ENVIRONMENTAL MONITORING

Assessment and verification of the adequacy of the aseptic compounding environment is essential. Environmental monitoring programs are designed to promptly identify potential sources of contamination, allowing for implementation of corrective actions in order to minimize the possibility of CSP contamination. This program provides information, which demonstrates that the engineering controls, disinfecting procedures, and employee work practices create an environment within the compounding area that consistently maintains acceptably low microbial levels. The compounding area includes the ISO Class 5 (see Table 1) primary engineering controls. ISO Class 7 (see Table 1) buffer room (cleanroom) and ISO Class 8 (see Table 1) anteroom or ante-area. The value of 13 CDC Guideline for Environmental Infection Control in Health-Care Facilities, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5210a1.htm).

An environmental monitoring program lies in the consistent, quantitative assessment of environmental conditions in these areas over time.

Sampling Plan

The evaluation of environmental quality is performed by measuring the number of airborne viable particles (microorganisms) in the ISO classified air environments within the compounding area and the total number of particles (nonviable and viable). The environmental quality of the ISO classified areas as it pertains to microbial bioburden is evaluated by assessing the number of viable and nonviable particles in the air.

An environmental sampling plan shall be developed for monitoring airborne viable particles. Selected sampling sites should include multiple locations within each ISO Class 5 (see Table 1) environment and in the ISO Class 7 and 8 (see Table 1) areas. The plan should include location, method of sampling, volume of air sampled, frequency of sampling, time of day as related to activity in the compounding area, and action levels.

Monitoring of the data generated by the program can detect changes in the microbial bioburden; such changes may be allowed for indication of changes in the state-of-control within the environment. It is recommended that compounding personnel refer to Microbiological Evaluation of Cleanrooms and Other Controlled Environments 1116 and the CDC Guidelines for Environmental Infection Control in Healthcare Facilities–20037,13 for more information. Although 1116 is an informational chapter and not applicable to controlled environments for use by licensed pharmacies, it can provide valuable information in helping compounding sites establish a robust environmental monitoring program. Changes in the microbial bioburden found during monitoring can allow for detection and resolution of problems in the system before loss of control of the environment.

Growth Media

A general microbiological growth medium such as Soybean–Casein Digest Medium (also known as trypticase soy broth or agar (TSA) should be used to support the growth of bacteria. Malt
extract agar (MEA) or some other media that supports the growth of fungi should also be used. Media used for surface sampling must be supplemented with additives to neutralize the effects of disinfecting agents (e.g., TSA with lecithin and polysorbate 80).

Air Sampling

Evaluation of airborne microorganisms in the controlled air environments (LAFWs, CAIs, BSCs, buffer or clean areas, and anterooms/areas) is performed by properly trained individuals using suitable electric air samplers. Impaction is the preferred method of active air sampling.

Use of settling plates for qualitative air sampling cannot be relied upon and shall not be used solely to determine the quality of air in the controlled environment. The settling of particles by gravity onto culture plates is highly dependent on the particle size and is strongly influenced by air movement. Given the unpredictable and uncontrollable nature of ambient particle movement, pharmacists or technicians cannot directly relate the number of colony-forming units (cfu) on a settling plate to the concentrations of the corresponding particles in the sampled environment.

Samples collected by gravity on settling plates are not suitable substitutes for volumetric air samples and should not be used to determine the relative air concentrations of different microorganisms because of the method's collection bias.

Air sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities like staging, labeling, gowning, and cleaning. Locations should include zones of air backwash turbulence within laminar airflow workbench and other areas where air backwash turbulence may enter the compounding area (doorways, in and around ISO Class 5 (see Table 1) engineering controls and environments).

The instructions in the manufacturer’s user manual for verification and use of these electric air samplers that actively collect volumes of air for evaluation must be followed. A sufficient volume of air should be tested per location in order to maximize sensitivity. These air sampling devices need to be serviced and calibrated as recommended by the manufacturer. Consideration should be given to the overall effect the chosen sampling method will have on the unidirectional airflow within a compounding environment.

Collection Methods—There are a number of different manufacturers of electric air sampling equipment. It is important that compounding personnel refer to the manufacturers’ recommended procedures when using the equipment to perform active air sampling procedures. It is recommended that compounding personnel also refer to Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms under Microbiological Evaluation of Cleanrooms and Other Controlled Environments 1116, which can provide more information on the use of active air samplers and the volume of air that should be sampled to detect environmental bioburden excursions.

Sampling Frequency—Active electronic air sampling that is designed not to interrupt airflow while sampling shall be performed and the results evaluated at least monthly for low- and medium-risk level compounding operations and at least weekly for high-risk level compounding operations. More frequent sampling will provide earlier detection of loss of environmental control.
Surface Sampling

Surface sampling is recommended but not required. Surface sampling can be an important component of the microbial environmental monitoring program in controlled environments. It is also useful to evaluate cleaning procedures and employee work practices. Surface sampling should only be performed when no compounding activity is occurring on or near the surface to be tested. For these reasons, sampling is often performed at the end of a shift or the end of the work day. Surface sampling may be performed in all ISO classified areas and can be accomplished using contact plates and/or swabs. Sample areas should be defined on the sample plan or form. The sample size usually ranges from 24 to 30 cm².

Contact plates are filled with general growth medium and neutralizing agents such as lecithin and polysorbate 80. Swabs should contain a transport medium and are most appropriate for irregular surfaces.

Collection Methods—To sample using a contact plate, gently touch the area with the agar surface and roll the plate across the surface to be sampled. The contact plates should be incubated as stated in the subsection Sampling Plate Incubation Period. The contact plate will leave a media residue behind. Therefore, immediately after sampling with the contact plate the sampled area should be thoroughly cleaned and disinfected prior to resuming compounding.

To sample an area with a swab, rub the swab in a twisting motion across the surface within a defined surface area template. After collection of the sample, the swab is placed in an appropriate media containing a neutralizer, processed by appropriate means, and plated to the desired nutrient agar. Results should be reported as cfu per surface area.

Sampling Frequency—Surface sampling should be performed when no other activities are occurring in critical areas and the results evaluated at least monthly for low- and medium-risk level compounding operations and at least weekly for high-risk level compounding operations. More frequent sampling will provide earlier detection of loss of environmental control.

Glove Fingertips Sampling

Personnel monitoring is required because direct touch contamination is the most likely source of introducing microorganisms into CSPs. Contact agar plates are used to sample gloved fingertips after compounding CSPs immediately after exiting the ISO Class 5 (see Table 1) environment. Glove fingertip sampling must occur outside of the ISO Class 5 (see Table 1) environment. Do not disinfect gloves with IPA immediately prior to sampling. Disinfecting gloves immediately before sampling will provide false negative results. The minimum sampling schedule is provided in Table 3. Plates filled with nutrient agar with neutralizing agents added are used when sampling personnel fingertips. Personnel should “touch” the agar with the fingertips of both hands in a manner to create a slight impression in the agar. The gloves must be discarded and hand hygiene performed after performing this procedure.
When a finger plate result for personnel monitoring after proper incubation exceeds the action limit, a review of hand hygiene and garbing procedures as well as glove and surface disinfection procedures and work practices should occur.

Air and Surface Sampling Frequencies

The sampling frequency table (Table 3) details the required sampling intervals for each of the respective CSP risk level compounding areas. If two or more risk levels of compounding (e.g., medium- and high-risk level) activity should occur in a pharmacy, then the more stringent frequency of sampling must be performed routinely. If compounding occurs in multiple locations within an institution (e.g., main pharmacy and satellites), environmental monitoring is required for each individual compounding area.

Table 3. Environmental Monitoring Sampling Schedule

<table>
<thead>
<tr>
<th>Low-Risk Level CSPs</th>
<th>Medium-Risk Level CSPs</th>
<th>High-Risk Level CSPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required air sampling</td>
<td>Once a month</td>
<td>Once a month</td>
</tr>
<tr>
<td>Required glove fingertipsa</td>
<td>Weekly</td>
<td>Weekly</td>
</tr>
<tr>
<td>Recommended ISO surface sampling</td>
<td>Weekly</td>
<td>Weekly</td>
</tr>
</tbody>
</table>

a At least one individual or 10% of the compounding personnel, whichever is larger, to be sampled.

Sampling Plate Incubation Period

At the end of the designated sampling or exposure period for all environmental monitoring activities (air, surface, or personnel), the plates are recovered, covers secured, inverted and incubated at a temperature and for a time period conducive to multiplication of microorganisms. Trypticase soy broth or agar (TSA) should be incubated at between 33 and 37 for 2 days. Malt extract agar (MEA) or other suitable fungal media should be incubated at between 26 and 30 for 7 days.

Action Limits, Documentation, and Data Evaluation

The greatest value of viable microbial monitoring in the air and on surfaces of the aseptic environment are realized when normal baseline cfu counts are determined over a period of time. Environmental monitoring data shall be collected and trended as a means of evaluating the overall control of the compounding environment.
The number of discrete colonies of microorganisms are counted and reported as cfu and documented on an environmental monitoring form. Counts from air monitoring need to be transformed into cfu/cubic meter of air and evaluated for adverse trends.

Action levels shall be determined based on baseline data gathered. Table 4 should only be used as a guideline or as interim levels until baseline data has been gathered. Determining the baseline cfu counts permits identification of an increasing trend of microbial cfu. An increasing trend in cfu counts should prompt a re-evaluation of the adequacy of cleaning procedures, operational procedures, personnel work practices, and air filtration efficiency within the aseptic compounding location. When action levels are exceeded, an investigation into the source of the contamination shall be conducted. Sources could include heating, ventilating, and air conditioning (HVAC) systems, damaged HEPA filters, and changes in personnel garbing habits or working practices. Eliminate the source of the problem, clean the affected area, and then resample.

Table 4. Action Levels (Counts) of Microbial Colony-Forming Units (cfu) per Cubic Meter of Air or Contact Platea

<table>
<thead>
<tr>
<th>ISO Class of Sampled Location</th>
<th>Sampled Sources and Their Action Levels (Counts) of Microbial cfu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active Air (required)</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>7</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>8</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

Sources and Their Action Levels (Counts) of Microbial cfu ISO Class of Sampled Location Active Air (required) Glove Fingertip (required) Inanimate Surfaces (recommended) 5 > 3 > 3 > 3

a The cfu action levels are adapted from those in Microbiological Evaluation of Cleanrooms and Other Controlled Environments 1116.
b At least one cubic meter, m3, or 1000 liters, L, of air must be sampled.

Nonviable Particle Facility Environmental Monitoring Program

A program to monitor nonviable particles differs from that of viable particles in that it is intended to directly measure the performance of the engineering controls used to create the various levels of air cleanliness, e.g., ISO Class 5, ISO Class 7, or ISO Class 8 (see Table 1).

Engineering Control Performance Verification

Primary (e.g., LAFWs, BSCs, and CAIs) and secondary (e.g., buffer and ante rooms/areas) engineering controls are essential components of the overall contamination control strategy for
aseptic compounding. As such, it is imperative that they perform as designed and the resulting levels of contamination are within acceptable limits. Certification procedures such as those outlined in the CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2005) should be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated, altered, or major service to the facility is performed. 

Total Particle Counts—Certification that each ISO classified area, e.g., ISO Class 5, ISO Class 7, and ISO Class 8 (see Table 1) is within established guidelines shall be performed no less than every 6 months and whenever the LAFW, BSC, or CAI is relocated or the physical structure of the buffer room or anteroom/area has been altered. Testing shall be performed by qualified operators using current, state-of-the-art electronic equipment with the following results:

- Not more than 3,520 particles 0.5 µm size and larger per cubic meter of air (ISO Class 5, see Table 1) for any LAFW, BSC, and CAI;
- Not more than 352,000 particles of 0.5 µm size and larger per cubic meter of air (ISO Class 7, see Table 1) for any buffer room;
- Not more than 3,520,000 particles of 0.5 µm size and larger per cubic meter of air (ISO Class 8, see Table 1) for any anteroom/area.

All certification records shall be maintained and reviewed by the supervising pharmacist or other designated employee to ensure that the controlled environments comply with the proper air cleanliness, room pressures, and air changes per hours. (Refer to Cleanrooms, CAIs, and Table 1 in the Environmental Quality and Control section.)

Pressure Differential Monitoring

A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the cleanroom and anteroom and the anteroom and the general pharmacy area. The results should be reviewed and documented on a daily basis in a log. The pressure between the ISO Class 7 (see Table 1) and general pharmacy area should not be less than 5 Pa (0.02-inch water column, w.c.). Facilities used to compound low-risk CSPs utilizing directional airflow should maintain a minimum velocity of 0.2 m/s (40 fpm).