



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Bureau of Health Professions Licensure
239 Causeway Street, Suite 500, Boston, MA 02114

Tel: 617-973-0800
TTY : 617-973-0988
www.mass.gov/dph/boards

Board of Registration in Pharmacy

Advisory: Remediation Considerations for Handling Above Action Level Environmental Monitoring (EM) Results

In an effort to reduce the risk to patients receiving compounded sterile preparations (CSPs), the Board of Registration in Pharmacy (Board) has developed this guidance document to assist licensees in addressing above action level environmental results within ISO-classified spaces.

The Board's policy, *"Sterile Compounding Pharmacy Response to Above Action Level Environmental Monitoring Results"*, outlines the required steps for a Pharmacy's response to environmental excursions including reporting requirements, conditions for continued compounding, and other key elements of response that must be instituted with each instance of above action level results.

This guidance document provides an in-depth approach to assessment and analysis of above action level contamination. The document incorporates USP <797> standards along with FDA aseptic processing standards for documentation and follow-up. Assessment of the situation at hand along with investigatory techniques can help to identify a root cause and develop a corrective action preventative action plan (CAPA) specific to the situation.

Preventative strategies focused on continuous monitoring of both personnel competency and proficiency along with the compounding environment are key elements in preventing product contamination and patient harm. Development of an intense monitoring program for personnel, products, and the environment is an important part of the quality program for compounded sterile preparations. In the event a sterile compounding facility has an environmental excursion, a comprehensive risk assessment of both the product and process is paramount to an appropriate response.

Proper use of this document will help to ensure a consistent and complete approach to environmental excursions. Continual assessment of work practices coupled with an in-depth root cause analysis (RCA) will result in a higher level of quality care to the patients served.

I. Overview

An above action level environmental monitoring (EM) result indicates a sterile compounding operation that may be at risk for microbial contamination. Therefore, the Board recommends the following:

- A. Sampling data should be collected and reviewed on a routine basis as a means of evaluating the overall control of the compounding environment. If data consistently shows elevated levels of microbial growth, competent microbiology personnel should be consulted.

Note: The Board recommends that a competent microbiologist be consulted in the event of any above action level microbiological result.

- B. Any colony forming unit (CFU) count that exceeds its respective action level should prompt a comprehensive re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the sterile compounding location.
- C. The root cause investigation should include an evaluation to determine compliance with USP <797>. Any significant gaps should be considered as potential root causes for the above action level result(s) and adequate CAPAs should be implemented in a timely fashion.
- D. The source of the problem should be eliminated, the affected area cleaned, and resampling performed.
- E. Ensure that your pharmacy is not preparing, packing, or holding sterile drug products under conditions which put your sterile drug processes / products at risk for contamination. Common risk factors are described in this document.
- F. A thorough review of data should be completed in order to determine the need to retrieve product that has or could result in patient related adverse events.
- G. Development of a Remediation Plan which contains the following critical elements:
 - i. Root Cause Investigation
 - ii. Product / Process Risk Assessment
 - iii. Corrective Action and Preventative Actions (CAPAs)
 - iv. Consider engagement of a qualified Microbiologist / Infection Control Professional / Industrial Hygienist to assist in the evaluation and remediation process.

- H. A prompt and thorough review of all policies and procedures associated with sterile compounding and aseptic work practices should be conducted and if necessary, modifications should be made.

II. Remediation Considerations

When determining what remediation would be necessary after receipt of a viable EM above action level result or if a pharmacy should stop compounding, several points need to be considered. An over-arching picture of the quality of the ISO classified space(s) needs to be considered:

- A. Was the above action level (AAL) result isolated to a specific area? Was the AAL confined to a single hood, a single buffer room, or the anteroom? Or is there evidence that microbial contamination is present throughout the space?

For example, was contamination identified at a single location inside the positive pressure buffer room but not found inside the primary engineering controls (PECs), anteroom and / or the negative pressure buffer room? Or was microbial contamination identified in numerous locations?

Note: Special consideration should be given to negatively pressurized areas and adjacent areas during remediation due to increased risk to compounded sterile preparations (CSPs).

- B. What is the typical reservoir for the microbe identified? Was containment identified in a location consistent with its typical reservoir or elsewhere?

For example, was a water-borne pathogen isolated in direct proximity to the anteroom sink vs. water-borne pathogen inside an ISO 5 PEC?

- C. Is there a documented history of viable environmental excursions (within a certain time frame) or is this an isolated incident?

- D. When was the sample collected vs. when growth was observed and identified? What microbial control provisions have occurred in the space since that time?

- i. What type (daily, weekly, and / or monthly) of cleaning activities have been performed since sample collection?
- ii. Is it probable that the organism is still present in the environment? Is the cleaning agent(s) effective against the microbe(s) identified?

- E. In some situations, it may be beneficial to work with industry specialists during the development phase of a viable EM program to aid in the development of robust policies and procedures.

III. Remediation Steps

Step 1: Evaluate Sample Results

A. Review the above action level results of the sample, including:

- i. Location and classification of the area / zone (ISO 5, ISO 7, etc.) where the sample was collected.
- ii. Organism(s) identity to a minimum of genus level.
- iii. Total number of CFUs observed in each area.
- iv. Did the AAL result from an air or surface sample?
- v. When was the sample taken? Was it under dynamic conditions? Include date / time of sample collection.
- vi. Why was the sample taken? Routine sample or in response to previous excursion, etc.
- vii. Was the person conducting the EM observed to ensure that proper procedures were followed?

B. Evaluate for adverse trends:

When was the location last sampled, and what was the result? This step should be crucial for determining proper remediation and if a sterile compounding facility should disengage from sterile compounding activities.

C. Consider enlisting a third party expert such as a microbiologist, industrial hygienist, or infection control professional to evaluate the results and assist with development of required response based on the results of evaluation.

Engagement of a third party expert is especially important if there are multiple environmental samples that are contaminated during routine EM or repeat EM indicating that the problem has not been eliminated.

Step 2: Evaluate Product / Process Risk for Microbial Contamination

In order to effectively evaluate product risk to microbial contamination, the following non-exhaustive list should be considered:

- Nature of the process
- Nature of the product (risk level, etc.)
- Delivery method (route of administration, etc.)
- Storage conditions and beyond-use-date (BUD) assignment
- Patient exposure risk

A. Microorganism Evaluation

- i. A full profile of the identified microorganism(s) (including gram negative / positive, aerobic / anaerobic, spore forming, etc.) should be conducted by a microbiologist.
 - a. Severity of the above action level incident.
 - b. Quantity of CFU and species of microorganism(s) isolated.
 - c. Pathogenicity of the organism(s) identified should be assessed including a health hazard evaluation for both human and veterinary patients, as applicable.
- ii. Perform a comprehensive history / trending review. This should not be limited to just EM results. It should include all microorganism-related testing where applicable (e.g. personnel monitoring, media-fill evaluations, finished product testing, non-routine monitoring, etc.).
- iii. Determine if the AAL represents isolated contamination or gross contamination throughout the sterile compounding areas.
- iv. Review EM reports specific to sites around doors and pass throughs for recent alerts / excursions.

B. Process / Product Impact Factors

- i. Evaluate potentially impacted products¹. The product contamination risk level of the compounded drug should be considered during evaluation, as well as the following non-exhaustive items:
 - a. What types of sterile compounding activities were being performed at the time the viable EM sample was collected (supply restocking, material transfer, etc.)?
 - b. Type of sterile compounding performed during the time frame in question (single unit or batch production, etc.).
 - c. BUD.
 - d. Compounded product storage conditions (room temperature, refrigerated, frozen).
 - e. Preservative use in compounded products.
 - f. Nutritive properties of the product (e.g., TPN, etc.).
 - g. Use of non-sterile starting ingredients.
 - h. Sterilization method of compounded products (sterile filtration or terminal heat).
 - i. Whether or not filtration is / was performed on sterile compounded preparations within the vicinity of the AAL.

¹ **MGL Chapter 112 Section 39D (e)** *If a pharmacy knows or should have reason to know that a drug preparation compounded, dispensed or distributed by the pharmacy is or may be defective in any way, the pharmacy shall immediately recall the drug preparation. Any of the same drug preparations remaining in the possession of the pharmacy shall be located and segregated and shall not be distributed or dispensed.*

- j. Product volume / units.
 - k. In-process hold-times.
 - l. Review of critical deviations that may increase product risk to microbial contamination.
 - m. Closure systems (closed system or open closure system).
 - n. Route of administration.
- ii. Visually inspect all available compounded products (current stock, retained product, etc.) for direct evidence of product contamination, including visible contamination.
 - iii. Review any instances of returned / recalled product which may reflect contamination.

C. Adverse Event Monitoring²

Thoroughly review complaint files / adverse event reports for issues which may reflect contamination (complaints of inflammation / infection / fever, visible contamination, etc.).

Step 3: Conduct a Root Cause Investigation

An evaluation of common risk factors should be considered as potential root causes for the above action level result(s) and adequate CAPAs should be implemented in a timely fashion. This list is non-exhaustive.

A. Equipment / Facility Deficiencies

- i. Visual inspections should be conducted paying special attention to the following common risk factors:
 - a. Visible signs of filth, dirt, dust, mold or mildew, insects, inappropriate items / debris, trash or other signs of inadequate cleanliness on floors, ledges, and other surfaces.
 - b. Equipment with difficult to clean surfaces due to poor construction, or meaningful degradation (rust, corrosion, etc.).
 - c. The critical zone (direct compounding area) within the sterile compounding area is open to the surrounding clean room with no (or minimal) physical barriers separating it from other non-aseptic activities (i.e. vertically integrated laminar air flow zones).

² **MGL Chapter 112 Section 39D** (c) *The manager of record of a pharmacy shall report any serious adverse drug event, as defined in section 51H of chapter 111, occurring as a result of the patient's interaction with any drug or pharmaceutical manufactured, produced or compounded at the manager of record's pharmacy, to the board, the federal Food and Drug Administration MedWatch Program and the Betsy Lehman center for patient safety and medical error reduction.*

- d. The layout of the facility is designed and / or operated in a way that allows influx of poor quality air into a higher classified area or permits poor flow patterns of personnel or materials.
- e. Sterile compounding area cluttered with equipment and material, making it difficult to clean adequately.
- f. Is the compounding area being used for storage?
- g. Are any classified spaces being used for activities that are not essential to the compounding process?
- h. Sinks in unclassified and classified spaces adjacent to the compounding areas where sterile compounding activities are performed.
- i. Drains are prohibited from sterile compounding buffer areas and should not be present in other classified areas or unclassified spaces adjacent to the compounding area.
- j. Refrigerators should not be in classified spaces.
- k. Ceiling surfaces in classified spaces are not impervious or hydrophobic.
- l. HEPA filters are not caulked around each perimeter to seal them to the support frame.
- m. Peeling paint, chipped drywall, acoustic ceiling tiles with cut-out holes or other breaches in the walls or ceilings.
- n. Exhaust vent(s) for the room is unclean or appears encrusted with foreign material.
- o. Review utilization of doors and pass throughs for proper functioning and closure. Are pass throughs interlocked and properly sealed?

Note: Review the FDA's guidance on insanitary conditions at compounding facilities:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf>

- ii. Review any recent changes in the facility design, or operational process including renovations to any classified or unclassified spaces.
- iii. Assess upstream issues affecting the clean room for possible impact on the classified areas (e.g. product, material, movement, water sources, etc.).
- iv. Determine if other environmental concerns (e.g. adjacent to warehouse, cardboard around perimeter, etc.) are impacting the classified areas.

B. Environmental Controls Deficiencies

- i. Conduct assessment of the PEC(s):
 - a. Ensure power to the PEC(s) is on.
 - b. Is the PEC on 24/7 or is there an “off” period? If there is an “off” period, was the PEC appropriately cleaned after the “off” period?
 - c. Perform visual inspection (general cleanliness, dirt, filter, grills/intakes, isolator gloves, etc.)
 - d. Assess HEPA filter (any dirt, damage or residue?)
 - e. Is the PEC vibrating or making noise in excess of normal operations?
 - f. Has the PEC been moved or relocated (since last certification)?
 - g. Does the PEC contain compounding equipment? If so, has it been moved or relocated?
 - h. Has a recent smoke study been performed within the PEC? If so, did the PEC smoke study identify any area(s) displaying turbulent air flow patterns?
 - i. Has the PEC been cleaned and maintained according to manufacturer specifications and facility policies and procedures?
 - j. Check for any condensation or other source of moisture around the PEC.
 - k. Changes in activities in area surrounding the PEC? (increased traffic, new procedure, etc.)
 - l. Noticeable changes in HEPA filtered supply air, coverage, or airflow over the area where sterile drug is exposed.
 - m. Review pressure gauges on PEC, if applicable, to assess loss of pressure.
- ii. Conduct assessment of secondary engineering controls (SECs).
 - a. Has a smoke study been performed within the SEC? If so, did the SEC show a general top to bottom dilution of air?
 - b. Lack of measurement of pressure differentials during operations? Ensure gauges are in working order.
 - c. Review temperature, humidity, and pressure differential logs for excursions and corrective actions.
 - d. Inadequate design / controls to ensure substantial pressure differentials between higher air cleanliness and lower air cleanliness (e.g., unclassified) including:
 - 1. Allowing multiple doors to be opened simultaneously.
 - 2. Allowing a door between two rooms to be open for an extended period.

3. Have there been any HVAC related issues (power loss, lack of airflow, etc.) since the last certification? If yes, were corrective measures taken? What were the remediation steps? Was recovery time measured?

Note: If the sterile compounding room is an open concept ISO 5 area and / or vertically integrated laminar flow (VLF), the HVAC operations must be checked.

iii. General assessments for both PEC(s) and SEC(s):

Review results of last certification, and any comments on the report.

- a. Does the PEC / SEC appear to be operating the same or similar to operating conditions at the time of certification (e.g., temperature, humidity, pressure, etc.)? Are one or more conditions drastically different?
- b. If yes or unsure, engage certification vendor / HVAC engineer.

C. Personnel Hand Hygiene / Garbing and Aseptic Work Practice Deficiencies

All sterile compounding personnel should be observed for compliance. Below is a non-exhaustive list.

- i. Review hand hygiene / garbing procedure, and personnel work practices:
 - a. Review garbing / gloving.
 - b. Do personnel change into scrubs at the facility, wear them in from home, or are street clothes worn in classified spaces?
 - c. Are dedicated shoes worn in classified spaces?
 - d. Appropriate order of garbing? (observe)
 - e. Appropriate coveralls or gowns used?
 - f. Coveralls or gowns donned appropriately? (observe)
 - g. Gloves donned properly?
 - h. Coverall or gown reuse consistent with policy?
 - i. Coverall or gown intended for reuse appropriately stored?
 - j. Review most recent gloved fingertip / thumb sample results.
 - k. Only essential items brought into hood?
 - l. Review aseptic technique. (observe)
 - m. Are gloves appropriately disinfected?
 - n. Assess practice for possible touch contamination (door opening, items brought into hood, etc.).
 - o. Review most recent media fill results.

- ii. The following list includes poor aseptic work practices which are common risk factors for microbial contamination:
- a. Performing sterile compounding activities during illness (coughing / sneezing).
 - b. Wearing non-sterile gloves while engaged in sterile compounding.
 - c. Performing aseptic manipulations with exposed skin. This includes hands, wrists, forehead, mouth, etc.
 - d. Gowning in a manner that may render the sterile gown contaminated. For example, gowning occurs in non-classified areas, gowning apparel allowed to touch floor, sterile gloves put on improperly. This includes touching the outside of a glove with bare hands, etc.
 - e. Leaving and re-entering clean room from non-classified areas without changing any personal protective equipment.
 - f. Manual handling of sterile components / containers should be done with extreme caution and in a manner that minimizes potential cross contamination (capping syringes or ophthalmic containers, utilizing stop-cocks multiple times etc.).
 - g. Performing a sterile compounding step that exposes the sterile product to conditions less than ISO 5.
 - h. Aseptic manipulations by personnel or equipment / supply placement such that it blocks the movement of first pass air around the exposed product.
 - i. Touching non-sanitized equipment or other items located outside of the ISO 5 area and then proceeding with aseptic manipulations without changing or sanitizing gloves.
 - j. Poor behavior or poor aseptic technique of operators, such as placing body or objects in the path of unidirectional airflow, contacting sterile materials with non-sterile instruments, exposed skin, infrequent or inadequate glove and surface sanitization (e.g., using a non-sterile disinfectant), and other movement that has potential to disturb the critical ISO 5 zone. Also, assess material transfer of supplies into and out of ISO 7 and ISO 8 zones.
 - k. Note practices for the reuse of gowning components and infrequent replacement throughout the day, such as after coughing and sneezing.
 - l. Any recent identified breaches (improper procedure by testing personnel, unauthorized access, etc.).
 - m. Processing area and countertops cluttered or used for equipment storage.

D. Review / Observe Cleaning Procedures and Logs

- i. Review cleaning logs
 - a. Has cleaning been consistently performed according to an established schedule based on the minimum required frequency?
- ii. Review cleaning procedures
 - a. Proper cleaning agents being used? (sterile vs. non-sterile?)
 - b. Proper cleaning equipment / supplies being used?
 - c. Cleaning equipment / supplies being maintained correctly?
 - d. Proper order of cleaning (e.g., cleanest to dirtiest)?
 - e. Compounding equipment moved for cleaning?
 - f. Condition (e.g., state of repair) of cleaning equipment assessed?
 - g. Difficult / hard to clean areas being cleaned appropriately?
- iii. Review waste removal process
 - a. Minimal agitation / movement, etc.
 - b. Is trash removed at the end of shift or during sterile compounding activities?
- iv. Ensure proper cleaning and disinfection was performed after sampling.
- v. Was sampling equipment properly cleaned and maintained according to manufacturer specification and facility policies and procedures?

E. Review Cleaning Agents

- i. Review cleaning agents for effectiveness
 - a. Verify EPA statement of antimicrobial activity or Certificate of Analysis.
 - b. Consider consultation with microbiologist, industrial hygienist, or infection control professional for facility-specific requirements (previous resistance, flora profile, etc.)
- ii. Review contact time of agents. Does cleaning policy reflect appropriate times?
- iii. Is a quaternary ammonium or phenolic based germicidal detergent being used?
- iv. Are chlorine and / or peroxide-based germicidal disinfectants being used?
- v. Is a sporicidal agent being used?
- vi. What is the frequency of application for all cleaning and disinfecting agents?

- vii. Are cleaning agents being used according to manufacturer specifications (RTU vs. diluted)? Is sterile diluent being used?
- viii. Review expiration dates of cleaning agents (RTU and upon dilution).
- ix. Review cleaning agent effectiveness against environmental monitoring analysis for comparable organisms and appropriateness.

F. Review Environmental Sampling Procedures

- i. Who conducted the sampling?
- ii. Are the required volumetric air samplers being used? Or settling plates?
- iii. Equipment / supplies being used correctly?
- iv. Proper preparation / labeling of collection plates?
- v. Proper gowning / gloving?
- vi. Appropriate aseptic technique?
- vii. Proper order of sample collection?
- viii. Proper incubation (time and temperature)?
- ix. In-date, appropriate media used?
- x. Controls used?
- xi. Check Certificate of Analysis for media selection to ensure growth.
- xii. Review sampling map:
 - a. Appropriate locations inside each PEC, or in a Class 5 open area, based on areas prone to contamination and flora profile?
 - b. Correct number of samples collected based on facility size, activities, normal flora, previous excursions, and trending of prior EM results?

Note: The Board recommends that licensees have service level agreements with testing vendors to assure that all of the facility's policies and procedures regarding hand hygiene, garbing, cleaning of testing equipment, aseptic technique, and utilization of classified spaces are followed to assure proper sampling processes and sample integrity as well as reduce contamination risk to the classified space. Licensees are responsible for preventing contamination to sterile compounding areas.

G. Common Errors / Failures in Root Cause Investigations

- i. The sequence of events is not outlined appropriately. The investigations should start from the beginning and include all items in a step-wise manner that could be associated with the event.
- ii. Focusing on policies and procedures. It is most important to find out what "actually" happened rather than what "should" have happened.
- iii. Exclusion of "at-risk behavior" from the report. A thorough risk assessment needs to be included in the investigation.

- iv. Identifying system errors that could result in repeat events but not acting upon them.
- v. No assessment of human factors or human error. Identifying areas prone to human error can help build stronger systems and minimize repeat events.
- vi. Minimal consultation with experts outside of the direct operation.
- vii. Failure to connect action and consequence.
- viii. Focusing on the weak risk-reduction strategies. Layering action plans to include all risk-reduction plans will result in success.
- ix. Failure to successfully implement the action plan.
- x. Information pertaining to the situation is not shared with the appropriate parties. (Infection control, leadership, pharmacy staff, etc.)
- xi. Invoking punitive action based on the result of the investigation.

Step 4: Implement Appropriate CAPAs

A. CAPAs should meet the following critical requirements:

- i. Appropriately address the root cause(s) of the above action level EM result.
- ii. Consider product / process risk.
- iii. Include EM re-evaluation of the associated sample location(s).
- iv. Include a training aspect.
- v. Implement in a timely fashion.

B. Other Considerations:

- i. No definitive root cause identified:
 - a. The following are considered inadequate responses under conditions in which no definitive root cause(s) of the above action level result is identified:
 - 1. One-time cleaning of the location where the above action level result was obtained following routine procedures.

Note: Having a qualified professional scientifically evaluate the cleaning procedure to ensure that it is appropriate for eliminating the organisms that were identified in the above action level EM result. Cleaning should be expanded to surrounding areas.

- 2. One-time EM re-evaluation of the location where the above action level result was obtained.

Note: Expanding the EM re-evaluation to surrounding areas and increasing the frequency of EM should be considered under these circumstances. Consider enlisting the help of a third party subject matter expert.

IV. Review and Complete the Remediation Plan

- A. Review of the final remediation plan including RCA and CAPA should be performed to ensure the process is thorough and complete.
- B. The remediation plan should be reviewed by at least the following:
 - i. Qualified Microbiologist / Infection Control Professional / Industrial Hygienist
 - ii. Pharmacist Manager of Record or pharmacist in charge of sterile compounding
 - iii. Administrative Leadership for facility (e.g., Quality, Directors, Chiefs, etc.), as applicable.
- C. Ensure that all required reporting forms and documentation (as detailed in the reporting forms) are submitted to the Board within the required timeframe.

Please direct any questions to: Pharmacy.Admin@MassMail.State.MA.US