PDA Midwest Microbial Contamination and Control

August 12th & 13th

Q: While performing Coupon test Is it necessary to mimic actual cleaning procedure followed in facility?

A: The best practice would be to test the antimicrobial chemistry against your environmental isolate. The cleaning should be evaluated separately. The problem with adding in the cleaning/wiping along with activity of the chemistry is that you can get very errant results due to the difference in technique of wiping and method of wiping.

Q: Are coupon studies required for every site for ATCC strains, or just house isolates?

A: The most critical study to obtain for FDA and other industry regulators is the testing of environmental isolates. You can include some ATCC or USDA strains in your coupon studies such as Gram Positives or Fungal spores, but the most critical part of the coupon testing is to test your environmental isolates.

Q: Would you recommend any specific publication for risk assessment for choosing the surfaces used for coupon testing?

A: There is a recent PDA Journal article from March-April 2020 that I would recommend. Disinfectant Efficacy: Understanding the Expectations and How to Design Effective Studies That Include Leveraging Multi-Site Data to Drive an Efficient Program. I have a couple of additional references if you want to send me an e-mail.

Q: For your triple clean recommendation, why use a disinfectant? Could you do a triple spore application?

A: The disinfectant is a critical part of the triple cleaning because most disinfectants are registered with US EPA as one step cleaner/disinfectants. The disinfectant adds the cleaning step prior to the sporicide step.

Q: Is it important to try to simulate the wild type state of vegetative challenge organisms? Cultured strains may not reflect the organism in its environmental state.

A: I would include your environmental isolates in your coupon testing based on hardest to kill/worst case and most frequently occurring. Some of the fungal and bacterial spores may in fact be more challenging to kill depending on the specific strain of microbe. An example would be Bacillus cereus strains.

Q: What percentage of hydrogen peroxide is effective as a sporicide? And contact time for it?

A: I would recommend 8-10% Hydrogen Peroxide which would be more effective against spores n 10 minutes than 6% Hydrogen Peroxide would be. The 6% Hydrogen Peroxide can be sporicidal but in contact time of 30-60 minutes.

Q: In regards to requalification of clean rooms. Would you perform both viable and non-viable measurements on the same day? If not necessary, can't you just use EM viable data from previous measurements?

A: I would take them at the same time. If you are specifically talking samples for the purpose of a requalification then new samples would be needed. If you are evaluating data for the purpose of creating a justification not to require that, you would utilize existing data.

Q: When do you expect the release of Annex 1?

A: Hopefully by end of this year, but, I would not be surprised if it is next year.

Q: Assuming you get 3 cfu on a contact plate sampled in a Grade B area. All three of them have the same macroscopic characteristics e.g. white, round, smooth etc. According to new Annex 1 you have to identify all them until the species level. Suppose that you can prove that indeed the plate had only 3 identical colonies i.e. by taking a photo (store it appropriately in regards to data integrity issues) and that the lab has already in place a comprehensive library concerning macroscopic characteristics of typical environmental recovered isolates (e.g. pictures of *S. epidermidis*, *M. luteus*, *B. megaterium* etc. followed by macroscopic traits). How "bold" would it be to identify only one out of the three colonies until the species level and the other 2 until the gram staining procedure, followed by microscopic observation?

A: It would not be acceptable to use macroscopic characterization of colonies to "ID" an organism in Grade B (nor any recovery over action limits in any lower grade rooms). The problem you have is that many genus of gram positive cocci look identical macroscopically and need to be properly identified in order to find a potential root cause and develop a CAPA.

An example scenario:

- You have a sterility failure and the organism was identified as *M. luteus*.
- You have no recovery or microorganisms in Grade A
- You have 3 CFU recovery in Grade B and you only identified one of the three colonies as S. epidermidis but considered the other two to be S. epidermidis based on morphological characteristics of the colony only
- *M. luteus* and *S. aureus* look identical on TSA plates.
- One microbiologist may see a beige color, another may see a white color and a third may see a yellow color. Color is EXTREMELY subjective, especially under different lighting conditions, eyeglasses, viewing angle, etc.
- You may have missed a potential route cause or source of contamination due to lack of sufficient.

Q: How would you exit the clean room (after cleaning) since you have dedicated airlocks for materials and personnel, without stepping on the already clean floor (assuming airlocks are not close)?

A: Aseptic facilities should have procedures in place for personnel and material flow through the area. These same procedures should be followed for cleaning and disinfection with the exit passthroughs cleaned last.

Q: In static conditions how many "WC should a room be allowed to fluctuate? How stable does a clean room positive pressure need to be when doors are closed and no operator movement?

A: A range of ±0.01 InWC around a setpoint is the generally recommended range. A room should be able to maintain this when the doors are closed, regardless of operator movement.

Q: Should you use one or two disinfectants in your cleaning program and how often?

A: The use of one or two disinfectants should be determine by your isolates to ensure you are able to control the spectrum of microorganisms in your environment. Typically, one high-level cleaner disinfectant is sufficient, however, consideration should be given to the specific regulations in the region. If two disinfectants are used in your program, it is recommended to keep their rotation simple to avoid non-compliance with cleaning procedures. I typically recommend rotation on a monthly basis, however, have seen everything from rotation weekly, quarterly, and other frequencies.

Q: Would you consider wearables (e.g. around the chest like pro athletes performing monitoring systems) under the undergarments, in order to manage operators fatigue?

A: No, I consider this a huge invasion of privacy, but some may want to choose a few individuals to gather this data for a short term study to determine best timing for breaks and scheduling of critical work. I personally feel this could be managed by feedback from operators and observation from front line managers and implementation of regularly scheduled breaks and rotation of work.

Q: In terms of dropping an item on the floor, are you recommending that someone can simply spray that item and their hands with IPA/EtOH and continue with operations?

A: No, if the item is critical to completion of an operation where it isn't product contact, for example, dropping a tablet/e-record/batch record, or calculator, timer, or tool, I recommended spraying the item off, spraying your gloved-hands off, and exiting the area to regown. Sometimes something is critical and needs to be recovered once dropped on the floor. This was to counter some individuals who state that absolutely nothing may be retrieved from the floor and that simply isn't practical in every case.

Q: Do you think IPA is an effective residue remover as compared to a detergent?

A: It depends on the residue. IPA is suitable for removing residues on stainless steel, glass, and mirrors after disinfection. If the residue is built up or on the floor, a detergent or WFI is generally recommended.

Q: Do you have a video showing the unidirectional cleaning importance?

A: I do not have a video showing the importance of unidirectional cleaning, but I do have a video demonstrating use of a triple bucket and unidirectional mopping on a wall. *https://youtu.be/ajZ5_QHErqU*

Q: Are firms using parametric release for a strictly aseptic processing line? Is it accepted from a regulatory perspective?

A: I'm not aware of any parametrically released aseptically filled drug products or any regulatory authorities that currently accept parametric release for aseptically filled products. That said, as manufacturing technology progresses and methods of sterility assurance improve, I think the option for parametric release of aseptically processed products should be considered.

Q: What is your recommendation for qualifying purchased sterile primary container closure components? Should a lot of closures be sent to an external lab every year for sterility/endotoxins testing?

A: As far as the FDA is concerned, testing should be conducted on every lot initially then intermittent testing can be incorporated once a satisfactory record of compliance and trust in the supplier is established. It's hard to give a time frame for the testing, it depends upon how many lots you go through in a year. See 21 CFR 211.84 for regulatory requirements.

Q: *P. acnes* - as it is a slow growing organism and not easily detected from typical environmental monitoring, how do we monitor for it?

A: If you've determined that *P. acnes* is a particular problem in your facility, I would conduct occasional anerobic environmental monitoring to make sure it can be detected within your manufacturing environment. That said, I've found it rare that a facility would have an issue with *P. acnes* and not other easier to detect aerobic microorganisms like *Staph* or *Micrococcus*. Generally, a robust EM program that can detect aerobic skin organisms is sufficient for ensuring that operator gowning and hygiene techniques are adequate to prevent *P. acnes* contamination in your environment.

Q: Which QRM techniques might be best for aseptic processing QRM exercises?

A: HACCP, Layers of Protection Analysis (swiss cheese model), and preliminary risk analysis can all be used depending upon the type of process you have and the level of control you're looking for.

Q: Could AP+ be applied to biologics?

A: Absolutely. Biologics are for the most part far more sensitive to sterilants like heat and radiation but some manufacturers have perfected methods for controlling the sterilization dose to allow for the terminal sterilization of biologics. Therefore, AP(+) is possible.

Q: How would you conduct a negative control during a sterility session when only testing glass vials? Use only rinsing solutions? Filled vials with media fill broth to mimic the process of opening vials?

A: I would use only the sterile rinse solution and be sure the technicians are adequately trained to aseptically open the vials to avoid false positives.

Q: What do you think of Grade C USP limits?

A: I believe these are good starting points for Contamination Recovery Rates (CRR); however, most areas, if designed appropriately (i.e., Infrastructure) and the correct process can easily be much lower than these recommended limits.

Q: Do all three types of data evaluation need to be used?

A: It would depend on your audience. Personnel from the floor may only care about the number of actions for a given area of responsibility. Others may care about actions and alerts, along with trends, to see if there are any indicators for a given area. Percent within Regulatory (PwiR) is beneficial for site senior management or corporate management, as it can quickly communicate the regulatory excursion rate, which has a negative impact on Quality Metrics and resource utilization for a site/facility. So, that is a long winded way to say yes, all data types can and should be used, but it is essential to know your audience and target your data analysis.

Q: For active air sampling what kind of equipment would you recommend?

A: I would recommend that you was Quality by Design and approved risk analysis to determine the most appropriate type of methodology to be used in the manufacturing environment.

Q: Impactors or impingers?

A: See answer above.

Q: Why everyone is in favor of impactors?

A: Each company should be using QbD along with approved risk analysis to determine the correct methodology for the sample type being gathered, and I cannot speak to why companies chose one type over another.

Q: Impingers could provide liquid media for rapid method analysis.

A: While I agree with the statement, I would go back to use of QbD and risk analysis to determine the appropriate methodology for the environment and other test methods used in the facility.

Q: When presenting a process control chart for a specific sampling EM sample, should OOS/OOT results be in there or separately?

A: It is recommended that all data be include, in some manner, when presenting process control data to your key stakeholders. However, there are many ways to do this for your classified environments. It may be best to only show actions if that is the most appropriate, or maybe alerts and actions. I would recommend that trends only be discussed when they occur and not represented on process control charts.

Q: When calculating alert limits should the above be excluded?

A: No, I would not recommend excluding any positive samples from the data pool when calculating your area / facility alert limits.

Q: Preferred method of calculating alert limits? Normal (if applicable), Poisson, negative binomial distribution, percentile method?

A: Working with statisticians, I always go to what they request or believe is the best fit for EM data. However, this is typically the difficult part of the process. In the past I have seen normal, if it is applicable (as you state above), but most of the time I would say that percentile method is utilized.