# CETA Certification Guide for Sterile Compounding Facilities
# CAG-003-2006
# December 18, 2007

*This document was developed to provide a uniform list of tests for certification of engineering controls specified in the proposed changes to USP chapter <797> dated December 3, 2007. It should be noted whether or until the proposed changes are officially adopted, this guidance is considered best of practice but not included in the current official version of the chapter. While use of this document will assure compliance with the proposed changes it may exceed the requirements of the existing standard . USP expects the currently posted changes to become official in June of 2008.*

## 1.0 Background:

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.

## 2.0 Cleanroom Certification

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>[1] are met. This section lists the tests appropriate to certify a cleanroom used in pharmacy. References are made to relevant industry standards for the specific procedures. Although the guide recommends specific tests and relevant standards, it does not detail the procedures to perform them. USP chapter <797> requires all environmental controls to be certified at least every 6 months.

## 2.01 Airflow Testing

### 2.01.1 Airflow Testing – Turbulent airflow

Cleanrooms employed in sterile compounding are usually dilution control (turbulent airflow) ISO class 7[2] buffer areas with ISO class 8 ante rooms. Criteria for airflow are established as a minimum of 30 ACPH with at least 15 ACPH coming from the air supply through the room HEPA[3] filters. The measurement of supply airflow volume is preferable to 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[4] Section 6.1.2.a

### 2.01.2 Airflow Testing – Unidirectional airflow

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-CC006.3 Section 6.1.2.b

### 2.01.3 Airflow Smoke Pattern Test

An airflow smoke pattern test should be performed on all unidirectional airflow cleanzones to verify unidirectional airflow. A visible source of smoke such as a glycol based fog generator 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 compounding area and to a return or out of the critical area. A parallel flow pattern with a minimum of turbulent flow around obstructions should be observed. Air exiting the critical area should not re-enter. This test is not appropriate for turbulent airflow cleanrooms.

It should be noted that water based fog generators such as $CO_2$ and liquid nitrogen create an effluent 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.

Specific procedures are not detailed in any cleanroom testing standards. The intentions are clearly stated, however, in the FDA guidance document for industry “Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice[5]”. “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”.

## 2.02 Room segregation

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

### 2.02.1 Room pressurization

Cleanrooms used for non-hazardous compounding must be positive pressure relative to the adjacent spaces. USP chapter <797> requires a minimum pressure differential of 0.02" w.c. (5 Pa) relative to adjacent spaces. Cleanrooms used for hazardous applications should be a minimum 0.01" w.c. (2.5 Pa) negative relative to adjacent spaces. Procedures are specified in the following document:

IEST-RP-CC006.3 Section 6.4

### 2.02.2 Airflow displacement

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.

ISO 14644:4[6] 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".

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 location, 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 (0.20 m/s) for the separation velocity but the specific criteria should be established by the manufacturer for each application.

## 2.03 HEPA Filter Installation Leak Test

All HEPA filters shall be leak tested at every certification with an aerosol challenge and a photometer. A challenge of 10-90 micrograms per liter should be used. Individual leaks should not exceed 0.01% of the upstream challenge for filters that can be scanned. For filters that can not be scanned the overall penetration shall not exceed the efficiency rating of the filter. Procedures are specified in the following document:

| | | |
|---|---|---|
| IEST-RP-CC034.2[7] | Section 6.2.1 | for filters that can be scan tested |
| IEST-RP-CC034.2 | Section 6.2.3 | for filters that cannot be scan tested |

## 2.04 Particle Count Survey

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 zone to be ISO class 7 (class 10,000) or cleaner and the ante room to be ISO class 8 (class 100,000) or cleaner. Ante areas adjacent to a negative pressure buffer/ cleanroom should meet ISO class 7 (class 10,000) as air will be drawn into the buffer room due to the affect of the negative pressure. Particle counts shall be taken under dynamic operating (operational) conditions at 0.5 µm and larger particles. Procedures are specified in the following document:

ISO 14644-1:1999

## 2.05 Optional Tests

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.

### 2.05.1 Lighting Level and Uniformity Test

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

### 2.05.2 Noise Level Test

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

### 2.05.3 General Temperature and Moisture Uniformity Tests

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% RH. The exact ranges are not specified in USP chapter <797>, therefore are at the discretion of the user. Test procedures are specified in the following document:

IEST-RP-CC006.3 Section 6.9

## 3.0 Biological Safety Cabinet Certification

Biological Safety Cabinets (BSCs) are tested at NSF International and performance criteria are published according to the results observed. Field certification professionals may also be accredited by NSF International to be competent to certify this equipment. 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 49-2004[8] Annex F for field certification

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. Procedures for particle count classification are detailed in the following standard:

ISO 14644-1:1999

## 4.0 Compounding Aseptic Isolator[9] Certification

Compounding Aseptic Isolators are relatively new to the compounding industry. As such, the criteria for their certification are just being established. It is important to insist the manufacturer test the isolator at the factory and the field certifier in the field according to recognized industry methods such as the CETA Compounding Isolator Testing Guide. Test procedures are specified in the following document:

CETA CAG-002-2006[10]

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. When compounding hazardous drugs, however, the room should be certified to have at least 12 ACPH and be at least 0.01” w.c. (2.5 Pa) negative to adjacent rooms and spaces.

## 5.0 Laminar Air Flow Workstation Certification

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 obsolete Federal Standard 209. Versions of this standard evolved from 209b to 209e[11], but the most cited version for certification of LAFWs was Federal Standard 209*b* because it was the last version of 209 to include tests other than particle count classification.

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:

### 5.01 Airflow Velocity Testing

Because unidirectional airflow equipment utilizes flow control, these should be measured in terms of velocity. Airflow velocities are typically set to a range of 80 to 100 fpm (0.41-0.51 m/s), but the actual range is best established by the device manufacturer and maintained there by the certifier. Uniformity should be confirmed as determined by the device manufacturer. Test procedures are specified in the following document:

IEST-RP-CC002.2[12] Section 6.1

### 5.02 HEPA Filter Leak Test

All HEPA filters shall be leak tested at every certification with an aerosol challenge and a photometer. 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-CC034.2 Section 6.2.1

### 5.03 Induction Leak/Backstreaming Test

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-CC002.2 Section 6.5

## 5.04 Airflow Smoke Pattern Test

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 laminarity of the air is undisturbed should be documented as part of the certification process.

## 5.05 Particle Count Survey

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

ISO 14664-1:1999

## 5.06 Optional Tests

Optional tests are detailed for the following:

IEST-RP-CC002.2

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|---|---|---|
| 5.06.1 | Section 6.10 | lighting |
| 5.06.2 | Section 6.11 | noise |

## 6.0 Definitions / Acronyms

| | | |
|---|---|---|
| 6.01 | CETA | Controlled Environment Testing Association |
| 6.02 | LAFW | Laminar Air Flow Workstation |
| 6.03 | BSC | Biological Safety Cabinet |
| 6.04 | IEST | Institute for Environmental Sciences and Technology |
| 6.05 | ISO | International Standards Organization |
| 6.07 | CAI | Compounding Aseptic Isolator |
| 6.08 | HEPA | High Efficiency Particulate Air (filter) |
| 6.09 | FPM | Feet Per Minute (air velocity measurement) |
| 6.10 | CFM | Cubic Feet per Minute (air volume measurement) |
| 6.11 | ACPH | Air changes per hour |
| 6.12 | NSF/ANSI | National Sanitation Foundation (NSF International)/ American National Standards Institute |
| 6.13 | µm | Micrometer 1 x $10^{-6}$ meters (particle size measurement) |
| 6.14 | HVAC | Heating Ventilation and Air Conditioning |
| 6.15 | m/s | meters per second (air velocity measurement) |
| 6.16 | Pa | Pascals (differential pressure measurement) |

[1] USP28-NF23: United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, USA, www.usp.org.

[2] 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

[3] IEST-RP-CC001.4: HEPA and ULPA Filters, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008-3841, USA, www.iest.org

[4] IEST-RP-CC006.3: Testing Cleanrooms, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008-3841, USA, www.iest.org

[5] 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

[6] 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

[7] IEST-RP-CC034.2: HEPA and ULPA Filter Leak Tests, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008-3841, USA, www.iest.org

[8] 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

[9] 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

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

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

[12] IEST-RP-CC002.2: Unidirectional Flow Clean-Air Devices, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008-3841, USA, www.iest.org