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Board of Registration in Pharmacy

Advisory: Environmental Monitoring

Based on recommendations from the Advisory Committee to the Board of Registration in Pharmacy, guidance has been developed regarding environmental monitoring ("EM") in sterile compounding pharmacies. This advisory is designed to supplement the requirements of United States Pharmacopeia ("USP") by providing additional practical guidance to optimize microbiological air and surface monitoring programs.

I. Environmental Monitoring Program

A. Sampling Plan

An EM monitoring program includes sampling for both air and surface viable organisms (bacterial and fungal) as well as for airborne particulate matter (non-viable). A good program will help detect "problem" areas to guide risk mitigation strategies.

In accordance with USP <1116>, "an environmental monitoring program should be tailored to specific facilities and conditions." Work with a qualified professional (e.g., microbiologist, industrial hygienist, or infection control professional) to develop a sampling plan that includes all ISO Classified areas and pass-throughs. The plan should include an appropriate number of sampling locations, a diagram (map) of such locations, and an optimal sampling frequency. Ensure there are an adequate number of sampling locations for the size and scope of the facility. Periodically revisit the sampling plan for any needed changes or updates.

Consider contamination risk factors such as frequently touched sites (e.g., doors, primary engineering control ("PEC") deck, pass-throughs, compounding equipment, etc.), water sources, and the compounding process / workflow when developing the sampling plan. Smoke studies can be used to identify sampling locations including zones of air turbulence within laminar airflow workbenches ("LAFW") and other areas where air turbulence may enter the compounding area (e.g., from doorways, in and around ISO Class 5 PEC(s), etc.). Smoke studies can also identify areas of stagnant

airflow or heating, ventilation, and air conditioning system ("HVAC") "dead zones" (where there is no / minimal HEPA-filtered air) in secondary engineering controls. These areas can be reservoirs of contamination and should also be included in the sampling plan.

B. Sampling Frequency

"Routine microbial monitoring should provide sufficient information to demonstrate that the aseptic processing environment is operating in an adequate state of control." (USP <1116>)

In accordance with USP <797>, the minimum frequency of routine EM sampling is based on the category of compounding and beyond-use-date ("BUD") assignment. Facilities should determine if the frequency of routine monitoring should be increased based on a contamination risk assessment. Consider factors such as volume (e.g., single unit, batch production, etc.), complexity of compounding (e.g., number of aseptic manipulations, non-sterile to sterile, etc.), and facility design (e.g., negative pressure environment, activities in adjacent unclassified areas, etc.). Also, any recent HVAC excursions (i.e., temperature, humidity, differential pressure) should prompt additional monitoring until remediated. Increased frequency would help to identify any patterns or trends providing a better picture of the environment, while a minimal testing frequency may only reflect seasonal changes. The overall goal would be to obtain more data without placing undue burden on compounding personnel or increasing risk to the cleanroom suite(s).

A trending analysis using a greater number of data points from more frequent testing may help identify environmental changes that could be indicative of a problem. Using a graph or other visual representation would illustrate the data well. "A trend analysis (can be) used to facilitate decision-making for requalification of a controlled environment or for maintenance and sanitization schedules." (USP <1116>)

Refer to USP <797> for when non-routine EM sampling must be conducted in response to specific incidents or trends.

C. Sampling Equipment / Media

Pharmacies must verify that any collection devices used for EM (e.g., volumetric air sampling device, electronic particle counter, etc.) have been calibrated in accordance with manufacturer's specifications and are in good working order. Also, confirm that collection devices are appropriately cleaned and disinfected prior to use. For instance,

air impaction sampler heads where the media device is placed must be carefully sterilized to avoid false positive EM results.

Refer to USP <797> and / or consult with a qualified professional to determine the proper sampling media for viable air and surface sampling. A “two-plate” method (bacterial and fungal media) for each sampling location may be used for additional risk mitigation in certain situations (e.g., non-sterile to sterile compounding, batch compounding, etc.) as well as to shorten the window for results (see “Incubation” below).

The use of negative controls is recommended to validate the testing. However, documentation such as a “Growth Promotion Certificate” for all EM media must be obtained to validate the ability to support microbial growth.

II. Procedural Considerations

A. EM must be conducted during dynamic operating conditions meaning that materials have been brought into the area, processing activities are ongoing, and a full complement of compounding personnel are working in the area. Document the time of day the samples are taken, the number of personnel present, and the activities taking place (e.g., during production, conclusion of compounding, etc.).

Passive air sampling procedures (e.g., settling plates, etc.) may be used to supplement a pharmacy’s quality assurance program but do not meet the requirement for dynamic sampling. Conducting EM immediately after a “deep clean” of ISO Classified areas is also inconsistent with USP and does not allow for the collection of meaningful data.

EM conducted in conjunction with the certification / recertification of facilities and equipment should be conducted immediately prior to the commencement of the “functional” testing (i.e., airflow testing, HEPA filter integrity test, smoke test) and be conducted by a qualified third-party professional.

When work is performed that could cause contamination (e.g., renovations, shutting down HVAC, etc.), collect samples after the work has been completed to assess / confirm the state of control prior to resuming compounding. BUDs should be reduced or limited as outlined in Policy 2023-09: *Action Level Environmental Monitoring Results* until EM results within action levels have been received.

If EM is to be performed by “in-house” personnel, develop and document proficiency training (e.g., collecting samples, incubating, etc.) in conjunction with a consultant or qualified professional.

B. **Incubation**

When using a third-party vendor for incubation, resulting, and identification of samples, utilize only fully compliant ISO-certified laboratories. Assure closures are secure and proper temperature control of the plates is maintained during storage and delivery / shipping.

If incubating EM samples “in-house”, properly prepare, handle, and store media devices and incubate them at the temperature ranges and duration specified by USP and / or the media manufacturer’s recommendations. Multiple incubators may be used to shorten the incubation period when utilizing a “two-plate” method. This involves incubating different media plates concurrently at each of the required temperatures to promote either bacterial or fungal growth. Restrict access to the incubation area and consider personal protective equipment (“PPE”) requirements to avoid introduction of contamination. Daily review of plates is not recommended as this can cause temperature fluctuations which may interrupt the growth process and introduce contamination.

To minimize temperature fluctuations, use caution when opening the door wide especially with small incubators as these units may be more temperature sensitive. Temperature fluctuations and humidity can contaminate incubators. Clean and disinfect incubators on a regular basis (monthly / quarterly) depending on the level of activity. It may be helpful to have more than one unit so they can be rotated.

Monitor the incubator temperatures either manually or by a continuous recording device. Temperatures should be reviewed and documented at least daily on the days the pharmacy is open. Calibrate incubators and temperature recording devices in accordance with manufacturer’s specifications.

C. **Results**

In accordance with USP <797>, “…results from microbiological air and surface sampling must be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination.”

Remember that even if there is no growth on a microbiological sample, this only means that growth was not recovered. It does not necessarily mean that the entire environment is free of contamination.

Determine if any microbial growth constitutes an action level result based on the number of colony-forming units ("CFU") and / or organism(s) identified. Any microbial growth resulting from EM in an ISO Class 5 area, ISO Class 7 **buffer room**, or any action level growth in any other ISO Classified areas must be identified to at least the species level. Refer to Board Policy 2023-09: *Action Level Environmental Monitoring Results* for EM action levels and associated reporting requirements.

Consider also establishing "alert levels" for ISO Classified areas with the help of a qualified professional. Alert level means an excursion limit value that when met or exceeded indicates an early warning of a drift from normal operating conditions but does not necessarily require corrective action. For alert level excursions, EM sampling should be more frequent, and the situation should be continually assessed so progression to an action level does not occur.

III. Corrective Action / Follow-up

Develop appropriate response plans for alert and action levels in ISO Classified areas. In the event of an action level excursion, it is important to respond to, and properly remediate these findings in accordance with Board Policy 2023-09: *Action Level Environmental Monitoring*.

IV. Documentation

Environmental sampling reports should include the following (minimum) elements:

A. date report prepared;
B. sample collection date and time;
C. identification of sampling locations;
D. type of sample (i.e., air or surface);
E. sampling conditions (i.e., dynamic);
F. number of personnel present and activities taking place during sampling;
G. sampling equipment and calibration certificate(s);
H. identification of individual(s) conducting the sampling;
I. media type(s);
J. media lot number, expiration date, and growth promotion confirmation;
K. date sample received by lab, if applicable;
L. incubation start date(s), duration, and temperatures;
M. dates of final results;

N. results of each sample (CFU count);
O. identity of any CFU that requires identification to at least the species level;
P. indication of any action level result(s);
Q. indication (i.e., signature) that the final report has been reviewed by a microbiologist (unless no growth was recovered); and
R. indication that the Manager of Record, Designated Pharmacist-in-Charge, or their pharmacist designee reviewed the final report.

Maintain all reports and any corrective actions in the pharmacy's records.

Please direct any questions to: **Pharmacy.Admin@mass.gov**

References

Draft 247 CMR 17.00: Sterile Compounding
https://www.mass.gov/doc/247-cmr-1700-sterile-compounding/download

USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations (Effective November 1, 2023) https://www.usp.org/compounding/general-chapter-797

USP <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments http://ftp.uspbpep.com/v29240/usp29nf24s0_c1116.html

FDA "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice" https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice

Contamination Control Basics Risk and Resolution, Microrite, Inc., Ziva Abraham, Ph.D., Parenteral Drug Association West Coast Chapter June 20, 2019
https://www.scribd.com/document/520295481/contamination-control-basics-risk-and-resolution