Environmental Monitoring of a Cleanroom Complex

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Designated Person(s)

The designated person must ensure that any person who enters the sterile compounding area maintains the quality of the environment.

The term “designated person” appears more than 25 times in the proposed USP<797>.

**Designated person:** One or more individuals assigned to be responsible and accountable for the performance and operation of the compounding facility and personnel in the preparation of CSPs.
In Connecticut, the designated person
• must be a pharmacist
• with 30 hours of approved education

Maintaining a Cleanroom Complex

• Well designed facility

• Cleaning and Disinfecting

  • Environmental Monitoring

• Contingency Plan – What to do if the cleanroom fails Environmental Monitoring

• Standard Operating Procedures
Goal: Reduce the risk of contamination of a CSP

- Test for “non-viable particles” per volume – every 6 months
- Test for viable particles per volume – every 6 months
- Test surfaces for viable particles – every month

These are minimums per Proposed USP<797>.

Air and Surface Monitoring Program

- Standard Operating Procedures include:
  - Diagram of the locations
  - Procedures for collecting samples
  - Frequency of collecting samples
  - Sample size (surface area or volume of air)
  - Time of day of sampling in relation to activities in the compounding area
  - Action levels that trigger corrective action

Proposed USP<797>
Non-viable airborne particles (per m³)

- Number of non-viable airborne particles per cubic meter (or 1,000 liters) of air must be determined in all ISO classified areas
  - Every 6 months
- Sample collecting devices should be placed in locations
  - well described in SOPs using location diagram
  - at most risk of contamination and
  - at locations representative of the entire space.
- Minimum number of sampling locations, \( N_L \) according to ISO 14644-1:1999 is:
  - \( N_L = \sqrt{A} \),
  - where \( A \) is the area (in m²) of the space (LAFW, buffer room or ante-room).
  - Round up to whole numbers.

ISO Classification of Rooms/Areas

<table>
<thead>
<tr>
<th>Room or Area</th>
<th>ISO Class</th>
<th>Maximum Particle Count (per m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ante-room</td>
<td>8</td>
<td>3,520,000</td>
</tr>
<tr>
<td>Buffer Room</td>
<td>7</td>
<td>352,000</td>
</tr>
<tr>
<td>LAFW (or other PEC)</td>
<td>5</td>
<td>3,520</td>
</tr>
</tbody>
</table>
Viable airborne particles (per m³)

- Number of viable airborne particles per cubic meter (or 1,000 liters) of air must be determined in all ISO classified areas
  - Every 6 months MINIMUM

- Minimum number of sampling locations, \( N_L = \sqrt{A} \)

- Once the 1,000 liters of air is sampled
  - Invert media and incubate (outside the cleanroom suite)
  - 30-35°C for ≥ 48 hrs & examine for growth
  - 20-25°C for ≥ 5 days & examine for growth

Action Levels for Viable Airborne Particle Air Sampling

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Air Sampling Action Levels (CFU/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>≥1</td>
</tr>
<tr>
<td>7</td>
<td>≥10</td>
</tr>
<tr>
<td>8</td>
<td>≥100</td>
</tr>
</tbody>
</table>

- No other action levels based on specific microorganism (e.g., fungus)
- If levels measured during viable air sampling exceed the levels in the table, the genus of any microorganism recovered must be identified with the assistance of a microbiologist.

Proposed USP<797>

What is the “Action”?
- Inform CT Drug Control!
- 12 BUD if not in ISO 5
- Start a remediation plan
Surface Sampling

- Frequency = monthly
- Locations
  - Interior of PEC and equipment therein
  - Frequently touched surfaces
  - Staging or work areas
  - All pass-through chambers
- For flat surfaces, use a contact plate or paddle
- For non-flat surfaces, use a swab

Use of positive control samples?

Surface Sampling Procedures

- Flat Surface Sampling
  - Fully gowned
  - Remove the cover from the contact sampling device.
  - Using a rolling motion, firmly press the media surface onto the surface to be sampled.
  - The contact sampling device will leave a residue of growth medium on the sample site. After sampling, use a low-lint sterile wiper to thoroughly clean the sampled area with sterile 70% IPA.
  - Cover each contact sampling device.

- Irregular Surface Sampling
  - Fully gowned
  - Sterile swabs wetted with sterile water or a sterile buffer.
  - After swabbing the area, place the swab in appropriate diluent or sterile packaging until it can be processed.
    - per manufacturer’s instructions

Proposed USP<797>
### Action Levels for Surface Sampling

**Proposed USP <797>**

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Work Surfaces Sampled Using Contact Plates (CFU/plate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&gt;3</td>
</tr>
<tr>
<td>7</td>
<td>&gt;5</td>
</tr>
<tr>
<td>8</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

How many cfu do you count?

How many?

In the PEC, is this passing?

In the buffer room, is this passing?

In the ISO 8 ante-room, is this passing?

(g) A sterile compounding pharmacy shall report, in writing, to the Department of Consumer Protection any known violation or noncompliance with viable and nonviable environmental sampling testing, as defined in the most recent United States Pharmacopeia, Chapter 797, Pharmaceutical Compounding - Sterile Preparations, as amended from time to time, not later than the end of the next business day after discovering such violation or noncompliance.

dcp.drugcontrol@ct.gov

Before you contact CT Drug Control → Have a plan.

https://www.cga.ct.gov/current/pub/chap_400j.htm#sec_20-633b

Selecting a growth medium

Soybean-Casein Digest Medium (SCDM) is suitable for environmental monitoring in most cases because it supports the growth of a wide range of bacteria, yeast, and molds. USP <1116>

SCDM = TSB [tryptic(ase) soy broth] = BAM Media M152

SCDA = TSA [tryptic(ase) soy agar] = BAM Media M154

Keep the Certificate of Analysis on file OR
Show a positive or several positive controls OR
Both

Biological Analytical Manual (FDA.gov)

M100  Trypsinase Neomycin (TN) broth
M101  Trypsinase-Peptone-Glucose-Yeast Extract Broth (TPGY)
M101a Trypsinase-Peptone-Glucose-Yeast Extract Broth with Tyrothricin (TPGY/T)
M102  Trypsinase (Trypticase) Soy Agar
M103a Trypsinase Soy Agar Magnesium sulphate-Neomycin (TSMN)
M103  Trypsinase Soy Agar with 0.6% Yeast Extract (TSAYE)
M104  Trypsinase (Trypticase) Soy Broth
M106  Trypsinase Soy Broth Modified (mTSB)
M108  Trypsinase (Trypticase) Soy Broth (TSB) with Ferrous Sulphate
M109  Trypsinase (Trypicase) Soy Broth (TSB) with Clorhexidine
M109a Trypsinase (Trypicase) Soy Broth with 10% NaCl and 1% Sodium Pyruvate
M117  Trypsinase Soy Broth with 0.4% Yeast Extract (TBSYE)
M120  Trypsinase Soy-Polynucleic Broth
M129  Trypsinase Soy-Supplemented Blood Agar
M160  Trypsinase Soy-Tryptose Broth
M164  Trypsinase (Trypticase) Broth, 1%
M161  Trypsinase Broth and Tryptose Sulf Broths
M162  Trypsinase Phosphate (TP) broth
M163  Tryptose Sulf (T-Na) Agar and T-Na Agar
M165  Trypsinase Yeast Extract Agar
M166  Trypsinase Blood Agar Base
Trend analysis

• Regular review of the sampling data must be performed to detect trends such as elevated levels of microbial bioburden, elevated levels of nonviable particulates, or other adverse changes within the environment.

• Evaluate cfu counts against the action levels and examine counts in relation to previous data to identify adverse results or trends.

Proposed USP<797>.
Who does the testing?

- External versus internal

If external folks do the testing:

- Qualifications?
- Training?
- Garbing?

New Mandates for Timing of Samples

Proposed USP<797>

- Viable Air Sampling
  - must be conducted in each classified area [e.g., ISO Class 5 PEC and ISO Class 7 and 8 room(s)] during dynamic operating conditions at least every 6 months.
- Surface Sampling
  - must be performed at the end of compounding activity or shift, but before the area has been cleaned and disinfected.

**Dynamic operating conditions:** Conditions in the compounding area in which operating personnel are present and simulating or performing compounding. The conditions should reflect the largest number of personnel and highest complexity of compounding expected during routine operations as determined by the designated person(s).