Certification Reports & Environmental Sampling

The North Carolina Board of Pharmacy Staff has received several questions concerning requirements related to certification reports and environmental sampling performed in sterile compounding pharmacies. The Board of Pharmacy requires compliance with the United States Pharmacopeia (USP) Compounding Compendium Chapter <797>, which references specific certification requirements including, Controlled Environment Testing Association (CETA) Certification Guide for Compounding Facilities (CAG-003-2006). USP Chapter <797> has specific requirements for the types of environmental sampling that must be performed including viable surface and air sampling.

It is the responsibility of the Pharmacy Manager and/or Designated Compounding Pharmacist to ensure that all certification testing and documentation are in compliance with USP Chapter <797> in accordance with Rule 21 NCAC 46.2801. The Pharmacy Manager and/or Designated Compounding Pharmacist should review certification and environmental sampling reports to ensure that appropriate tests are performed and are in compliance with USP Chapter <797> and that the results are compliant with the action levels set forth in USP Chapter <797>.

The following document provides guidance on Certification tests and documentation that is required for a sterile compounding facility and sterile compounding equipment. It also provides guidance on environmental sampling and documentation requirements. This document can be used to provide guidance to third party certification organizations so that the organization meets the pharmacy's requirements for compliance with USP Chapter <797> and Rule 21 NCAC 46.2801.

NOTE: USP Chapter <797> is currently under revision. North Carolina Board of Pharmacy is aware that once the revisions are finalized the requirements for clean room certifications and environmental sampling may change. This document will be updated once the new revisions of USP Chapter <797> are finalized.

Secondary Engineering Controls:

Secondary Engineering Controls (SEC) are the rooms or spaces containing the Primary Engineering controls (PEC).

Secondary Engineering Controls must be certified at least every six months.

1. **Air Changes Per Hour (ACPH):**

- Non Hazardous Buffer Room ISO 7 = 30 Air Changes Per Hour (ACPH) total. A minimum of 15 ACPH must be provided by the area supply HEPA filters. At most 15 ACPH can be provided by the Primary Engineering Controls (PECs).
- Anteroom classified as ISO 7= A minimum of 30 ACPH.
- Anteroom classified as ISO 8= Recommended 20 ACPH (CAG-003-2006).
- Hazardous Drug Buffer Rooms ISO 7= A minimum of 30 ACPH or a non-classified space containing a Compounding Aseptic Containment Isolator (CACI) must have at least 12 ACPH.

2. **Differential Pressures:**

- For rooms providing a physical separation through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of -0.02 to -0.05 inch water column is required.

    - Where is the different pressure measured? Buffer room to anteroom; anteroom to general pharmacy (unclassified space).

- Pressure differentials must be documented on the certification report, and they must be continuously monitored and documented daily by the pharmacy.

3. **HEPA Filter Leak Testing (CAG-003-2006):**

- All HEPA Filters must be leak tested with each certification utilizing an aerosol photometer and an appropriate aerosol challenge medium.

- Individual leaks should not exceed 0.01% of the upstream challenge for filters that can be scanned.

4. **Non-Viable Particle Count Testing:**

- Must be performed for all ISO classified areas (ISO 5, 7, and 8).

- **Must be performed under dynamic conditions. Dynamic operating conditions are defined in CAG – 003-2006-12 section 5.7 as *the actual conditions in which the engineering control is used. All actual operating personnel are present and performing actual or simulated operations*.**

- Must be performed every 6 months **AND** whenever the PEC is relocated, the physical structure of the buffer or ante area has been altered, or major service to the facility is performed.

- ISO Class 7: Not more than 352,000 particles (of 0.5 micron size and larger) per cubic meter.

- ISO Class 8: Not more than 3,520,000 particles (of 0.5 micron size and larger) per cubic meter.

5. <u>Environmental Sampling (May be performed by a certification company or in-house):</u>

Note: Environmental Sampling includes surface sampling and viable air sampling.

Pharmacy managers should review documentation of media used during sampling, specifically lot number and expiration date of media used.

- Environmental sampling shall occur as part of a comprehensive quality management program and shall occur 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 re-certification of facilities and equipment (i.e., every 6 months);
  • in response to identified problems with end products or staff technique; or
  • in response to issues with compounded sterile product (CSPs), observed compounding personnel work practices, or patient-related infections (where the CSP is being considered as a potential source of the infection).

A. <u>Viable Air Sampling:</u>

- **Sampling Plan—**USP Chapter <797> states, "an appropriate environmental sampling plan **<u>shall</u>** 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 environment and in the ISO Class 7 and 8 areas and in the segregated compounding areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 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.

- Shall be performed at least every six months.

- If compounding occurs in multiple locations within an institution (e.g., main pharmacy, satellites), an environmental sampling plan is required for **each** compounding area.

- A sufficient volume of air (400 to 1000 liters) shall be tested at each location in order to maximize sensitivity. Please note action levels for viable air sampling are based on 1000 liters of air, so if the volume of air sampled is less than 1000 liters then the results must be multiplied to reflect a volume of 1000 liters. Eg: If 400 liters are tested the results must be multiplied by 2.5 to provide colony forming units (cfu) per 1000 liters of air.

If action levels are exceeded:

- Any colony forming unit (cfu) count that exceeds its respective action level 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 (see Table below).

- An investigation into the source of the contamination shall be conducted. Sources of this contamination could include HVAC systems, damaged HEPA filters, and changes in personnel garbing or work practices. The source of the problem shall be identified and eliminated, and the affected area cleaned, and resampling performed before resuming compounding. The compounding area must be resampled to determine that cfu are within appropriate limits and then compounding activities can resume.

- 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.

- Regardless of the number of cfu identified in the pharmacy, required corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden captured as a cfu using an impaction air sampler.

- **Highly pathogenic organisms** (e.g. Gram-negative rods, coagulase positive staphylococcus, molds and yeasts) must be immediately remedied regardless of cfu count, with assistance of a competent microbiologist, infection control professional, or industrial hygienist.

Recommended Action Levels for Microbial Contamination* † (cfu per cubic meter [1000 liters] of air per plate)	
Classification	**Air Sample †**
ISO Class 5	>1
ISO Class 7	>10
ISO Class 8 or worse	>100

* Guidance for Industry–Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice–US HHS, FDA September 2004.

This table is found as Table 2 in USP Chapter <797> Environmental Viable Airborne Particle Testing Program.

B. <u>Surface Sampling</u>

- Sampling can be accomplished by using contact plates or swabs on surfaces in the compounding area. Locations sampled must be defined in the sampling plan.

- Surface sampling shall be performed in all ISO classified areas on a periodic basis.

- It shall be done at the conclusion of compounding

Recommended Action Level for Microbial Contamination*	
Classification	**Surface Sample (Contact Plate) (cfu per plate)**
ISO Class 5	**>3**
ISO Class 7	**>5**
ISO Class 8 or worse	**>100**

* Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products Annexes PE 009-6, 5 April 2007.
This table is found as Table 4 in USP Chapter <797> Action Levels, Documentation, and Data Evaluation.

- Regardless of the number of cfu identified in the compounding facility, required corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden captured as a cfu.

- **Highly pathogenic organisms** (e.g. Gram-negative rods, coagulase positive staphylococcus, molds and yeasts) must be immediately remedied regardless of cfu count, with assistance of a competent microbiologist, infection control professional, or industrial hygienist.

Primary Engineering Controls (PECs):

- PEC are the devices in which sterile compounding activities occur. These include: Biological Safety Cabinet (BSC), Compounding Aseptic Containment Isolator (CACI), Compounding Aseptic Isolator (CAI), Laminar Airflow Work Bench (LAFW).
    - *For certification requirements for CAI and CACI, please see Guidance Document for Certification testing for CAI and CACI and Report Documentation.*

- Primary Engineering Controls must be certified at least every six months.

1. Airflow Velocities:

- Airflow velocities are typically set to a range of 80 to 100 feet per minute (fpm), but the actual range is best established by the device manufacturer and maintained there by the certifier.

- Must be done every 6 months.

2. **Particle Count Testing:**

- PECs shall maintain ISO Class 5 or better conditions for particles (0.5 micron or larger) (dynamic operating conditions) while compounding CSPs.

- Shall be performed no less than every 6 months and whenever the LAFW, BSC, CAI, or CACI is relocated or the physical structure of the buffer area or ante-area has been altered.

- ISO Class 5: not more than 3520 particles (0.5micron and larger size) per cubic meter of air for any LAFW, BSC, CAI, and CACI.

3. **HEPA Filter Leak Testing (CAG-003-2006):**

- All HEPA Filters must be leak tested during each certification utilizing an aerosol photometer and an appropriate aerosol challenge medium.

- Individual leaks should not exceed 0.01% of the upstream challenge for filters that can be scanned.

4. **Airflow Smoke Pattern Test (Smoke studies):**

- In airflow smoke pattern tests (smoke studies) shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under **dynamic conditions**. Refer to definition of dynamic conditions in Non-Viable Particle Count Testing.

- Pharmacy staff should observe airflow smoke pattern testing and video documentation of this test should be maintained in the pharmacy.

5. **Environmental Sampling** (May be performed by a certification company or in-house)**:**

   Note: Environmental Sampling includes Viable Air Sampling and Surface Sampling

   Pharmacy managers should review documentation of media used during sampling, specifically lot numbers and expiration dates of media used.

   A. **Viable Air Sampling for Primary Engineering Controls (PEC):**

   - **Sampling Plan-** USP Chapter <797> states "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 environment and in the ISO Class 7and 8 areas and in the segregated compounding areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 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".

- Shall be performed at least every six months.

- If compounding occurs in multiple locations within an institution (e.g., main pharmacy, satellites), an environmental sampling plan is required for each compounding area.

- A sufficient volume of air (400 to 1000 liters) shall be tested at each location in order to maximize sensitivity. Please note action levels for viable air sampling are based on 1000 liters of air, so if the volume of air sampled is less than 1000 liters then the results must be multiplied to reflect a volume of 1000 liters. Eg: If 400 liters are tested the results must be multiplied by 2.5 to provide colony forming units (cfu) per 1000 liters of air.

If action levels are exceeded:

- Any cfu count that exceeds its respective action level 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 (see table below).

- An investigation into the source of the contamination shall be conducted. Sources could include HVAC systems, damaged HEPA filters, and changes in personnel garbing or work practices. The source of the problem shall be identified and eliminated, and the affected area cleaned, and resampling performed before resuming compounding. The compounding area must be resampled to determine that cfu are within appropriate limits and then compounding activities can resume.

- 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.

- Regardless of the number of cfu identified in the pharmacy, further corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden captured as a cfu using an impaction air sampler.

- **Highly pathogenic organisms** (e.g. Gram-negative rods, coagulase positive staphylococcus, molds and yeasts) must be immediately remedied regardless of cfu count, with assistance of a competent microbiologist, infection control professional, or industrial hygienist.

Recommended Action Levels for Microbial Contamination* †(cfu per cubic meter [1000 liters] of air per plate)	
Classification	**Air Sample †**
ISO Class 5	>1
ISO Class 7	>10
ISO Class 8 or worse	>100

* Guidance for Industry–Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice–US HHS, FDA September 2004.

This table is found as Table 2 in USP Chapter <797> Environmental Viable Airborne Particle Testing Program.

B. <u>Surface Sampling:</u>

- Surface sampling shall be performed in all ISO classified areas on a periodic basis.
- It shall be done at the conclusion of compounding.
- Regardless of the number of cfu identified in the compounding facility, further corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden captured as a cfu.
- **Highly pathogenic organisms** (e.g. Gram-negative rods, coagulase positive staphylococcus, molds and yeasts) must be immediately remedied regardless of cfu count, with assistance of a competent microbiologist, infection control professional, or industrial hygienist.

Recommended Action Level for Microbial Contamination* -	
Classification	**Surface Sample (Contact Plate) (cfu per plate)**
ISO Class 5	**>3**
ISO Class 7	**>5**
ISO Class 8 or worse	**>100**

* Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products Annexes PE 009-6, 5 April 2007.

This table is found as Table 4 in USP Chapter <797> Action Levels, Documentation, and Data Evaluation

Documentation:

CETA documentation requirements are outlined in CAG-003-2006, section 14.0. This section lists the minimum documentation requirements:

- Name, address, and contact information of the certification company
- Key personnel and appropriate accreditations of the certification company
- Confirmation that the most recent CAG was reference and the date of certification
- Identification of locations for data collection relative to facility layout, including equipment
- Specific and clear nomenclature for data locations
- Explanation of test procedures and justification for any deviations from established industry practices
- Collected data is compared to expected values or specific performance criteria. This is outlined in Standard Operating Procedures outlined by the client (pharmacy). In absence of SOPs, the certifier's SOPs or industry accepted standards are used.
- List of equipment used including make, model, serial number, and calibration date. When requested, current calibration documentation for each piece of equipment should be available.

Guidance for Certification Testing for CAIs & CACIs and Report Documentation:

- The specific type and placement of a facility's PECs plays a large role in the certification tests that must be performed as well as the level of sterile compounding and assigned beyond use dating. The current USP <797> chapter requires that PECs be located within an ISO 7 buffer area, but there are a few exceptions for a CAIs and CACIs.
    - CAIs and CACIs must be placed in an ISO 7 buffer area unless they provide an ISO 5 environment during **dynamic operating conditions*** including transfer of ingredients, components, devices, as well as during preparations of CSPs.
    - Particle counts must be sampled 6 to 12 inches upstream of critical exposures sites and must maintain ISO 5 conditions.
    - Not more than 3520 particles (sized 0.5 micron and larger) per cubic meter shall be counted during material transfer.
- This information can be found in USP <797> in the section labeled "Placement of Primary Engineering Controls". This section also references the CETA Applications Guide CAG-002-2006.

***Dynamic operating conditions are defined in CAG – 003-2006-12 section 5.7 as *the actual conditions in which the engineering control is used. All actual operating personnel are present and performing actual or simulated operations*.**

Mandatory Field Tests for CAIs/CACIs per CETA guidelines are:

Airflow:

- Performed for Ante and Main Chambers.
- Must be a repeatable method for determining airflow in each chamber.
- Samples taken at equal points across the tested plane.

Acceptance Criteria

- Determined by the manufacturer for the particular design.
- USP Chapter <797> requires unidirectional airflow.

Chamber Pressure Test:

- Performed for Ante and Main Chamber.
- Includes Test 1, Test 2, Test 3a, Test 3b found in CETA Compounding Isolator Testing Guide (CAG-002-2006).

Acceptance Criteria-

- Pressure range determined by manufacturer for the particular design.
- Pressure shall not change from positive to negative or negative to positive during any manipulations.

Site Installations Assessment Tests:

- Determines airflow or pressure setpoint(s) for audible/visual alarms, functionality of pass-through door interlock operations, proper canopy or exhaust connection performance.
- Includes: Test 1- Airflow or Pressure Alarm Test, Test 2- Door Interlock Verification Test, Test 3- Exhaust System Performance (a-Canopy or b- Hard ducted connections).

Acceptance Criteria

- Setpoints determined by manufacturer for Airflow or Pressure and Door Interlock Verification tests.
- Exhaust System Performance Tests- no smoke shall enter the room once it enters the exhaust system.

HEPA Filter Integrity Test:

- Performed for Ante and Main Chambers.
- For filters that cannot be scanned the manufacturer shall develop a test procedure for probe testing.

Acceptance Criteria:

- Sustained aerosol penetration shall not exceed 0.01% of the upstream concentration.
- Filters that cannot be scanned: sustained aerosol penetration shall not exceed 0.005% of the upstream concentration.
- Filter patch size shall not exceed 3% of the effective filter area, maximum patch size shall not exceed 1.5 inches.

Particle Containment Integrity and Enclosure Leak Test:

- Compounding Aseptic Containment Isolators (CACIs) only.
- Includes areas in Ante and Main chambers, seams and seals in each chamber.

Acceptance Criteria

- Detected leaks do not exceed ISO 5 conditions per cubic meter at 0.5 µm size particles and larger when probe held within 1 inch of the leak.

Airflow Smoke Pattern Test:

- Performed within the Main chamber.
- Smoke is passed along work area, over gloves/gauntlets, IV bars, interior lights, other extruding features.

Acceptance Criteria

- Smoke shall show smooth downflow with minimum dead spots or reflux at obstructions and critical work area.
- Smoke is removed to returns without reentry.

Preparations Ingress and Egress Test:

- Determines that Ante chamber can support material transfer while maintaining cleanliness classification.
- Need to verify background particle count in the testing room is at least 3,532,000 particles per cubic meter. If too low, use aerosol generator or smoke generator.
- Particle counter is set for one minute count with no more than one second hold time
- Use manufacturer's recommended purge time.
- Document Particle counts during transfer and for one minute after transfer.

Acceptance Criteria –

- Particle counts shall not exceed ISO 5 of 3520 particles (0.5 micron and larger) at any time during test.

Particle Count Tests:

- Two part test to determine that Main chamber operates within ISO 5 of 3520 particles (0.5 micron and larger) during Static (At-Rest) and Dynamic Operating Conditions. The Ante chamber is tested in Static state for this test.
- Need to determine particle count locations that address the entire work surface. Sample locations include Ante and Main Chamber.
- Test requires surrogate manipulations using both gloves.

Acceptance Criteria

- ISO 5 of 3520 particles (0.5 micron and larger) during Static (At-Rest) *and* Dynamic Operating Conditions.

Documentation:

- CAG-003-2006-12 (see section 14.0 Documentation).
- Test results shall be informative and comprehensive and provide a statement of compliance or non-compliance with requirement guidelines. At minimum a formal report will include, but is not limited to:
    - Name, address, and contact information for the certifying organization, including a list of key personnel with appropriate accreditations.
    - A remark confirming that the most current version of CAG was referenced and the date certification was completed.
    - Simple and clear identification of approximate location of data collected.
    - Explanation of test procedure(s) with justification for deviations from industry standards.
    - Collected data will be compared to expected values or specific performance criteria established by the client's standard operating procedures (SOPs), certifying organization's SOPs, or manufacturer's specifications.
    - The report will provide a list of equipment used for data collection including make, model, serial number, and calibration date.

References:

USP Compounding Compendium Chapter <797> Pharmaceutical Compounding-Sterile Preparations

Controlled Environment Testing Association (CETA) Certification Guide for Sterile Compounding Facilities CAG-003-2006 (Revised May 20, 2015)