ENVIRONMENTAL MONITORING Q & A

PMFList

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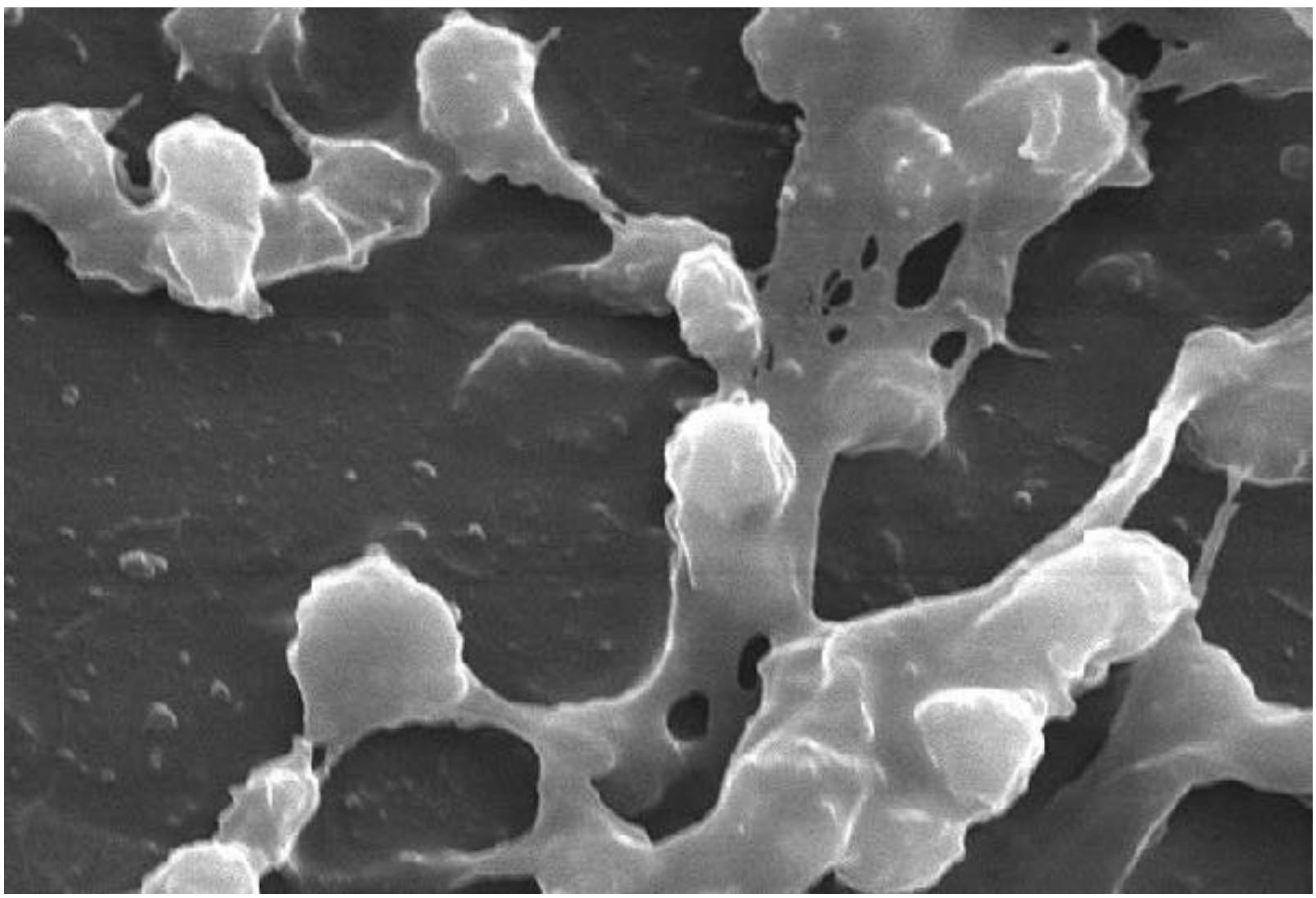

compiled by David A. Porter, Ph.D.

from the PMFList Archives

PREFACE

This ebook contains numerous questions and answers compiled from the PMFList archives related to environmental monitoring. They span from February 2021 through June 2023, and are provided in chronological order. Some editing may have been done to remove attributions, and for clarification. The purpose is to provide a digest of questions and answers submitted by subscribers to the PMFList pertaining to environmental monitoring issues in the pharmaceutical and related industries. The information contained in these questions and answers, and in this ebook, includes the professional opinions of individuals and does not represent the policies or operations of any corporation or government agency to which they may be associated. The information in this ebook is solely for informational purposes and is developed from sources believed to be reliable. Statements expressed constitute current opinions derived through analysis of available information and professional networking and are not necessarily the views of the PMF board or regulatory agencies. The PMF cannot make any representations as to the accuracy or completeness of the information presented and it cannot be held liable for errors.

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QUESTION 1

My company is looking at reducing the use of SDA plates in routine environmental monitoring. Currently, both TSA and SDA are used for every sampling session. The goal is to change SDA sampling to quarterly or stop the use of SDA altogether. What would be the best approach in justifying this reduction? Can historical data, roughly 3 years, be used solely or is some type of designed experiment required?

ANSWER

1. I'm not sure which room classifications you're referring to but there are definitely options for reducing or eliminating the SDA plate. Assuming your data don't suggest a problem with molds in the facility, then you can analyze the data you have and write a justification for removing the SDA plates. There are multiple publications you can use to support your rationale as it is well known that TSA will recover some yeasts/molds. Here are a few relevant references.

USP<1116> recommends a 35°C incubation to promote recovery of skin flora from aseptic processing sites which are the most common contaminations in critical areas.

FDA Pharmaceutical Microbiology Manual states "When targeting fungal populations only, it is necessary to use an appropriate fungal media such as Sabouraud Dextrose or Malt Extract media." This allows for single media when fungal isolates are not of particular concern.

QUESTION 2

I am looking for some discussion on which path industry is moving to. There has been an ongoing discussion (or debate) on the use of Environmental Isolates during Method Verification. This is not a recommendation by Compendia Chapters, but more and more observations by Regulatory are coming through in industry for this.

What is the path industry is taking or moving to?

ANSWERS

1. The method suitability requirements are detailed in the compendial chapter.

See Guilfoyle, D. E. and A. M. Cundell 2022. Do Plant Isolates have a Role in Method Suitability and Growth Promotion Testing in the Microbiology Laboratory? Is it a Matter of Science versus Compliance? PDA Journal of Pharmaceutical Science and Technology February 2022, pdajpst.2021.012675; DOI: https://doi.org/10.5731/pdajpst.2021.012675

2. Please clarify what assays or compendial chapters you are referring to.

3. Just this week the PDA Journal published an article by Tony Cundell and Dennis Guilfoyle that addresses this topic as well as EM isolates for GPT: PDA J Pharm Sci and Tech 2022, 76 444-460

Their overall argument was that for method validation, yes, plant/EM isolates are useful but not for routine GPT of media. The article is very good and I recommend it for everyone interested in this topic. I personally agree with their conclusion as well....not that it matters.

4. Yes, Method Suitability requirements are detailed in the Chapter but not for Plant Isolates.]
Chapters <51>, <61>, <71>.

5. Yes, no details on plant isolates as they are not a compendial requirement.

6. I expect that this is a bandwagon type observation ("I heard that these should be used, so it MUST be something this firm isn't doing").

EM isolates have a place in their usefulness. For growth promotion challenges (EM plates, APS, sterility, etc.) perhaps…. But there's a few considerations.

* Once you take the wild type strain and preserve it, store it and revive/resuspend it, it is not much different than a "store bought" strain purchased from any manufacturer.
* I would also take a hard look at how different is that EM isolate than any organism that I am already challenging your assays with. If you recover an organism that is unique to YOUR environment and vastly different from your compendial challenge panel, then MAYBE I would take it into consideration.

I can't tell you how many times I have seen folks perform suitability assays with a half dozen different personnel/operator recovered gram positive cocci microorganisms because they felt they ALL needed to be included. Craziness.

If you already have representative microorganisms demonstrating recovery in your assay, then why the need to expand the panel?

Ultimately it depends on what method/assay you're verifying and which microorganisms you've recovered. I am more apt to say it is NOT needed given the narrow bandwidth of species we normally find in our cleanrooms. If you have something that keeps popping up in your EM, that should be an investigation in and of itself.

Don't forget, EM isolates shouldn't wind up in your product if you have a solid control strategy.

I know, a long-winded answer, barely worth more than $0.02!

QUESTION 3

I have recently got to learn about petriplate stands that can be utilised during environmental monitoring using the settle plate method. Does anyone know what the recommended height of these settle plate stands should be and any design recommendations for the stands, i.e, i have been reading about these stands coming either as horizontally surfaced stands or inclined/slanted stands. How would these two factors possibly affect the quality of the settle plate method during environmental monitoring?

ANSWERS

1. I have seen stands at an angle but I'm not sure where or why that originated. I don't know of any document that states the settling plate should be at an angle. That being said, the plate should be at working height, capturing particles out of the air where they may fall into the product or surface.

2. Earlier in my career at the NY Blood Center we used retort stands which hold the Petri plates and standardized their location.

That reflected my organic chemistry training as an undergrad.

3. Settle plates should ideally be positioned such that laminar flow is hitting it directly. I've never seen them not pointing straight up (i.e. no angle). Positioning could be determined and justified via recorded smoke studies.

4. The angled plate was the result of a study by Upjohn in the mid 80s, where they showed the air flow pattern over a plate on a flat surface and an angled surface in a unidirectional airflow area was better on the plate on an angled surface. I am still looking to see if I have the paper in my files.

QUESTION 4

Is there any reference document or guideline for incubation conditions for environmental monitoring plates i.e first two days 30-35°C and after 20-25°C for three days. Mostly guidelines provide only limits but not incubation conditions. Please suggest.

ANSWERS

1. There is no one set incubation scheme. There is data showing 20–25° first followed by 30-35° and vice versa. If you'd like one plate and two incubation conditions, you'll need to show equivalent recoveries of the scheme you choose compared to the recoveries you get at different temps or different media with different temps. There really is no "one way".

2. Your incubation conditions will be dependent on the type of manufacturing (pharmaceutical, medical device, consumer care, etc.) for and the type of test (surface, viable air, etc.). Standards will state different conditions depending on the manufacturing. For example, standards like USP <797 (Sterile Compounding) or USP <795> (Nonsterile Compounding).

Example USP <797> proposed revision on Active Air Sampling:

1. Two samples may be collected for each sample location and incubated concurrently.

    1. Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., malt extract agar [MEA] or sabouraud dextrose agar [SDA]).
    2. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 h, and incubate the other sample at 20°– 25° for no less than 5 days. If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.

Another Example USP <1116> Microbiological Control and Monitoring of Aseptic Environments

1. Selection of Culture Conditions

* For general microbiological growth media such as SCDM, incubation temperatures in the ranges of approximately 20°–35° have been used with an incubation time of not less than 72 hours.

USP website has numerous standards and proposed revisions. Hope this helps!

3. There is mention in <1116> in the section for culture conditions relating to the topic of using single plates at both temperatures, that reads "Incubating at the lower temperatures first may compromise the recovery of Gram-positive cocci that are important because they associated with humans" so would relate to EM/PM monitoring.

QUESTION 5

Can folks recommend articles re. EM [edit note: environmental management] in pharma context?

ANSWERS

1. PDA TR No. 13 (Revised)

2. Here are some other resources on EM:

Reducing Risk in Your Environmental Monitoring Program | Pharmaceutical Outsourcing - The Journal of Pharmaceutical & Biopharmaceutical Contract Services (pharmoutsourcing.com)<https://www.pharmoutsourcing.com/Featured-Articles/564781-Reducing-Risk-in-Your-Environmental-Monitoring-Program/>

Reducing Microbiological Risk and Using Quality Tools in the Pharmaceutical Industry (biopharma-asia.com)<https://biopharma-asia.com/webinars/reducing-microbiological-risk-using-quality-tools-in-the-pharmaceutical-industry/>

Best Practices for Environmental Monitoring and Risk Management | Charles River (criver.com)<https://www.criver.com/resources/webinar-pi-ms-best-practices-environmental-monitoring-and-risk-management>

Environmental Monitoring: Identify & Track Resident Microbes with a Contamination Control Program | Charles River (criver.com)<https://www.criver.com/resources/webinar-pi-ms-environmental-monitoring-identify-track-resident-microbes-contamination-control-program>

Welcome to the MicroLearning Microbiology Series | Charles River (criver.com)<https://www.criver.com/resources/welcome-microlearning-microbiology-series>

QUESTION 6

I am looking for information regarding regulatory requirements for objectionable organisms as it pertains to environmental monitoring. Is the expectation that specific actions be undertaken if an objectionable organism is found during either batch related or routine sampling? Do EM programs even need to consider objectionable organisms or is this concern only related to finished product testing?

ANSWERS

1. Just to make your job/life easier, from here on out we are not going to refer to EM recovered microorganisms as "objectionable" or not. We are going to, properly, leave that term specific to the microorganisms listed in USP <62> (and <60>).

With that out of the way, yes, all agencies expect that you will have some type of appropriate response when you recover microorganisms from EM program that are a "cause of concern". This is like finding Waldo.

I simply use the term "qualitative excursions", which can be applied to the following examples of recoveries and are separate from the number/qualitative of CFU recovered:

1. Mold
2. Bacterial spore formers
3. New flora
4. Strange flora (I.e. microorganisms that you just do not expect to recover in a clean room). This includes microorganisms that originate from foreign habitats such as those aquatic in nature, animal, infectious agents, etc. If it causes you to wonder "how the hell is this in my cleanroom"? Investigate it.
5. Unique morphologies. Admittedly, it's a lot of fun to ID really colorful or nasty looking colonies albeit this is budget dependent. Don't forget finance departments hate micro departments!
6. Repeat offenders (you found Waldo more than once or in multiple locations).

This doesn't mean you need a full scale, all hands on deck, CSI-level investigation, it simply means you should look into what caused the microorganism to make its way into your facility.

Again, we're not going to use the term "objectionable" anymore to describe EM recoveries microorganisms (that term, for the rest of your career is reserved for use with non-sterile testing). Every microorganism recovered in a cleanroom is a cause for concern. You are just going to categorically determine what level of response is appropriate for an investigation (refer to ICH Q9) for support.

Hope that helps. And yes, again, this is what any regulatory agency would expect you to do.

2. Just to address my typo:

"I simply use the term "qualitative excursions", which can be applied to the following examples of recoveries and are separate from the number/qualitative of CFU recovered"

The second use of the word "qualitative" should be "quantitative" and read as follows:

"I simply use the term "qualitative excursions", which can be applied to the following examples of recoveries and are separate from the number/quantitative of CFU recovered:"

3. I would agree with [name redacted] in terms of the terminology of an objectionable microorganism in that it should be limited to microorganisms excluded from a specific non-sterile dosage form.

I would point out that the tests for specified microorganisms in USP <60>, and <62> are limited to specified microorganisms that are product monograph specifications and are not a substitute for the GMP requirement to exclude objectionable organisms from your non-sterile drug products.

The best source of guidance continues to be PDA Technical Report No. 67 *Exclusion of Objectionable Microorganisms from Non-sterile Pharmaceutical and OTC Drug Products, Medical Devices and Cosmetics* 2014

4. Please identify which "we" you mean. Are you talking for the industry? This is not necessarily what FDA inspectors have said in inspections.

5. Hear, Hear. There is good guidance for what is an organism of concern, an objectionable organism, etc.

I know of places that are doing investigations because *S. aureus* was recovered in an active air sample in a CNC manufacturing zone for non sterile oral drug products, and was seen only once in the last year, because it is a <62> indicator organism. Could not convince anyone that it was an indicator that a human had been in the area. The suggested capa to this recovery is that the sampling technicians would fully gown as if going into a sterile suite, before they took samples.

6. When I say "we", I mean myself and anyone who wants to use the proper terminology or discussion points.

If any inspector is referring to "objectionable organisms" in regards to EM recovery, it is not the correct term. It's not "wrong" in a pure sense of the word and we certainly understand what that are trying to allude to, however "we" (myself, a few friends, family and whomever else) should strive to use the proper terms.

As I've stated "objectionable organisms" should be reserved for MLT of non-sterile drugs.

If anyone wants to break away from the pack and use the MLT term elsewhere, I won't throw stones. They just need to explain what they mean.

QUESTION 7

What is the best way to do this and comply with GMP?
Do you have any advice/guideline on how to make EM monitoring easier for ourselves?

ANSWERS

1. You are definitely thinking along the correct lines. Any changes to an EM program should involve a risk analysis and be based on historical data when possible. It sounds like you have a couple of years' worth of historical data. You can begin by reviewing this data and determining if there are some sampling locations that may no longer need to be sampled. Or perhaps some locations could be sampled less frequently. You can also perform a risk analysis on each sampling location to determine if the criticality for sampling has changed.

Be sure that whatever changes you decide upon are documented, justified, and defendable to potential questions from auditors.

2. Actually there is no regulation that requires solid oral dosage form to be manufactured in a Grade D environment.

Evidence of this belief in the September 2021 Draft Guidance For Industry Microbiological Quality Considerations in Non-sterile Drug Manufacturing that make no reference to this requirement

I would refer you tas the best source of guidance.o USP <1115> Bioburden Control in Non-sterile Drug Substance and Drug Product Manufacturing

I believe you are wasting your company's resources. by monitoring this aggressively.

3. Please refer to USP 1115 which guides to prepare a risk assessment to fix an EM program. A whole set of parameters to be considered in the risk assessment are specified. The results of previous trends are always helpful to assess a meaningful data of the EM and to reduce the frequency and (or) sampling sites.
In general I have seen companies following a frequency ranging from once in a month to once quarterly.
4. You can minimise the sampling location based on historical data, Use risk based approach for selection of sample location.

Refer USP <1115> for Microbial assessment of nonsterile product manufacturing environment.

If you are performing active as well as passive sampling, then you can select only active air sampling method.

Swab sampling also minimize, rationalize with cleaning validation of equipment in place.

5. I agree with the comments already made by others on this topic. It does seem like a huge amount of work. However, if you are unsure about how to perform the risk assessments mentioned in some of the responses, I urge you to consult with any of the consultants who regularly post on this site. The cost of a good consultant, I am sure, can overcome all of your annual costs to perform this testing.

QUESTION 8

I’m looking to assess our current EM frequency for non-sterile products (nasal an inhalation products). Areas are classified as ISO8/ EU Grade D for limits. We currently monitor based on numbers of shifts. e.g 2 shift pattern we measure twice per month, 3 shift pattern we measure three times per month and I’m not in agreement with this and think we can possibly reduce to once per month or even less.

I can’t see any actual documented guidance (USP, EP or Orange guide) that provides some example time periods that we can refer to support our decision.
If we decide that once a month or once a quarter is acceptable, who is to say that an auditor will agree and not have their own opinion. Therefore, I'm trying to at least have some basic frequency guidance to be comparing against.

ANSWER

1. Solid oral dosage forms are manufactured in grade D area. We monitor it monthly and we have over 11 000 samples yearly.

It takes a whole team to manage this - we do all the media preparation, sampling (swab method) and testing/reading the results, trending etc.

Superiors demand we reduce the testing according to historical data. I have some ideas on how to do it (analyse perhaps last two years of results, once again decide whether the sampling spot is critical etc.).

QUESTION 9

Is there guidance on EM for viruses and mycoplasma in cleanrooms? Can someone point me in the right direction?

ANSWERS

1. There is not. There is no practical method for conducting EM sampling for viruses or mycoplasma.

What leads you to believe this is necessary?

2. Viruses and mycoplasma of clinical significance usually do not survive outside the human body and are readily destroyed by disinfectants used in cleanrooms.

Absence of guidance documents for viral environmental monitoring should be viewed as indicative that it is not necessary.

The issue is briefly discussed in the article I co-authored: Cundell, A.M., D. Guilfoyle, T. R. Kreil and A. Sawant 2020 Controls To Minimize Disruption of the Pharmaceutical Supply Chain During the Covid-19 Pandemic PDA J. Pharm. Sci. & Technol. May 2020, pdajpst.2020.012021; DOI: https://doi.org/10.5731/pdajpst.2020.012021

3. Bad move. Sounds like a "bug hunt" intended to find microorganisms that may have an impact on product quality. There is no such guidance that you're looking for. Dr. Sutton eloquently described the purpose of an EM program several years ago:

“The purpose of the EM program is to document the state of control of the facility, not to determine the quality of the finished product.”

Sutton S. The Environmental Monitoring Program in a GMP Environment. J GXP Compliance 2010:14(3)23-30

QUESTION 10

When dealing with deviations occurring during microbiological environmental monitoring in facilities manufacturing non-sterile pharmaceutical products, how can we do calculation of the number of microorganisms from the deviating sampling location that would theoretically be present in the product, or product bioburden testing results?

ANSWERS

1. You cannot make a theoretical calculation/derivation. If you recover a microorganism in an EM sample and also recover the IDENTICAL microorganism then you can infer a probable cause and effect.

This also assumes that you are able to determine the the location of the EM sample excursion had a direct influence or contact with product. This would be part of your investigation. Then you also have a multitude of other situations (lack of recovery in EM or bioburden, external influences, multiple recoveries, etc). Keep in mind very few micro investigations lead to the exact root cause. This is especially true in non-sterile manufacturing applications.

EM and bioburden (and microbiology, in general) is funny like that (not always “ha ha” either).

Sadly, no formula or theoretical calculation can be applied.

2. Environmental monitoring data cannot be directly correlated to product contamination. Your investigation should take into consideration the type of sample (ex: air vs surface) sample location, type of organism, and most probable root cause of the excursion. Is your sample location close to product stream? Is the organism mold? Gram positive? Gram negative? Is the root cause related to an activity that would impact your product quality/ patient safety? You may wish to consider increased product testing as well.

If you wish to provide more information, the group may be able to help further.

3. My calculation of the number of bacteria in a controlled environment like a non-sterile product manufacturing facility entering the product would be close to zero. Yes that got your attention!

I would refer you to USP <1115> Bioburden control in Non-sterile Pharmaceutical Product for a discussion of the hierarchy of microbial contamination risk. The pharmaceutical ingredients, water system, and process equipment cleaning and storage are much greater sources of contamination.

QUESTION 11

Is grade 8 for oral solids, but i normally have results less than 20 UFC/m^3 and we want to do less time in the monitoring.

ANSWERS

1. If you are comfortable to sample 500 liters then multiply the result with 2 factor. Then equal to 1000 liters.

2. A couple of comments.

With a limit test you typically must sample the amount specified in the limit. For example CFU/g or ml for non-sterile drug testing and CFU/m^3 or 1000 mL for environment.

Other than the Grade D requirements in the EU GMP Annex 13 I know of no regulatory requirement for a specific air cleanliness standard for non-sterile products.

3. Why “must” you sample 1000L individually for both bacteria and fungi? There’s no requirement to perform dual sampling at each EM site.

No reason you couldn’t perform an individual sample on TSA at each location with a validated incubation scheme and obtain sufficient bacteria and fungal counts on the same plate.

4. An answer most don’t like hearing, but if you need to sample 50 rooms and don’t have the time, you may need to look at expanding resources. It is a basic quality requirement to be adequately staffed such that you’re not prone to considering cutting corners when performing quality tests regarding the health of your facility.

5. I would like to provide suggestions

1. I would suggest to perform Risk assessment with respect to product risk and reduce the sampling locations instead of performing at 500 litres.

2. Logically sampling at 500 litres and Interpreting by multiplying with 2 sounds ok but expressing of results at cfu/m^3 might be questionable. There is no specific guideline

requirement for Non sterile facility, upcoming WHO guideline for OSD may provide insight in this topic.

5. You are correct that there is no regulatory standard for air cleanliness in the manufacturing environments for non-sterile products. In general, non-sterile product manufacturing occurs in rooms that are not classified. In the absence of a microbial standard, most people will often start using the microbial air standard of a Class D environment for these areas and establish an internal standard based upon generated data. It is not common to see the presence of HEPA filters in non-sterile manufacturing environments. Instead, the air filters for a non-sterile manufacturing area have a classification called Merv that has a lower filter particulate retention in comparison to HEPA filters.

QUESTION 12

We have tablet, capsule manufacturing area along with oral liquids and ointments mfg area. All are non-sterile dosage forms.
My question is only settle plate sufficient? Many auditors/customers point out to do air sampling in the manufacturing of these dosage forms.
Can we perform air sampling at a frequency of once in three months? Or there is no need to do air sampling and only settle plate exposure is sufficient?
Any reference apart from USP <1115>, please let me know.

ANSWERS

1. Thank you all, for your feedback. In case I sample less than 1000L air (in non-sterile production) how I will address the results, since in sterile production it is addressed as CFU/m^3.

QUESTION 13

I have a question for improve the time taking the air of the environmental monitoring. Can I change the quantity of liters taken for less liters for example 1000L to 500L?

What can I do for do it the change?

ANSWERS

1. I assume you are referring to viable sampling.

I am not a fan of taking less than a cubic meter of air, ever. Depending on your sampler, you are sampling for only 5-35 minutes in order to take 1000L of air, which is providing good dynamic data. Why cut that short?

I will step off my soapbox and understand that some firms may decide to go with smaller sample sizes in Grades C and D areas and calculate the results per cubic meter (again, air is not homogenous and you are over/under estimating your counts).

If you decide to do so, it should include a risk assessment and rationale with supporting data to justify the change in sampling volume.

You can make the adjustment from your samplers' user menu (either time or volume, depending on the model).

2. In general the answer is "no", since we can't extrapolate air contamination as we do in other microbiology tests because air isn't homogenous and each sample is a snapshot. Some firms do this in non-critical areas but that's usually in a much less regulated environment. What grade is your room that you're looking to reduce sampling?

3. What about the air sampling in non-sterile production? In which you must sample 1000L air for bacteria and 1000L for fungi. And also the same air volume for the compressed air in the same room. What do you do when you have to sample 30-50 rooms? Can you consider the application of passive settle plates method instead of active air sampling method?

4. Why “must” you sample 1000L individually for both bacteria and fungi? There’s no requirement to perform dual sampling at each EM site.

No reason you couldn’t perform an individual sample on TSA at each location with a validated incubation scheme and obtain sufficient bacteria and fungal counts on the same plate.

5. Avoid excessive environmental monitoring in non-sterile manufacturing areas. Periodic monitoring may be useful depending on the products manufactured.

USP <1113> states:

"In general, environments for tablet and powder- and liquid-filled capsule manufacturing should require no monitoring or infrequent monitoring. Monitoring programs should be risk based, and the frequency and number of sampling sites should reflect the risk level. Manufacturing areas for higher-risk dosage forms such as inhalant products require more frequent monitoring and typically are manufactured in rooms classified to a particulate air quality level, e.g., ISO 8."

"For most non-sterile product manufacturing environments, because of their limited environmental controls and comparatively low product risk, the establishment of alert and action levels may not be required. Environmental monitoring is considered an informational survey of the general hygienic conditions of the environment and should not be used in product-release decisions. Monitoring of unclassified environments is not required”.

6. For non-sterile product manufacturing there is no requirement to sample 1000 L of air. Depending on the area classification and gowning requirements sampling 1000 L of air may yield too many colonies to count. You can reduce the air volume per sampling site. This along with the other suggestions already provided, use one plate for both bacteria and fungi (this is quite common), and periodic sampling per USP <1115> should reduce your environmental monitoring.

QUESTION 14

I am hoping someone, anyone, can help me with guidance on environmental monitoring. We currently monitor air and water in our non-sterile pharmaceutical manufacturing plant based on our trending data. However, we are going to begin touch plates and swabbing, and I am a little overwhelmed. I have quantified swabs before by swabbing and immersing the swab in broth, vortexing, and then plating. However, how would you quantify touch plates such as RODAC plates? What if an organism spreads all over the plate and you cannot get an accurate count? Would these be used more as an indication of the environment rather than providing passing or failing results? For a non-sterile facility, is it best to perform swabbing and touch plates on high touch areas from people and not product? If I were to swab a tank, they have to re-clean the entire tank which takes time. Any suggestions are greatly appreciated!

ANSWERS

1. Environmental monitoring is generally performed in the background environment. Sampling of equipment internals may be done to support cleaning validation efforts or as part of your routine cleaning verification program. Though you can certainly swab the background environment, most EM programs focus on nonviable particulate monitoring, active viable air monitoring, and touch plates. In manufacturing steps of high risk to your product, you may also wish to expose settling plates (ex: a compounding step in a biosafety cabinet). Personnel monitoring is also a common component of EM programs.

Your procedure should dictate how you handle spreaders. You may count it as a TNTC and follow your action limit response (typically a clean of the area and then re-sampling) or you can indicate it is a spreader and unable to obtain a valid count. This should also lead to a re-sampling event to obtain a valid result.

Environmental monitoring of your background environment is typically not used alone as release criteria. That is, a "failing" EM result (action limit excursion) does not necessarily mean you have to hold/scrap your batch. There are, of course, a lot of nuances, but it really depends on how you build your program and which samples you consider "environmental monitoring" vs something like in-process monitoring of your process.

I'm not sure which regulatory authority you fall under, but PDA tech report 13 covers environmental monitoring, and EU GMP Annex 1 does as well. ISO 14644-1 helps guide non-viable particulate monitoring.

2. There are no standards in the ISO charts for gloves in a non-sterile environment so you'd sort of be starting from scratch as to how to establish your alert and action levels. Environmental monitoring is just that...monitoring so it's not a "release test"...but if you continually have very high counts that exceed your alert and action levels, that will draw some attention. Also, there are many studies that you can find that talk about recoveries of organisms on contact plates...and those numbers vary. You'll also need to take into account the sanitizer/disinfectant you're using and whether or not your media can neutralize it. If you'd like to contact me directly, you can reach me at [link redacted] for documentation on recoveries and neutralization.

3. The use of swabs and contact plates are considered Class O standard methods, e.g., Standard Methods For the Examination of Dairy Products and have been subject to a thorough evaluation and are widely used so may be considered grandfathered.

The surface contracted with a plate is wiped down with an alcohol wipe to remove media residuals while swabs are not expected to leave residues.

As discussed in USP <1115> Bioburden Control of Non-sterile Drug Substances and Products do not overdo the EM in non-sterile manufacturing areas.

4. Sorry for being late to the party. I agree with [redacted names]. I haven't seen a company use touch plates for personnel in non-sterile manufacturing yet, but there is always a first time.

The touch plates will be dirty considering you will be monitoring the dirty gloved fingers of operators in a non-sterile environment. I would recommend doing a feasibility study for a period of time. Monitor the operator's gloved hands at several intervals and time points over a period of time (e.g. month). And then review the data to determine realistic action limits that are fit for your purpose.

5. In general, the performance of doing touch plates in a non-sterile environment is never performed. Swabbing of equipment surfaces is perform to either validate the sanitization processes or to monitor the compliance with a validated sanitization procedure. RODAC plates may be used to take samples of flat surfaces of the building such as walls and floors after sanitization. Air samples are usually taken of the manufacturing environment by using either gravity settling plates or a mechanical air sampler.

Touch plates using RODAC platted are normally performed for workers who normally work in a Class 100 environment and wear sterile PPE and uniforms. From my experience, I have never seen anyone to perform particulate (non-viable) counts in a non-sterile manufacturing environment, but there can always be someone that does it because they have a classified manufacturing environment. For non-sterile manufacturing, the manufacturing environment is generally never classified to meet even a Class D or Class 100,000 environment. Why conduct particulate counts in the first place? Workers do not wear sterile uniforms. It is hard for workers to maintain clean uniforms in this type of environment depending the work area such as compounding. I have seen many times workers wear non-sterile gloves, hair nets, beard covers and disposable arm sleeves to cover bare arms if they are wearing a short sleeve shirt or blouse of a uniform to prevent contamination of a non-sterile finished product. By the way, I have seen companies in which there are different color worker uniforms for the identification of job function in a non-sterile manufacturing environment. I have even seen some companies to have their workers wear a non-sterile surgical mask over their face during the manufacturing of non-sterile finished products. During a workday, it is very normal for workers to change their non-sterile gloves immediately if they become soiled and to use alcohol hand sanitizers several times a day if their gloves are not soiled. I will be honest that I do not see the purpose of conducting touch plates of workers in a non-sterile manufacturing environment because you are allowed to have a low microbial count in a non-sterile product unlike sterile products. I suspect that workers in a non-sterile manufacturing environment will normally have higher counts than workers in a Class 100 room if samples were ever taken by using a touch plate.

6. Only because a dozen opinions are never enough when it comes to EM!

[redacted name], let's try make this simple (and I apologize ahead of time if I am unable to do so). As to your original question:

Any EM activity that occurs in unclassified/non-sterile operations are risk-based (for information, please have a read of <USP 1115>) with little, if none, regulatory guidance given. I'll assume by touch plate you are referring to surface monitoring via contact plate. My question would be are you then targeting facility surfaces (e.g. walls, windows, floors) with your contact/RODAC plates and swabs or equipment surfaces? You can quantify swabs and contact plates as they are designed as such, assuming you are using a sterile diluent with your swabs. One method is to vortex the swab head (aseptically snapped off from the stalk) in the diluent and membrane filter for a count (whereas using TSB as your swab liquid is qualitative only and should be reserved for use in ISO 5 environments, which is not applicable for you). If you are swabbing a tank and exceeding your alert level or action limit, then you would clean the tank as it would be an indication of poor cleaning/disinfection (unless you have personnel in your tanks, in which case, STOP doing that).

For your direct quantification of contact plates, you just count them. That is all (I wish I could offer more than that). If there are spreaders, then you would want to incorporate an interim read on your plates during your incubation period. Spreaders, in my opinion, are always a qualitative excursion and should be investigated as such.

Both methods have limitations on recovery and you can conduct a study demonstrating your recovery percentages with your media or swabs, in your facility, on your representative surfaces by conducting a coupon evaluation with known counts of appropriate microorganisms.

From an indication standpoint, all EM is in fact, an indication of the environment! The passing/failing is somewhat misleading based on the capabilities and data generated, which is why alert levels and action limits are established. You will have to look at each sampling location and determine what your course of action would be for alert/action excursions. EM data should be utilized to determine state of control and when you are drifting from that happy state of being. Therefore action limit (or multiple alert level) excursions, which would prompt an investigation and CAPA, can be directed towards cleaning & disinfection improvement, facility improvements, personnel behavior improvement or process improvement. The choice is yours and is based on the outcome of your investigation.

Ultimately, I will answer your question with "it depends".

7. We also produce non-sterile solid dosage forms and implemented all of the mentioned (exception: settle plates) for our non-classified production area.
As we now changed to GMP class D (by EU-GMP-Guideline), I may give you a short overview on our previously used system:

1) We called it class E in the style of GMP class A-D (suggested by our authority).

2) We defined limits based on historical data, balanced by GMP class D limits and some literature.

3) Sampling points were defined risk based.

4) We used contact plates for non product contacting surfaces (floors, walls, etc.). -> monitor the cleaning and disinfection process within the rooms.

5) We used contact plates for product contacting surfaces (inner side of the systems, etc.). -> monitor the cleaning and disinfection process for the systems (cleaning validation).

6) If not reachable, we also used swabs for testing product contacting surfaces (tubes, etc.). -> monitor the cleaning and disinfection process for the systems (cleaning validation).

7) We measured the viable air particles by an active air sampler. -> monitor the HVAC-systems and personnel activity in the production area.

8) We measured the non-viable air particles by a particle counter. -> monitor the HVAC-systems and personnel activity in the production area.

9) We used contact plates for personal samples (hands & gowning). -> monitor the personnel hygiene (did they wash, gown and disinfect properly?).

10) We take samples from utilities (soap, creme, detergent) within the production area. -> hand dispensers cleaned and disinfected properly?

11) We take samples from cleaning agents and detergents used in the cleaning areas and for cleaning and disinfection of the rooms. -> removal tools cleaned properly?