CETA Certification Matrix for Sterile Compounding Facilities
(Secondary Engineering Controls)
CAG-008-2010
January 31, 2012

The following table provides a matrix for reviewing the certification of secondary engineering controls (cleanrooms) used in sterile compounding facilities designed to comply with USP chapter <797>. The Controlled Environment Testing Association has developed the applications guide, CAG-003-2006 (2012), which is referenced in chapter <797>. The table assumes the certification professional follows this applications guide for general guidance. The certifier should provide specific details of each test conducted either directly in the certification report or in a Standard Operating Procedure (SOP) referenced in the certification report. All calculations including intermediate values should be documented on the certification report. Calibration certificates should be provided for every test instrument used and the specific model number and serial number of each test instrument should be documented on the certification report. The certification report should include the name and address of the testing agency, the name and qualifications of the certification technician (including accreditations), the name and version of any referenced standards, and a clear identification of the physical location of the equipment being tested.

The actual acceptance criteria for each test should be agreed to between the owner and certifier based on industry guidance. Good documentation practices include stating an acceptance range for each test. The acceptance values listed in this document are customary and standard for cleanrooms. Where no criteria exist, those used for FDA aseptic drug manufacturing have been used.

This review does not include the viable environmental sampling (See CAG-009-2012 for guidance on environmental monitoring). It is limited to the engineering control performance verification (certification) procedures covered in the CETA document as referenced in chapter <797>. The control points of interest are:

1. Assuring adequate HEPA filtered air supplied to the rooms and proper airflow velocities in unidirectional cleanroom spaces (airflow testing)
2. Assuring separation from rooms of different cleanliness classification and purpose (differential pressure and displacement airflow)
3. Assuring that the HEPA filters are leak-free (HEPA filter integrity test)
4. Providing visual verification that air flows from clean to less clean areas and that unidirectional airflow areas are free from turbulence and reverse flows (airflow smoke pattern test)
5. Assuring that the design when operating properly yields the intended cleanliness classification under dynamic operating conditions (particle count test)
6. Assuring the temperature within the compounding facility is appropriate for sterile compounding (temperature testing)
7. Assuring the humidity within the compounding facility is appropriate for sterile compounding (humidity testing)

CETA Certification Matrix for Sterile Compounding Facilities
(Secondary Engineering Controls)
CAG-008-2010
January 31, 2012

Item	Basis for compliance	Minimum reported values	Test equipment requirement
Airflow (Non-Hazardous Compounding rooms) (1)	Non-hazardous sterile compounding rooms must maintain a minimum of 30 total HEPA filtered Air Changes Per Hour (ACPH). At least 15 HEPA filtered ACPH must come from air sources outside the room(e.g. HVAC, Fan Filter Units, recirculation system, etc.) Up to half of the total HEPA filtered air can be generated by the recirculated primary engineering control. The minimum ACPH requirement for an ISO class 8 ante area is not specified in USP <797>. A minimum of 20 ACPH is commonly referred to by the FDA and others.	Air Volume through each supply HEPA filter __CFM. Total HEPA Filtered air volume supplied to the room__CFM. Total HEPA filtered air volume added to the room total from the PEC__ CFM. Room volume __Ft^3. Dimensions used to calculate the room volume__inches. If the primary engineering control is used for a portion of the minimum 30 total ACPH, specific calculations for this source should be documented. All calculations along with the total HEPA filtered room __ACPH should be documented.	The preferred test equipment is the airflow capture hood used to measure directly in airflow volume (CFM). When this method cannot be employed a secondary method may be used. The alternative methods may include thermal anemometers for velocity measurements. Maximum recommended calibration interval – 12 months for electronic capture hoods - 6 months for thermal anemometers.

Airflow (Hazardous compounding rooms) (1)	Hazardous sterile compounding rooms must maintain a minimum of 30 total HEPA filtered Air Changes Per Hour (ACPH). Since most primary engineering controls used for compounding hazardous drugs are vented from the building, all of the HEPA filtered air will be from outside the room. In the rare case where the low-volume exception is used and the primary engineering control is vented back into the room, a total of 15 ACPH must come from outside the room when the re-circulated HEPA filtered exhaust air from the BSC is used as part of the 30 total ACPH. The air exchange rate criteria for an ISO Class 7 ante area serving a negative pressure buffer room should maintain a minimum 30 ACPH. If a CACI is used, the room must maintain a minimum of 12 ACPH.	Air Volume through each supply HEPA filter __CFM. Total air volume supplied to the room__CFM. Room volume __Ft^3. Dimensions used to calculate the room volume__inches. All calculations along with the total HEPA filtered room __ACPH should be documented. A statement of pass or fail should be clearly made for every the room air exchange rate within each room tested.	The preferred test equipment is the airflow capture hood used to measure directly in airflow volume (CFM). In some rare cases, a capture hood will not fit in the given space and a thermal anemometer will need to be used to measure in velocity (FPM) and those readings converted to volume by multiplying the average velocity times the effective filter area. Maximum initial recommended calibration interval – 12 months for electronic capture hoods - 6 months for thermal anemometers.

Airflow (Velocities in a unidirectional zone) (1)	Some sterile compounding facilities integrate a Vertical Laminar Flow (VLF) area directly into the cleanroom design. This area is typically segregated from the ISO Class 7 buffer area in which it is placed with Lexan shields. On rare occasions, the entire buffer area can be classified as an ISO class 5 unidirectional space. USP does not specify a velocity range but does require the primary engineering control to be unidirectional and to verify that the air sweeps over and away from the product under dynamic operating conditions. A velocity profile across the entrance plane into the work area is required to establish and prove maintenance of a state of control over this critical space. The actual acceptable velocity range should be confirmed with an airflow smoke pattern test (see #4). Most VLF spaces operate at an entrance plane velocity of between 80 – 100 fpm. The entrance plane is typically 6" below the HEPA filter or diffuser.	Individual velocity readings displayed on a grid corresponding to reading locations in ___ FPM Average velocity through the entrance plane to the work area in average ___ FPM. Listing of the acceptable velocity range as validated with smoke pattern testing. A statement of pass or fail	The preferred test equipment is the thermal anemometer or an electronic manometer with a multipoint tube array Maximum initial recommended calibration interval –12 months for thermal anemometers – 6 months for electronic capture hoods

Room Segregation (Non-hazardous compounding rooms) (2)	One of two segregation strategies must be proven a) Differential pressure A minimum differential pressure of 0.02" w.c. positive from the cleanroom to the ante room and all adjacent spaces and between the ante room and all adjacent spaces with the doors closed. -or- b) Displacement airflow for low and medium risk non-hazardous rooms only. A minimum differential velocity of 40 FPM from the cleanroom to the ante room. Note that it is very important to maintain this velocity across the entire opening.	Differential pressure at every door or opening from each sterile compounding room and ante room to every adjacent space __ inches w.c. displayed on a room layout diagram clearly identifying which direction the pressure is flowing. Displacement velocity across every opening between rooms of different classification in __ FPM. A comprehensive grid should be taken across every opening to assure that the airflow is consistent across the entire opening. Every individual reading displayed on a schematic grid should be documented along with the average velocity across every opening. Statement of a visual confirmation in the form of an airflow smoke pattern test that the air is flowing out of a non-hazardous compounding room into the ante room and out of the ante room to adjacent spaces. This is performed for both pressure controlled and flow controlled spaces.	The preferred equipment is an electronic manometer with a resolution to at least thousandths of an inch water column. Maximum recommended calibration interval-12 months.

Room Segregation (Hazardous compounding rooms) (2)	The only acceptable room segregation strategy for hazardous compounding rooms is differential pressure*. A minimum differential pressure of 0.01" w.c. negative from the cleanroom to the ante room and 0.02" positive from the ante room to all adjacent spaces must be proven. *Maintenance of room pressure requires the use of physical barriers such as walls and doors.	Differential pressure at every door or opening from each hazardous sterile compounding room and ante room to every adjacent space in __ "w.c. displayed on a room layout diagram clearly identifying which direction the pressure is flowing. While not required in most cleanroom standards, a Statement of a visual confirmation in the form of an airflow smoke pattern test that the air is flowing into a hazardous compounding room from the ante room and out of the ante room to adjacent spaces is recommended.	The preferred equipment is an electronic manometer with a resolution to at least thousandths of an inch water column. A magnehelic gage can be substituted but it is ideally a monitoring device and not as good of a field certification device as a digital electronic manometer. Maximum recommended calibration interval-12 months.

HEPA filter Integrity Test (3)	All HEPA filters should be leak tested at every certification using an aerosol photometer and an appropriate aerosol challenge. A challenge aerosol is introduced into the air handling system upstream of the filters and the upstream concentration is compared to the downstream concentration to determine if there are any penetrations in excess of the maximum allowed. The maximum allowable leakage is 0.01% of the upstream aerosol concentration.	Aerosol introduction location and upstream measurement location and the measured upstream aerosol concentration in __ micrograms per liter. Note that in some rare occasions, an upstream concentration cannot be measured. In those cases, an upstream aerosol concentration can be calculated and reported as such. If a calculated challenge is used, all of the calculations should be reported along with a reason that a challenge was not measured. A diagram of the filter along with an indication of where leaks were found, if any, and the percent penetration of leaks or a statement that no leaks in excess of the maximum allowable 0.01% were detected. A statement of pass or fail should be clearly made for every HEPA filter.	An aerosol photometer that is capable of indicating a 100 % upstream concentration with an aerosol challenge of 10 micrograms per liter of polydispersed Poly Alpha Olefin (PAO) particles or equivalent. Unit must have a threshold sensitivity of at least 10^{-3} per liter and be capable of measuring concentrations over a range of 10^5 times the threshold sensitivity. The sampling rate shall be 1 CFM with an inlet probe having maximum open area of 1.7 in2 and a minimum dimension of 0.5 inches. Maximum recommended calibration interval-12 months. An aerosol generator should be capable of supplying a polydispersed aerosol by blowing compressed air through a laskin type nozzle into oil such as Poly Alpha Olefin (PAO) or another approved generation method.

Airflow smoke pattern test (4)	Primary engineering controls including built-in laminar airflow, LAFW, and BSCs must be properly integrated into the buffer area. A visual medium is used to observe airflow patterns during dynamic operating conditions. The buffer room must be segregated from the ante area and all adjacent spaces. A visual observation using smoke is used to prove the pressure/ flow differential is consistent across the entire opening.	A description of the test along with the results of the airflow pattern observation should be documented for each engineering control and around every room penetration. The language used to describe the results should be descriptive. For example: Sweeping, smooth, steady, flowing, controlled, fluid, turbulent, unidirectional, backward flow, slow, lazy. Statement of the occupancy state (at rest, as built, or operational (dynamic operating conditions)). A statement of pass or fail should be clearly made for every test.	A visual airflow observation medium such as ventilation smoke tubes. The delivery velocity of the "smoke tubes" should not overcome the airflow patterns being observed. Laskin nozzle generators typically generate too high of a velocity to be an appropriate medium for airflow observation.

Particle Count Survey (5)	All buffer rooms used for sterile compounding must maintain at least ISO class 7 during actual or simulated dynamic operating conditions. Ante areas that do not serve a negative pressure hazardous drug buffer area must maintain at least ISO class 8 under dynamic operating conditions. Ante areas that serve a negative pressure hazardous drug buffer area room must maintain at least ISO class 7 under dynamic operating conditions. An airborne optical particle counter is used to sample particle levels within the buffer area and ante area. Counts should be taken under dynamic operating conditions; during actual compounding operations	All individual readings or applicable averages of the readings for each location along with a diagram to illustrate the location of each reading displayed in __particles per cubic foot (ppcf) or __ particles per cubic meter (ppcm). Where the number of locations requires Upper 95% statistical analysis or other consideration, show the average of the room readings along with any applicable statistics and calculations Statement of the occupancy state (at rest, as built, or operational (dynamic operating conditions)). Note that particle counts for sterile compounding facilities should be taken under dynamic operating conditions. The permitted concentration of airborne particles and applicable classification for the space (e.g. ISO Class 7 or ISO Class 8). A statement of pass or fail should be clearly made for every clean zone.	Discrete particle counter capable of detecting 0.5 micrometer size particles. Maximum recommended calibration interval is 12 months.

Temperature (6)	USP <797> requires facilities to "provide a comfortable and well-lighted work environment, which typically includes a temperature of 68° F(20°C) or cooler". This is not a mandatory test for compliance per USP <797>. It is a recommendation for worker comfort and required to demonstrate a state of control over the operation.	For each location, report the measurement time and temperature in __degrees Fahrenheit This test is often performed as part of the initial certification and then it is considered monitoring.	A temperature sensor capable of indicating a change in temperature of 0.1 Celsius degree or equivalent. Maximum recommended calibration interval-12 months.
Humidity (7)	This is not a mandatory test for compliance per USP <797>. It is a recommendation for worker comfort and required to demonstrate a state of control over the operation. Relative Humidity levels between 35% and 60% are recommended. Below 35% allows static levels above recommended values. Above 60% promotes microbial growth.	For each location, report the measurement time and relative humidity. This test is often performed as part of the initial certification and then it is considered monitoring.	Humidity sensors should capable of indicating a change in relative humidity of 1%. Maximum recommended calibration interval-12 months.

CETA Certification Matrix for Sterile Compounding Facilities
(Secondary Engineering Controls)
CAG-008-2010
January 31, 2012

Acronyms, abbreviations

BSC Biological Safety Cabinet
CAI Compounding Aseptic Isolator
CFM Cubic Feet per Minute
PEC Primary Engineering Control
W.C. Water Column
LAFW Laminar Air Flow Workstation
CACI Compounding Aseptic Containment Isolator
FPM Feet per Minute
SEC Secondary Engineering Control

Definitions

Primary engineering control (PEC) – A unidirectional airflow ISO class 5 device such as Laminar Air Flow Workstation, Biological Safety Cabinet (BSC), Compounding Aseptic Isolators (CAI), and Compounding Aseptic Containment Isolators (CACI) used to prepare sterile preparations.
Secondary engineering control (SEC) – The facilities used to house the primary engineering control and support the sterile compounding operation; the buffer room and the ante room.
Water column (w.c.) – The unit of measurement used to measure static pressure.
Feet Per Minute (FPM) – The unit of measurement used to measure airflow velocity.
Effective Filter Area – The portion of the HEPA filter where air actually flows through – the filter medium.
Unidirectional Airflow – An airflow moving in a single direction in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical processing or area.

Common Formulas

100 mg/m^3 = 100 µg/l
1milligram (mg) = 1,000 microgram (µg)
1 liter = 0.001 cubic meter (m^3)
Q = VA (CFM = velocity (fpm) x area (ft^2))
1 fpm = 0.0051 m/s
1 m/s = 196 fpm
1 cfm = 0.000472 m^3/s
1 m^3/s = 2118 cfm
33.8°F = 1°C