CETA Certification Guide
for Sterile Compounding Facilities
CAG-003-2006 *-13*
Revised May 20, 2015

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1.0 Revision History

1.1 Revision 12: Effective March 11, 2015

1.1.1 Revised as follows: Complete revision

2.0 Background

2.1 The purpose of this guide is to establish an industry-based minimum set of criteria appropriate for performance evaluation and certification of facility and environmental controls used for compounding sterile preparations. It is intended to assist compounders, facilities managers and certification professionals in determining appropriate tests and procedures to be employed on the various engineering controls. This guideline has been established to create a uniform approach for field certifiers to allow consistent and repeatable testing at all facilities. The approach of this guide is to reference the applicable accepted industry guidelines, standards or recommended practices along with the specific tests within that document. When industry guidance documents are not available for a specific procedure, guidance will be provided here for developing an appropriate procedure.

2.2 The recommendations in this report are intended to guide the certification process for compliance with USP Chapter <797>. USP does not enforce the chapter or inspect facilities for compliance. The individual State Boards of Pharmacy, Departments of Health, or other inspection agencies enforce the standard or their own versions of the standard. When individual state or agency standards conflict with USP, the standards which the facility is inspected against shall be used and clearly identified in the certification documentation.

2.3 Traditional sterile compounding (Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)) is typically regulated by state boards of pharmacy and typically inspected against USP Chapter <797>. Operations serving as registered compounding facilities (Section 503B of the FD&C Act) are regulated by the Food and Drug Administration (FDA) and inspected to current Good Manufacturing Practices (cGMP). This document is directly related to traditional compounding. Certification of registered compounding facilities may require additional consideration.

3.0 Precautions/Considerations

3.1 The following information is to provide a basic understanding of concepts applicable to cleanroom testing and certification. In some cases, more than one method may be considered correct. The methodologies listed here are for the purpose of providing an industry consensus for terminology and methods that should be used for testing sterile compounding cleanrooms.

3.2 Test equipment shall be normalized to room temperature prior to use per manufacturers' recommendations. Typical temperature ranges are between 35° F and 105° F.

4.0 References

4.1 USP 35 <*797*> *Pharmaceutical Compounding—Sterile Preparation*

4.2 ISO 14644-1:1999: *Cleanrooms and associated controlled environments-Classification of air cleanliness*

4.3 IEST-RP-CC001.5: *HEPA and ULPA Filters*

4.4 IEST-RP-CC006.3: *Testing Cleanrooms*

4.5 FDA 2004 *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Guide*

4.6 ISO 14644-4:2001 *Cleanrooms and associated controlled environments-Design, construction and start-up*

4.7 IEST-RP-CC034.3: *HEPA and ULPA Filter Leak Tests*

4.8 NSF/ANSI 49 *Class II (laminar flow) Biosafety Cabinetry*

4.9 CAG-001-2005: *CETA Applications Guide for the use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities*

4.10 CAG-002-2006: *CETA Compounding Isolator Testing Guide*

4.11 IEST-RP-CC002.3: *Unidirectional Flow Clean-Air Devices*

4.12 IEST-RP-CC013.2: *Calibration Procedures and Guidelines for Select Equipment*

4.13 IEST-RP-CC014.1*: Calibration and Characterization of Optical Airborne Particle Counters*

5.0 Acronyms/ Definitions

ACPH	Air changes per hour
BSC	Biological Safety Cabinet
CAI	Compounding Aseptic Isolator
CACI	Compounding Aseptic Containment Isolator
CETA	Controlled Environment Testing Association
CFM	Cubic Feet per Minute (air volume measurement)
CSP	Compounded Sterile Preparation
DCA	Direct Compounding Area
FPM	Feet Per Minute (air velocity measurement)
HEPA	High Efficiency Particulate Air (filter)
HVAC	Heating Ventilation and Air Conditioning
IEST	Institute for Environmental Sciences and Technology
ISO	International Organization for Standardization
LAFW	Laminar Air Flow Workstation
µm	Micrometer 1 x 10-6 meters (particle size measurement)
NSF/ANSI	NSF International/ American National Standards Institute
PEC	Primary Engineering Control
VLF	Vertical Laminar Flow
SCA	Segregated Compounding Area
SEC	Secondary Engineering Control

5.1 **Ante Area:** An ISO Class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate –generating activities are performed. It is also a transition area that (1) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas and (2) reduces the need for the HVAC control system to respond to large disturbances.

5.2 **Beyond Use Date:** for the purpose of USP Chapter <797>, the date or time after which a CSP shall not be stored or transported. The date is determined from the date or time the preparation is compounded.

5.3 **Buffer Area:** An area where the primary engineering control (PEC) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs.

5.4 **Critical Area:** An ISO Class 5 environment

5.5 **Critical Site:** A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampules, needle hubs) exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

5.6 **Direct Compounding Area;** A critical area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

5.7 **Dynamic Operating Conditions:** The actual conditions in which the engineering control is used. All actual operating personnel are present and performing actual or simulated operations.

5.8 **First Air:** The air exiting the HEPA filter in a unidirectional air stream that is essentially particle free.

5.9 **Line of Demarcation:** A visible line on the floor that separates the room into areas for different purposes. For example, in the ante area the line separates the cleaner and less clean sides of the room. When the line of demarcation separates two different ISO classification areas, it must be accompanied by a minimum air velocity of 40 fpm from the cleaner area to the less clean area.

5.9.1 **Gowning Line:** A line of demarcation on the floor used to identify where the booties are donned in the gowning process. When this line does not identify a demarcation between ISO Classes it does not require airflow displacement of 40 FPM.

5.10 **Primary Engineering Control:** A device or room that provides a unidirectional airflow ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to LAFWs, BSCs, CAIs, CACIs, and built in VLFs.

5.11 **Segregated Compounding Area:** A designated space, either a demarcated area or room, that is restricted to preparing low-risk level, nonhazardous CSPs with 12-hour or less BUD. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of CSPs and shall be void of activities and materials that are extraneous to sterile compounding.

5.12 **Secondary Engineering Control:** The room or suite of rooms used to support sterile compounding operations. Primary engineering controls are placed inside secondary engineering controls. Secondary engineering controls include: ante areas, buffer areas, and segregated compounding areas.

5.13 **State of Control:** State of control is the practice of controlling variables to achieve the expected results. For the purposes of sterile compounding facility certification, a state of control is achieved when critical parameters used to achieve an appropriate environment for sterile compounding are managed and under control. Adequate HEPA filtered

air is supplied to the room or PEC and the cleaner space is protected from less clean spaces by overpressure or displacement airflow.

5.14 **Unidirectional Airflow:** Controlled airflow from the entrance plane of the work zone that makes a single pass along generally parallel streamlines to the exit plane of the work zone with minimal turbulence, without back-flow, refluxing, and/or re-entrainment and at a velocity sufficient to sweep particles away from critical areas. Air is generally delivered to the work area through a HEPA or ULPA filter system or a diffuser that encompasses the entire entrance plane of the work zone.

6.0 Equipment and Materials

6.1 See individual sections for required equipment

7.0 Effective area of HEPA filters

7.1 The effective area of a HEPA filter refers to the actual face area of the filter medium through which air is passing. This area is obtained by multiplying the length and width of the filter medium, measured to the inside edge of the potting compound or caulk bead. If the filter frame includes a center bar, the face area of the bar is subtracted. (per IEST-RP-CC006.3)[5]

7.1.1 For general purposes, subtracting 2" off of each outside filter dimension will yield a representative effective filter area. The 2 inches is based on ¾" for the filter frame and ¼" for the potting compound for a total of 1" for each of the two dimensions. For example, a filter with outside dimensions of 24" x 48" has an overall area of 8 ft^2 (24 x 48 / 144) and an effective area of 7.03 ft^2 (22 x 46 / 144). If filter frame or potting compound dimensions are different than this example, actual measurements should be used.

8.0 Establishing Acceptance Criteria

8.1 USP Chapter <797> and this document specify **minimum** acceptance criteria for many of the tests required for compliance with the chapter. These values, however, do not establish the **specific** acceptance criteria for each application. For example, if a cleanroom was designed for 60 HEPA Filtered supply ACPH, the USP <797> mandated minimum is too low for this application. The acceptance criteria should be based on the design criteria as long as that criterion is within the limits established by USP. The acceptance criteria for airflow and room segregation in a SEC must be established based on the design criteria whenever possible.

8.1.1 The USP mandated minimum of 30 ACPH may not be adequate for some applications. When the cleanroom designer specifies a

higher air exchange rate, this should be used as the minimum acceptable certification value.

8.1.2 The FDA recommended 20 ACPH minimum air change value for an ISO Class 8 area is often used for ISO Class 8 ante areas. This may not be adequate to maintain cleanliness in light of the activities that occur in these areas. When the cleanroom designer specifies a higher air exchange rate, the higher value should be used as the minimum acceptable certification value.

8.1.3 When the initial certification is performed and the room pressures are significantly higher than the USP mandated minimum values, these higher values should be used for establishing acceptance criteria.

8.1.3.1 It should be noted that negative pressure in an HD buffer room should ideally be maintained as close to -0.01" w.c. as possible. Higher vacuum may result in increased airborne contamination due to particulate laden air infiltrating through cracks and crevices.

8.1.4 Acceptance criteria of baseline +/- 20% may be appropriate for establishing an acceptance criteria range as long as that range exceeds the USP minimum values. Whenever possible, these values should be based on the cleanroom design and supported by environmental monitoring data.

8.2 Room pressure

8.2.1 All readings and acceptance criteria shall be documented to one thousands of an inch water column (e.g. 0.020" w.c. and not 0.02" w.c.)

8.2.1.1 By specifying an acceptance criteria for room pressure to the third decimal place, rounding takes place at a thousands of an inch.

8.2.1.1.1 0.01855" w.c. reading on the micro manometer will be reported as 0.019" w.c. and the room would fail to meet the minimum 0.020" w.c. specified in <797>. If rounding was done at the second decimal place, a meter reading of 0.0185 would be rounded to 0.02" w.c. and the room would pass.

9.0 Cleanroom Certification

For the purpose of this document, certification of the cleanroom in a sterile compounding facility shall be done with the intent to prove that the requirements set forth in USP chapter <797> are met. This section lists the tests appropriate to certify a cleanroom used in sterile compounding. References are made to relevant industry standards for the specific procedures. Although the guide recommends specific tests and relevant standards, it may or may not detail the procedures to perform them. When possible, the guide refers to other industry recognized

standards or guides. USP chapter <797> requires all environmental controls to be certified at least every 6 months, whenever the device or room is relocated or altered or when major service to the facility is performed.

9.1 Airflow Testing

9.1.1 Airflow Testing – Turbulent airflow

9.1.1.1 Cleanrooms employed in sterile compounding are usually dilution control (turbulent airflow) ISO class 7 buffer areas with ISO class 7 or ISO class 8 ante areas. Criteria for the buffer area (hazardous and non-hazardous) airflow are established as a minimum of 30 ACPH with at least 15 ACPH coming from the air supply through the room HEPA filters. Minimum air exchange criteria are not prescribed in USP Chapter <797> for an ISO Class 8 ante or buffer area. The FDA aseptic processing guide recommends a minimum of 20 ACPH for ISO Class 8 zones. Acceptable air exchange rates should be determined on a case by case basis taking into consideration particle generators such as personnel and processes. Higher air exchange rates are often justified.

9.1.1.2 The measurement of supply airflow volume is preferable to the measurement of airflow velocity and is a more representative test of the final filter air supply. Tests to determine airflow supply volume are specified in the following document:

IEST-RP-CC006.3 Section 6.1.2.a

9.1.1.3 USP Chapter <797>[2] is clear that room air change rates are to be based on supply air volume. Traditional air change rules base calculations on the predominant airflow for a particular room. For positive pressure rooms, the supply airflow would establish the exchange rate and for negative pressure rooms, the exhaust airflow would establish the exchange rate. However, for the certification of ISO Class 7 or cleaner sterile compounding facilities USP <797> specifies HEPA filtered supply air exchange rates within the room.

9.1.1.3.1 Measuring the air exchange rates is intended to determine that there is sufficient airflow to dilute and remove airborne contaminants in both positive and negative pressure rooms. Therefore, the air change measurement under USP <797> only involves the SUPPLY HEPA filtered air. Exhaust or return airflow is not

used (for negative pressure rooms) to determine room air changes.

9.1.1.4 For rooms using a line of demarcation between two areas of different purpose, calculation of room air exchange rates takes on additional levels of complexity. If the line of demarcation is simply to divide the clean side of a room from the dirty side for purposes of gowning and process separation, both sides of the line will be the same ISO classification. In this case, the entire room (walled area) should be used to calculate one air exchange rate.

9.1.1.5 For rooms where a line of demarcation separates two separate ISO classifications such as an ISO Class 7 or cleaner buffer area and an ISO Class 8 ante area, the areas on each side of the line are considered independently only when there is HEPA filtered supply for each ISO classified space. In this case, the room air change would use the line of demarcation as an imaginary wall to establish the size of the two areas.

9.1.1.6 When the supply air is delivered only to one side of the line of demarcation (typically on the ISO Class 7 buffer area side) the air exchange rate incorporates both sides of the line of demarcation and the entire space (walled area) is used to calculate one air exchange rate. Similarly, where a HEPA filter is installed directly above the line of demarcation, the walled area would be used to calculate the air exchange rate. Reporting for these situations would identify the combined spaces (ISO Class 7 and ISO Class 8) on both sides of the line of demarcation.

9.1.1.7 All supply outlets served by a common air handler should be measured as a single task without interruption to minimize system variations over time.

9.1.1.8 Backpressure compensation should be used when measuring airflow volume with a capture hood as recommended by the device manufacturer. The backpressure compensation process requires special attention when used to measure air flow at individually controlled constant volume air terminals. The non-backpressure compensated and the backpressure compensated air flow readings should be essentially equal for fast acting constant volume air terminals. The controller responds to the additional backpressure and maintains the preset air flow. If the controller is slow acting, the capture hood must be held in place long enough for the controller to re-attain the set point.[1]

9.2 Airflow Testing – Unidirectional airflow

9.2.1.1 In some cases, the cleanroom will also include the ISO class 5 unidirectional zone as a part of the cleanroom. Unidirectional clean-zones utilize flow control instead of dilution control and should be measured in terms of velocity. Tests to determine airflow velocity are specified in the following document:
IEST-RP-CC002.3 Section 6.1.1

9.2.1.2 The use of a thermal anemometer or an electronic manometer with a multipoint tube array sensor is acceptable for this test.

9.2.1.3 Typical grid patterns used to test unidirectional airflow devices used in sterile compounding are 6 to 12".

9.2.1.4 Grid areas typically begin 6" from the outside edge of the HEPA filter media.

9.2.1.5 Grid zones are typically 6" from the HEPA filter diffuser screen.

9.2.1.6 Unless specified otherwise by the device manufacturer, average velocity should be between 80 and 100 FPM.

9.2.1.6.1 Alternative velocity ranges can be assigned if airflow visualization tests indicate smooth airflow with no refluxing or dead air spots within the DCA and air is drawn away from the critical site to the return or out of the PEC.

9.3 Room segregation

9.3.1 Rooms used to compound sterile preparations need to be isolated from surrounding spaces. Traditionally, this segregation is done through pressurization, however, some situations allow for the separation to be accomplished with airflow displacement.

9.4 Room pressurization

9.4.1 Cleanrooms used for non-hazardous compounding must be positive pressure relative to the adjacent spaces. USP chapter <797> requires a minimum pressure differential of 0.020" w.c. relative to adjacent spaces. Cleanrooms used for hazardous applications should be a minimum 0.010" w.c. negative relative to adjacent spaces. Pressure gauges shall be installed in order for pharmacy personnel to monitor pressures between the buffer area(s) and the ante area(s), and between the ante area(s) and the uncontrolled space. The resolution for each pressure monitor should be adequate for the specified range.

9.4.1.1 Pressure gauges should be performance verified at every certification.

9.4.2 When cart pass-throughs are employed, the cleanroom designer should specify the pressure relationship between the cleanest room, the cart pass-through, and the less clean room.

9.4.2.1 When the cart pass-through is used as a cleaning space, material prep space, HEPA filtered air should be supplied to the pass-through and the recommended pressure relationship is 0.020" w.c. positive from the cleanest room to the cart pass-through, and 0.020" w.c. positive from the cart pass-through to the less clean room (0.040" w.c. positive from the cleanest room to the less clean room).

9.4.2.2 When the cart pass-through is not used as a prep space, HEPA filtered air is typically not provided to the cart pass-through and the pressure relationship is 0.020" w.c. through the cart pass-through to the less clean room.

IEST-RP-CC006.3 Section 6.4

9.5 Airflow displacement

9.5.1 The concept of space separation with airflow is not as well documented as is room separation with pressurization. The inclusion of this test procedure should not be taken as an endorsement of the concept but rather an acknowledgement that the practice does exist and as such facilities must at least be tested to the manufacturers design concept.

9.5.2 ISO 14644:4[7] discusses the displacement concept (low pressure differential, high airflow) in section A.5.2. as follows: "A low pressure differential can effectively separate clean and less clean adjacent zones, i.e. by means of a low turbulent "displacement" airflow, e.g. larger than 0.2 m/s (40 fpm). Displacement airflow velocity should be typically above 0.2 m/s (40 fpm), from the cleaner zones towards the less clean zones. The necessary airflow velocity should be selected considering important conditions such as physical obstacles, heat sources, exhausts and contamination sources".

9.5.2.1 It should be noted that the velocity mentioned above is at the lower limits of the airflow measurement range of equipment typical for field certification applications. The statement also indicates an important consideration is for the airflow to be "low turbulent" indicating an importance to uniformity. The cleanroom manufacturer should be responsible for determining an appropriate set of measurement parameters including sample locations, minimum average velocity, and uniformity range. The airflow velocity measurements should be supported with a visual smoke pattern analysis. USP chapter <797>

specifies a minimum of 40 fpm for the separation velocity but the specific criteria should be established by the manufacturer for each application.

9.5.3 Displacement airflow velocity test

9.5.3.1 Divide the open area to be tested (opening between two adjacent cleanliness class spaces) into a grid of equal areas. Individual areas should not exceed 1 ft^2 and should not be taken within 6" of all opening edges unless the opening is too narrow that this is not possible. If the opening is less than 12" in one direction then a single row should be taken 6" from the sides with reading not more than 12" apart.

9.5.3.2 Measure the airflow velocity at each test location. Allow at least 5 seconds for each measurement and record the average reading at each position once the reading has stabilized.

9.5.3.3 All individual readings shall be 40 feet per minute or greater.

9.5.3.4 Airflow visualization procedure

9.5.3.4.1 Generate a neutrally buoyant airflow visualization medium across the entire area being tested. A separate pass should be made along the entire perimeter as well as across the entire opening itself. Attention should be paid to thermal and flow gradients across the opening to verify that the air flows from the cleanest to less clean area across the entire opening with no reverse flow.

9.5.3.4.2 A video documentation of the results is recommended.

9.6 HEPA Filter Installation Leak Test

9.6.1 All HEPA filters shall be leak tested every certification utilizing an aerosol photometer and an appropriate aerosol challenge medium. A challenge of 10-90 micrograms per liter should be used. Individual leaks should not exceed 0.010% of the upstream challenge for filters that can be scanned. For filters that cannot be scanned, a probe test in the duct or discharge into the room can be performed at a location downstream of the HEPA filter that results in good mixing. For filters that cannot be scanned the overall penetration shall not exceed the efficiency rating of the filter.

9.6.2 Accepted industry practice is to use a photometer scan probe with a maximum area of 1.7 in^2 and a minimum dimension of 0.5" and a maximum scan rate of 2"/second. Overlapping strokes should be used when scanning the filter media. A separate scan should be

performed at the perimeter of each filter to locate leaks in the bond between the filter and the frame.

9.6.3 When developing a filter leak test plan, ensure that smoke detectors, if present, are disabled for the duration of the test. If the aerosol is introduced into the HVAC system at a remote location upstream of the blower, care should be taken to ensure that all duct outlets are HEPA filtered. Unfiltered outlets on a remotely challenged system will result in smoke being released into the room served by that outlet. Procedures are specified in the following document:

IEST-RP-CC034.3[8] Section 6.2.1 for filters that can be scan tested

IEST-RP-CC034.3 Section 6.2.3 for filters that cannot be scan tested

9.7 Airborne Non-Viable Particle Counting

9.7.1 Classification of cleanliness levels is done with a particle count survey. Rooms shall be certified to the cleanliness level specified by the owner. USP chapter <797> requires the buffer area to be ISO class 7 (class 10,000) or cleaner and the ante area for non-hazardous applications to be ISO class 8 (class 100,000) or cleaner. Ante areas adjacent to a negative pressure buffer area should meet ISO class 7 (class 10,000) because this air will be drawn into the negative pressure buffer area.

9.7.2 A discrete particle counter capable of detecting particles of 0.5 microns shall be used. The particle counter shall have been calibrated within one year with traceability to a recognized organization such as NIST. A zero-filter should be used in conjunction with discrete particle counter prior to testing to verify performance. The volume sampled at each location shall be at least 2 liters, with a minimum sampling time at each location of 1 minute.

9.7.3 Verify that all aspects of the cleanroom system which contribute to its operations integrity (air handling, filtration systems, walls, floors, ceilings etc.) are complete and functioning normally in accordance with the requirements of the type of cleanroom and the operational mode under test.

9.7.4 Set up the particle counter in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate. Establish a test point grid pattern at the working level and into the airstream. The direction of probe should be oriented into the direction of the airflow for unidirectional applications. If

the airflow is not unidirectional (non-unidirectional), affix the sampling probe vertical pointing upward. Divide the test zone into grids of equal area. Minimum number of sample locations shall be no less than the square root of the clean space area in square meters.

9.7.5 Reporting: Nonviable samples shall be expressed in ISO classification; occupancy state; considered particle size. Room cleanliness class acceptance will be based on ISO Standard 14644-1[3] analysis for the room classification assigned to each room ISO 14644-1:1999

9.8 Optional Tests

9.8.1 In addition to the criteria specified by USP, the following tests may yield valuable information. These tests are performed at the discretion of the owner.

9.9 Lighting Level and Uniformity Test

9.9.1 This test is recommended on a new cleanroom to verify the contractor provided a finished product that meets design criteria. Test procedures are specified in the following document:

IEST-RP-CC006.3 Section 6.6

9.10 Noise Level Test

9.10.1 This test is recommended on a new cleanroom to verify the contractor provided a finished product that meets design criteria. Test procedures are specified in the following document:

IEST-RP-CC006.3 Section 6.7

9.11 General Temperature and Moisture Uniformity Tests

9.11.1 Temperature is an important issue when considering worker comfort. Temperature ranges typical for cleanroom applications are between 66 (18.9º C) and 70 (21.1º C) degrees Fahrenheit. Humidity ranges are typically between 35% and 60%. The exact ranges are not specified in USP chapter <797>, however, USP does recommend temperatures below 68 degrees Fahrenheit (20˚C).

IEST-RP-CC006.3 Section 6.9

10.0 Biological Safety Cabinet (BSC) Certification

10.1 Class II Biological Safety Cabinets (BSCs) are tested at NSF International and performance criteria are published according to the results observed. Field certification professionals should be accredited by NSF International for certification of Class II BSCs. Selection of certifiers accredited by NSF International gives the end user confidence in their understanding of this complicated process. Test procedures for certification of BSC are detailed in the following standard:NSF/ANSI 49[9] Annex F for field certification

10.2 In addition to the NSF certification process, the BSC must be certified to meet ISO class 5 at 0.5 µm and larger particles during dynamic operating conditions.

10.2.1 A discrete particle counter capable of detecting particles of 0.5 microns shall be used. The particle counter shall have been calibrated within one year with traceability to a recognized organization such as NIST. A zero-filter should be used in conjunction with discrete particle counter prior to testing to verify performance. The volume sampled at each location shall be at least 2 liters, with a minimum sampling time at each location of 1 minute.

10.2.2 Procedure: Verify that all aspects of the BSC are functioning normally in accordance with the manufacturer's recommended parameters for the operational mode under test.

10.2.3 Set up the particle counter in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate. Establish a test point grid pattern at the working level and into the airstream. The direction of probe should be oriented into the direction of the airflow. Divide the test zone into grids of equal area. Minimum number of sample locations shall be no less than the square root of the clean space area in square meters.

10.2.4 For BSCs typically used in sterile compounding, ISO recommendations result in one sample location which may not adequately prove an environment to be suitable for compounding sterile preparations. An example of a reasonable plan is one where the locations are in each of the four corners (6" from interior walls) and one at the geometric center of the work area. A minimum of one sample location should be positioned 6 to 12" directly upstream of the critical site.

10.3 Reporting: Nonviable samples shall be expressed in ISO classification; occupancy state; considered particle size. Room cleanliness class acceptance will be based on ISO Standard 14644-1.

ISO 14664-1[3]

10.4 BSCs used to compound hazardous drugs shall be equipped with an exhaust alarm. The exhaust alarm shall be performance verified at every certification.

10.4.1 NSF/ANSI 49[9] Annex F.7, site installation tests for field certification

11.0 Compounding Aseptic Isolator[2] (CAI) and Compounding Aseptic Containment Isolator (CACI) Certification

11.1 USP Chapter <797> references the following applications guide for testing and certification of CAIs. This includes positive pressure isolators used for non-hazardous sterile compounding (CAI) and negative pressure isolators used for compounding hazardous sterile preparations

(CACI):CETA CAG-002-2006

11.2 It is crucial to note that isolators are often used for compounding outside of a cleanroom. USP does not currently specify conditions for the room when compounding non-hazardous drugs in an isolator that meets the conditions specified in Chapter <797>. When compounding hazardous drugs, however, the room should be certified to have at least 12 ACPH and be at least 0.01" w.c. negative to adjacent rooms and spaces.

CETA CAG-003-2006 Sections 2.1.1 and 2.1.4.1

11.3 CACIs used to compound hazardous drugs shall be equipped with an exhaust alarm. The exhaust alarm shall be performance verified at every certification.

12.0 Laminar Air Flow Workstation Certification

12.1 The Laminar Air Flow Workstation (LAFW) has been the staple of sterile compounding since the inception of the trade. Historically, LAFWs were certified to the now sunset Federal Standard 209. Versions of this standard evolved from 209b to 209e, but the most cited version for certification of LAFWs was Federal Standard 209b because it was the last version of 209 to include tests other than particle count classification.

12.2 Laminar flow devices are certified to two sets of criteria; physical tests and particle count for cleanliness classification. The following standards and recommended practices are used to specify appropriate certification procedures:

12.3 Airflow Velocity Testing

12.3.1 Because unidirectional airflow equipment utilizes flow control, these should be measured in terms of velocity. Average airflow velocities are typically set to a range of 80 to 100 fpm, but the actual range is best established by the device manufacturer. Acceptance criteria should be 80 - 100 fpm unless an alternative velocity range has been supported by smoke pattern studies to be more appropriate. Uniformity should be confirmed as determined by the device manufacturer. Test procedures are specified in the following document:

IEST-RP-CC002.3[13] Section 6.1

12.3.2 Airflow velocity readings should be taken in a plane 6-12 inches from the filter, protective screen or diffuser screen. The actual plane location should be chosen based on the most repeatable position for that particular device. The distance from the filter or screen should be clearly identified on the test report.

12.3.3 Unless otherwise recommended by the device manufacturer, a maximum 12” grid beginning 6” from the inner edge of the filter frame (or LAFW sidewall) positioned 6” from the filter or screen is recommended.

12.3.4 Acceptance criteria should be 80 - 100 fpm unless an alternative velocity range has been supported by smoke pattern studies to be more appropriate.

12.4 HEPA Filter Leak Test

12.4.1 All HEPA filters shall be leak tested at every certification utilizing an aerosol photometer and an appropriate aerosol challenge medium. A challenge of 10-90 micrograms per liter should be used. HEPA filters should be certified to be free from leaks in excess of 0.01% of the upstream challenge concentration. Test procedures are specified in the following document:

IEST-RP-CC034.3 Section 6.2.1

12.5 Induction Leak/Backstreaming Test

12.5.1 This test verifies the LAFW is free from unsealed construction joints and that room airflow patterns or bench location do not introduce particulate contamination into the critical work area. Test procedures are specified in the following document:

IEST-RP-CC002.3 Section 6.1.3

12.6 Non-Viable Particle Counting

12.6.1 LAFWs shall be certified to ISO class 5 at 0.5µm and larger particles under dynamic operating conditions.

12.6.2 A discrete particle counter capable of detecting particles of 0.5 microns shall be used. The particle counter shall have been calibrated within one year with traceability to a recognized organization such as NIST. A zero-filter should be used in conjunction with discrete particle counter prior to testing to verify performance. The volume sampled at each location shall be at least 2 liters, with a minimum sampling time at each location of 1 minute.

12.6.2.1 Procedure: Verify that all aspects of the LAFW are functioning nominally in accordance with the manufacturers recommended parameters for the operational mode under test.

12.6.2.2 Set up the particle counter in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate. Establish a test point grid pattern at the working level and into the airstream. The direction of probe should be oriented into the direction of the airflow. Divide the test zone into grids of equal area. Minimum number of sample locations shall be no less than the square root of the clean space area in square meters.

12.6.2.3 For LAFWs typically used in sterile compounding, ISO recommendations result in one sample location which may not adequately prove an environment to be suitable for compounding sterile preparations. . An example of a reasonable plan is one where the locations are in each of the four corners (6" from interior walls) and one at the geometric center of the work area. A minimum of one sample location should be positioned 6 to 12" directly upstream of the critical site.

12.6.3 Reporting: Nonviable samples shall be expressed in ISO classification; occupancy state; considered particle size. Room cleanliness class acceptance will be based on ISO Standard 14644-1.[3]

ISO 14664-1

12.7 **Optional Tests**

12.7.1 Optional tests are detailed for the following:IEST-RP-CC002.2

Section 6.10 lighting

Section 6.11 noise

13.0 Airflow Visualization Test (Smoke Pattern)

13.1 Two types of smoke pattern tests are performed on all primary engineering controls used to compound sterile preparations. A test to determine if the device is performing as designed and is properly integrated into the facility is done under "at rest" conditions. A test to ensure that the device provides adequate unidirectional airflow to support aseptic operations as required for the intended tasks is performed under "dynamic operating conditions".

13.2 Select a visual smoke/fog tracer that can be conveniently deployed within the unidirectional flow zone to visualize airflow without disrupting the airflow patterns. A video recording device should be available to document the airflow patterns. Depending on the layout of the room and/or PEC, a tripod may be needed to support and aim the video recording device.

13.2.1 An airflow smoke pattern test should be done at every certification to verify that the device is properly integrated into the facility. Cross drafts caused by traffic patterns, HVAC airflow, opening and closing of doors, and poorly placed products and materials may interfere with the unidirectional airflow. Visual verification that the flow of the air is undisturbed should be documented as part of the certification process.

13.2.2 A dynamic smoke pattern test shall be performed to ensure that the device adequately supports the actual process and that the staff is using the device properly. The dynamic smoke pattern test shall be done with the actual compounding personnel performing simulations of all of the actual compounding processes in which critical sites are potentially exposed.

13.2.3 Dynamic smoke pattern testing shall prove that the device provides unidirectional airflow with no dead spots or refluxing at the DCA for the operating velocity at which the unit was certified.

13.2.4 The dynamic smoke pattern test shall be performed at every certification.

13.2.5 The smoke pattern test should be a critical component of the compounding technician training program. It is therefore required that the dynamic smoke study be performed at every certification to:

13.2.6 Determine the optimum layout within the DCA.

13.2.7 Show the compounding personnel the correct way to take advantage of unidirectional airflow.

13.2.8 Indicate suitability of the unidirectional airflow device for the intended purpose.

13.3 A visible source of smoke such as a glycol based fog generator or ventilation smoke tube is used to observe air patterns within the unidirectional space. Smoke is generated directly downstream of the diffuser and then observed as it flows across the critical site and the direct compounding area (DCA) and to a return or out of the critical area. Air exiting the critical area should not re-enter. This test is not appropriate for turbulent airflow cleanrooms.

13.4 The smoke pattern tests should be witnessed by the compounding facility supervisors so they can determine optimal operating set-ups based on airflow patterns within the space.

13.5 Water based fog generators such as CO^2 and liquid nitrogen create a fog that is heavier than air and do not always provide for an accurate representation of the actual air patterns. The smoke source should be as close to neutrally buoyant as possible. For example, when generating the fog in an area with no detectable airflow, it should not "fall out" or "drop". Fog streams that are heavier than air may not detect updrafts and turbulence that are detected with a generally neutral buoyant detection stream.

13.6 The intentions of unidirectional airflow are clearly stated in the FDA guidance document for industry "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice". "In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions".

13.7 A written report detailing the airflow patterns with a definitive statement of acceptability for the intended purpose should be provided. The final documentation should clearly identify the DCA along with the appropriate aseptic technique performed by compounding personnel.

13.7.1 The preferred method of documenting airflow patterns is to support the written statement with a video.

14.0 Documentation

14.1 Documentation of test results in an informative and comprehensive report shall be provided as a formal completion to the certification process. The report will include a statement of compliance or non-compliance regarding the requirements and guidelines outlined in this Application Guide. A formal report will include as a minimum, but not limited to, the following items:

14.1.1 Name, address and contact information for the certifying organization also listing key personnel with appropriate accreditations.

14.1.2 Confirming remark that the most current version of this CAG was referenced for this certification and the actual date the certification was completed.

14.1.3 Simple and clear method of identification of the approximate location of the collected data in relation to the physical layout of the equipment or facility tested, including specific and clear nomenclature for the data locations.

14.1.4 Explanation of test procedure used for data collection and justification for any deviations from established industry practices encountered during the certification process.

14.1.5 Collected data will be compared to expected values or specific equipment performance criteria established in Standard Operating Procedures supplied by the client. In the absence of client SOPs, the certifying organizations SOPs or industry accepted standards, recommended practices and manufacturer's specifications would be used.

14.1.6 Provide a list of equipment utilized in data collection to include make, model, serial number, and calibration date and when requested a facsimile of the current calibration documentation for each piece of equipment, when applicable.

15.0 Test equipment calibration

Test equipment used for certification of sterile compounding facilities should be calibrated on a calibration frequency not to exceed 12 months or more frequently if recommended by the manufacturer. Calibration certificates should be provided upon request by the customer for all calibrated test equipment.

IEST-RP-CC013.2[14]
IEST-RP-CC014.1[15]

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[1] Shortridge owner's manual section **12.4 CONSTANT VOLUME CONTROLLERS**

[2] USP33-NF28: United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, USA, www.usp.org.

[3] ISO 14644-1:1999: Cleanrooms and associated controlled environments-Classification of air cleanliness, International Organization for Standardization, Case Postale 56, CH-1211 Geneve 20, Switzerland www.iso.org

[4] IEST-RP-CC001.5: HEPA and ULPA Filters, Institute of Environmental Sciences and Technology, 2340 S. Arlington Heights Road, Suite 100, Arlington Heights, IL 60005-4516, USA, www.iest.org

[5] IEST-RP-CC006.3: Testing Cleanrooms, Institute of Environmental Sciences and Technology, 2340 S. Arlington Heights Road, Suite 100, Arlington Heights, IL 60005-4516, USA, www.iest.org

[6] Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, U.S. Department of Health and Human Services Food and Drug Administration, September 2004, http://www.fda.gov/cder/guidance/index.htm

[7] ISO 14644-4:2001 Cleanrooms and associated controlled environments-Design, construction and start-up, International Organization for Standardization, Case Postale 56, CH-1211 Geneve 20, Switzerland www.iso.org

[8]IEST-RP-CC034.3: HEPA and ULPA Filter Leak Tests, Institute of Environmental Sciences and Technology, 2340 S. Arlington Heights Road, Suite 100, Arlington Heights, IL 60005-4516, USA, www.iest.org

[9] NSF/ANSI 49-2004: Class II (laminar flow) Biosafety Cabinetry, NSF International, P.O. Box 130140, Ann Arbor, MI 48113-0140, USA, www.nsf.org

[10] CAG-001-2005: Applications Guide for the use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607, USA, www.cetainternational.org

[11] CAG-002-2006: CETA Compounding Isolator Testing Guide, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607, USA, www.cetainternational.org

[12] Federal Supply Services Bureau, Specifications Section, Suite 8100, 470 East L'Enfant Plaza, SW Washington, DC 20407, USA

[13] IEST-RP-CC002.3: Unidirectional Flow Clean-Air Devices, Institute of Environmental Sciences and Technology, 2340 S. Arlington Heights Road, Suite 100, Arlington Heights, IL 60005-4516, USA, www.iest.org

[14] IEST-RP-CC013.2: Calibration Procedures and Guidelines for Select Equipment, Institute of Environmental Sciences and Technology, 2340 S. Arlington Heights Road, Suite 100, Arlington Heights, IL 60005-4516, USA, www.iest.org

[15] IEST-RP-CC014.1: Calibration and Characterization of Optical Airborne Particle Counters, Institute of Environmental Sciences and Technology, 2340 S. Arlington Heights Road, Suite 100, Arlington Heights, IL 60005-4516, USA, www.iest.org