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CETA Application Guide CAG-003

Certification of Sterile Compounding Facilities for USP Compliance

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Foreword

The Controlled Environment Testing Association (CETA) is an international organization. One of CETA's objectives is to promote quality assurance through the review of existing standards and the development of new methodologies. One of the main vehicles for obtaining this goal is our CETA Application Guides (CAGs). The CETA Application Guides have proven to be an immeasurably valuable tool to a wide variety of professionals in our industry. They have been used by many safety professionals, industrial hygienists, facility engineers and quality control personnel.

The standards and other documents normatively referenced, in whole or in part, in this CETA Application Guide are indispensable for its use and application. The content of this CAG has its origin in material found in these reference documents. Preparation and development of these guides are the outcome of work completed by technical committees that are formed by the CETA Board of Directors.

Abstract

Certification of sterile compounding facilities and equipment must be performed in a consistent manner and in such a way that the tests are easily repeatable and well understood by the compounding facility and certification company. CAG-003 provides a basic understanding of concepts applicable to cleanroom and sterile equipment testing and certification. This guide, along with USP Chapters <797>, <800> and <825>, provide minimum acceptance criteria for many of the tests required for compliance to state boards of pharmacy regulations and other regulatory bodies. This guide explains the testing required and provides industry best practices where possible.

Certification of Sterile Compounding Facilities for USP Compliance

1 Introduction

Sterile compounding facilities must maintain a specific minimum standard of quality within their facilities and compounding equipment. The certification of sterile compounding facilities and equipment is a complex process that requires communication and planning between the Designated Person of the pharmacy and a representative of the certification company. The certification must be performed in a consistent manner and in such a way that the tests are easily repeatable and well understood by everyone involved. This guide provides a basic understanding of the required cleanroom tests and the certification of primary engineering controls and provides industry best practices where possible.

2 Scope

This guide is intended to be used for the certification of sterile compounding facilities by both certification and compounding professionals as a means for compliance to USP Chapters <797>, <800> and <825>. The guide references minimum industry accepted/current standards and recommended and/or best practices to perform the certification process and properly document the results.

The definitions, acceptance criteria and minimum requirements listed in this document are based on, USP <797>, <800> and <825>.

2.1 Limitations

This guide does not apply to nonsterile compounding facilities. It is intended to support regulation, not replace existing regulation.

This guide specifies **minimum** acceptance criteria for USP compliance. In most cases the facility's acceptance criteria will be more stringent and specific to each application as well as facility design.

This guide was made specifically for USP chapter compliance but may be relevant to other industries and countries.

3 Target Audience

This guide is intended for sterile compounders, facility managers, compounding supervisors, regulators/inspectors, regulatory affairs, consultants and certification professionals.

4 References

For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

4.1 Reference Documents

CAG-002: Compounding Isolator Testing Guide (2008). Controlled Environment Testing Association (CETA), Raleigh, NC, US.

CAG-009: Viable Environmental Monitoring for Sterile Compounding Facilities (2020). Controlled Environment Testing Association (CETA), Raleigh, NC, US.

CAG-011: Gloved Fingertip Testing for Sterile Compounding Personnel (2020). Controlled Environment Testing Association (CETA), Raleigh, NC, US.

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CAG-014: Airflow Visualization Study (2022). Controlled Environment Testing Association (CETA), Raleigh, NC, US.

IES Lighting Handbook (2020). Illuminating Engineering Society, New York, NY, US.

IEST-RP-CC002.4: Unidirectional Flow Clean-Air Devices (2016). Institute for Environmental Standards and Technology (IEST), Schaumburg, IL, US.

IEST-RP-CC006.3: Testing Cleanrooms (2004). Institute for Environmental Standards and Technology (IEST), Schaumburg, IL, US.

IEST-RP-CC013.2: Calibration Procedures and Guidelines for Select Equipment Used in Testing Cleanrooms and Other Controlled Environments (2012). Institute for Environmental Standards and Technology (IEST), Schaumburg, IL, US.

IEST-RP-CC034.5: HEPA and ULPA Filter Leak Tests (2016). Institute for Environmental Standards and Technology (IEST), Schaumburg, IL, US.

ISO 14644-1: Cleanrooms and associated environments - Part 1: Classification of air cleanliness by particle concentration (2015). International Organization for Standardization (ISO), Geneva, Switzerland.

ISO 21501-4: Determination of particle size distribution – Single particle light interaction methods – Part 4: Light scattering airborne particle counter for clean spaces (2018). International Organization for Standardization (ISO), Geneva, Switzerland.

NSF/ANSI 49 Biosafety Cabinetry: Design, Construction, Performance and Field Certification (2020). NSF International (NSF), Ann Arbor, MI, US.

U.S. Department of Health and Human Services, Food and Drug Administration (CDER,CBER,ORA): Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (2004). Food and Drug Administration, Rockville, MD, US.

USP General Chapter <797>: Pharmaceutical Compounding - Sterile Preparations (2021 Proposed revision). United States Pharmacopeia, Rockville, MD, US.

USP General Chapter <800>: Hazardous Drugs - Handling in Healthcare Settings (2019). United States Pharmacopeia, Rockville, MD, US.

USP General Chapter <825>: Radiopharmaceuticals - Preparation, Compounding, Dispensing and Repackaging (2019). United States Pharmacopeia, Rockville, MD, US.

4.2 Cited Bibliography

International Organization for Standardization. (2015). ISO 14644-1: Cleanrooms and associated controlled environments- Classification of air cleanliness

NSF International. (2020). NSF/ANSI 49: Biosafety Cabinetry: Design, Construction, Performance and Field Certification, Annex N-1.4.2, page 35.

NSF International. (2020). NSF/ANSI 49: Biosafety Cabinetry: Design, Construction, Performance and Field Certification, Annex N-5.5.2.1, page 98.

NSF International. (2020). NSF/ANSI 49: Biosafety Cabinetry: Design, Construction, Performance and Field Certification, Annex N-5.5.2.2, page 98.

United States Pharmacopeia. (2021). USP General Chapter <797>: Pharmaceutical Compounding - Sterile Preparations, Section 4.2, page 11.

5 Nomenclature

The terms and definitions here are intended to clarify generally accepted industry positions or to provide specific guidance as needed to understand the testing requirements of this application guide. Where applicable, industry positions have been used in full or in part to define processes.

ACPH - Air changes per hour

Adverse Air Currents - Air currents that adversely affect the HEPA filtered unidirectional air flow of a buffer room or primary engineering control.

Aerosol Diluter - A device used for measuring total particle levels in a high concentration of aerosol providing a representative sample that meets the input specifications of the discrete particle counter.

Airlock - A space with interlocked doors constructed to maintain air pressure control when items move between two adjoining areas (generally with different air cleanliness standards). The intent of an airlock is to prevent ingress of particulate matter and microbial contamination from a lesser-controlled area.

Allergenic Extracts Compounding Area (AECA) - A designated, unclassified space, area, or room with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.

ANSI - American National Standards Institute

Anteroom - An ISO Class 8 (or cleaner) room with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels may be performed. The anteroom is the transition room between the unclassified area of the facility and the buffer room. It is also a transition area that provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas.

As-Built Conditions - Condition where the cleanroom or clean zone is complete with all services connected and functioning but with no equipment, furniture, materials or personnel present.

Aseptic Processing - A method by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. In most cases, the components can be purchased as sterile. Nonsterile components can be separately sterilized prior to combining (e.g., by membrane filtration, autoclave).

At-Rest Conditions - Condition where the cleanroom or clean zone is complete with all normal equipment and supplies used for compounding installed and operating, but with no personnel present (see static conditions).

AVS - Airflow Visualization Study (see Visual Smoke Study and Dynamic Airflow Smoke Pattern Test)

AVS Output Manifolds - Diffusers remote to the visible medium source intended to release the medium in a method appropriate to the airflow visualization test being performed.

Backstreaming - Airflow currents that travel in the opposite direction (upstream) of the HEPA filtered unidirectional airflow due to the turbulence created by an object within the airstream.

Beyond Use Date (BUD) - 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.

Biosafety Cabinet (BSC), Class II - A ventilated cabinet with an open front and inward and downward unidirectional HEPA-filtered airflow and HEPA-filtered exhaust. A BSC used to prepare a CSP must be capable of providing an ISO Class 5 or better environment for preparation of the CSPs.

Buffer Room - An ISO Class 7 or cleaner room with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer room may only be accessed through the anteroom.

Category 1 CSP - A CSP that is assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less refrigerated that is compounded in accordance with all applicable requirements for Category 1 CSPs.

Category 2 CSP - A CSP that is assigned a BUD of greater than 12 hours at controlled room temperature or greater than 24 hours refrigerated that is compounded in accordance with all applicable requirements for Category 2 CSPs.

Category 3 CSP - A CSP that undergoes sterility testing, supplemented by endotoxin testing when applicable, and has more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequency of environmental monitoring, and stability determination.

CFM - Cubic Feet per Minute (air volume measurement)

Classified Area - An area that maintains an air quality classification based on the ISO standards (see also the definition for ISO class).

Cleaning Agent - An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Cleanroom Suite - A classified area that consists of both an anteroom and buffer room.

Compounded Sterile Preparation (CSP) - A preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance.

Compounding - The process of combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication.

Compounding Area - The area where compounding is occurring (i.e., a cleanroom suite, inside the perimeter of the SCA, or AECA).

Compounding Aseptic Containment Isolator (CACI) - A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for the compounding of sterile HDs.

Compounding Aseptic Isolator (CAI) - A type of RABS that uses HEPA filtration to provide an ISO Class 5 unidirectional air environment designed for compounding of sterile non-HDs.

Critical Area - An ISO Class 5 environment

Critical Site - A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, and beakers) or openings (e.g., opened ampules and needle hubs) that are 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.

Designated Person(s) - One or more individuals assigned to be responsible and accountable for the performance and operation of the compounding facility and personnel in the preparation of CSPs.

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

Direct Processing Area (DPA) - An area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air”

Dynamic Airflow Smoke Pattern Test - A PEC test in which a visible medium (smoke source), which is close to neutrally buoyant, is used to observe air patterns within the unidirectional space (i.e., the DCA) under dynamic operating conditions (see Dynamic operating conditions). This test is not appropriate for ISO Class 7 or ISO Class 8 cleanrooms that do not have unidirectional airflow (see Visual Smoke Study).

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

First Air - The air exiting the HEPA filter in a unidirectional air stream.

FPM - Feet Per Minute (air velocity measurement)

Hazardous Drug (HD) - Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing HDs in structure or toxicity.

High-efficiency Particulate Air (HEPA) Filtration - Being, using, or containing a filter designed to remove 99.97% of airborne particles measuring 0.3-micron or greater in diameter passing through it.

Hot Cell - A device used for the shielding and containment of radioactive materials. A hot-cell may also be referred to by other designations (e.g., shielded isolator with laminar flow, PET dispensing station, manipulator hot-cell, shielded isolators for dispensing, radiopharmaceutical dispensing isolator).

HVAC - Heating Ventilation and Air Conditioning

IEST - Institute for Environmental Sciences and Technology

Integrated Vertical Laminar Flow Zone (IVLFZ) - A designated ISO Class 5 area serving as the PEC within an ISO Class 7 or cleaner buffer room. In the IVLFZ, unidirectional airflow is created by placing HEPA filters over the entire surface of the work tables and effective placement of air returns.

ISO - International Organization for Standardization

ISO Class - An air-quality classification from the International Organization for Standardization 14644-1.

LAFW Total Work Area - The area inside the workbench between the sidewalls, horizontal flow diffuser or rear wall, ceiling top or bottom of the downflow diffuser, and top of the work surface. The total work area definition is applicable only for purposes of design and construction and for testing.

LAFW Work Zone - The space within the total work area where the user can perform the process, identified by the manufacturer and airflow visualization studies as appropriate for user activities to maintain product protection.

Laminar Airflow System (LAFS) - A device or zone within a buffer room or SCA that provides an ISO Class 5 or better air quality environment for sterile compounding. The system provides a unidirectional HEPA-filtered airflow.

Laminar Airflow Workbench (LAFW) - A device that is a type of LAFS which provides an ISO Class 5 or better air quality environment for sterile compounding. The device provides a unidirectional HEPA-filtered airflow.

Line of Demarcation - A visible line on the floor that separates the clean and dirty sides of the anteroom. In some cases, different colored flooring is used.

Micrometer (µm) - 1 x 10^{-6} meters (particle size measurement)

Negative-pressure Room - A room that is maintained at lower pressure than the adjacent accessible (through a door) spaces, and therefore the net airflow displacement is into the room.

NIST – National Institute of Standards and Technology

NSF - NSF International

PAO - Poly Alpha Olefin, a testing medium used in an aerosol generator, typically used in HEPA filter leak testing.

Pass-through - An enclosure with sealed doors on both sides that should be interlocked or procedures in place to assure only one door is opened at a time. The pass-through is positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.

Positive-pressure Room - A room that is maintained at higher pressure than the adjacent spaces, and therefore, the net airflow is out of the room.

Primary Engineering Control (PEC) - A device or zone that provides an ISO Class 5 air quality environment for sterile compounding.

Radioactive Materials (RAM) License - A document(s) issued by the US NRC or an Agreement State agency that authorizes various activities involving the use of radioactive materials. These uses can include possession, research and development, distribution, medical use, and other purposes not included in this list.

Restricted-access Barrier System (RABS) - An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air that allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. Examples of RABS include CAIs and CACIs.

Secondary Engineering Control (SEC) - The area where the PEC is placed (e.g., a cleanroom suite or an SCA). It incorporates specific design and operational parameters required to minimize the risk of contamination within the compounding area.

Segregated Compounding Area (SCA) - A designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Category 1 CSPs only.

Segregated Radiopharmaceutical Processing Area (SRPA) - A designated, unclassified space, area, or room with a defined (by facility procedures) perimeter that contains a PEC. An SRPA is only suitable for radiopharmaceutical preparation (with and without minor deviations), dispensing, and repackaging. If the SRPA is used to elute radionuclide generators it must have ISO Class 8 total particle count air quality.

Simulated Compounding - Compounding performed by a trained pharmacy technician or pharmacist which replicates the typical compounding procedures performed in the compounding facility but does not utilize active pharmaceutical ingredients.

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.

Static Conditions - See At-Rest conditions

Unclassified Space - A space not required to meet any air cleanliness classification based on the ISO.

Unidirectional Airflow - Air within a PEC moving in a single direction in a uniform manner and at sufficient velocity to sweep particles away from the DCA.

Visual Smoke Study - A test, used in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow, in which a visible source of smoke, which is close to neutrally buoyant, is used to verify an absence of stagnant airflow where particulates can accumulate. This test does not need to be performed under dynamic operating conditions and is not appropriate for PECs (see Dynamic airflow smoke pattern test). This test is done when an ISO Classified room has ceiling mounted air returns. It only needs to be done when the room is first commissioned and again when any changes to the room configuration which may affect the room's performance are made.

6 Materials and Equipment

See individual sections for required equipment.

7 Precautions/Safety

7.1 Precautions

Observe all facility safety signage, personal protective equipment requirements and facility procedures. Ensure safety data sheets are readily available for products used in the certification process.

8 Testing Guidelines

The certification of sterile compounding facilities consists of several elements to accomplish the process. The first being cleanroom (SEC) certification and airflow visualization studies followed by certification of primary engineering controls (e.g., BSCs, Laminar airflow workbenches).

All testing instrumentation used must be calibrated in accordance with IEST-RP-CC013 or manufacturer's recommendation and be NIST traceable where possible.

8.1 Cleanroom Certification – Secondary Engineering Control (SEC)

This section lists the tests appropriate to certify a cleanroom used in sterile compounding. USP <797> requires all environmental controls to be certified at least every 6 months or whenever PECs or compounding devices within PECs are relocated/altered or when major service to the facility is performed. It is strongly recommended that certification technicians are CETA Registered Certified Professionals for Sterile Compounding Facilities.

Verify that all aspects of the cleanroom system which contribute to its operational integrity are complete (construction is complete) and functioning as designed in accordance with the requirements of the type of cleanroom and under dynamic operating conditions.

USP <797> and this document specify minimum acceptance criteria for many of the tests required for compliance with the chapter. However, these values do not establish the specific acceptance criteria for each application. For example, if a cleanroom was designed for a minimum of 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 specifications 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 SEC Airflow Testing

Apparatus

A calibrated air multimeter with an accuracy of ± 3% of reading ± 7 CFM (± 12 m^3/h), in conjunction with;

A capture hood with properly sized shroud **or** a multi-point tube array with proper stand offs (typically 6" (15 cm) are used)

A calibrated thermal anemometer with an accuracy of ± 3 ft/min (± 0.015 m/s) or 3% of the indicated velocity, whichever is larger in conjunction with a rigid probe holder that will not distort airflow

ISO Classified Turbulent Airflow Area Testing Procedure

In ISO classified rooms, 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.

Cleanrooms employed in sterile compounding are usually designed as dilution control (turbulent airflow) ISO class 7 buffer rooms with ISO class 7 or ISO class 8 anterooms. The criteria for ISO 7 area (hazardous and/or non-hazardous) airflow is established as a minimum of 30 ACPH. ISO 8 areas must have a minimum of 20 ACPH. If a certified HEPA filtered device is used (e.g., LAFW, FFU, BSC, room air cleaner, etc.), as part of the overall ACPH, at least 15 ACPH must come from the building's HVAC system through room ceiling terminal HEPA filters. Acceptable air exchange rates must be determined on a case-by-case basis taking into consideration sources of airborne contamination, such as personnel and processes. Higher air exchange rates are typically justified. The acceptance criteria for air exchange rates and room segregation in a SEC should be established based on the design criteria. Where design criteria are not available or sufficient, air exchange rates should be based on successful environmental monitoring results from past testing, the minimum ACPH values mentioned above and agreed upon by the cleanroom operator and the certifier.

USP <797> 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 8 or cleaner sterile compounding facilities, USP <797> specifies HEPA filtered supply air exchange rates are to be calculated within the room.

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

Backpressure compensation should be used on all air volume measurements, but must be used to measure airflow volume with a capture hood when the supply air volume is in excess of 500 CFM or as recommended by the instrument manufacturer. All air volume from any source must be captured in totality with the properly sized shroud. Readings added together from sections of a HEPA filter are unacceptable regardless of backpressure compensation use.

For the purpose of calculating airflow volume from velocity measurements on exposed HEPA filters and for proper calculation of patch percentage, the effective area of a HEPA filter refers to the actual face area of the filter medium through which air is passing. Where a HEPA filter diffuser is in place, the outside dimensions of the open area of the diffuser, or plane that the velocity measurements are taken in, shall be used.

Any time an oversized shroud is used for measurements, the measured grill needs to be centered in the shroud.

Non-ISO Classified Negative Pressure Turbulent Airflow Area Testing Procedure

ACPH requirements for containment segregated compounding areas and hazardous drug storage areas, must be a minimum of 12 exhaust ACPH. Because these rooms/areas are not ISO classified airflow measurements should be taken on the exhaust of negative pressure differential rooms.

ISO Classified Turbulent Airflow Area Reporting and Documentation

- Record all airflow measurements and their corresponding filter or diffuser locations or grid identifications on a diagram
- Calculate and report room volume
- Calculate and report the average total room airflow volume
- Calculate and report the total air changes per hour of the room (include LAFW and/or Non-ducted BSC HEPA exhaust to room, if applicable)
- Report any correction factors used or deviations from the primary method
- Name of test (e.g., Room Airflow Analysis)
- Report acceptance criteria
- Provide a Pass or Fail statement based on the results of the test

Non-ISO Classified Negative Pressure Turbulent Airflow Reporting and Documentation

- Record all airflow measurements and their corresponding exhaust filter or exhaust grill locations
- Calculate and report room volume
- Calculate and report the average total room airflow volume
- Calculate and report the total air changes per hour of the room
- Report any correction factors used or deviations from the primary method
- Name of test (e.g., Unclassified Negative Pressure Room Airflow Analysis)
- Report acceptance criteria
- Provide a Pass or Fail statement based on the results of the test

SEC Airflow Testing Frequency

Airflow testing must be performed at least every six months or after any modification to the HVAC system or renovation to the pharmacy cleanrooms.

8.1.2 SEC HEPA Filter Leak Testing

Apparatus

A calibrated aerosol photometer that complies with the specification of IEST-RP-CC034.5 section 6.1.1 shall be used. The instrument shall be capable of measuring concentrations of up to 100 µg/L and have a threshold sensitivity capable of measuring 0.0001 µg/L. The photometer should have a detection limit of at least 0.1 x the designated leak and a volumetric flow rate of 1.0 CFM (28.3 L/min). The scanning probe shall have a maximum open area of 1.7 in² (1100 mm²) and a minimum dimension of 0.50 inches (13 mm).

An aerosol generator of the Laskin nozzle type, thermal generator type or equivalent shall be used to create an aerosol. The aerosol generator shall comply with the specifications of IEST-RP-CC034.5 section 6.1.4.

SEC HEPA Leak Testing Procedure

All HEPA filters shall be leak tested every certification cycle utilizing an aerosol photometer and an appropriate aerosol challenge medium. A minimum challenge of 10 micrograms per liter should be used. Individual leaks shall not exceed 0.010% of the upstream challenge.

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 testing aerosol being released into the room served by that outlet.

Aerosol shall be introduced upstream of the HEPA filters at a distance far enough to ensure adequate mixing. Aerosol introduction ports should be provided with a minimum diameter of ½” (1.25 cm) Inner Diameter. Whenever possible, an upstream aerosol concentration measurement should be taken.

HEPA filter field repairs shall not block or restrict more than 3% of the filter face area and no single repair shall have a lesser (width) dimension exceeding 1.5” (3.8 cm).

Patch Size Calculation Procedure

For the purpose of calculating proper calculation of patch percentage, 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, and if present, caulk bead, is subtracted.

For general purposes, subtracting 2” (5 cm) off of each outside filter dimension will yield a representative effective filter area. This estimation is based on 3⁄4” (2 cm) for the filter frame and 1⁄4” (0.5 cm) for the potting compound for a total of 1” (2.5 cm) for each of the two dimensions four sides. If the filter contains a center bar, it can generally be estimated at 1 ¼” (3 cm) in width.

For example:

A filter with outside dimensions of 24” x 48” (61 x 122 cm) and that has a center bar, has an overall area of 8 ft^2 (24” x 48” / 144) or 0.744 m^2 (61 cm x 122 cm / 10,000).

Using the general estimates listed above, this filter would have an effective area of 6.84 ft^2 (22” x 44.75” / 144) or 0.638 m^2 (56 cm x 114 cm / 10,000).

If filter frame or potting compound dimensions are different than this example, actual measurements shall be used.

SEC HEPA Filter Leak Test Reporting and Documentation

- Record upstream aerosol challenge concentration
- List method used to report concentration (measured or calculated)
- Record maximum leak penetration in percent
- Name of test (HEPA Filter Leak Test)
- Report acceptance criteria
- Provide a Pass or Fail statement based on the results of the test

Room HEPA Filter Leak Test Frequency

HEPA Filter Leak testing must be performed at least every six months or after any modification to the HVAC system or renovation to the pharmacy cleanrooms.

8.1.3 SEC Room Pressure Differential/Room Pressurization

Apparatus

A calibrated manometer, capable of meeting the following requirements;

- Accuracy: ±2% of reading
- Resolution: 0.001” w.g. (0.1 Pa) when reading at 0.5” w.g. (125 Pa) or less

Visible medium generation device

SEC Room Pressure Testing Procedure

Cleanrooms used for non-hazardous compounding must be positive pressure relative to the anteroom. USP <797> requires a minimum pressure differential of 0.020” w.g. (5.0 Pa) measured at the door(s).

USP Chapter <800> requires all HD buffer and SCA rooms used for hazardous applications to maintain a pressure differential between 0.010” w.g. (2.5 Pa). and 0.030” w.g. (7.5 Pa) negative at the door(s) to the anteroom and/or support areas.

All anterooms must have a positive pressure of at least 0.020” w.g. (5.0 Pa) to the unclassified space.

Pressure gauges shall be installed in order for the Designated Person to monitor pressures between the buffer room(s) and the anteroom(s), and between the anteroom(s) and the support areas. The resolution of each pressure monitor shall be adequate for the specified range. Ideally, the pressure gauge is equipped with an audible and visual alarm, and located in a manner that the compounding personnel will be notified in the event of a loss of the state of control.

Pressure gauges shall be performance verified at every certification. Performance verification consists of measuring room differential pressure with a calibrated instrument and confirming that the room gauge matches the calibrated instrument reading, within the tolerances of the calibrated instrument and the room pressure gauge. A zero reading on the room gauge can be confirmed by opening the door to equalize room differential pressure.

Doorways within the anteroom and cleanroom must be verified for proper direction of airflow and that certification test equipment and facility room pressure monitoring equipment are reporting correctly.

Entry doors shall be opened slightly (e.g., ¼” - 1”, [0.5 - 2.5 cm]) and a visible medium is passed around the entire perimeter, demonstrating airflow direction as designed.

Pass the visible medium along the perimeter of the openings between rooms (at doorways) and visually verify that the smoke is moving in the proper direction around the entire perimeter. If the door is tightly sealed, open the door slightly to perform this test. Note on the report that the airflow direction was visually confirmed. Unlike a dynamic smoke study, a video recording of this test is not required.

When cart pass-throughs are employed, the cleanroom specifications must include the pressure relationship between the cleanest room, the cart pass-through, and the less clean room.

When an airlock is used as a cleaning or material prep space, HEPA filtered air should be supplied to the airlock. The recommended pressure relationship is as follows:

- ≥ 0.020” w.g. (5.0 Pa) positive from the cleanest room to the airlock
- ≥ 0.020” w.g. (5.0 Pa) positive from the airlock to the less clean room
- ≥ 0.040” w.g. (10 Pa) positive from the cleanest room to the less clean room

When the airlock is not used as a prep space, HEPA filtered air may or may not be provided to the airlock, and the pressure relationship is from the cleanest space, through the airlock to the less clean space.

Report all measured values as displayed on the calibrated instrument to at least the nearest 0.001” w.g. (0.1 Pa) and report the pressure cascade direction.

Door sweeps are not recommended in USP <797>, but if the door being tested has a door sweep, use rigid tubing under the door to ensure the tubing does not compress during the test.

Note: All readings and acceptance criteria shall be documented to at least one thousandths of an inch water column (e.g., 0.020” w.g. and not 0.02” w.g.) or one tenth of a pascal (e.g., 2.5 Pa). By specifying an acceptance criteria for room pressure to the third decimal place, rounding takes place at a thousandths of an inch.

A reading of 0.01855” w.g. on the micro manometer can be reported as 0.019” w.g. and the room would fail to meet the minimum 0.020” w.g. specified in USP <797>. If rounding was done at the second decimal place, a meter reading of 0.0185 would be rounded to 0.02” w.g. and the room would pass. This rounding rule is less of an issue when measuring in the metric equivalent, pascals (Pa).

SEC Room Pressure Reporting and Documentation

- Report room pressure differential relative to an adjacent room/space
- Report and compare performance of room pressure monitor
- Report whether smoke dispersed at entry doors follows correct direction
- Name of test (Room Pressure Differential Test)
- Report acceptance criteria
- Provide a Pass or Fail statement based on the results of the test

SEC Room Pressure Frequency

SEC Room Pressure testing must be performed at least every six months or after any modification to the HVAC system or renovation to the pharmacy cleanrooms.

8.1.4 SEC Airflow Visualization Studies (AVS) - Visual Smoke Studies

For information regarding Airflow Visualization Study tests reference CETA CAG-014. Some AVS tests are mandatory at each certification interval.

8.1.5 SEC Airborne Total Particle Counting

Rooms shall be classified to the most current version of ISO 14644-1.

Classification of cleanliness levels is done with a particle count survey. Rooms shall be certified to the cleanliness level specified by the owner. USP <797> requires the buffer room to be ISO class 7 or cleaner and the anteroom providing access to positive pressure buffer rooms to be ISO class 8 or cleaner. Anterooms adjacent to a negative pressure buffer room must meet ISO class 7 or cleaner because this air will be drawn into the negative pressure buffer room. Compounded sterile preparations must be manipulated in a unidirectional airflow ISO class 5 or cleaner environment.

Apparatus

A discrete particle counter capable of accurately detecting particles ≥0.5 microns shall be used. The particle counter shall have been calibrated within one year with a recognized organization such as NIST. The particle counter shall be calibrated per ISO 21501-4:2018. A zero-filter may be used in conjunction with a 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.

SEC Airborne Total Particle Counting Testing Procedure

Sample collection shall occur under dynamic operating conditions.

Set up the discrete 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 the probe is oriented into the direction of the airflow for unidirectional applications. If the airflow is not unidirectional, affix the sampling probe vertically pointing upward. The probe height should be located within the plane of work activity (e.g., 48" (122 cm) from the floor, or 12" (30 cm) from the work surface). Divide the room being tested into grids of equal area. Refer to the most current version of ISO-14644-1 table A.1 for the minimum number of sample grids. Samples should be taken within the grid underneath a section of ceiling that is a good representation of the ceiling within that grid (i.e., if most of the ceiling area within that grid is not made up of HEPA filters, the sample should not be taken under a HEPA filter).

SEC Airborne Total Particle Counting Reporting and Documentation

Reporting shall be completed following ISO 14644-01 [2015] section 5.4 “Test report” and shall include the following:

- The name and address of the testing organization, and the date on which the test was performed
- The number and year of publication of this part of ISO 14644 (i.e., ISO 14644-1:2015)
- A clear identification of the physical location of the cleanroom or clean zone testing (including reference to adjacent areas if necessary), and specific designations for coordinates of all sampling locations (a diagrammatic representation can be helpful)
- The specified designation criteria for the cleanroom or clean zone, including the ISO Class number, the relevant occupancy state(s), and the considered particle size(s)
- Details of the test method used, with any special conditions relating to the test, or departures from the test method, and identification of the test instrument and its current calibration certificate
- The test results, including particle concentration data for all sampling locations
- Report acceptance criteria
- Provide a Pass or Fail statement based on the results of the test

SEC Airborne Total Particle Counting Frequency

Airborne Total Particle Counting must be performed at least every six months or after any modification to the HVAC system or renovation to the pharmacy cleanrooms.

8.1.6 SEC Viable Sampling

See CAG-009 for information regarding Viable Sampling.

See CAG-011 for information regarding Gloved Fingertip Sampling.

See CAG-013 for information regarding Media Fill Testing.

8.1.7 SEC General Temperature and Moisture Tests

USP 797 states “The cleanroom suite should be maintained at a temperature of 68°F (20°C) or cooler and a relative humidity below 60% to minimize the risk for microbial proliferation” and “Temperature and humidity monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.” (USP 797 section 4.2, 2021).

Relative humidity over 60% may increase the risk for microbial proliferation. Additional microbial air and surface sampling should be utilized to verify that acceptable conditions have been maintained when the relative humidity exceeds 60%. Remediation should be considered to keep the relative humidity below 60%.

Apparatus

“Thermometers, resistance temperature devices (RTPDs), high-grade Type T (copper/constantan) thermocouples, thermistors, or other known temperature sensors used with readout devices calibrated to standards and capable of indicating a change in temperature of 0.1 Celsius degree or equivalent” as per IEST (IEST-RP-CC006.3, section 6.9.1, page 17, 2004).

“Dielectric thin-film-capacitor humidity sensors with a range of 10% to 95% relative humidity, a sling psychrometer, or a few point sensor. Humidity sensors should be calibrated to known standards and be capable of indicating a change in relative humidity of 1%. (In use, these devices are positioned to records data in conjunction with the temperature sensors listed in section 6.9.1a)” as per IEST (IEST-RP-CC006.3, section 6.9.1, page 17, 2004).

General Temperature and Moisture Testing Procedure

Measure the temperature and humidity at a minimum of one location for each room. Ideally one reading is taken at each particle count location. Place each sensor at the designated location at work-level height. Allow sufficient time for the sensor to stabilize at each location.

General Temperature and Moisture Reporting and Documentation

- Report all measurements and corresponding grid locations
- Name of test (e.g., Temperature and moisture uniformity test)
- Report acceptance criteria
- Report overall results of the test and recommendations based on the results

General Temperature and Moisture Frequency

General Temperature and Moisture testing must be performed at least every six months or after any modification to the HVAC system or renovation to the pharmacy cleanrooms.

8.1.8 SEC Lighting Level and Uniformity Test - Optional

This optional test is performed at the discretion of the owner.

This test is recommended on a new cleanroom to verify the contractor provided a finished product that meets design criteria and to set a benchmark for the lighting intensity and uniformity within the room. Test procedures are specified in IEST-RP-CC006.3, section 6.6.

Apparatus

"A portable photoelectric illuminance meter as described in *The Lighting Handbook*, Section 9.8.1. The meter shall be accurate within ± 10%, cosine and color corrected. The illuminance meter shall be calibrated in accordance with the manufacturer's instructions." as per NSF (NSF/ANSI 49: Annex N-1.4 page 35, 2020).

Photo-electric illumination meters should be calibrated and certified every 12 months.

SEC Lighting Level and Uniformity Testing Procedure

Illuminance measurements should be made under actual working conditions at the working level.

Measurements should be taken at the working level, in an equally spaced grid pattern. Grid pattern spacing for each measurement should not exceed 430 ft² (40 m²).

Illuminance measurements shall be compiled to show the minimum value, average value, maximum value, and uniformity calculations including maximum:minimum ratio and average:minimum ratio.

Ideally the illuminance should be within 10% of the design measurements, but acceptable illumination levels shall be determined by the owner.

Recommended illumination levels can be found in the IES Lighting Handbook.

SEC Lighting Level and Uniformity Reporting and Documentation

- Report all measurements and corresponding room locations
- Report overall average lighting intensity
- Name of test (Lighting level and uniformity test)
- Report acceptance criteria
- Report overall results of the test and recommendations based on the results

SEC Lighting Level and Uniformity Frequency

Lighting level and uniformity testing is performed as requested by the pharmacy owner.

8.1.9 SEC Noise Level Test - Optional

This optional test is performed at the discretion of the owner.

This test is recommended on a new cleanroom to verify the contractor provided a finished product that meets design criteria and to set a benchmark for the noise

level within the room. Test procedures are specified in the following document: IEST-RP-CC006.3.

Apparatus

Calibrated octave band analyzer or calibrated sound level meter, or both

Suitable support stand

Measurement equipment should be calibrated every 12 months.

SEC Noise Level Testing Procedure

Divide the work zone entrance plane into a grid of equal areas. The areas should not exceed 430 ft² (40 m²). Support the sound level meter on the stand with the microphone approximately 5 ft (1.5 m) above the floor. Measure and record the sound pressure level for each octave band (63 Hz to 8000 Hz), or record the decibels A scale, or both, as specified, in the center of each grid.

SEC Noise Level Reporting and Documentation

- Report all measurements (Octave bands or dBA) and corresponding grid locations
- Report maximum reading
- Name of test (Noise Level Test)
- Report acceptance criteria
- Report overall results of the test and recommendations based on the results

SEC Noise Level Frequency

Noise level testing is performed as requested by the pharmacy owner.

8.1.10 Troubleshooting Using Room Recovery Rate Testing

The purpose of this test is to establish the time required for a non-unidirectional (turbulent flow) cleanroom to achieve a steady state of cleanliness after a brief introduction of particles. This test can be used to help identify locations to include in the environmental sampling plan. It is a valuable tool for troubleshooting a cleanroom that is unable to maintain a state of control. It is also helpful for the pharmacy to have an understanding of the recovery rate of each room when they are creating processes such as writing a garbing procedure that allows for a specific purge time between actions. Typically, test methods for room recovery rates have focused on quantitative test procedures due to the accuracy and repeatability associated with them. However qualitative testing procedures can prove to be an acceptable substitute when carried out and reported properly. Note that the different methods of room recovery testing may not be comparable to each other. If comparing results of an earlier recovery test, ensure the same test method is used.

Quantitative Particle Count Method

Apparatus

A discrete particle counter that complies with section 8.1.5. Apparatus

An aerosol generator (non-oil based preferred)

An aerosol diffusion apparatus (output manifold)

A time keeping device

An aerosol diluter

Ideally, multiple particle counters would be used for each of the sample locations around the room. Where this is not possible, up to four sample locations can be measured using one particle counter. Tubing shall not exceed the maximum length listed by the particle counter manufacturer.

An aerosol diluter should be used to avoid coincidence loss and to avoid damaging the discrete particle counter optics. Sampling large amounts of aerosol can lead to ineffective readings and if an oil-based aerosol is used, the optics can quickly become contaminated.

Quantitative Particle Count Testing Procedure

Place discrete particle counters or particle count probes in locations that will provide a good mix of room air. Test locations should not be located directly under a supply HEPA filter, or directly next to a return/ exhaust grill. Where needed as a guide, the locations used for room particle count testing to ISO 14644-1 can be used. Locations should be measured and recorded so the test can be recreated if desired.

Set the discrete particle counter(s) to sample for 10 seconds. The number of samples to be taken should be set to infinite and there should be a 5 second delay between samples. If multiple probes are being used on one particle counter, the probe tubes must be switched during the 5 second delay period.

Start all discrete particle counters and obtain the room's baseline reading. Allow for at least 3 samples to be logged at each location. If a diluter is to be used, it should be connected after the baseline has been determined.

Once the baseline has been established, start the aerosol generation source. The particle generation period will vary based on room. The particle level in the room must be raised 1,000 to 10,000 times the baseline. Once the particle level has been raised to the appropriate level, note the particle level, stop aerosol generation and start the time keeping device.

Monitor all discrete particle counters and record the time when each location's particle level has decreased by two orders of magnitude (e.g., from 500,000 particles to 5,000 particles). The location with the slowest recovery shall be used as the room recovery time. Additional testing can continue to determine how long the room takes to return to the original baseline, but this may take quite a while and the result may not carry much value.

Quantitative Photometer Method

Apparatus

An aerosol photometer that complies with section 8.1.2 Apparatus

Aerosol generator suitable for use with an aerosol photometer (e.g., laskin nozzle, thermal generator, etc) and suitable reagent such as PAO

An aerosol diffusion apparatus (output manifold)

A time keeping device

Quantitative Photometer Testing Procedure

Sample in locations that will provide a good mix of room air. Test locations should not be located directly under a supply HEPA filter, or directly next to a return/exhaust grill. Multiple locations can be sampled by setting up tubing throughout the room. Tubing length shall not exceed the maximum length recommended by the photometer manufacturer. Where needed as a guide, the locations used for room particle count testing to ISO 14644-1 can be used. Locations should be measured and recorded so the test can be recreated if desired.

Set the photometer to 100 µg/l. Establish room baseline by sampling at each location. Monitor photometer reading at each location for about 10 seconds. The baseline readings are typically 0.001 % or less.

Once the baseline reading has been established, start the aerosol generator and disperse aerosol into the room as evenly as possible. Monitor photometer readings. Raise the aerosol level in the room by 1,000 to 10,000 times the baseline. If the baseline was found to be zero, use 0.001 % as the baseline. Example: with a baseline of 0.001%, raise the particle level in the room until the photometer reads between 1.0 and 10.0%. Once this particle level has been achieved, stop the aerosol generating source and start the time keeping device.

Sample with the photometer at each location for 10 sec with a 5-30 second break between samples. If multiple locations are being used, ensure one 10 second sample is obtained at least every 60. Example, if four locations are being sampled by one photometer, sample for 10 seconds, then switch the tube within 5 seconds to the next location. Continue to monitor each sample location until the photometer reading has been reduced by two orders of magnitude. Example, from a reading of 10% to 0.1%. Record the time at each location when this result has been achieved. The room recovery time is the slowest location to recover. Additional testing can

continue to determine how long the room takes to return to the original baseline, but this may take quite a while and the result may not carry much value.

Qualitative Visual Testing Method

Apparatus

A high-volume visible smoke generator

Laser(s) or high intensity directional lights

An aerosol diffusion apparatus (output manifold)

A time keeping device

Qualitative Visual Testing Test Procedure

Set up laser(s) or directional lights throughout the room. A hand-held laser or light can also be useful. Disperse the visible medium through the entire room. Once visible medium has been evenly distributed throughout, stop generator and start time keeping device.

Observe the visible medium throughout the room. It can be helpful to make comments on the air flow patterns at this point, if any are observed. Monitoring the lasers or lights, and/or utilizing a hand-held laser or light, scan room until the line created by the laser or high intensity light is no longer visible. Focus on all areas of the room, especially within the work zone. Stop the time keeping device and record the time as the room recovery rate.

8.2 Biosafety Cabinet (BSC)

Class II Biosafety Cabinets (BSCs) are typically type tested at NSF International to NSF/ANSI 49 and performance criteria are listed according to the results observed. Field certification professionals then use this listed performance criteria to field certify BSC performance. 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 for compliance to NSF/ANSI 49. Test procedures for certification of BSC are detailed in the following standard: NSF/ANSI 49 Annex N5 for field certification. It is preferable to use an NSF-49 listed BSC or modified NSF-49 listed BSC over a non-listed BSC.

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 as detailed in ISO-14644-1 (current version).

8.2.1 BSC Testing

Apparatus

Per NSF/ANSI 49 Annex N5.

BSC Testing Procedure

Verify that all aspects of the BSC are functioning normally in accordance with both NSF/ANSI 49 Annex N5 and the manufacturer's recommended parameters for the operational mode under test.

BSC Reporting and Documentation

- Reporting shall be to the minimum reporting requirements of NSF/ANSI 49 Annex N5.

8.2.2 BSC Airborne Total Particle Counting

Apparatus

A discrete particle counter capable of accurately detecting particles ≥0.5 µm shall be used. The particle counter shall have been calibrated within one year with a recognized organization such as NIST. The particle counter shall be calibrated per ISO 21501-4:2018. A zero-filter may be used in conjunction with a 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.

BSC Airborne Total Particle Counting Testing Procedure

Sample collection shall occur under dynamic operating conditions.

Set up the discrete particle counter in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate. The direction of the probe will be oriented into the direction of the airflow.

For PECs typically used in sterile compounding, ISO recommendations result in one sample location based on ISO 14644-1 Table A.1. However, sampling must be performed upstream of any/all critical sites, preferably within 6" (15 cm). For example, in basic compounding, only one location may be needed. In PECs where an automated compounding device is being used, 3 or more locations may be needed (locations of sterile connections or penetrations).

BSC Airborne Total Particle Counting Reporting and Documentation

- Reporting shall be to ISO-14644-1 [2015] section 5.4 (Test Report).

8.2.3 BSC Viable Sampling

See CAG-009 for information regarding Viable Sampling.

8.2.4 BSC Airflow Visualization Studies (AVS) - Visual Smoke Studies

See CAG-014 for information regarding Visual Smoke Studies.

8.2.5 BSC Testing Frequency

All of the above BSC tests must be performed every six months and after a HEPA filter change, if maintenance or repairs are made to internal parts or if the BSC is relocated.

8.3 Compounding Aseptic Isolator (CAI) and Compounding Aseptic Containment Isolator (CACI)

8.3.1 CAI/CACI Testing

Apparatus

See CAG-002 for a listing of the appropriate test equipment.

CAI/CACI Testing Procedure

Compounding Aseptic Isolators used for non-hazardous sterile compounding and Compounding Aseptic Containment Isolators used for hazardous sterile compounding are performance tested by the manufacturer to meet the requirements of CETA CAG-002. USP <797> references both CAIs and CACIs as Restricted Access Barrier Systems (RABS).

Field certification professionals then use this manufacturer test criteria to field certify performance. Test procedures for certification of CAI's and CACI's are detailed in CETA CAG-002 Field Test for field certification.

CAI/CACI Reporting and Documentation

- Reporting shall be to the minimum reporting recommendations of CETA CAG-002.

8.3.2 CAI/CACI Airborne Total Particle Counting

Apparatus

A discrete particle counter capable of accurately detecting particles ≥0.5 µm shall be used. The particle counter shall have been calibrated within one year with a recognized organization such as NIST. The particle counter shall be calibrated per ISO 21501-4. A zero-filter may be used in conjunction with a 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.

CAI/CACI Airborne Total Particle Counting Testing Procedure

Sample collection shall occur under dynamic operating conditions.

Set up the discrete particle counter in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate. The direction of the probe will be oriented into the direction of the airflow.

For PECs typically used in sterile compounding, ISO recommendations result in one sample location based on ISO 14644-1 Table A.1. However, sampling must be performed upstream of any/ all critical sites, preferably within 6" (15 cm). For example, basic compounding, only one location may be needed. In PECs where an automated compounding device is being used, 3 or more locations may be needed (locations of sterile connections or penetrations).

CAI/CACI Airborne Total Particle Counting Reporting and Documentation

- Reporting shall be to ISO-14644-1 [2015] section 5.4 (Test Report).

8.3.3 CAI/CACI Viable Sampling

See CAG-009 for information regarding Viable Sampling.

8.3.4 CAI/CACI Airflow Visualization Studies (AVS) - Visual Smoke Studies

See CAG-014 for information regarding visual smoke studies.

8.3.5 CAI/CACI Testing Frequency

All of the above CAI/CACI tests must be performed at least every six months and after a HEPA filter change, if maintenance or repairs are made to internal parts or if the CAI/CACI is relocated.

8.4 Laminar Air Flow Workbench (LAFW)

Laminar Air Flow Workbenches are used for compounding sterile products, provide either horizontal or vertical unidirectional airflow and are designed to meet manufacturers test criteria as referenced in IEST and FDA. Field certification professionals then use the manufacturer test criteria to field certify performance. Test procedures for field certification of Laminar Air Flow Workbenches, at a minimum, must include air velocity, HEPA integrity, induction leak and backstreaming, airborne total particle counts and viable sampling.

8.4.1 LAFW Testing

Apparatus

A calibrated air multimeter with an accuracy of ± 3% of reading ± 7 ft_3/min (± 12 m_3/h) in conjunction with;

A multi point tube array with proper stand offs **or** a thermal anemometer with an accuracy of ± 3 ft/min (± 0.015 m/s) or 3% of the indicated velocity, whichever is larger in conjunction with a rigid probe holder that will not distort airflow

“A calibrated aerosol photometer with linear or expanded logarithmic scale shall be used. The instrument shall be capable of indicating 100% upstream concentration with a minimum aerosol concentration of µg/L of polydisperse dioctylphthalate (DOP) particles, or an equivalent fluid that provides the same particle size distribution (e.g., polyalpha olefin [PAO] di[2-ethylhexyl], sebecate, polyethylene glycol, and medicinal-grade light mineral oil)[39] produced by the generator described in Section N-1.3.2.2 or equivalent. It shall also be capable of detecting an aerosol concentration in the downstream equal to 10^{-5} of the upstream concentration of the same particles. The sampling rate of air shall be 1 ft^3/min (28 L/min) ± 10%. Probe area shall have a maximum open area of 1.7 in^2 (1100 mm^2) and a minimum dimension of 0.50 inches (13 mm). The photometer shall be set up in accordance with the photometer manufacturer's instructions or IEST-RP-CC-013 if instructions are not provided.” as per NSF (NSF/ANSI 49, Annex N-5.5.2.1, p. 98, 2020).

“An aerosol generator of the Laskin Nozzle type conforming to Annex N-1, Figure 12 or equivalent shall be used to create an aerosol by flowing air through liquid DOP or equivalent substitute. When a Laskin nozzle generator is used, the compressed air supplied to the generator should be adjusted to a minimum of 20 psi (140 kPa), if using DOP or 23 psi (160 kPa) if using PAO, measured at the generator manufacturer’s recommended location. The nozzles shall be covered with liquid to a depth not to exceed 1.25 inches (31 mm).” as per NSF (NSF/ANSI 49, Annex N-5.5.2.2, p. 98, 2020).

LAFW Airflow Velocity Testing Procedure

Airflow velocity shall be measured per the manufacturer’s recommended range, or the FDA guidance range which is typically 72 - 108 FPM (0.37 - 0.55 m/s). Velocity uniformity should fall within the manufacturer’s specification and must be confirmed with visual smoke studies. An alternative velocity range that has been supported by smoke pattern studies may be acceptable.

The testing apparatus shall be a calibrated thermal anemometer with an accuracy of +/- 3 ft/min (+/- 0.015 m/s) or 3% of indicated velocity, whichever is larger.

Airflow velocity readings, as defined by the manufacturer, are typically taken in a plane 6-12 inches (15 - 30 cm) from the filter, protective screen or diffuser screen. The airflow probe shall be held rigidly in a free-standing fixture. The distance from the filter or screen shall be clearly identified on the test report. Unless otherwise specified by the device manufacturer, a maximum 12” (30 cm) grid beginning 6” (15 cm) from the inner edge of the filter frame (or LAFW sidewall) positioned 6” (15 cm) from the filter or screen is recommended.

LAFW HEPA Filter Leak Testing Procedure

All HEPA filters shall be scan leak tested at every certification utilizing an aerosol photometer and an appropriate aerosol challenge medium. A minimum challenge of 10 µg/L must be used to verify all HEPA filters are free from leaks in excess of 0.010% of the upstream challenge concentration.

Aerosol photometer, scanning probe and aerosol generator shall be in compliance with IEST-RP-CC034.5 section 6.1.1 and 6.1.4.

The sampling rate of air shall be CFM (28.3 L/min) ± 10%. Probe area shall have a maximum open area of 1.7 in^2 (1100 mm^2) and a minimum dimension of 0.50 inches (13 mm). An aerosol generator of the Laskin Nozzle type or equivalent shall be used to create an aerosol by flowing air through liquid DOP or equivalent substitute. When a Laskin nozzle generator is used, the compressed air supplied to the generator should be adjusted to a minimum of 20 psi (140 kPa), if using DOP or 23 psi (160 kPa) if using PAO, measured at the generator manufacturer's recommended location. The generator nozzles shall be covered with liquid to a depth not to exceed 1.25 inches (31 mm).

With the end of the probe held not more than 1 inch (2.5 cm) from the area being tested, scan the entire downstream side of the HEPA filter(s) and the perimeter of each filter pack by passing the photometer probe in slightly overlapping strokes at a traverse rate of not more than 2 in/s (5 cm/s). Separate passes shall be made around the entire periphery of the filter, along the bond between the filter pack and frame, and around the seal between the filter and the device.

LAFW Induction Leak Testing Procedure

This test verifies that the LAFW workzone maintains ISO class 5 quality air, with penetrations present, and sufficiently isolates the DCA from the surrounding room. The Induction Leak Test must be performed with all materials and equipment in the work area as used.

Set up the discrete particle counter in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate. The particle counter is set up to sample continuously for the duration of the test. The particle counter probe should be held in hand and oriented into the direction of the airflow. Particle count readings should be taken at least 1" (2.5 cm) away from side walls and sampling 1" (2.5 cm) downstream of the penetration or seam in question. During sampling, a localized visible medium is passed over the penetration from the outside of the LAFW. A visible medium source that produces a strong visual amount of medium must be used. The visible medium must not be directed at the penetration, but rather indirectly passed in the immediate vicinity, ensuring the entire area of the penetration is being covered with the visible medium. The discrete particle counter is monitored to ensure there is not a continual increase in 0.5 µm particles (e.g., 100 particle increase per second) which would indicate a failure. This process is repeated for all penetrations and welds in the work zone.

LAFW Backstreaming Testing Procedure

This test verifies that air from the surrounding room environment does not enter the total work area of the LAFW or integrated work zone. The backstreaming test must be performed with all materials and equipment in the work zone as used.

Using a localized visible medium source scan the plane of the face access opening. Visible medium source is positioned 2” (5 cm) outside of the plane of the face access opening. Special attention must be given to corners and upper edges of the face access opening. The LAFW must not have any visible medium entering the total work zone which would indicate a failure.

LAFW Airflow Velocity Testing Reporting and Documentation

- Record grid dimensions used
- Record distance from screen or diffuser
- Record individual velocity readings in the applicable grid
- Record overall average of the velocity readings
- List acceptance criteria for average airflow velocity
- Name of test (Airflow Velocity Test)
- Report acceptance criteria
- Give a Pass or Fail statement based on the results of the test

LAFW HEPA Filter Leak Testing Reporting and Documentation

- Record upstream aerosol challenge concentration
- List method used to report concentration (measured or calculated)
- Record maximum leak penetration in percent
- Name of test (HEPA Filter Leak Test)
- Report acceptance criteria
- Provide a Pass or Fail statement based on the results of the test

LAFW Induction Leak Testing Reporting and Documentation

- Source of visual smoke
- Provide a Pass or Fail statement based on the results of the test

LAFW Backstreaming Testing Reporting and Documentation

- Source of visual smoke
- Provide a Pass or Fail statement based on the results of the test

8.4.2 LAFW Airborne Total Particle Counting

Apparatus

A discrete particle counter capable of accurately detecting particles ≥0.5 µm shall be used. The particle counter shall have been calibrated within one year with a recognized organization such as NIST. The particle counter shall be calibrated per ISO 21501-4:2018. A zero-filter may be used in conjunction with a 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.

LAFW Airborne Total Particle Counting Testing Procedure

Sample collection shall occur under dynamic operating conditions.

Set up the discrete particle counter in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate. The direction of the probe will be oriented into the direction of the airflow.

For PECs typically used in sterile compounding, ISO recommendations result in one sample location based on ISO 14644-1 [2015] Table A.1. However, sampling must be performed upstream of any/all critical sites, preferably within 6" (15 cm). For example, in basic compounding, only one location may be needed. In PECs where an automated compounding device is being used, 3 or more locations may be needed (locations of sterile connections or penetrations).

LAFW Airborne Total Particle Counting Reporting and Documentation

- Reporting shall be to ISO-14644-1 [2015] section 5.4 (Test Report).

8.4.3 LAFW Viable Sampling

See CAG-009 for information regarding viable sampling.

8.4.4 LAFW Airflow Visualization Studies (AVS) - Visual Smoke Studies

See CAG-014 for information regarding visual smoke studies.

8.4.5 LAFW Testing Frequency

All of the above LAFW tests must be performed at least every six months and after a HEPA filter change, if maintenance or repairs are made to internal parts or if the LAFW is relocated.

8.4.6 LAFW Optional Tests

Optional tests are detailed in the following documents and are performed at the request of the pharmacy owner:

Lighting: IEST-RP-CC002.2 Section 6.10

Noise: IEST-RP-CC002.2 Section 6.11

8.5 General Report Documentation

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:

- Name, address and contact information for the certifying organization also listing key personnel with appropriate accreditations.
- Confirming remark that facility/equipment was tested “in accordance with CETA CAG-003-[Current version]” The most current version of this CAG must be referenced. *Note: USP <797> is not a certification specification.
- Explanation of test procedure used for data collection and justification for any deviations from established industry practices encountered during the certification process.
- The required reporting values listed in each test section of this document.
- A list of test equipment utilized in data collection. List shall include; make, model, serial number, and calibration date.

A copy of the current calibration documentation for each piece of equipment when requested.

8.6 Specific Considerations for Certification of Radiopharmaceutical Preparation Facilities

This section is meant to identify the requirements for radiopharmaceutical facilities that fall under USP<825> where they differ from or are not mentioned by USP<797>. When not mentioned here, any specific test, procedure or criteria found in the other sections of this guide will apply to the engineering controls (e.g., minimum air change rates and methods for collecting particle count data).

8.6.1 Radiopharmaceutical Preparation Facility Requirements

Table 1: Radiopharmaceutical Preparation Facility Requirements (CETA, 2021)

Worked Performed	Engineering Controls Needed	Pressure Requirement	Temperature Requirement
Radionuclide Generator Storage/Elution (12 Hour BUD)	• ISO 8 or better SRPA.	Positive pressure. Adjacent to a negative pressure unclassified space when volatile/airborne drugs are present.	No greater than 77°F (25℃) - **required** Below (RH) 60% - recommended
Radionuclide Generator Storage/Elution (24 Hour BUD)	• ISO 8 or better buffer room. • ISO 8 or better anteroom.	Positive pressure. Adjacent to a negative pressure unclassified space when volatile/airborne drugs are present.	No greater than 77°F (25℃) - **required** Below (RH) 60% - recommended
Dispensing, repackaging, preparation and preparation with minor deviations (12 hour BUD)	• ISO 5 vertical flow PEC. • Unclassified SRPA.	Must be negative pressure to the unrestricted area when volatile/airborne drugs are present.	N/A
Dispensing, repackaging, preparation and preparation with minor deviations (24 hour BUD)	• ISO 5 vertical flow PEC. • ISO 8 or better buffer room. • ISO 8 or better anteroom.	Positive pressure. Adjacent to a negative pressure unclassified space when volatile/airborne drugs are present.	No greater than 77°F (25℃) - **required** Below (RH) 60% - recommended
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using sterile components (96 hour BUD) *24 hour BUD when compounding using a nonsterile component and performing sterilization procedure	• ISO 5 vertical flow PEC • ISO 7 or better buffer room. • ISO 8 or better anteroom.	Positive pressure. Adjacent to a negative pressure unclassified space when volatile/airborne drugs are present.	No greater than 77°F (25℃) - **required** Below (RH) 60% - recommended
Radiolabeled blood components (6 hour BUD)	• ISO 5 BSC. • ISO 7 or better buffer room. • ISO 8 or better anteroom.	Positive pressure. Adjacent to the ISO 8 anteroom.	No greater than 77°F (25℃) - **required** Below (RH) 60% - recommended

*Refer to the pharmacy's RAM license for acceptable pressure ranges in negative pressure cleanrooms.

8.6.2 Testing a Hot-Cell

Certification of a Hot-Cell must include the following:

Certification testing shall be performed to the manufacturer's specifications.

Leak testing of the HEPA filter(s) shall be performed to IEST-RP-CC034.

Particle count to verify the demarcated work area meets ISO 5 shall be performed to ISO 14644-1 (2015).

An ingress/egress particle count and airflow visualization test shall be performed to CETA CAG-002.

9 Addresses and Contacts

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