these relate to aseptic processing, the highest-risk area of pharmaceutical manufacturing.

The previous draft of the Annex was reviewed by this author for CACR[5] and the aim is not to repeat those aspects that have not changed between the two drafts; instead the focus is to outline what differs in relation to cleanroom operations and management.

Main changes in the new draft for cleanrooms and clean air devices

Cleanroom design and qualification

Compared with the previous draft of the Annex, reference continues to be made to Annex 15 of the EU GMP guide ("Qualification and Validation")[6] in relation to ensuring that equipment has been suitably qualified. However, the reference to the ISO 14644 standard has been dropped (except for particle counts) and instead the text makes reference to the specific series of tests required when a cleanroom is qualified. These tests are (where relevant to the design):

- Installed filter leakage and integrity testing.
- Airflow measurement - Volume and velocity.
- Air pressure difference measurement.
- Airflow direction and visualisation.
- Microbial airborne and surface contamination.
- Temperature measurement.
- Relative humidity measurement.
- Recovery testing.
- Containment leak testing.

Notable here is the task of microbiological monitoring to assess cleanroom suitability (described as a determination of "microbiological concentration"). This would involve using established sampling methods (active air samples, settle plates and surface samples) with a risk-based method used to determine appropriate sampling locations.[7] Adding this microbiological aspect to the qualification of cleanrooms is being addressed in the biocontamination control standards ISO 14698[8] (under review) and EN 17141[9] (in preparation) and is a required part of the issuing of cleanroom certificates under the new draft Annex 1.

With particle assessments, the Annex keeps the requirement to count airborne particulates equal to or greater than 0.5 and 5 µm. However, for Grade A zone and Grade B at rest, classification only needs to be for particles equal to or greater than 0.5 µm (hence the argument

about the statistical limitations of measuring larger size particles which formed part of the 2015 ISO 14644 Part 1 update seem to have been accepted). The measuring of larger size particles for Grade A and Grade B areas is referenced as something that can be considered. The cleanroom classification expectations apply to the 'at rest' and 'in operation' states. With the 'in operation' state there is a suggestion that for aseptic processing areas that the exercise is undertaken during media fills, in order to represent worst-case.

For selecting particle sampling locations the draft Annex states that the ISO 14644 methodology is to be followed, along with the additional expectation that, for aseptic processing areas, sampling locations are positioned so that all critical processing zones like the point of fill and stopper bowls are included and based on a documented risk assessment.

Whilst there are no changes to requalification intervals (Grades A and B six-monthly and Grade C and D annually) additional text has been added stipulating that re-qualifications should be undertaken following any remedial works needed on equipment or where the facility requires work or where new equipment is added to the cleanroom, as assessed through change control. Other reasons for undertaking a re-qualification include change of room use and following a loss of power.

Outside of classified cleanrooms, reference is made to 'controlled but not classified areas'. Here the movement of material from controlled but not classified to Grade C needs to be based on risk management principles, which means that the level of cleaning and disinfection and the control of materials needs to be commensurate which the level of risk assessed.

Cleanroom occupancy

An emphasis throughout the Annex is placed on the numbers of operators permitted in cleanrooms and changing rooms. For aseptic processing areas, the media fill sets the maximum numbers, whereas for other cleanrooms the expectation is that this is assessed through a risk assessment.

New guidance for Grade D

For the first time the draft Annex provides guidance for Grade D particles, albeit for 'at rest' rather than for 'in operation'. Here a value of 29,000 particles for the ≥0.5 µm size particle is provided as the limit. The current Annex simply lists Grade D particles as 'separately determined', with no further guidance supplied.

More flexibility over unidirectional airflow velocity

The draft Annex offers more scope with unidirectional airflow velocities (notably 'unidirectional' is now consistently used throughout the text and all references to the archaic term 'laminar' expunged). With air speed, while the range of 0.36 – 0.54 m/s remains the general requirement at working height, this is presented in less stringent terms. Hence there is scope for companies to design and operate clean air devices outside of this range provided that this is scientifically justified and detailed in the contamination control strategy. Included in this justification is the location for measurement and verification as to the appropriateness of the air speed as supported by airflow visualisation studies ('smoke studies').

The draft Annex requires that following an adjustment to air velocities for qualified devices that part of the acceptance of the adjusted volume includes an airflow visualisation to be conducted. For isolators that are 'closed' the Annex acknowledges that the airflow may not necessarily be unidirectional.

Barrier technology

The Annex does not go as far as mandating the use of barrier technology; however, there is a recommendation that manufacturers consider adopting "appropriate technologies", such as Restricted Access Barriers Systems (RABS) or isolators. The recommendation extends to consideration of robotic systems, which will reduce the need for human intervention. With the emphasis upon barrier technology the Annex requires that any alternative must be robustly risk assessed.

With isolator technology, the text states that entry of materials during processing should be minimised and preferably be supported by rapid transfer technologies or transfer isolators. Gloves are recognised as the weakest point with an isolator system, so consequently there is the requirement for glove leak testing at a minimum interval of before and after each batch. Also with gloves, there is reference to the importance of selecting the correct isolator gloves; those with good mechanical and chemical resistance.

Environmental conditions

The current version of the Annex sets limits for temperature for Grade B areas. This limit is no longer stated, and instead there is the requirement to adopt a risk-based approach for setting temperature and humidity requirements for any cleanroom grade. While the draft Annex does not go into specifics, maintaining operator comfort is important for both the operator and reducing excessive skin cell shedding into the environment.

The current Annex requires all connections for aseptic processing (such as vessel to manifold) to be performed under Grade A. The draft acknowledges advances in sterile processing technology, permitting aseptic connections that use intrinsic sterile connection devices, designed to minimise any potential contamination from the immediate environment, to be performed in lower classified environments provided that the connection device has been appropriately validated to show no ingress of microbial contamination.

Viable monitoring

In relation to viable monitoring expanded information is provided in relation to sample site selection, stating that this needs to be risk based and, where applicable, determined through a review of airflow visualization studies.

A change is made to the EU GMP Grade A limit; which changes from 1 CFU to 'no growth'. This change is both a reflection of the expectation that microorganisms are not typically recovered from Grade A environments (and that every recovery requires an investigation) and with the different types of techniques that could be applied as replacements to the classic culture-based methods (the use of rapid and alternative microbiological methods are permitted provided the facility has demonstrated their equivalency or superiority). There are no other changes to microbiological limits.

A further change with the tone of the Annex in relation to environmental monitoring is the requirement for continuous monitoring. This is mandatory for Grade A and recommended for Grade B. By continuous monitoring this means air samples (either settle plates or volumetric air samplers).

Gowning and Operator qualifications
The requirements for entering changing areas for access into Grade B and C areas have been strengthened. The draft now states that outdoor clothing (other than personal underwear) cannot be brought into changing rooms (whereas in the previous draft this was a 'recommendation'). Changes include the need for suits to be full sleeves for Grade C (this always the case for Grade B) and for cleanroom socks to be worn for both grades prior to entry as part of the process to minimise contamination entering the change areas. In terms of what is not permitted to be taken into clean areas, the Annex now calls out mobile devices (reflecting the ubiquity of smartphones and the like).

For cleanroom operators entering aseptic processing areas a gowning test is required (which is a combination of visual assessment and microbiological monitoring). The new draft expands the list of recommended locations on an operator's gown that require monitoring as part of the gowning qualification: hands, arms, chest and forehead. Each one of these locations presents a different microbial contamination risk, in terms of the types of organisms and the route of contamination transfer. In addition, microbiological limits are presented for gown plates for the first time (these are afforded the same maximal values as finger plates).

Finally, with gowning, the new draft now requires the maximum time that a gown can be worn for to be defined.

Suitably qualified personnel
All staff working in cleanrooms are expected to have knowledge of hygiene, cleanroom practices, contamination control, aseptic techniques, and potential safety implications to the patient of a loss of product sterility and in the basic elements of microbiology. As well as requiring that personnel are suitably qualified to work in cleanrooms, the new draft of the Annex states that each facility must have staff who are specifically experienced in microbiology, environmental monitoring regime and with conducting microbiological investigations.

Other changes
Other revisions to the Annex which impact on operations conducted within cleanrooms include additional information about media fills (aseptic process simulations), where more 'time based' criteria have been added (such as assessing filling machine hold times and sterilised equipment hold times as part of the exercise). Greater detail is provided for assessing the success of autoclave operations, such as the requirement to inspect sterilised packaging for its integrity and dryness. Such changes are designed to strengthen controls around sterile products manufacture.

The Annex does not go as far as mandating the use of barrier technology; however, there is a recommendation that manufacturers consider adopting "appropriate technologies", such as Restricted Access Barriers Systems (RABS) or isolators. The recommendation extends to consideration of robotic systems, which will reduce the need for human intervention.

The controversial issue of pre-use post sterilization integrity testing (PUPSIT) has been softened for small volume products, with a list of criteria to be taken through a risk assessment provided so that a risk-based alternative to this stage of filter integrity testing can be considered as an alternative.

General updates
With general updates to the text the terminology has been tightened up. Gone are confusing references to "Grade A/B", "Grade A conditions", "Grade A air", or to "critical areas". Now exact cleanroom grades are specified. In terms of what has not been addressed is the background grade for isolators; this is left to the user to decide. Some guidance as to Grade C or D would have been helpful. Furthermore, it remains that the requirements for classification and 'routine' monitoring are contained in different sections and separated by twenty or so pages.

In the new draft, the section on disinfectants is far more detailed than in the current Annex, with references to rotation with a sporicide and the need to qualify each disinfectant against different surface materials. There are also references to the use of single-use systems (SUS) and technologies, which continue to be encouraged, albeit with the caveats that the adsorption and reactivity of the product with product contact surfaces under process conditions is carefully understood and the extractable and leachable profile of the SUS and any impact on the quality of the product is evaluated.

Summary

The new draft Annex (version 12) is a step-forward from the previous draft in relation to cleanroom management, with greater clarity and with some of the concerns being addressed. The text will, however, not satisfy all parties and the window is open for additional comments to be made. How different the final draft will be is a matter of conjecture. The key takeaways of interest to CACR readers would appear to be:

- The expectation for each facility to have in place a formal, holistic contamination control strategy, focused on minimising contamination control with respect to sterile manufacturing.
- Additional requirements for cleanroom qualification (beyond ISO classification which relates to particle concentration only).
- A major focus on risk-based approaches.
- Recommendations for the wider use of barrier technology.
- A focus on personnel controls, such as gowning, and training.

Nonetheless, the broad requirements are unlikely to alter greatly and sterile product manufacturers and equipment providers to the pharmaceutical sector should be getting to grips with the forthcoming changes and putting in plans to meet the new requirements.

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Tim Sandle's biographical note may be found on page 13.

An update on 14644 Cleanroom Standards: Parts 8, 9, 10 and 16

Dick Gibbons, Convenor ISO TC 209 Working Groups 8 and 13

Parts 8, 9 and 10 to be updated in 2020

The ISO family of International standards are reviewed periodically for updating, replacement or in some situations total removal. This ensures that the content remains practical and up to date.

Recently ISO 14644 Parts 8, 9 and 10 reached this milestone and ISO TC 209, the ISO Technical Committee responsible for the ISO 16444 series of standards, decided to redefine them so that they are no longer described as Cleanroom Classification standards. The work was assigned to ISO TC 209 Working Group 8. The decision was taken in order to clarify the position that ISO 14644 Classification relates only to levels of airborne particulate measured within the cleanroom. Parts 8, 9 and 10 were designed to quantify the additional, optional attributes of airborne chemical, surface particulate and surface chemical contamination present in the room. Measurement of these specific attributes is not required for all cleanrooms and there has been some confusion concerning what constitutes classification and a classified cleanroom.

Accordingly, the term 'classification' will be removed from the three documents and replaced by the term 'assessment'. This will allow airborne chemical concentration and surface chemical and particulate residue to be quantified and ratified where necessary. There will be a change of title from Classification to Assessment for each of the three standards. There will be no changes to the technical content or to the recommended methodology originally used to establish the classification levels. All charts, graphs and grading lists have been renamed retaining the original demarcation levels. International document preparation work is currently in process and the new standards should be released by the end of this year.

Part 16: Energy efficiency in cleanrooms and separative devices, released in May 2019

This document was produced by ISO TC 209 Working Group 13 as an international progression of UK's BS 8568:2013 - Cleanroom energy – Code of practice for improving energy efficiency in cleanrooms and clean air devices. As an international document it contains much additional material, focusing closely on the formulae and methodology for defining airflow volumes for cleanrooms. It also introduces the concept of benchmarking to encourage the comparison of energy consumption between companies using established energy measurement criteria. An extra annex defines the metrics used in France, Holland, the US and ISO itself to establish the agreed evaluation parameters. Other sections draw extensively on the experience of cleanroom experts from Australia, Europe, Japan, Russia, Scandinavia and USA. These are supplemented by the recent experiences of our UK experts in this field which enabled large reductions to be achieved in reducing airflow volume for critical industries.

As in BS 8568, the new document identifies airflow conditioning and airflow circulation as the main contributors to cleanroom energy cost. The document further develops the parameters for the airflow volume calculation by moving away from the traditional air change rate methods as used in the 14644-4:2001 cleanroom design guide. These often lead to excessive and wasteful results. Airflow volumes may now be determined by an accurate assessment of particulate loading challenges, related to the type of garment worn and particles generated in the process. The prediction is further improved by estimating the ventilation effectiveness of the room design for factoring into the calculations and by allowing a contingency factor to be used with the result. Where appropriate, a suitable REVHA Contamination Removal Efficiency factor may also be used.

Proving work should then be carried out in the cleanroom using an iterative testing system developed in Russia by Professor Fedotov. This allows the various factors to be adjusted in order to arrive at an optimum result. Essentially the cleanroom is tuned for economic performance.

The new document also covers the significance of correct gowning, education and training in energy conservation whilst retaining the maintenance, leak prevention, filter and motor selection material used in BS 8568. The reduction technique selection tables are also retained to illustrate the benefits or dangers of certain reduction techniques.

Most of these new principles are supported by reference to the original work carried out to establish theoretical and practical low volume air flow production by experts such as Bill Whyte and Nigel Lenegan in the UK and Wei Sun in the US. The bench marking work was pioneered in France by ASPEC and the EDF as a major industrial study and we are fortunate to have shared in their results in the development of this new document.

Dick Gibbons, CEng, IMechE, FSEE, has an extensive career in contamination control and runs a consultancy specialising in the processing of cleanroom product. He has been a major contributor to the work of BSI LBI/30 and ISO TC 209 for many years and he is or has been Convenor for all the BS and ISO Working Groups for all the standards in this report, with the exception of ISO 14644-9:2012, where he was the UK technical expert

An update on 14644 cleanroom standards: Parts 14, 15 and PWI 23294

Richard Roberts, UK Expert to ISO TC 209 Working Group 11

Overview

Within the activity scope of ISO Technical Committee 209 (ISO/TC 209), Working Group 11 has been tasked with preparing standards under the subject heading of "cleanroom suitability".

Commencing in 2012, the working group has created and published two cleanroom suitability standards, and is currently working on a PWI (Proposed Work Item) for a third.

ISO 14644-14:2016 Cleanrooms and associated controlled environments – Part 14 Assessment for suitability of use of equipment by airborne particle concentration

By following the normative section of the standard for a candidate piece of equipment, used in a representative manner, it is intended that a suitability statement can be generated following comparison to cleanroom classification levels for airborne particles. The testing procedure initially identifies the location of any high particle concentration zones in a qualitative manner. This allows both a judgement of where high particle concentrations are located in relation to product locations, and importantly, ensures that at least one high particle concentration zone is included in the subsequent quantitative particle concentration test matrix, for all agreed zones around the equipment.

As the standard does not normatively address microbiological cleanliness attributes, or determine overall emission rates, it is likely that the standard will be more widely used within the Microelectronics, Aerospace, Optics and Semiconductor sectors.

Published in 2016, the next systematic review of this standard is currently scheduled for July 2021.

ISO 14644-15:2017 Cleanrooms and associated controlled environments – Part 15 Assessment for suitability of use of equipment and materials by airborne chemical concentration

For a candidate piece of equipment used in a representative manner; or a material sample tested in a representative form, the intention is to enable a suitability statement to be generated by comparison to cleanroom concentration levels, for airborne chemicals, for an agreed chemical species.

It should be noted that TC209 has passed a resolution to ensure that cleanrooms and controlled environments shall be classified using airborne particle concentrations only. The intention is to revise 14644 parts 8, 9 and 10 so that they become standards to determine assessment levels, rather than classification levels, for attributes such as airborne and surface chemicals and surface particles.

Within 14644-15, the testing procedure has three sampling environments described in order to assess emission rates:

- Closed design. The equipment or material is contained within the testing environment
- Closed design, special application. Usually for material samples, e.g. sheet materials for construction, whereby the material sample forms part of the test enclosure.
- Open design. Suitable for larger scale or operational equipment, where the test environment can be a cleanroom or controlled environment.

It is most likely that this standard is applicable to the Microelectronics, Aerospace, Semiconductor and Optics sectors.

Published in 2017, the next systematic review of this standard is currently scheduled for October 2022.

ISO Proposed Work Item (PWI) 23294: Assessment of suitability of consumables for use in cleanrooms

Unlike 14644-14 and 14644-15 this proposed standard will not provide a mechanism whereby the cleanliness attributes of a consumable item can be related to a particle classification level or chemical assessment level for a cleanroom or controlled environment. The intention here is to provide a rigorous comparison procedure between documented customer requirements and supplier design attributes and requirements for a given consumable use case. Broadly the comparison involves attributes within the following groups:

- Functional properties
- Cleanliness attributes
- Special properties

Consumable items are considered in two groups; personal and non-personal items. It is intended to be able to make a selection of a consumable, either following a straightforward comparison of readily available data, or through the incorporation of additional specific test data for a consumable destined for more critical applications/environments.

The PWI aim is to develop a standard that is applicable for use within all cleanroom user sectors.

It is foreseen that the PWI will be submitted to the TC before the end of 2020. If accepted as part of the 14644 family of standards (possible part 18), it is anticipated that the international review, comment and amendment stages leading to publication will be completed by 2023.

Richard Roberts has over 30 years' experience, primarily within the micro-electronics sector and has undertaken a variety of technical and management roles in both the development and the manufacture of contamination sensitive products and their processing equipment. He has been a member of BSI LBI/30 since 2008 and has served as the UK technical expert on two ISO TC 209 working groups including Working Group 11 covering the standards in this report.

"Honey I shrunk the cleanroom"

James Akers

Abstract

This article comprises comments from James Akers received directly by Tim Coles as four e-mails in response to the publication of his article "*Standards for pharmaceutical isolators: an overview*" in CACR40. The comments are reproduced here in the form of an informal article by kind permission of James Akers and Tim Coles. The proposal for specific isolator standards is supported, since isolators are very different from cleanrooms. There is concern about using log 6 reduction as the target for bio-decontamination, and the value of continuous environmental monitoring is questioned. It is suggested that an isolator standard might be developed with international co-operation.

Comments from e-mail 1

I certainly think you are on to something with the idea of taking isolators out of the cleanroom sphere of ISO 14644 and creating their own space. I think an argument can be made that isolators and perhaps some other separative environments are different enough from manned cleanrooms to be served best by their own unique standards. The entire "honey I shrunk the cleanroom" notion of isolators which dates to the 90s is wrong. While there are common principles in some respects isolators are different enough that linking them to clean room air quality requirements will eventually stifle innovation, in fact I'd argue that doing so already has had a chilling effect on innovation.

I think in somewhat different ways we are both arguing for the uniqueness of isolators and we are both highlighting the performance aspect of these attributes. Also, as I think about this more I think we can begin to develop some engineering "control points" to supplant a fruitless reliance on clean room monitoring, which is rather pointless in the context of isolators given their design and operational considerations (absent people).

Comments from e-mail 2

I'm very interested in your thoughts because I am very concerned that the advantages of isolators have not been fully recognized by most regulatory authorities. Just my 2 cents-worth, but I think isolators are so different from cleanrooms that traditional clean room validation and process control requirements are inapplicable.

Once the risk of human contamination is reduced effectively to the point of elimination, the nature of the aseptic risk is completely changed.

I also feel that the concerns about biological indicators, and 6 log spore reduction have been widely exaggerated. We certainly don't sterilize the environment in human scale aseptic processing, so why should we treat the inside of an isolator as though it were an autoclave chamber?

Comments from e-mail 3

(Further expansion on initial comments)

Your article makes interesting reading and clearly you wrestled with some of the same issues we considered as far back as PDA TR #34, in the advanced aseptic processing book J. Agalloco and I edited, and more recently in some of the USP information chapter work we have underway. Ed Tidswell is in fact leading a project for our USP committee now to tackle head-on some of the definitions we've long used in aseptic processing that make no real microbiological sense. If stated another way, they make no objective microbiological sense.

Thinking about Parkinson's Laws, if you assign a committee the task of determining the process capability of an aseptic filing line, or determining where the coffee machine should be located in the conference room, they will spend most of their time on the latter. Now you might ask what does that have to do with isolators or sterility assurance?

There are many factors which impact sterility assurance as we call it, but inevitably, the one people perceive to be the least complicated, is environmental monitoring. As a microbiologist I can affirm that it is a rather trivial consideration in the area of "sterility assurance" as it has no demonstrable connection to process conditions, because it is not a measure of process and even more importantly, low numerical counts are statistically unreliable. Worse still, even if EM did apply directly to the process, it could never measure or even adequately evaluate sterility assurance, or the condition of sterility, because one cannot measure that attribute microbiologically. We cannot prove a negative absolute. That would require an infinite sample size, and an assay capable of detecting a single cell of any potential contaminant, both of which are unachievable.

In our field, non-microbiologists are very comfortable in trivializing microbiology because it seems to be ridiculously easy. You expose a simple petri dish under procedurally defined conditions, you use the standard media, you incubate under prescribed conditions, you count the resulting colonies, and you have a result! That result is either in specification, or out, and if it is out you conduct an investigation using risk analysis tools of someone's choosing, which leads to the recommendation of CAPAs which you then implement with the belief that you've done something positive in the attainment of sterility assurance. Except, this is all scientific rubbish.

Microbiological assays don't have a limit of detection of one, > 99% of all samples exposed in ISO 5 cleanrooms are growth free, which those who trivialize microbiology confuse with "sterile". Actually, it means only that nothing grew, and the limit of detection is more likely somewhere in the one log range of 10^1 to 10^2. Obviously, since EU Grade A says the average count must be <1cfu that's pretty easy to meet, and utterly pointless. Now, if we turn to isolators or any aseptic processing method that reduces reliance on personnel, it is obvious that the rate at which we see contamination will be lower still. This is true because contrary to popular belief H13 and even H12 HEPA filters are very good at removing viable contamination, which of course is why, when you run an isolator for days at a time at rest, you typically don't find

0.3um particulates, and it is even less likely that you'll grow something on a EM sample plate. I have never tested an isolator at rest for any period of time that did not meet or exceed ISO 4 conditions at rest. The thing is though, at rest measurements don't take into consideration the contribution of the process equipment which is where most contamination that a particle counter would detect, comes from.

The same principle applies to microbiological testing. Humans generate ~100% of the contamination in a clean room. ISO 5 clean rooms have a higher number of air changes per hour than ISO 7 rooms, but both have the same filtration. So, at rest with no people they will give the same result. However, put people in the room and an ISO 5 room will do better because it has a higher air exchange rate. I would thus, argue that the fewer people are involved in aseptic processing the more pointless EM becomes. A modern ISO 5 filling clean room with an automatic fill line, and one or two people to recharge parts feeders, and correct momentary jams, with an HVAC system with full HEPA coverage producing 600 or so AC/hour, will have a contamination recovery rate in EM of <0.5%. This means 995 out of 1000 exposed samples will be null data. To any logical scientist shouldn't that mean that we are doing too much sampling already? Yet, to some inspectors it says we should be doing continuous monitoring.

This is just absurd, more sampling under the standard operating conditions I just described, will continue to produce 995 negative samples out of a 1000, no matter how much sampling we do. You can't detect what the analytical method will not detect.

So, then we are wrestling with the question when do you simply say in standardizing an isolator that EM is pointless? The only thing stopping us is regulatory push back, because the reality is, it is already pointless to expand EM further, and we should be reducing our emphasis in manned clean rooms as well. We learn nothing from it. I am currently doing an audit of a facility with two aseptic lines both installed in the early 90s both have full HEPA coverage over the fill line, both lines had no microbiological deviations in the last 5 years. They haven't had a media fill positive in 12 years and haven't had a sterility test failure in 23 years. Obviously, their rooms aren't sterile because they have people in them! But they are operating below the limit of detection of the method. So, does the $2million they spend a year on monitoring give them useful information? No, it does not in the statistical sense, but it does make the regulator happy. This is a scientific disconnect.

So, what we at USP have done already, is to propose the elimination of alert and action levels (limits) and a tabulation based only on contamination recovery. The reason for this is both analytical and statistical. A plate count with a recovery of 2 cfu has a relative standard deviation of about 50%. 1 cfu is 100%, so FDA's guideline targets of 0 cfu with an "action limit" of 1 cfu is scientifically illegitimate. They are requiring firms to work below the accurate quantal range of the method, just as the EU has tasked us with a zero 5um particle recovery limit which they finally addressed. You simple can't measure a negative absolute!

We think the EM requirements for isolators should be dramatically reduced. Perhaps for some isolators eliminated entirely. It is quite simply a waste of time and money. Regulators often trivialize the measure of things because it seems to be so simple. You put a plate in a sampler push the start button take the sample out, incubate it and count it. Easy, simple. A clear measure of room quality. Except it is none of those things, it isn't easy, it is not an accurate measure, it can't even grow 10% of the likely contaminants, it is prone to some false positives through the aseptic technique required to load and unload samplers, and it does not have a limit of detection of zero. Anybody can understand microbiological air sampling, right? No, not really, every single standard we have today was obviously set by someone who didn't understand what they were actually doing.

I could also say that those who require a 106 "complete kill" of a *G. stearothermophilus* BI to establish the suitability of an isolator for use are also confused regarding the objective and therefore have established a standard that isn't really accomplishing what they imagine it is. They have failed to understand both the logarithmic nature of microbiology, and first order kinetics. They have taken something to be simple which isn't simple, and as Parkinson predicted, trivialized it. The objective of decontaminating an isolator is not to sterilize an environment it is to create a safe environment for the conduct of aseptic primary packaging. Isolators, because we've separated the people from the aseptic environment, would be safer than clean rooms if we didn't decontaminate them at all! People have always been the only significant source of contamination in aseptic processing and in isolators there are no people.

The saddest aspect of this is that real scientists have known for decades what was going on here, but sat silent rather than challenge conventional wisdom, which in this case has not been wise.

My good friend Jim Agalloco and a couple of other industry experts used to be fond of saying that an isolator is nothing else but a "shrunken clean room". This seemed like a reasonable observation in the early days of isolator usage, but experience has taught us that it is clearly not true. Once direct human occupancy of a space is not possible you have something that isn't really a room, and which no longer utilizes humans for direct intervention. The simple elimination of people, as La Calhene understood from the outset, changes everything. Yet, most isolator recommendations and regulatory review or inspection approaches have in fact treated isolators like clean rooms. We look for the same engineering "things" with parameters like 0.45m/s air flow, air overpressure, classification approaches, EM approaches, and validation activities we have required in clean rooms. Worse still, even though the isolator lacks the innate source of contamination which is humans, we do not want it disinfected, which is adequate for a clean room. No, we demand it be sterilized. Then remarkably once sterilized, we want it monitored continuously, even though we may find only one positive plate in 10,000 or 100,000 and we can't establish that contaminant is not a false positive result.

To sum up I believe we are going to suggest that we don't need to do routine monitoring in an isolator at all. We are also going to suggest that the number of air changes per hour can be quite low, depending on how much particulate matter is produced by the process, and, that air over pressure need only be sufficient to ensure that there exists an air seal at the mouse hole. We will further suggest that static leak testing is

rather a waste of time for isolators run at a positive pressure to the room in which they are located. We would probably stick with the current Glove Box standards. We have also learned that turbulent flow and unidirectional air flow are less pertinent in isolators as well. They both generally meet ISO 4 or better at rest and in operation it all depends on the generation of particles by the process which is mitigated by the air exchange rate or air changes/hour.

We are also not convinced that media fill testing is helpful in isolators. The reality is we can't measure sterility assurance microbiologically and the sterility test doesn't measure sterility because it doesn't have a limit of detection of zero. So why not parametric release in isolators? The reality is in modern aseptic processing patient safety (sterility assurance) is dependent on engineering, and not microbiological testing which teaches us little or nothing. I'm a microbiologist, just reporting the facts. In fact, we really already parametrically release product in aseptic processing because we certainly would reject product which was manufactured outside defined and validated processing specifications, even if we passed a sterility test. So, we've really long recognized that the 'sterility' test doesn't prove sterility.

Comments from e-mail 4

In fact, I think there is already a lot of enthusiasm for an isolator standard embodying much of what we've discussed. I would love to see this be a joint UK/USA effort and I think I can bring Japan along as well. Japan is in many respects leading in the implementation of isolators in cell processing, Dr. Kino-oka, a Bioengineering Professor at the University of Osaka, has presented some extremely well designed studies regarding the technical performance benefits of automation in isolators over human technicians, even extremely skilled ones, working in clean rooms, most interesting. It seems that the benefits of automated isolators extend well beyond microbiological safety and extend to improved cell culturing outcomes as well.

Jim Akers PhD is President and Co-Owner of Akers Kennedy & Associates and has been a Technical Consultant to Shibuya Kogyo, Co. Ltd since 1991. Jim received his BA in Biology from the University of Kansas in 1971. After earning a PhD in medical microbiology with a concentration on virology at the University of Kansas School of Medicine in 1976, he spent five years in academia teaching and doing research in virology. He left academia for the pharmaceutical industry in 1981. Jim now has 35 years of experience working in, evaluating and providing design input for clean environments used in research and manufacturing applications. He is past president of the Parenteral Drug Association (PDA) and is Chairman of the Microbiology and Sterility Assurance Committee of Experts for the United States Pharmacopeia (USP). He has written over 100 articles and 28 book chapters on subjects including aseptic processing, validation, biologics manufacturing, isolation technology, and environmental monitoring. His principal areas of interest are aseptic processing technologies, sterilization, contamination control, and analytical microbiology.

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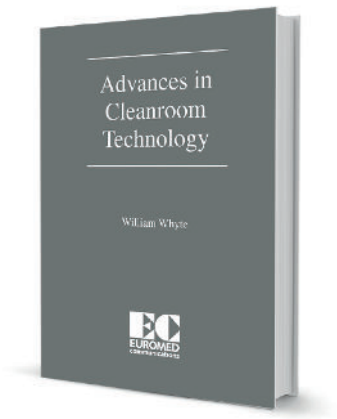

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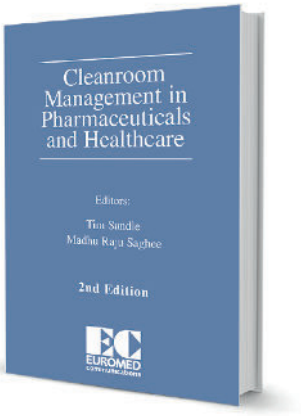

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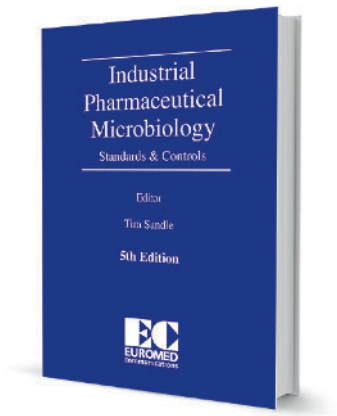

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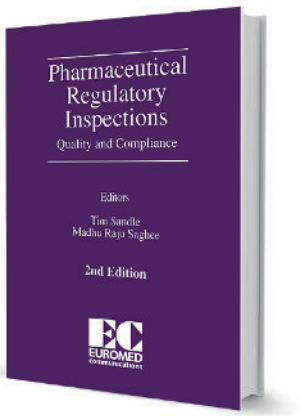

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Is log 6 overkill for an isolator?

Rick Nieskes

Abstract

This article comprises comments from Rick Nieskes received directly by Tim Coles in response to the publication of his article "*Standards for pharmaceutical isolators: an overview*" in CACR40. The comments are reproduced here in the form of an informal article by kind permission of Rick Nieskes and Tim Coles. Concern is expressed over appropriate levels of environmental monitoring and particle counting in isolators. There is some discussion on leak rates, and there is a suggestion that an intermediate Class 3.5 leak rate is required. Doubts are also expressed over the legitimacy of log 6 reduction as the target for bio-decontamination.

Comments

First off, I applaud your desire to standardize isolators as this a daunting task with all the isolator manufacturers out there. That said, here are my initial comments upon my first reading. I sincerely hope this helps or adds to our cooperative discussions.

1. The direction you are taking related to acceptable particulate levels for > or = to 0.5µm is a step in the right direction, although I am not certain if I agree with how low you are proposing. It has been a year or two since I have performed IQ/OQ on an isolator (as I am delegating this to the isolator manufacturer due to my availability), but I would be concerned about the amount of particles generated from a transfer door, for example. Since you can only detect particulates where the isokinetic probe is placed, your proposal would have to be evaluated so that the maximum permissible particles are appropriate anywhere sampling is performed.
2. Regarding viable environmental monitoring, I see essentially continuous Active Air Viable (AAV) as the goal (although this is indeed a laborious process that has the potential to disrupt normal operation). Passive Air Viable (PAV) has its place too, but is a supplement to AAV in my opinion.
3. There are standards/expectations related to the height and location of the isokinetic probe and these should be established so as to not disrupt airflow detrimentally in areas deemed "critical" to the process. I know that is pretty ambiguous, but "it is what it is".
4. The time required to achieve acceptable particulate levels from Grade D to Grade A, for example, needs to be validated. I do this by opening the isolator to the room, closing it, and letting the particulate counter run until acceptable levels are obtained. 15 minutes is common.
5. I suggest not using the acronym "DOP"[1] because there is also "DEHS"[2]. I would change to "aerosol challenge" or something similar.
6. I have seen time and time again where a positive pressure isolator (let's say around 60 Pascals) will "blip" negative pressure during a rapid glove sleeve withdrawal. For this reason, isolator manufacturers often incorporate a 3-second delay in this alarm.
7. I believe that an intermediate LR of Class 3.5 is needed between ISO Class 3 and 4.[3] For example, in a relatively small airlock transfer chamber I have seen an LR of 3% chamber volume per hour. In my opinion, this is because it is hard with current sensors, fluctuations in room pressure, operator(s) entering/exiting the room, the overall size of the room, etc. to precisely control pressure in such a small enclosure.
8. In many cases HEPA filter flow rate is somewhat variable and is a function of the Variable Frequency Drive (VFD) or AC to DC converter, or other fans control system (ed.).
9. Pressure drop across the main filter is often measured, but not necessarily tied to an alarm based upon my experiences. That said, it could be. But in operation, I typically see this bounce around quite a bit.
10. LR can, and in many cases is measured, and alarms are set prior to the initiation of the biocide decontamination cycle. This is achieved via a pressure sensor built into the design of the isolator, also used to generate a specified test pressure, typically double that of the normal operating pressure.
11. I do not agree that the only critical alarms you have listed are the only ones. This depends on the application. For example, an incubator isolator temperature would be critical. For a powder filling application, the humidity would be critical. For an inert atmosphere, the oxygen concentration would be critical. And the list goes on and on.
12. I do not agree that "failures other than HEPA filter integrity and leak rate will show up as changes in these three parameters and therefore do not need to be alarmed as such". This oversimplifies isolator design and performance.
13. Keep in mind a log 6 reduction does not equate to "kill" as there is always a probability of a positive BI. The use of a 10^6 BI is simply too much. The box shows an excerpt from one of my protocols on this subject matter. I will let Jim (James Akers – Ed.)

1. Editor's note: DOP is the abbreviation for Dioctyl Phthalate but is often used as an abbreviation for Dispersed Oil Particulate.
2. DEHS (Di-Ethyl-Hexyl-Sebacat) is a non-soluble, colourless and odourless liquid which is suitable for producing steady aerosols. The main proportion of droplets generated by aerosol generators series ATM can to be stated in the most penetration particle size (MPPS 0.2…0.3µm). DEHS is a proven aerosol liquid for challenging clean rooms and laminar flow boxes.
3. In accordance with ISO 14644-7:2004, Table E.1

chime in on this one, as he is the leading industry expert on this topic and I know this fires him up!

The biological indicator (BI) used in this protocol contains 10^6 viable *Geobacillus stearothermophilus* (spores) inoculated at the end of a piece of stainless steel ribbon measuring approximately 0.6 cm W x 7.0 cm L. The inoculum area is approximately 0.6 cm^2. By calculation, the density of microorganisms on the BI per unit area equals 10^6 CFU / 0.6 cm^2 or ≈ 1.67 x 10^6 CFU / cm^2. According to the publication entitled, "Approximate Challenges for the Validation of Hydrogen Peroxide Vapour Sanitization Cycles", the mean bioburden count in an isolator **before cleaning** is in the range between 14 and 63 CFU per 25 cm^2 (based on the area of RODAC™ plate). By calculation, the density of microorganisms associated with this mean bioburden is at most 63 CFU / 25 cm^2 or ≈ 2.5 CFU / cm^2. Therefore, the use of this BI containing 10^6 viable *Geobacillus stearothermophilus* (spores) exceeds mean bioburden density levels by a factor of [(1.67 x 10^6 CFU / cm^2) / (2.5 CFU / cm^2)] or 6.7 x 105. (This means the challenge exceeds the natural bioburden by a factor of more than 100,000 – Ed.)

14. I know you know this, but in some cases, aeration down to 1 PPM is simply not enough.
15. Standards for the room are essential so that you have a consistent, controlled base-line particle level, temperature range, humidity range, etc. I feel strongly about this and believe discussions otherwise are incorrect.
16. Generally speaking, how are older isolators with proven historical data going to fit in with these proposed standards that cannot be met? This is certainly not limited to this technology, but is a manifestation of progress. At what point do you call an isolator "obsolete" such that it must be decommissioned? I don't know the answer to these questions, but I believe you/we must proceed cautiously down this path.

Rick Nieskes has a BSc in Bacteriology from the University of Wisconsin-Madison. He started his career with a major pharmaceutical company as a Sterility Testing Microbiologist utilizing isolation technology. Following this he worked as a Process Engineer for a manufacturer of equipment that used a patented technology for vaporized hydrogen peroxide biodecontamination. In 1994, with this unique combination of experiences, Rick founded Ardien Consulting Services which offers customized isolator validation to the pharmaceutical industry. Ardien Consulting Services has successfully validated over 100 isolators for Aseptic Manufacturing, Quality Control Laboratory Sterility Testing and Containment applications from over 40 different pharmaceutical companies throughout the world. For more information about Rick Nieskes and Ardien Consulting Services please visit www.ardienconsulting.com.

Life-lines

Quotations of George Bernard Shaw

The single biggest problem in communication is the illusion that it has taken place.

The moment we want to believe something, we suddenly see all the arguments for it, and become blind to the arguments against it.

Choose silence of all virtues, for by it you hear other men's imperfections, and conceal your own.

England and America are two countries separated by the same language.

We learn from experience that men never learn anything from experience.

Miracles, in the sense of phenomena we cannot explain, surround us on every hand: life itself is the miracle of miracles.

Progress is impossible without change, and those who cannot change their minds cannot change anything.

You see things; and you say 'Why?' But I dream things that never were; and I say 'Why not?'

The first condition of progress is the removal of censorship.

Censorship ends in logical completeness when nobody is allowed to read any books except the books that nobody reads.

A government that robs Peter to pay Paul can always depend on the support of Paul.

Life isn't about finding yourself. Life is about creating yourself.

We don't stop playing because we grow old; we grow old because we stop playing.

Ecolab on top of regulatory trends

Ecolab are reiterating their commitment to customers by staying on top of regulatory trends in the pharma industry. By monitoring the FDA 483 observations over several months, the company is able to advise what types of activity, or lack of them, is likely to attract such citations.

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- Inadequate validation of cleaning procedures – 37 observations
- Inadequate validation of the disinfectant products – 8 observations
- Inadequate cleaning/sanitizing (including inadequate cleaning procedures) – 31 observations
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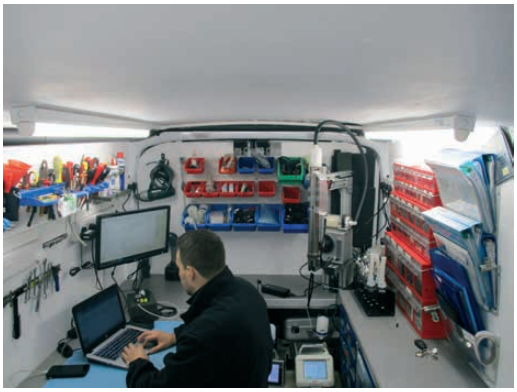
In order to help protect their customers against a potentially costly 483 in these areas, Ecolab can help them navigate through the regulatory requirements for cleaning, sanitization and contamination control.

Ecolab provide the technical and validation support needed to help ensure that customers' cleaning and disinfection processes have been optimized and are audit ready. They can also assist with selection of the most appropriate agents and parameters to reduce the risk of cross contamination and/or residues, thereby providing a high assurance of safety to patients, compliance and operational efficiency.

For further information on how Ecolab's Global Technical Consultants can help you adhere to current regulatory standards, contact Emily Buck on +44 (0) 1606 721999 or email emily.buck@ecolab.com or visit. www.ecolab.com/expertise-and-innovation/experts/life-sciences-experts

ATI UK launches mobile testing and calibration laboratory



ATI UK has recently added a new mobile laboratory to its service department to attend customers' sites where it can carry out service and calibration of aerosol photometers and generators for HEPA/ULPA filter testing, and particle counters and microbial air samplers for cleanroom testing and monitoring. ISO9001 quality certification ensures standards compliance including particle counter calibration to ISO21501-4 and photometer service to manufacturers' specification.

ATI's premier range of HEPA/ULPA filter testing instruments, flat sheet media and special filter penetrometers, respirator filter testers focus on protection for people, product and the environment.

ATI also supplies particle counting solutions from Lighthouse and designs Environmental Monitoring Systems for particles, microbiology, temperature, humidity and pressure within cleanroom facilities across all applications.

ATI's Academy for Cleanroom Testing provides popular and informative theoretical and practical courses on all aspects of cleanroom testing and certification.

Come and visit ATI's UK facility in Letchworth Garden City, email salesuk@atitest.com, call +44(0)1462 676446, or click www.atitest.com to learn about ATI's full range of products and services.

EECO2 Limited installs MEMUs monitoring 22 Air Handling Units in the USA

EECO2's largest Mobile Energy Monitoring Unit (MEMU) installation yet has been taking place This involves 10 MEMUs covering 22 Air Handling Units (AHUs) at a customer site in Maryland, USA. The AHUs serve 3 buildings, containing a combination of labs, cleanrooms and admin areas on the pharmaceutical manufacturing site.

The measuring devices will provide evidence of energy savings from sustainability projects identified by EECO2. The benefit of any proven savings above that guaranteed originally by EECO2, will be shared between EECO2 and the customer.

Unlike most other metering, monitoring and targeting systems, the MEMU allows for granular monitoring, enabling EECO2 to provide customers with detailed proof of real savings from implemented sustainability projects.

For more information on the MEMU or possible sustainability projects for your site, contact EECO2 Limited at info@eeco2.com or visit www.eeco2.com.

The Sound of Silence from Biopharma

What does your perfect working environment sound like? Absolute silence? A little noise?

Whatever your preference it's nice to be able to hear yourself think, especially in a lab environment. The modern laboratory is filled with equipment and people, all emitting noise which can combine to reach an unbearable level. In fact, noise exposure above 55 dBA has been linked to depression. Research has proven that prolonged experiences of noise increases the bodies levels of the stress hormone cortisol.

The Faster Premium model of class II microbiological safety cabinet, is known to be the quietest in the market, with dBA of 49 (1.2m model) and that's not using clever noise testing equipment, that's the result of noise testing in a real life lab! We combine, low pressure drop filters with, textile plenum, deep back wall and DC motors to produce the quietest and most energy efficient safety cabinet in the market.

Biopharma is the UK distributor for Faster products. For further information, please visit www.fasterair.co.uk

CRC's tech investment drives cleanroom success

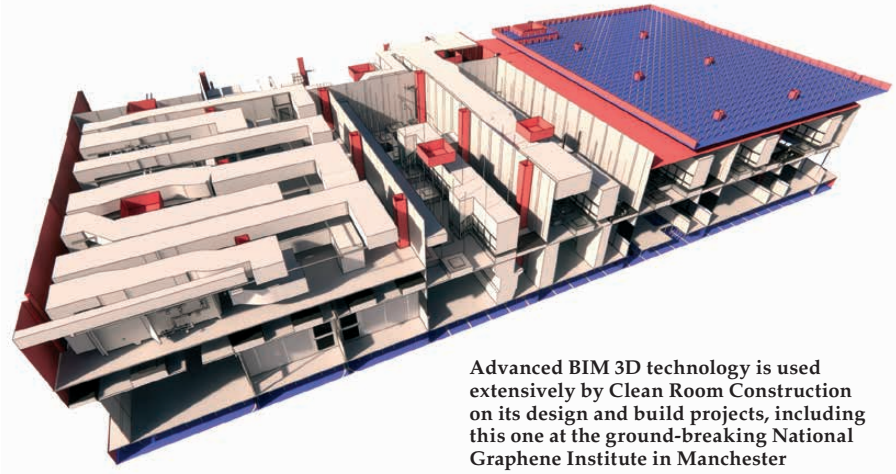
New BIM technology is driving innovation and success in 2020 for leading cleanroom design and build specialist, Clean Room Construction (CRC).

In its latest contract win, CRC has been awarded a million-pound design and build contract for a global leader in sustainable technologies in the Swindon area. The 300 sq.m full turnkey project pushes the boundaries in terms of accurately controlling a wide range of environmental parameters.

Clean Room Construction has also started work on a prestigious contract to build a high precision performance cleanroom for a global power systems company with complex manufacturing processes. This project has involved a long lead-in time to enable CRC to plan the work, together with the client, to coincide with a major factory production shutdown and also to facilitate the procurement of specialist materials. Both projects have been designed using the company's extensive BIM 3D capability.

Managing Director Steve Lawton, said: "CRC's investment in BIM 3D technology over recent years puts us at the forefront of cleanroom design and innovation."

www.crc-ltd.co.uk



Advanced BIM 3D technology is used extensively by Clean Room Construction on its design and build projects, including this one at the ground-breaking National Graphene Institute in Manchester

Cherwell announces new Microbiology Sales Specialist

Thomas Parkhill – Cherwell Laboratories' new Microbiology Sales Specialist

Cherwell Laboratories are pleased to announce the appointment of Thomas Parkhill as Microbiology Sales Specialist. Thomas will work closely with new and existing customers across the UK to fully understand and help Cherwell to satisfy its customers' future environmental monitoring and process validation needs.

Thomas studied Molecular Biology at the University of Dundee in Scotland, before moving to Biocatalysts, an enzyme manufacturer, based in Cardiff. During his five years with Biocatalysts, Thomas progressed to the role of Business Manager for Northern Europe territory; particularly working closely with Blue-Chip companies to deliver complex new developments within the food and beverage industry.

Andrew Barrow, Sales Manager of Cherwell, commented, "Tom brings valuable additional experience of technical sales and project management to our team. This combined with his energy and enthusiasm in microbiology will help us to continue to deliver added value to our customers."

For more information about Cherwell Laboratories, please visit www.cherwell-labs.co.uk.

Argonaut Manufacturing Services and Particle Measuring Systems partner for top tier results

Argonaut Manufacturing Services, a contract development and manufacturing organization (CDMO) for biopharmaceuticals, and Particle Measuring Systems (PMS), a contamination monitoring solutions company, have announced their ongoing partnership. The companies have been partnering for over a year to achieve manufacturing results that exceed industry standards.

The partnership was initiated in 2019 when Argonaut purchased a state-of-the-art Bausch+Ströbel VarioSys filling. PMS instruments are not the default on the line, but Argonaut's previous experience with various environmental monitoring solutions and their desire to use only premier partners led the team to select PMS instruments including particle, microbial, and data management.

"Argonaut is a top tier contract manufacturer, and we partner with other industry-leading companies such as Particle Measuring Systems to ensure that we provide our customers with the highest standards and safest products", said Stacy Sutton, VP Regulatory and Quality at Argonaut. She continued, "After being in this industry for decades I know the various players; we chose PMS because of their proven reliable track record and complete solutions".

"As the industry experts in our field, we fit well with companies such as Argonaut who strive for excellence", said Giovanni Scialo, VP Life Sciences at PMS. "We provide complete solutions to help ensure our customers meet relevant regulatory requirements and identify problems before they happen".

For more information on PMS visit www.pmeasuring.com or contact nmorton@pmeasuring.com

Envair represented in Ireland ... and reappointed for their Royal Liverpool Hospital project

Envair is delighted to announce that it now has representation covering all of Ireland. Eirdata Environmental Services Ltd operates from offices in Dublin, Cork and Limerick and as from February 2020 provides Sales and routine Servicing of the entire Envair product range. Established in 2001, Eirdata are proven specialists in cleanroom validation, commissioning & compliance within the pharmaceutical, medical devices and healthcare sectors primarily.

...and in other News

Having secured the management contract to finish the Royal Liverpool Hospital project, after the collapse of Carillion, Laing O'Rourke has recently reappointed Envair to finish the supply and installation of rapid gassing pharmacy isolators, laboratory fume cupboards and downdraft ventilated workstations within the CSSB Building.

For further information please contact info@envair.co.uk or visit www.envair.co.uk

Events

2020	Event	Organiser
April 27-30	ESTECH, Minniapolis/St.Paul, Minnesota **POSTPONED**	IEST
April 28-29	Making Pharmaceuticals, Coventry, UK	Step Exhibitions
May 25-27	51st R3Nordic Symposium in Cleanroom Technology & Contamination Control, Naantali Spa, Finland	R3Nordic
June 2-3	Cleanroom Technology Conference 2020, Birmingham, UK	HPCi Media
June 2-3	Manufacturing Chemist Live 2020, Birmingham, UK	HPCi Media
June 6	PHSS Sterile Product Manufacture Conference 2020, Knutsford, UK	PHSS
June 22-24	EP and Clean Tech China, Shanghai, China	Informa Markets Sinoexpo
August 16-18	Cleanroom Guangzhou,2020, Guangzhou (Canton), China	Guangdong Grandeur International Exhibition Group
September 29-30	Making Pharmaceuticals Ireland, Dublin, Eire	Step Exhibitions
October 13-15	25th International Symposium on Contamination Control, ICCCS'20, Antalya, Turkey	TTD
November 4-5	Lab Innovations, Birmingham, UK	Easyfairs
November 17-19	International Congress A3P, Biarritz, France	A3P
November 18-19	Cleanzone, Frankfurt, Germany	Messe Frankfurt Exhibition GmbH
November 24-25	Cleanroom Technology Conference 2020, Hyderabad, India	HPCi Media
December 1-2	Cleanroom Technology Conference 2020, Singapore	HPCi Media

Training courses

IEST (Institute of Environmental Sciences and Technology) www.iest.org		
2020	**Event**	**Location**
April 27	Basics of Cleanroom Design, HVAC System Design, and Engineering Fundamentals **POSTPONED**	ESTECH Minneapolis/ St. Paul, Minnesota
April 28	Cleanroom Basics: What is a Cleanroom and How Does it Work? **POSTPONED**	ESTECH Minneapolis/ St. Paul, Minnesota
April 29	Beyond Cleanroom Basics: Fundamental Information for Cleanroom Operations **POSTPONED**	ESTECH Minneapolis/ St. Paul, Minnesota
April 30	Cleanroom Classification Testing and Monitoring **POSTPONED**	ESTECH Minneapolis/ St. Paul, Minnesota
May 12-15	Requirements Needed for Compounding Pharmacies Using USP 797 **POSTPONED**	Lee's Summit, Missouri
June 16	Understanding the Cornerstone Cleanroom Standards: ISO 14644-1 and 14644-2	Schaumburg, Illinois
June 17	Application of ISO 14644-3	Schaumburg, Illinois
June 18	Universal Cleanroom Operations Guidelines with ISO 14644-5	Schaumburg, Illinois

CCN (Contamination Control Network) www.theccnetwork.org		
2020	**Event**	**Location**
May 19-21	CTCB-I Testing and certification course	Liphook, England
November 10-12	CTCB-I Testing and certification course	Liphook, England

ICS (Irish Cleanroom Society) www.cleanrooms-ireland.ie		
2020	**Event**	**Location**
September 24	CTCB-I Advanced Cleanroom Technology course, 1 day	Dublin. Ireland
November 26	CTCB-I Cleanroom Testing & Certification, 2/3 days	Dublin. Ireland

R3Nordic (Scottish Society for Contamination Control) www.r3nordic.org		
2020	**Event**	**Location**
For courses run by R3Nordic see https://r3nordic.org/		

VCCN (Association of Contamination Control Netherlands) www.vccn.nl/cursusaanbod		
2019	**Event**	**Location**
For a complete list of courses including CTCB-I courses, please see http://www.vccn.nl/cursusaanbod		

Note:
CTCB-I Certification: Cleanroom Testing and Certification Board International Certification,
see CTCB-1 website: www.ctcb-i.net/index.php

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To find out more, please speak to your Ecolab account manager today or visit ecolablifesciences.com

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