Recent well-publicized compounding errors have demonstrated the rapidity by which contamination in the pharmacy can lead to patient infections via contaminated CSPs. As such, implementing an effective environmental monitoring (EM, also called environmental sampling) program is vital. However, the details of a pharmacy EM program are subject to some confusion in the current regulatory environment, leaving many to wonder what sample sites, testing frequency, and investigations into excursions should be included in a comprehensive EM program.

A cursory reading of USP <797> may leave the false impression that EM plays a role only during the biannual certification of the classified areas, meaning the EM program should include only two sampling intervals per year. USP <797> offers some potentially conflicting guidance on this point. In the Environmental Quality and Control section, USP <797> states:

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This text seems to indicate that biannual testing is expected. However, a few paragraphs further in the section, the following text counters that assumption:

> This passage seems to clearly instruct the pharmacy to use the EM program as a metric to monitor the ongoing state of control of the facility. Moreover, USP <1116> explicitly states that pharmacy should use the EM program for this purpose. With this in mind, deeper evaluation of the role of EM in the pharmacy is warranted.

**What Is the Intent of the EM Program?**

Integral to establishing an EM program is defining its scope and purpose. The FDA is clear on this point:

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**Viable and Nonviable Environmental Sampling (ES) Testing**

The ES program should provide information to staff and leadership to demonstrate that the PEC is maintaining an environment within the compounding area that consistently ensures acceptably low viable and nonviable particle levels. The compounding area includes the ISO Class 5 (see Table 1*) PEC (LAFWs, BSCs, CAIs, and CACIs), buffer areas, ante-areas, and segregated compounding areas.

Environmental sampling shall occur as part of a comprehensive quality management program and shall occur minimally under any of the following conditions:

- As part of the commissioning and certification of new facilities and equipment;
- Following any servicing of facilities and equipment;
- As part of the recertification of facilities and equipment (ie, every 6 months);
- In response to identified problems with end products or staff technique; or
- In response to issues with CSPs, observed compounding personnel work practices, or patient-related infections (where the CSP is being considered as a potential source of the infection).

* Table 1 is available on page 2 of USP <797>.

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**Abbreviations**

- BSC = biological safety cabinet
- CACI = compounding aseptic containment isolator
- CAI = compounding aseptic isolator
- CSP = compounded sterile preparation
- LAFW = laminar airflow workbench
- PEC = primary engineering control

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**Environmental Viable Airborne Particle Testing Program—Sampling Plan**

- An appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed.
- Selected sampling sites shall include locations within each ISO Class 5 (see Table 1*) environment and in the ISO Class 7 and 8 (see Table 1*) areas and in the segregated compounding areas at greatest risk of contamination (eg, work areas near the ISO Class 5 [see Table 1*] environment, counters near doors, pass-through boxes).
- The plan shall include sample location, method of collection, frequency of sampling, volume of air sampled, and time of day as related to activity in the compounding area and action levels.1
- It is recommended that compounding personnel refer to USP <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments and the CDC's Guidelines for Environmental Infection Control in Healthcare Facilities, 2003 for more information.

* Table 1 is available on page 2 of USP <797>.

1 Review of the data generated during a sampling event may detect elevated amounts of airborne microbial bioburden; such changes may be indicative of adverse changes within the environment.

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**Environmental Monitoring—General Written Program**

In aseptic processing, one of the most important laboratory controls is the environmental monitoring program. This program provides meaningful information on the quality of the aseptic processing environment (eg, when a given batch is being manufactured), as well as environmental trends of ancillary clean areas. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs (211.42 and 211.113). And later, FDA states:

> Environmental monitoring data will provide information on the quality of the manufacturing environment.
By monitoring bioburden levels in the facility, the EM program provides a measure of the state of control underpinning the pharmacy’s operations. One criticism of microbiological assays used in EM is that they can be subject to variability, which may reduce the precision and predictive ability of the data they provide. But rather than negate the value of the assays based on their imperfect predictive ability, pharmacy leaders should capitalize on the data these assays provide—namely, their ability to elucidate trends over time. EM data derives its value in establishing and monitoring facility trends, rather than in the evaluation of single data points. USP <1116> reinforces this idea, stating:

> It is important that locations posing the most microbiological risk to the product be a key part of the program. It is especially important to monitor the microbiological quality of the critical area to determine whether or not aseptic conditions are maintained during filling and closing activities. Air and surface samples should be taken at the locations where significant activity or product exposure occurs during production. Critical surfaces that come in contact with the sterile product should remain sterile throughout an operation. When identifying critical sites to be sampled, consideration should be given to the points of contamination risk in a process, including factors such as difficulty of setup, length of processing time, and impact of interventions . . .

All environmental monitoring locations should be described in SOPs with sufficient detail to allow for reproducible sampling of a given location surveyed. Written SOPs should also address elements such as (1) frequency of sampling, (2) when the samples are taken (ie, during or at the conclusion of operations), (3) duration of sampling, (4) sample size (eg, surface area, air volume), (5) specific sampling equipment and techniques, (6) alert and action levels, and (7) appropriate response to deviations from alert or action levels.

In other words, the sites used in the routine EM program must be identified and justified. Section X.A.2 states:

> Microbiological monitoring levels should be established based on the relationship of the sampled location to the operation. The levels should be based on the need to maintain adequate microbiological control throughout the entire sterile manufacturing facility . . . Environmental monitoring data will provide information on the quality of the manufacturing environment.

The virtue of a microbiological monitoring program lies in its ability to confirm consistent, high-quality environmental conditions at all times. Monitoring programs can detect changes in the contamination recovery rate that may be indicative of changes in the state of control sustaining the environment.

While FDA inspections are likely to invoke trepidation, they also can serve as opportunities to evaluate and improve operations. FDA has posted approximately 160 Form 483 reports from pharmacy inspections on their Web site since 2012. Of these, approximately 78% cite specific issues with the pharmacy’s EM program. Clearly, EM is an area where many pharmacies can, and should, improve performance.

Environmental Monitoring as a Part of a Contamination Control Program
Developing and maintaining a contamination control program can be challenging. USP <797> describes the system of increasing control for the facility in terms of a bull’s eye diagram (see FIGURE 1), where the decreasing size of the concentric circle indicates an increasing level of contamination control.

In general terms, bioburden (microbial) contamination management can be divided into control activities and monitoring activities (see ONLINE-ONLY TABLE 1). Both aspects of contamination management—the control activities that affect levels of microbial contamination, as well as the monitoring activities that allow evaluation of those controls—are necessary to build a successful contamination control program.

Components of Environmental Monitoring

Testing Methods
Microbiological testing methods are subject to operator and methodology affects. Therefore, it is critical to determine your testing methods at the outset and to continue with those methods throughout the program. Surface sampling, for example, should be done by agar transfer, if possible; while air sampling can be performed in a variety of ways. Viable air monitoring can be undertaken using both passive (settle plates) and active (drawing a set volume of air in for sampling) methods, while non-viable air monitoring should be conducted using active methods (see USP <1116> and Sutton 2010 for reviews).

Sample Sites
Identification of sample sites for the EM program is vital to enable a comparison of a facility’s state of control over time. For example, the FDA Aseptic Processing guideline (Section X.A.1) states:

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

Environmental microbial monitoring and analysis of data by qualified personnel will permit the status of control to be maintained in clean rooms and other controlled environments. The environment should be sampled during normal operations to allow the collection of meaningful, process-related data. Microbial sampling should occur when materials are in the area, processing activities are ongoing, and a full complement of operating personnel is onsite.

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For low-, medium-, and high-risk level compounding, air sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities such as staging, labeling, gowning, and cleaning. Locations shall include zones of air backwash turbulence within LAFW and other areas where air backwash turbulence may enter the compounding area (doorways, in and around ISO Class 5 [see Table 1] PEC and environments). Consideration should be given to the overall effect the chosen sampling method will have on the unidirectional airflow within a compounding environment.

The expectation is that sample sites be chosen based on an evaluation that takes into account dynamic activities in the pharmacy, and that these sites will remain constant.

**Frequency of Sampling**

USP <797> also provides requirements for data evaluation:

The value of viable microbial sampling of the air in the compounding environment is realized when the data are used to identify and correct an unacceptable situation. Sampling data shall be collected and reviewed on a periodic basis as a means of evaluating the overall control of the compounding environment. If an activity consistently shows elevated levels of microbial growth, competent microbiology personnel shall be consulted . . .

Counts of cfu are to be used as an approximate measure of the environmental microbial bioburden. Action levels are determined on the basis of cfu data gathered at each sampling location and trended over time.

As noted above, it is possible to interpret the language in USP <797> regarding sampling frequency in different ways, but there is little ambiguity in FDA’s expectations, as has been made abundantly clear in recent years. Rather than full cGMP expectations of sampling in the aseptic core during every batch and shift, review of 483 commentary makes it clear that FDA is setting a standard that daily testing is required. *3

**Investigating Excursions**

Any excursion in the EM program must be investigated to determine if it is a random occurrence or part of a larger pattern. If present, a larger pattern may indicate a problem in the contamination control program. The effect of the excursion (and any associated excursions, equipment failures, or related events) on sterile compounding as a process should be addressed. USP <797> states:

Any cfu count that exceeds its respective action level (see Table 2) should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location. An investigation into the source of the contamination shall be conducted. Sources could include HVAC systems, damaged HEPA filters, and changes in personnel garb-

| * * * |

Each investigation should be driven by an SOP and should include:

- Determination of whether the excursion was due to sampling or lab error
- If not, then:
  - Determination of the threat the event poses to sterile compounding in the pharmacy, especially to released CSPs
  - Identification of the root cause of the excursion
  - Determination of a Corrective Action/Preventative Action Plan (CAPA) to fix the problem
  - Follow up to demonstrate that the problem is not recurring

**Conclusion**

Investing time, effort, and resources into developing an effective EM program is a necessary part of doing business to ensure patients receive safe, effective CSPs. The expectations for EM programs include identifying well-defined sample sites, frequent sampling that enables data trending to monitor the facility, and investigations into any excursions from expected values. Recent regulatory changes are removing ambiguity in expectations for compounding pharmacies, with EM taking on a larger role in the contamination control program for production of CSPs. As a result, now is the time to develop a comprehensive approach to EM as part of an overall contamination control program.

**References**


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The opinions expressed in this article are the author’s alone and do not necessarily reflect the policies or positions of any organization with which he is associated.
### ONLINE-ONLY TABLE 1

**Elements of Microbial Contamination Control**

<table>
<thead>
<tr>
<th>Control Activities</th>
<th>Monitoring Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleaning and sanitization</td>
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<td>Sporicidal treatment</td>
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<td>Procedures to prevent microbial contamination</td>
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<td>Personnel gowning and hygiene</td>
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<td>Facility and physical barriers</td>
<td>Raw material and in-process monitoring</td>
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<tr>
<td>Water sanitization</td>
<td>Finished product testing</td>
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<tr>
<td>Admission, Discharge, and Transfer Software</td>
<td>Identify late transactions relative to patient location during encounter (e.g., dispensation before or after case, or after transfer)</td>
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