REVISED

Meeting Notice

Missouri Board of Pharmacy
Sterile Compounding Sub-Committee

January 12, 2016 3:00 p.m.

Hilton Garden Inn, Rose Room
3300 Vandiver Drive
Columbia, MO 65202

Three designated members of the Board will be meeting to review the sterile compounding rule. The full Board will not be meeting. In the interest of full compliance with Chapter 610, public notice of the meeting is being provided as detailed herein.

If any member of the public wishes to attend the meeting, s/he should be present at the Hilton Garden Inn, Rose Room, 3300 Vandiver Drive, Columbia, Missouri at 2:00 p.m. on January 12, 2016.

Notification of special needs as addressed by the Americans with Disabilities Act should be forwarded to the Missouri Board of Pharmacy, P O Box 625, 3605 Missouri Blvd., Jefferson City, Missouri 65102, or by calling (573) 751-0091 to ensure available accommodations. The text telephone for the hearing impaired is (800) 735-2966.

Please see attached tentative agenda for this meeting.

REVISED

TENTATIVE AGENDA
January 12, 2016 3:00 p.m.

Missouri Board of Pharmacy
Sterile Compounding Rule Review

Hilton Garden Inn, Rose Room
3300 Vandiver Drive
Columbia, MO 65202

1 Approval of Sterile Compounding Subcommittee Minutes (8/26/15, 9/23/15 and 11/13/15)

2 Discussion of Action Items from 12/15 Subcommittee Meeting

3 Review/Discuss Comments on Draft USP Chapter 797 Impact on Nuclear Pharmacy

4 Review/Discussion of CETA Guidelines and Procedures for Certifying Sterile Compounding Facilities/Isolators and Potential Fiscal Impact

5 Impact of Clinical Laboratory Improvement Amendments (CLIA) on Draft Sterile Compounding Rule.

6 Review of Sterile Compounding Rule/Draft Revisions to 20 CSR 2220-2.200

7 Review of Proposed USP Chapter 797

8 Future Meeting Dates/Times

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
	Action Level: A situation in which action must be taken in order to maintain compliance with this rule, USP Chapter 797 or both.
	Adverse Event: Any incident related to or resulting from the compounding process that did or may have resulted in an adverse patient outcome.
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.	
Ante-area: An ISO Class 8 or cleaner area where personnel hand hygiene and garbing procedures and other activities that generate high particulate levels are performed. The ante-area is the transition area between the unclassified area of the facility and the buffer area. [NOTE– The ante-area is sometimes referred to as an anteroom when solid doors and walls are present.	**Ante-Area**: An area in which the concentration of airborne particles is controlled to meet ISO Class 8 or better air quality and that provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas.
Aseptic processing or preparation: A process by which separate, sterile components (e.g., drugs, containers, or closures) are brought together under conditions that maintain their sterility. The components can either be purchased as sterile or, when starting with nonsterile components, can be separately sterilized prior to combining (e.g., by membrane filtration, autoclave)	**Aseptic processing**: A mode of processing pharmaceutical and medical CSPs in an ISO Class 5 area that involves procedures designed to produce a CSP that meets a predetermined sterility assurance level and to preclude or prevent contamination by microorganisms during processing or preparation.
Batch: More than one unit of CSP prepared in a single process and intended to have uniform characteristics and quality, within specified limits.	**Batch**: Batch compounding includes: (1) compounding multiple CSP units in a single discrete process, by the same individual(s), carried out during one limited time period, (2) compounding in advance of receiving a prescription and (3) compounding a quantity in excess of the filling of an individual prescription or medication order.

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
Beyond-use date (BUD): The date or time after which a CSP cannot be used and must be discarded. The date or time is determined from the date or time when the preparation was compounded.	**Beyond-Use Date**: For purposes of this rule, the date or time after which a CSP should not be used.
Biological safety cabinet (BSC): A ventilated cabinet with unidirectional HEPA filtered airflow and HEPA-filtered exhaust to protect the worker from hazardous drugs. A BSC used to prepare a CSP must be capable of providing an ISO Class 5 environment for preparation of the CSP.	**Biological Safety Cabinet**: A ventilated cabinet for CSPs and for staff, preparation and environmental protection that has an open front with inward airflow for staff protection, downward high-efficiency particulate air (HEPA) filtered laminar airflow for CSP protection, and HEPA-filtered exhausted air for environmental protection.
Buffer area: An ISO Class 7 (or ISO Class 8 if using an isolator) or cleaner area where the PEC that generates and maintains an ISO Class 5 environment is physically located.	**Buffer Area**: An ISO 7 area where a primary engineering control is physically located
Category 1 CSP: A CSP assigned a BUD of 12 hours or less at controlled room temperature or 24 hours or less refrigerated.	
Category 2 CSP: A CSP 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 standards for Category 2 CSPs in this chapter.	
Certificate of analysis (COA): A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.	
	CFU: Colony forming units.
Classified space: A space that maintains an air cleanliness classification based on the International Organization for Standardization (see also definition for ISO Class).	
Cleanroom: An ISO-classified room in which the concentration of airborne particles is controlled to meet a specified airborne-particulate cleanliness class to prevent particle and microbial contamination of CSPs.	

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
	Compounding: The preparation, incorporation, mixing, packaging or labeling of a drug or drug containing device: (1) as the result of a prescriber's prescription or medication order based on the prescriber/patient/pharmacist relationship in the course of professional practice, or (2) in anticipation of a prescription or medication order as provided herein, or (3) for or incident to research, teaching or chemical analysis and not for sale or dispensing purposes.
	Compounding Area: The area designated for preparing CSPs and includes the ante-area and buffer area.
Compounding aseptic containment isolator (CACI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 clean air environment designed for the compounding of sterile hazardous drugs.	**Compounding Aseptic Containment Isolator (CACI)**: A compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment for CSPs.
Compounding aseptic isolator (CAI): A type of RABS that uses HEPA filtration to provide an ISO Class 5 clean air environment designed for compounding of sterile nonhazardous drugs.	**Compounding Aseptic Isolator (CAI)**: A form of isolator specifically designed for compounding pharmaceutical ingredients or CSPs and to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes.
	Compounding Equipment: Equipment, instruments, apparatuses, and devices used to compound CSPs.
	Compounding Staff: Any person who engages or participates in any aspect of sterile compounding regardless of employment status.**W**

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
Compounded sterile preparation (CSP): A preparation intended to be sterile that is created by combining, diluting, pooling, or otherwise altering a drug product or bulk drug substance. A product produced by reconstituting a conventionally manufactured product for an individual patient strictly in accordance with the directions contained in the approved labeling provided by the product manufacturer is not considered a CSP for the purposes of this chapter.	**Compounded Sterile Preparation (CSP)**: Any low risk, medium risk or high risk CSP prepared by a pharmacy, including: a. Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that must or are required to be sterile when they are administered to patients, including, but not limited to the following dosage forms: bronchial and inhaled nasal preparations intended for deposition in the lung, baths and soaks for live organs and tissues, epidural and intrathecal solutions, bladder/wound solutions, injectables, implantable devices and dosage forms, inhalation solutions, intravenous solutions, irrigation solutions, ophthalmic preparations, parenteral nutrition solutions, and repackaged sterile preparations. Nasal sprays and irrigations intended for deposit in the nasal passages may be prepared as nonsterile compounds; b. An FDA approved manufactured sterile product that is either prepared according to the manufacturers' approved labeling/recommendations or prepared differently than published in such labeling; and c. Assembling point-of-care activated systems.
Compounded stock solution: A compounded solution to be used in the preparation of multiple units of a finished CSP.	
Container–closure system: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection.	
	Controlled Room Temperature: A controlled room temperature as defined by USP.

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an FDA-approved application, and manufactured under current good manufacturing practice conditions. Conventionally manufactured products are not compounded preparations.	
	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 ampuls 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.	**Critical Site:** Any surface, pathway or opening (e.g., vial septa, injection ports, beakers, needle hubs) that provides a direct pathway between a CSP or other ingredient used to compound a CSP and the air, environment or moisture or that poses a risk of touch contamination.
Direct compounding area: A critical area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.	**Direct Compounding Area (DCA)**: An area within an ISO Class 5 primary engineering control where critical sites are exposed to unidirectional HEPA-filtered air also known as first air.
Disinfectant: A chemical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria, but not necessarily their spores.	**Disinfectant**: An agent applied to inanimate objects that frees from infection and destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores.
	Experiential Training: Training based on experience and observation.
Expiration date: Date placed on a conventionally manufactured product to limit the time during which it can be used.	
Filter integrity test: A test (e.g., bubble point test) of the integrity of a sterilizing grade filter performed after the filtration process to detect whether the integrity of the filter has been compromised.	
First air: The air exiting the HEPA filter in a unidirectional air stream.	**First Air**: The air exiting a HEPA filter in a unidirectional air stream that is essentially particle free.
	Frozen: The temperature range for a freezer as defined by USP.
Hazardous drug: 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 hazardous drugs in structure or toxicity.	**Hazardous Drugs**: A hazardous drug as indicated on the National Institute for Occupational Safety and Health's (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
	High-Efficiency Particulate Air (HEPA) filter: A particulate filter that directs the flow of air forced through the filter in a uniform parallel flow and that is: (1) capable of retaining airborne particles and microorganisms while allowing gases to pass freely through and, (2) a minimum of 99.97% efficient when tested using 0.3-µm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.
	• **ISO Class 5:** An area with less than 3,520 particles (0.5 µm and larger in size) per cubic meter. • **ISO Class 7:** An area with less than 352,000 particles (0.5 µm and larger in size) per cubic meter. • **ISO Class 8:** An area with less than 3,520,000 particles (0.5 µm and larger in size) per cubic meter.
In-use time: The time before which a conventionally manufactured product or a CSP must be used after it has been opened or needle punctured (e.g., after a container closure of a vial has been penetrated).	
ISO Class: An air quality classification from the International Organization for Standardization.	
Isolator: An enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and is decontaminated using an automated system. It uses only decontaminated interfaces or rapid transfer ports for materials transfer.	
Label: A display of written, printed, or graphic matter on the immediate container of any article.	
Labeling: All labels and other written, printed, or graphic matter that are 1) on any article or any of its containers or wrappers, or 2) accompanying such an article.	

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
Laminar airflow system (LAFS): A device or zone within a buffer area that provides an ISO Class 5 or better environment for sterile compounding. The system provides a unidirectional HEPA-filtered airflow.	
Laminar airflow workbench (LAFW): A device that is a type of LAFS that provides an ISO Class 5 or better environment for sterile compounding. The device provides a unidirectional HEPA-filtered airflow.	
	Line of Demarcation: A visible line or barrier on the floor that separates a room into distinct and identifiable separate areas for the performance of sterile compounding from general pharmacy activities.
Media fill test: A simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to produce sterile CSPs without microbial contamination.	**Media-Fill Test**: A test using a growth medium to verify aseptic compounding techniques or processes that are able to produce a CSP without microbial contamination.
Microbial contamination: The presence of microorganisms in, or on, an item.	
Multiple-dose container: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed to contain more than one dose of the medication. A multiple-dose container is usually required to meet the antimicrobial effectiveness testing criteria. See *Container Content for Injections □697□, Determination of Volume of Injection in Containers, Multi-Dose Containers*.	**Multiple-Dose Container**: A multiple-unit container for articles or CSPs that contains more than one dose of medication and an antimicrobial preservative.
Pass-through: An enclosure with seals on interlocking doors that are positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.	
	Parenteral: A CSP intended for injection through one (1) or more layers of skin.

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
	Peer-Reviewed Literature: Literature that has been evaluated by other qualified scientific, academic or qualified professionals for quality or accuracy and has been nationally published in a pharmaceutical, scientific, compendial or other medical publication.
Pharmacy bulk package: A conventionally manufactured sterile product for parenteral use that contains many single doses intended for use in a pharmacy admixture program. A pharmacy bulk package may either be used to prepare admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes.	**Pharmacy Bulk Package:** A manufactured sterile product that contains many single doses intended for use in pharmacy compounding.
	Point of Care Activated System: A closed system device that creates a physical barrier between diluents, fluids or other drug components and is designed to be activated by the end user by allowing the components to mix prior to administration.
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.	
Preservative: A substance added to inhibit microbial growth or to prevent decomposition or undesirable chemical changes.	
Primary engineering control (PEC): A device or zone that provides an ISO Class 5 environment for sterile compounding.	**Primary Engineering Control (PEC)**: A device that provides an ISO Class 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but may not be limited to, laminar airflow workbenches, biological safety cabinets, compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs).
	Product: A commercially manufactured drug or nutrient that has been evaluated for safety and efficacy by the United States Food and Drug Administration (FDA).
Pyrogen: A substance that induces a febrile reaction in a patient.	
Pyrogen-free: A substance lacking sufficient endotoxins or other fever-inducing contamination to induce a febrile or pyrogenic response.	

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
Quality assurance (QA): A system of procedures, activities, and oversight that ensures that operational and quality standards are consistently met.	
Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the preparation.	
Reconstitution: The process of adding a diluent to a powdered medication to prepare a sterile solution or suspension.	
	Refrigerated. A cold place in which the temperature is maintained thermostatically between 2° and 8° (36°C and 46°F).
Release testing: Testing performed to ensure that a preparation meets appropriate quality characteristics.	
Repackaging: The act of removing a conventionally manufactured sterile product from its original primary container and placing it into another primary container, usually of smaller size.	
Responsible person: The individual accountable for an activity.	
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.	
Segregated compounding area: A designated, unclassified space, area, or room that contains a PEC and is suitable for preparation of Category 1 CSPs only.	**Segregated Compounding Area**: A designated area or room within the pharmacy that is restricted to preparing Low Risk or Medium Risk CSPs as allowed by section 8 of this rule.
Single-dose containers: A container of sterile medication for parenteral administration (e.g., injection or infusion) that is designed for use with a single patient as a single injection/infusion. A single-dose container usually does not contain a preservative.	**Single-Dose/Single-Unit Container/vial**: A container/vial of medication intended for administration that is meant for use in a single patient for a single case, procedure or injection.

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
Specification: The tests, analytical methods, and acceptance criteria to which a drug substance, drug product, CSP, component, container–closure system, equipment, or other material used in drug preparation must conform to be considered acceptable for its intended use.	
Stability: The extent to which a CSP retains physical and chemical properties and characteristics within specified limits throughout its BUD.	
	Sterile Alcohol: Alcohol that contains 70% by volume USP grade Isopropanol (isopropyl alcohol) and 30% USP purified water and is free of viable organisms.
Sterility: The freedom from viable microorganisms.	
Sterility testing: A documented and established laboratory procedure for detecting viable microbial contamination in a sample or preparation.	
	Sterilization: A validated USP recognized process used to render a CSP free of viable organisms.
Sterilization by filtration: Passage of a gas or liquid through a sterilizing-grade membrane to consistently yield filtrates that are sterile.	
Sterilizing-grade membranes: Filter membranes that are documented to retain 100% of a culture of 107 microorganisms of a strain of *Brevundimonas diminuta* per cm2 of membrane surface under a pressure of not less than 30 psi. Such filter membranes are nominally 0.22-µm or 0.2-µm pore size.	
Terminal sterilization: The application of a lethal process (e.g., dry heat, steam, irradiation) to sealed containers for the purpose of achieving a predetermined SAL of greater than 10−6 or a probability of less than one in one million of a nonsterile unit.	**Terminal Sterilization**: The application of a lethal process for the purpose of achieving a predetermined sterility assurance level of less than 10^{-6}, or a probability of less than one nonsterile unit in one million units.
Unclassified space: A space not required to meet any air cleanliness classification based on the International Organization for Standardization (ISO).	

Comparison of USP vs. Draft Missouri Definitions

USP DEFINITION	MISSOURI DRAFT
Unidirectional airflow: Air within a PEC moving in a single direction in a uniform manner and at sufficient speed to reproducibly sweep particles away from the direct compounding area or testing area.	**Unidirectional Flow**: An airflow moving in a single direction in a robust and uniform manner and at a sufficient speed to reproducibly sweep particles away from the critical processing or testing area.
	USP: The United States Pharmacopeia and the National Formulary (USP-NF) as adopted and published by the United States Pharmacopeial Convention, effective May 2013. Copies of the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway, Rockville, MD 20852-1790 or online at http://www.usp.org/. The USP-NF is incorporated herein by reference. This rule does not include any later amendments or additions to the USP-NF.
Verification: Confirmation that a method, process, or system will perform as expected under the conditions of actual use.	

CETA Certification Guide for Sterile Compounding Facilities
CAG-003-2006
Revised December 8, 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 sterile compounding. 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 7 or 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 clean-zones 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. relative to adjacent spaces. Cleanrooms used for

hazardous applications should be a minimum 0.01" w.c. 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 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 for non hazardous applications 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%. The exact ranges are not specified in USP chapter <797>, however, USP does recommend temperatures below 68 degrees Fahrenheit (20˚C).

IEST-RP-CC006.3 Section 6.9

3.0 Biological Safety Cabinet Certification

Class II 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[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

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 in an isolator that meets the conditions specified in Chapter <797>. When compounding hazardous drugs, however, the room should be certified to have at least 12 ACPH and be at least 0.01" w.c. negative to adjacent rooms and spaces.

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, 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

5.06 Optional Tests

Optional tests are detailed for the following:

IEST-RP-CC002.2

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	CACI	Compounding Aseptic Containment Isolator
6.09	HEPA	High Efficiency Particulate Air (filter)
6.10	FPM	Feet Per Minute (air velocity measurement)
6.11	CFM	Cubic Feet per Minute (air volume measurement)
6.12	ACPH	Air changes per hour
6.13	NSF/ANSI	NSF International/ American National Standards Institute
6.14	µm	Micrometer 1 x 10^{-6} meters (particle size measurement)
6.15	HVAC	Heating Ventilation and Air Conditioning

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[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

CETA Certification Matrix for Sterile Compounding Facilities
CAG-008-2010
October 26, 2010

The following table provides a matrix for reviewing the certification of secondary engineering controls (cleanrooms) used in sterile compounding facilities designed to comply with USP chapter <797>. The Controlled Environment Testing Association has developed the applications guide, CAG-003-2006 (2008), which is referenced in chapter <797>. The table assumes the certification professional follows this applications guide for general guidance. The certifier should provide specific details of each test conducted either directly in the certification report or in a Standard Operating Procedure (SOP) referenced in the certification report. All calculations including intermediate values should be documented. Calibration certificates should be provided for every test instrument used and the specific model number and serial number of each test instrument should be documented on the test report. The certification report should include the name and address of the testing agency, the qualifications of the tester (accreditations), the name and version of any referenced standards, and a clear identification of the physical location of the equipment being tested.

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

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

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

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

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

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

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

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

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

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

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

CETA Certification Matrix for Sterile Compounding Facilities
CAG-008-2010
October 26, 2010

Acronyms, abbreviations

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

Definitions

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

CETA Applications Guide for the use of Compounding Aseptic Isolators in Compounding Sterile Preparations in Healthcare facilities
CAG-001-2005
Revised December 8, 2008

The introduction of USP Chapter 797[1] in January 2004 (revised in June 2008) along with increased pressure from some State Boards of Pharmacy has led to more robust implementation of environmental controls by facilities involved in the compounding of sterile preparations. In some cases, isolators intended for compounding sterile preparations are used either as an alternative or as an adjunct to traditional methods. Isolator use for sterile compounding is relatively new to the United States. Few isolator standards exist and none of those that are in place have been developed with pharmacy compounding in mind. This guide is intended to provide an overview of isolators and assist individuals considering their use in purchasing, installation and commissioning issues.

Scope

This guide will focus on isolator applications appropriate for use in facilities that compound sterile preparations. We will define compounding isolators, describe isolator types and applications as well as describe minimum performance expectations. The definitive standard for compounding sterile preparations in the United States is USP Chapter 797. This document provides application guidance specifically for compounding sterile preparations as dictated by USP. We address both positive pressure isolators used for sterile compounding and negative pressure containment isolators used for sterile compounding of hazardous drugs.

Overview

Isolators have become an effective option in the effort to develop compliance strategies for compounding facilities. Traditional equipment that is used to provide the critical sterile manufacturing zone (ISO Class 5[2]) protects the product with a unidirectional flow of particle free (HEPA filtered) air. Compounding Isolators go one-step farther. The use of gloves and view-screens provides a physical barrier between the operator and the product. A well-designed positive pressure isolator, supported by adequate procedures for its use, maintenance, monitoring, and control, may offer tangible advantages over classical aseptic processing, including fewer opportunities for microbial contamination during processing. However, users should not adopt a false sense of security with these systems. There are no uniform industry standards for the manufacture of Compounding isolators and as you will see, there are significant differences in design applications. Furthermore, positive pressure isolators are not appropriate for compounding hazardous drugs and negative pressure isolators designed to contain hazards present some real challenges to sterile compounding (as we describe later in this Guide). Pharmacists should also be aware of the need to establish new procedures addressing issues unique to isolators. We have seen different types of isolators applied to the pharmacy application.

Some are more effective than others. It is critical that you match the proper isolator to the application.

Definition

Compounding Isolator: A class of isolator designed for use during pharmacy sterile drug compounding. Compounding isolators utilize an airtight glove/glove port design that allows the user to perform hands-on tasks inside the isolator without compromising the intended performance of the isolator.

There are two types of compounding isolators, each named according to their design objective: *Compounding Aseptic Isolator*, and *Compounding Aseptic Containment Isolator*. Among other features, the compounding isolator achieves its design objective through the following:

- The full enclosure of the drug compounding process.
- The intentional use of air pressure relationships that define the direction of airflow in/out of the cabinet.
- The use of airflow capture velocities to capture and remove aerosolized drug product near its point of generation.
- The use of high-efficiency filtration system (HEPA minimum) to capture aerosolized drug preparations and particulate contamination.
- The use of external venting to remove vaporized hazardous drugs from work chamber and from the pharmacy.
- The use of material transfer processes that allow material transfer in/out of the compounding isolator without compromising worker exposure to undesirable levels of airborne drug or unwittingly compromising the sterility of the compounding environment.

Compounding Aseptic Isolator: A form of isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless it has first passed through a microbially retentive filter (HEPA minimum).

Compounding Aseptic Containment Isolator:

A compounding aseptic isolator designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless it is first passed through a microbially retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile hazardous drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation.

Design Characteristics:

1. Prerequisite Features:

A. A Compounding Isolator is supplied with air through a microbially retentive filtration system (IEST Type C or J HEPA minimum) [3].

B. Compounding Aseptic Isolators may discharge unfiltered air from the isolator venting directly into the room. Compounding Aseptic Containment Isolators may discharge air from the isolator through an exhaust HEPA filter into the room only in the absence of volatile hazardous drugs. Where volatile hazardous drugs are compounded, the isolator design must be a total exhaust (non-recirculating) design where discharge must be passed through an exhaust HEPA filter and properly vented from the building[4].

C. Compounding Aseptic Containment isolators must maintain containment of the specific hazard through all aspects of normal operation and material transfer. Containment tests are recommended in the CETA Compounding Isolator Testing Guide[5] .

D. The cleanliness classification of the Compounding Isolator work zone must meet ISO class 5 at 0.5µm and larger particles under dynamic operating conditions.

E. The Compounding Isolator must be designed to allow for safe and effective disinfection.

F. The preparation is never directly exposed to the compounding personnel or the outside environment. Access to the preparation is through gloves.

G. Ingress and egress of product is through either aseptic connection (Closed system) or specially engineered doors or openings (Open system). Isolators used in sterile compounding are typically open isolators where material is transferred via pass-throughs.

2. Closed system vs. open system:

Closed isolator systems exclude external contaminants from the isolator's critical zone by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations and use only decontaminated (where necessary) interfaces or Rapid Transfer Ports (RTPs) for material transfer.

Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g., using continuous overpressure) to exclude the entry of external contamination into the isolator. Typically, pressurized pass-throughs are used to isolate the interior of the isolator from the surrounding atmosphere when material is transported in and out of the isolator.

3. Air Recirculation:

Compounding Isolators vary by design of air recirculation. End user understanding of these design aspects is important as these relate to placement, economy of operation, and the appropriate safety of air removed from the isolator.

Non-recirculating: Compounding Isolators that use a single pass of filtered air that is completely exhausted from the chamber. Compounding Aseptic Isolators may exhaust air to the surrounding space either through HEPA filters or without filtration. Non-recirculating Compounding Aseptic Containment Isolators must exhaust air through a HEPA filter, and where volatile hazardous drugs are prepared, this exhaust air must be properly vented from the building. CETA recommends that only non-recirculating compounding isolators utilizing total exhaust through HEPA filters and connected to a properly designed building exhaust system be used for preparing hazardous drugs that volatilize.

Partial recirculating: Compounding Isolators that are designed to reuse exhaust air by routing a portion of exhaust air back to the supply HEPA filter, expelling the remaining exhaust air from the isolator in a manner consistent with the level and type of hazard. CETA recommends that partial recirculating compounding isolators not be used with hazardous drugs that volatilize.

Full recirculating: Compounding Isolators that are designed to reuse all the exhaust air by routing the exhaust air back to the supply HEPA filter. CETA recommends that full recirculating compounding isolators not be used with hazardous drugs that volatilize.

4. Airflow:

It is critical that the end-user of the Compounding Isolator considers the process and makes an educated decision about the airflow type that best fits their needs. The two fundamental differences in isolator design are in supply airflow utilization and pattern.

Air will be delivered to the process chamber through one of two methods; ***Flow Control*** (produced by unidirectional airflow) or ***Dilution Control*** (achieved through turbulent airflow). Aseptic processing is traditionally carried out in unidirectional or laminar flow areas. Non-aseptic processes are more often associated with a turbulent flow environment, such as with the surrounding support areas. **It should be noted that USP Chapter 797 requires unidirectional airflow for all primary engineering controls used in sterile compounding operations.**

Unidirectional Airflow: An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area[5].

A. A flow-controlled Compounding Isolator will provide protection by sweeping HEPA filtered air over the preparation and carrying particulates away from the critical zone to an air return. The FDA guideline for Sterile Drug Products Produced by Aseptic Processing and USP Chapter 797 states "Air in critical areas should be supplied at the point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations"[6]. Realizing that the ultimate objective of the USP Chapter 797 document is to provide guidance sterile operations, we use this to provide direction to the following recommendations.

The unidirectional airflow velocity should be sufficient to sweep particles away from the compounding area within the isolator work-zone. Traditionally, airflow velocity of unidirectional flow clean-air devices is recommended to be 90 fpm (.45m/s) per IEST-RP- CC002.2[7]. However, application of unidirectional airflow velocity may be higher or lower to achieve specific desired results. It has been demonstrated and validated within the NSF/ANSI 49:2004[5] standard for Class II Biosafety Cabinetry that lower velocities can provide sufficient sweeping action for aseptic processing.

The unidirectional airflow velocity, at whatever value is used, should be proven by the manufacturer to repeatedly achieve the required particle sweeping action. The demonstration will normally include an airflow velocity profile along with a visual smoke pattern test. The manufacturer-determined unidirectional airflow parameters will be established based on its ability to assure that particle generation from work practices, work product and packaging will not cross-contaminate associated product during and/or after subsequent work practices within the isolator work zone. This process of verification should be repeatable during a field test at the user site under dynamic operating conditions.

The unit shall be designed to achieve a smooth, even flow absent of turbulence and upward reflux. A documented demonstration of flow from the point of filtration across the product exposure area to the returns (front, side, and rear air grilles) should give the user confidence that the unidirectional isolator is well designed for compounding sterile drugs. This is typically demonstrated using an airflow smoke pattern test.

Turbulent Airflow: The process of introducing a supply of filtered air that mixes with and dilutes airborne contaminants, thus reducing the concentration within the environment. Most contaminants are ultimately removed from the environment through the air exhaust system. Contamination removal takes longer to achieve than in a unidirectional isolator because the air turbulence keeps particles suspended and the dilution process is dependent on the volume of air cycling through the space. More chamber volume requires more time or a higher air exchange rate.

A. A dilution-controlled Compounding Isolator provides a state of control by replacing unconditioned air with HEPA filtered air. An estimate of the effectiveness of the level of control can be determined by calculating the number of times the air within the space is replaced with HEPA filtered air. This is referred to as Air Changes per Hour (ACPH) and in an isolator used for critical operations, greater than 300 ACPH is typical.[9]

The FDA guideline[6] on aseptic processing states that turbulent flow is normally acceptable within closed isolators. While this is a defendable position, it is important to understand that most pharmacy compounding is performed in *open* isolators meaning materials are generally brought in and out of the isolator through an interchange chamber having sealed doors from the main chamber.

Room air may be allowed to enter the interchange chamber and subsequently pass into the main chamber during the material transfer process. Closed isolators use aseptic Rapid Transfer Ports (RTPs) or direct connection for material transfer to prevent room air from entering the main chamber.

Another factor that would affect the ability of a dilution-controlled isolator to perform in a compounding facility is Recovery Time. Recovery time is how long it takes to return to original base-line particulate levels after an elevation to the particle counts. The number of air changes per hour will have a direct affect on recovery time. Increased air exchange rates should decrease recovery times.

The following variables affect the impact of recovery time:
1. How many different preparations will be compounded in the same isolator and the frequency of these operations? If you plan to compound more than one preparation and are concerned about cross contamination, recovery time is an extremely important factor. The amount of time needed to recover after manipulation of one preparation before introduction of another must be determined. Tests can be conducted to determine this, but the test procedure must be carefully documented.

2. How effective is the pass-through at isolating the inside of the main work chamber from the room? In the event particulate is allowed to enter the main work chamber in the process of product introduction, the recovery time needs to be considered before compounding can begin. Well designed pass-throughs will minimize transferred contamination; Static pass-through systems do not adequately protect the isolator environment during material transfer. Recovery time of the pass-through and the compounding chamber should be considered when determining how long the isolator should be allowed to purge after material transfer before compounding.

3. How clean is the material that is being brought into the Compounding Isolator? Outer packaging for all disposables can create particulate contamination as packages are opened or manipulated. In a dilution-controlled environment, these particles may travel across clean areas, contaminating items thought to be sterile. In a flow-controlled environment, this contamination will be swept away with minimal cross contamination.

5. Pressurization:
Compounding Isolators that bring product in through pass-throughs have a potential for compromise in achieving complete physical separation from the external environment.
Compounding Aseptic Isolators use positive air pressure relative to the surrounding space to reduce the ingress of external airborne particles during both product transfer and compounding operations. A positive air pressure differential adequate to achieve this full separation should be employed. Pressure differential will typically maintain a minimum of 0.1” water gauge. The appropriate minimum pressure differential will depend on the system’s design. The isolator manufacturer should validate the appropriate positive pressure differential for each unit. As a point of reference, the FDA guideline for

aseptic processing suggests a pressure range between 0.07 and 0.2" w.g[6]. Additionally the manufacturer should validate that the pressure will not change state from positive to negative or vise versa during glove manipulation or normal operations.

Compounding Aseptic Containment Isolators are either recirculating or total exhaust and use negative air pressure relative to the surrounding space and exhaust airflow to contain the escape of hazards during the compounding process and during a breach of containment (e.g. glove failure) to protect the operator.

6. Venting:

HEPA filters are designed to contain particles and aerosols but not vapors or fumes from volatile substances. Compounding Aseptic Containment Isolators used to prepare hazardous preparations that volatilize must be properly vented through HEPA filtration and then outside the building (not into the surrounding space) in order to protect the worker from harm[4].

Compounding Isolator exhaust air that is vented to the outside environment should be done so with a building exhaust blower using direct-drive motors, when possible. Belt-driven devices are more susceptible to failure and loss of exhaust volume due to belt slipping, stretching, or breaking.

The exhaust blower should be on the roof (per NSF/ANSI Standard 49 - 2004)[8] or in a top-floor unoccupied equipment room if it is the final component of the exhaust system prior to discharge from the building to maintain containment (negative air pressure) in the exhaust ductwork. Equipment rooms should have adequate ventilation.

Exhaust air must be 100% exhausted to the outside atmosphere. The exhaust system shall not re-circulate air back into the building. Exhaust stacks should extend at least ten feet above the adjacent roofline to protect maintenance workers from direct exposure to the effluent from the top of the stack. Care must still be taken as this may not be sufficient to guarantee or prevent re-entrainment of isolator exhaust air back into the building or nearby buildings[10] through open doorways, windows, or air intake systems.

An exhaust airflow alarm to alert the operator of an exhaust system failure should be either part of the isolator or the exhaust system. If it exists, its performance must be verified and documented.

Name of Isolator	Type of Isolator	Purpose	Building Exhaust Requirements	Placement
Compounding Aseptic Isolator	Positive Pressure and positive pressure recirculating	Compounding of sterile preparations	None	If located in an uncontrolled room, it should be proven that the isolator prevents transfer of unfiltered room air into the isolator during material transfer or compounding operations
Compounding Aseptic Containment Isolator - Recirculating	Negative Pressure Recirculating	Compounding hazardous drugs that do not volatilize.	Optional	Must be located in an area devoted to hazardous drug handling. If located in an uncontrolled room, it should be proven that the isolator prevents transfer of unfiltered room air into the isolator during material transfer or compounding operations. The room should be a minimum of 0.01" w.c. negative and have a minimum of 12 ACPH.
Compounding Aseptic Containment Isolator – non-recirculating	Negative Pressure Total Exhaust	Compounding hazardous drugs including those that volatilize.	Must be properly connected and vented from building	Must be located in an area devoted to hazardous drug handling. If located in an uncontrolled room, it should be proven that the isolator prevents transfer of unfiltered room air into the isolator during material transfer or compounding operations. The room should be a minimum of 0.01" w.c. negative and have a minimum of 12 ACPH.

7. Decontamination/ Disinfection:

The isolator design should facilitate physical disinfection of all work surfaces. Interior seams should be shaped and sized to facilitate easy cleaning. All interior surfaces should be easily reached through the gloves to accommodate cleaning. If the interior is designed in a manner that does not permit easy physical disinfection of all surfaces, an alternative gaseous decontamination process must be developed and validated.

8. Gloves/Sleeves:

Manipulations within a isolator are conducted through a glove/sleeve (gauntlet) assembly. Two types of glove/sleeve assemblies are available:

A. *One-Part*: The one-part assembly is where the glove and sleeve are of a single, unbroken unit.
B. *Two-Part*: The two-part assembly is where the glove and sleeve are separate and are connected at the sleeve (gauntlet) by some type of seal system. The two-part system allows for the relatively simple change-out of gloves.

The type of work conducted in the isolator and the disinfectants that will be used should be taken into consideration in determining the glove material. Commonly used materials include Neoprene®, Nitrile®, Hypalon® and latex. The gloves must have sufficient chemical resistance to stand up to decontaminating chemicals, cleaning agents, and process materials. Special gloves developed for use with Chemotherapy agents may be appropriate for certain applications.

It is common practice to use a double glove system to minimize the possibility of a tear or leak to compromise the environment within the isolator. An ordinary latex glove can be worn underneath the isolator glove and changed as needed. Glove life will be affected by the cleaning agents, solvents, and process materials. A faulty glove will represent a potential route of exposure to the product. Gloves should be inspected daily for pinholes as well as breaches at seams, gaskets and seals. A regular replacement program should be established so gloves are replaced before a breach of integrity occurs.

9. Pass-through considerations:
The transfer of materials into and out of the isolator is one of the greatest potential sources of contamination. There are three basic types of pass-throughs that are employed in the design of an open Compounding Isolator system - Static Air, Dilution Airflow, and Unidirectional Airflow. In all cases, the pass-through must be designed to effectively isolate the interior of the isolator from the room when materials are transported in and out, and where containment is required, isolate the operator and room from the hazardous drugs.

Static Pass-through: In its most basic form, a static pass-through is a box with doors on 2 sides that is sealed to the isolator. Materials are placed into the pass-through from the outside door. After the materials are placed inside, the outside door is closed. The inside door can then be opened and materials passed through to the isolator. The process is reversed for material removal from the isolator.

Static pass-throughs generally are not considered appropriate for sterile compounding applications.

Dilution and Unidirectional Airflow Pass-through: Improvements over the static air pass-through are dilution control and unidirectional pass-throughs because the particulate level in the pass-through can be reduced before opening the door to the main body of the isolator. Airborne particulate levels can be reduced with a dilution-controlled pass-through or virtually eliminated with a unidirectional pass-through.

To prevent direct exposure between the Compounding Isolator main chamber and the room, both pass-through doors should not be open at the same time. The installation of

door interlocks may be used to prevent simultaneous opening, and timers may be used to aid operators. The interior pressure of the Compounding Aseptic Isolator should be sufficient to prevent air movement from the pass-through to the main work chamber and in the case of Compounding Aseptic Containment Isolators; both prevent air movement from the pass-through to the main work chamber and contain the hazardous preparation for operator protection. Manufacturer validation of the appropriate time required and procedures before opening either the exterior or the interior door should be provided.

Regardless of the isolator type, opening and closing the pass-through to the room may allow some room air into the pass through. Additionally, there will be some surface contamination on the material that is brought into the unit via the pass through. A dilution-controlled isolator dilutes out the airborne contamination over time. A unidirectional isolator will flush out the contamination almost immediately with a continuous bath of HEPA filtered air. Any airborne contamination that is brought in through the pass-through with the product is swept away, carried to the return, and removed from the work zone. Note that for both unidirectional and turbulent flow isolators, provisions should be made to address the issue of surface contamination on inbound materials.

Care should be taken to avoid the ingress of any airborne particles from the external environment by induction at product ingress locations such as the pass-through door. This induction can occur from local turbulent flow causing air swirls or backflows into the isolator from the room in both positive and negative pressure isolators. Additionally, negative pressure isolators are more susceptible to drawing room air in to the work chamber, so the operation of the pass-through must incorporate this condition into the overall design of the isolator.

10. Materials of Construction:

Suitable materials should be selected for construction. Considerations include cleanability, durability and functionality. Stainless steel and glass interior surfaces are common materials. High performance plastics have been used for the viewing panels. The use of plastics in the design of the glove panel allows flexibility of design that would be made difficult with glass. The plastics employed should be scratch resistant and compatible with common cleaning materials and work products used within the isolator.

11. Ergonomic Considerations:

Working in an isolator can often involve long periods of time with arms in a relatively still position. Comfortable working conditions are obviously very important. Consideration to worker comfort is recommended as part of any isolator purchase. Most manufacturers have height adjustors available as part of their units. Some form of height adjustment is strongly recommended to provide easy transition from short to tall operators or from sitting to standing working positions. Also, the design should have front view screen and glove ports sized and positioned to allow comfortable and efficient work. It should be noted that height adjustors may not work with units connected to an external exhaust system. Flexible duct connections may help but may limit the length of travel.

Conclusions:

Type of Design

Compounding Isolators are designed to be surface disinfected, not decontaminated in a manner that would penetrate all hidden areas of the isolator. Therefore, contamination may remain and could become airborne during the operation of the compounding isolator. The capability of the compounding isolator to supply and maintain filtered air at the work zone level becomes critical to successful aseptic practices. Because turbulent airflow compounding isolators do not use a continuous fully diffused top to bottom piston of clean air, it is possible that contamination may be harbored in stagnate air zones within the critical work zone space and therefore are not recommended.

Additionally, the frequency of chamber air changes determines the recovery time to acceptable levels in the event particles are drawn into the chamber during a transfer, or through normal operation. Compounding isolators with unidirectional airflow designs remove particles from the work zone more rapidly than do turbulent flow designs and because of lower air change rates, turbulent flow compounding isolators recover more slowly from particle excursion the than do unidirectional flow equipment. Unidirectional airflow will more quickly remove particles carried in on preparations during a transfer and reduce opportunity for particle transfer to the critical work zone.

Airborne Particle Level Testing

USP Chapter 797 requires the compounding isolator critical work zone meet ISO Class 5 particle levels and be regularly tested to this requirement. CETA recommends that the classification of all cleanliness levels should be done under dynamic operating conditions to ensure that acceptable particle levels are met during routine operation not just during an "At Rest" state. CETA also recommends that the particles to be counted should be 0.5µm and larger both in the compounding isolator work zone and surrounding cleanroom space. This particle level is consistent with ISO 14644-1 (1999) methodology.

Placement and Clean Zone Classification

USP Chapter 797 requires a minimum cleanliness classification of ISO class 5 (FS209E class 100) for the compounding zone within the isolator. ISO class 5 should be stated as follows; ISO class 5 at 0.5 µm particles under dynamic operating conditions.

Compounding Isolators should be placed in an ISO class 7 cleanroom unless they can meet all of the following conditions:

a. The isolator shall provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.
b. Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO class 5 levels during compounding operations.
c. Not more than 3,520 particles per cubic meter shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer. [4]

Isolator Testing and Commissioning

Isolator testing to CETA CAG-002-2006 is recommended in USP Chapter 797. The isolator manufacturer should provide specific procedures for testing and use of their product along with acceptance criteria. When choosing a compounding isolator, it is strongly recommended that you verify that the manufacturer has considered field certification and has accommodated that eventuality.

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

[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, USA, www.iest.org

[4] NIOSH Alert for Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings, Department of Health and Human Services, CDC, NIOSH, NIOSH – Publications dissemination, 4676 Columbia Parkway, Cincinnati, OH 45226-1998, www.cdc.gov/niosh

[5] CAG-002-2006 *(revised 12/08/2008*): CETA Compounding Isolator Testing Guide, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607, www.cetainternational.org.

[6] USFDA: Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice, September 2004, Centers for Drug Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, MD 20852-1448, www.fda.gov/cber/guidelines.htm

[7] IEST-RP-CC002.2: Unidirectional Flow Clean-Air Devices, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Rolling Meadows, Il. 60008-3841

[8] NSF/ANSI 49-2004: Class II (laminar flow) Biosafety cabinetry, NSF International, P.O. Box 130140, Ann Arbor, MI 48113-0140

[9] Design of Barrier Isolators for Aseptic Processing: A GMP Perspective" Pharmaceutical Engineering Volume 18 No. 2 March April 1998

[10] ANSI/AIHA Z9.5-2003: American Industrial Hygiene Association, 2700 Prosperity Ave., Suite 250, Fairfax, VA 22031, www.aiha.org

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CETA Compounding Isolator Testing Guide
CAG-002-2006
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1.0 Overview:

The purpose of this document is to establish an industry-based minimum set of testing criteria appropriate for all Compounding Isolators used pursuant to USP Chapter 797 [1]. Compounding Isolators consist of Compounding Aseptic Isolators used for compounding sterile preparations and Compounding Aseptic Containment Isolators used for compounding sterile hazardous drug preparations in pharmacy applications. While this document gives general guidance or referenced guidance through relevant industry documents, it is not the intention to set the specific acceptance criteria. It is the manufacturer's responsibility to determine exact testing procedures consistent with these guidelines and assign appropriate values pertaining to acceptance criteria that is consistent with user requirements. This guide has also been established to create a uniform approach for field certifiers to allow consistent and repeatable testing at all facilities.

1.01 General Responsibilities:

The criteria outlined are intended to describe currently accepted practice. Responsibility for test performance lies with the manufacturer during design and production, and field certifiers at the installation site. INFORMATIONAL NOTES are inserted to aid users of this guide by providing a format or general reference for the information desired. The engineering and design concepts employed are up to the individual manufacturer's discretion. The general assumptions in determining the minimum criteria for Compounding Aseptic and Compounding Aseptic Containment Isolators covered in this document are:

- used for compounding sterile preparations
- used in either a classified or unclassified space
- use of "open" design, using pass-through chamber systems to transfer material in and out
- may be either positive or negative pressure depending on the hazard of the drugs
- no expectation of end user employing gaseous decontamination of the Compounding Isolator

An isolator certified by the manufacturer as meeting the criteria established in CETA CAG-002-2006 shall post the following on the front of the cabinet in a location readily visible to the user:

1. Notice of pass or failure of the Preparation Ingress and Egress Test (2.09).
2. Whether or not designed for use with volatile hazardous drug compounds, toxic, flammable or explosive materials.
3. Indication of the results of the Recovery Time Determination Test (2.07).

NOTE: Instructions for material transfer should be developed by individual user/ facility, based on their SOPs taking into account purge and recovery times listed by the isolator manufacturer.

a. Purge time for the pass through
b. Purge time after materials are entered into the isolator

An isolator field certified to the statement "in accordance to CETA CAG-002-2006" shall have the following information posted on the front of the cabinet in a location readily visible to the user:

1. Information to be completed by testing technician:
   - A. Date tested
   - B. Reference report number
   - C. Due for retest date (month and year)
   - D. Tested by:
     - 1) Name printed
     - 2). Signature

E. If the cabinet does not have manufacturer's listed information noted above.
   1) Pass/ fail status of the material ingress/ egress test
   2) Recovery time of the main chamber.
   3) Indication that the operator has to wait at least the recovery time before initiating operations after material transfer.
   4) Ventilation appropriate for use with volatile / non-volatile hazardous drugs.

2. Information to be pre-printed on label:

   A. Company name
   B. Address
   C. Phone number

1.02 Test Responsibility

Procedure	Manufacturer	Field Test
2.01 Airflow Test	**X**	**X**
2.02 Chamber Pressure Test	**X**	**X**
2.03 Site Installation Assessment Tests	**D**	**X**
2.04 Gauntlet Breach Air Velocity Test	**D**	**O**
2.05 HEPA Filter Integrity Test	**X**	**X**
2.06 Particle Containment Integrity and Enclosure Leak Test	**X**	**X**
2.07 Recovery Time Determination Test	**D**	**O**
2.08 Airflow Smoke Pattern Test	**X**	**X**
2.09 Preparation Ingress and Egress Test	**D**	**X**
2.10 Particle Count Tests	**X**	**X**
2.11 Volatile Hazardous Drug Containment Tests	**D**	**O**
2.12 Hazardous Particle Containment Test	**D**	**O**
2.13 Pass-through Particle Purge Time Determination Test	**D**	**O**

X = Mandatory
O = Optional
D = Design criteria qualification

1.03 Glossary of Terms

- **Ambient**
  Environment external to the compounding isolator

- **Compounding Aseptic Isolator:**
  A form of isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbially retentative filter (HEPA minimum).

- **Compounding Aseptic Containment Isolator:**
  A compounding aseptic containment isolator is designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes, and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless it is first passed through a microbially retentive filter (HEPA [3] minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile hazardous drugs are prepared, the exhaust air from the isolator shall be appropriately removed by properly designed building ventilation. [2]

- **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, beakers) or openings (e.g. opened ampule, needle hubs) exposed and at risk of direct contact with air (e.g. ambient room or HEPA filtered), moisture (e.g. oral and mucosal secretions), or touch contamination. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

- **Critical Work Zone:**
  The defined specific localized area starting 6" (15.2 cm) below the IV bar including horizontal and vertical space within the work area where aseptic manipulations are performed.

- **Design Acceptance Test:**
  A manufacturer test performed to verify that the design meets intended criteria. Must be successfully completed on at least 2 units of each model and size upon introduction and modification of that design.

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

- **HEPA (high-efficiency particulate air) Filter** [3]
  An extended-medium, dry-type filter in a rigid frame when tested at rated airflow having a minimum particle collection efficiency of 99.97% for 0.3-µm mass median diameter particles of DOP when tested in accordance with MIL-STD-282 [4].

- **Main Chamber:**
  The primary chamber containing the work area, critical work zone, and means for manipulation of the preparation. This includes plenums and areas covered with diffusers.

- **Pass-through Chamber:**
  The chamber designed to separate the surrounding ambient space from the main chamber while facilitating the movement of materials between the two areas.

- **Particle Elevation:**
  Airborne room particles elevation to enable certain tests. This elevation may be accomplished through the use of aerosol generator, theatrical smoke generator, or other smoke sources that provide suitable particle size and quantity

- **Primary Engineering Control (PEC)**
  A device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow work-benches (LAFWs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs).

- **Surrogate Manipulation:**
  A manipulation of a preparation that involves the use of substituted materials that closely resemble actual materials used in sterile compounding to provide a similar impact upon the environment tested and to resemble actual operational conditions during testing

- **Unidirectional Airflow:**
  An airflow moving in a single direction in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

- **Volatile**
  A gas, vapor, or micro-aerosol potentially generated during the pharmacy compounding process that can pass through a High Efficiency Particulate Air (HEPA) filter.

- **Work Area**
  The horizontal and vertical space within the isolator from wall to wall and from the base or floor to the top within the main chamber. This excludes plenums and areas covered with diffusers.

1.04 Safety Concerns

Testing in accordance with this document may involve hazardous materials, equipment and operations. It is the responsibility of the user to consult and establish appropriate safety and health practices and to determine the applicability of regulatory limitations prior to use of this document.

2.00 Compounding Isolator Tests:

The following tests are offered to establish that the Compounding Isolator design is appropriate for the task, that test methods are repeatable and accurately reproducible in the field, to provide detailed guidance for the field certifier through a specific field test documentation and / or through a designated section of the product owner's manual, and to set appropriate acceptance values.

The manufacturer shall be responsible for identifying special accommodations, or ancillary equipment that may be needed for accurately field testing the Compounding Isolator design. These may include, but are not limited to the methods, sources, or devices to provide accurate and repeatable testing such as:

- correcting for impact of operating pressures where applicable
- provision of ports to support the use of diagnostic equipment
- supplementary equipment, materials, products to facilitate tests
- providing and updating performance information as necessary
- For turbulent flow isolators, provide chamber volume needed to calculate air changes.

INFORMATIONAL NOTE:
Metric equivalents (SI) are provided in parentheses ( ) behind English measurement values throughout this document as an aid or cross-reference.

2.01 Airflow Test:

Purpose:

This test verifies the appropriate airflow parameters are met for the manufacturer's design intent.

Apparatus:

- A calibrated thermal anemometer with an accuracy of ± 3.0 fpm (0.015 m/s) or ± 3% of the indicated velocity, whichever is greater.

Procedure:

Main Chamber:

Measure the air velocity in the Compounding Isolator using equally spaced points in the horizontal plane that produces the most repeatable readings.

INFORMATIONAL NOTE:
As an example, the horizontal plane would be set at X inches (cm) below the filter diffuser using a X inch (cm) grid.

An example of uniformity ranges may be a) +/- Y % of the average or +/- X fpm (m/s), whichever is greater, or b) +/- Y % of the average velocity.

Procedure – All Compounding Isolators:

Pass-through Chamber

In a purged pass-through chamber, the manufacturer shall develop a repeatable method of determining airflow volume or velocity to achieve the stated purge objective.

1. For unidirectional purged pass-through, measure the air velocity at multiple points across the pass-through using equal points in a plane that produces the most repeatable readings or determine an alternate repeatable method to determine that the specified purge objective is met.

2. For non-unidirectional purged pass-through, the manufacturer will determine the optimum location and method that produces the most repeatable readings or determine an alternate repeatable method to determine that the specified purge objective is met

INFORMATIONAL NOTE A: *Airflow velocity and / or volume and chamber pressurization will interact with each other. Both tests should be verified before recording final airflow and pressure values.*

INFORMATIONAL NOTE B: Id*eally the manufacturer's recommended pass-through purge time should relate to and specify an acceptable level of airborne particulate at conclusion of the purge time. For example, a purge time of X seconds or minutes should result in airborne particle levels consistent with ISO Class Y at 0._ µm and larger size particulate classification* [5] *within the pass-through chamber.*

Acceptance Criteria:

- The manufacturer will determine the appropriate acceptance criteria for the particular design. **Unidirectional Airflow Compounding Isolator** velocity criteria shall be expressed in terms of a range of velocities in feet per minute (fpm) (meters per second (m/s)) along with a velocity uniformity designator. For example, a statement would be presented as *the average velocity shall fall between __fpm (m/s) and __fpm (m/s) and __% uniformity from the average*

INFORMATIONAL NOTE: *Airflow velocity and / or volume and chamber pressurization will interact with each other. Both tests should be verified before recording final airflow and pressure values.*

2.02 Chamber Pressure Test:

Purpose:

This test is performed to determine that pass-through and main chamber pressures are adequate to aid in providing Compounding Isolator separation between the main chamber and ambient spaces.

Apparatus:

- A calibrated mechanical or electronic differential pressure indicating device.

> **INFORMATIONAL NOTE**: Differential pressure indicating devices should have a fast reaction or update capability (time constant) of less than 1 second in order to detect momentary or large changes in differential pressure.

Procedure:

1. Utilize the factory installed test port or sealed access location to main and pass-through chambers.
2. Attach test instrument tubing into chamber and allow pressure levels to stabilize.

Test 1:

- Record pressure level of main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended into Compounding Isolator.
- Fully open outer pass-through door. Document any change to the pressure.
- Confirm that the pressure does not change from positive to negative or from negative to positive.
- Close outer pass-through door. Document any change to the pressure.

Test 2:

- Record pressure level of main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended into isolator.
- Using Compounding Isolator glove, fully open inner door. Document the change to the pressure.
- Confirm that the main chamber pressure does not change from positive to negative or from negative to positive.
- Close inner door. Determine if pressure level returns to original levels.

Test 3a:

- Record pressure level of Compounding Aseptic Isolator main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended into isolator.
- Insert hands into gloves and pull back from isolator to simulate operator hand removal. An example of a reasonable pull back time is no greater than 3 seconds from fully extended to fully extracted (gloves at a point even with the view panel)
- Determine the change in pressure and verify that the pressure does not change from positive to negative.

Test 3b:

- Record pressure level of Compounding Aseptic Containment Isolator main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended outside isolator.
- Insert hands into gloves and push into main chamber to simulate operator hand insertion.
- Determine the change in pressure and verify that the pressure does not change from negative to positive.

Acceptance:

- Compounding Isolator operating pressure range shall be determined by the manufacturer.
- The pressure shall not change from positive to negative or from negative to positive during any manipulations.

2.03 Site Installation Assessment Tests:

Purpose:

These tests are performed to verify:

- The airflow or pressure setpoint(s) where an audible and/or visual alarm will activate to signify unfavorable operating conditions within the compounding isolator and/or the remote exhaust blower.
- Functional pass-through door interlock operation.
- Proper canopy or exhaust connection performance.

Apparatus:

- A calibrated thermal anemometer with an accuracy of ± 3.0 fpm (0.015 m/s) or ± 3% of the indicated velocity, whichever is greater.
- A calibrated mechanical or electronic differential pressure indicating device.
- Alarm adjustment/alignment tool.
- A source of visible smoke - such as a chemical smoke tube.

Procedure:

Test 1: Airflow or Pressure Alarm Test:

- Verify the alarm setpoint(s) using the compounding isolator or alarm manufacturer's performance verification procedures.
- Adjust as necessary.
- Return isolator to certification setpoint.

Test 2: Door Interlock Verification Test:

- Verify the inner and outer door interlock system operates as per manufacturer's design criteria.

Test 3a: Exhaust System Performance – Canopy Connections:

- Using a visible smoke source, verify negative pressure at the gap.
- Measure the duct static pressure between the air gap and any duct-mounted balancing dampers.

Test 3b: Exhaust System Performance – Hard ducted connections:

- Measure the duct static pressure between the isolator discharge point and any duct-mounted balancing dampers.

Acceptance:

Airflow or Pressure Alarm Test

- The setpoint(s) shall be determined by the manufacturer as appropriate for operator safety, product sterility and/or containment.

Door Interlock Verification Test

- Determined by the manufacturer.

Exhaust System Performance

- No smoke shall escape into the room once it enters the exhaust system

2.04 Gauntlet Breach Air Velocity Test:

Purpose:

This test is performed on containment Compounding Isolators to assure some level of operator protection in the event of a significant glove or gauntlet integrity failure.

Apparatus:

- A calibrated thermal anemometer with an accuracy of ± 3.0 fpm (0.015 m/s) or 3% of the indicated velocity, whichever is greater.

Procedure:

1. Determine that all other operating parameters have been met.
2. Remove one gauntlet from chamber view screen.
3. Measure velocity at the geometric center of the opening. A minimum of 3 samples at a minimum of 1 location shall be taken.
4. Record results.

Acceptance:

- The velocity shall be determined by the manufacturer as appropriate for operator safety.

> **INFORMATIONAL NOTE**: *Published sources show various ranges of airflow velocities that pertain to gloveboxes and other containment devices.*
> *These sources include:*
> - **NSF/ANSI Standard 49 (75 to 100 lfpm) (0.38 to 0.51 lm/s)**[6]
> - **ANSI/AIHA Z9.5-2003 (≥ 100 lfpm) (0.51 lm/s)** [7]

2.05 HEPA Filter Integrity Test:

Purpose:

This test determines the integrity of the all HEPA filters, filter housings, and filter mounting frames. The cabinet shall be operated at operational airflow for this test.

Apparatus:

- A calibrated Aerosol Photometer capable of indicating 100% upstream concentration with an aerosol of between 10 and 90 µg per liter of polydispersed dioctylphthalate (DOP or DEHS) CAS# 117-81-7, polyalphaolefin (PAO) CAS# 68649-12-7 or an equivalent fluid. Unit must have a threshold sensitivity of at least 10^{-3} micrograms per liter and be capable of measuring concentrations over a range of 10^5 times the threshold sensitivity. The sampling rate shall be 1 CFM (28.3 lpm) (±10%) with an inlet probe having sufficient area (1.7 square inches) (11.0 cm^2) as to maintain a probe inlet velocity of 90 fpm (0.46 m/s) or slightly higher.
- Laskin Nozzle aerosol generator or equivalent.

Procedure:

Main and Pass-through Chamber HEPA filters:

1. Turn on the Compounding Isolator blowers and lights.
2. Remove the HEPA filter diffuser screen(s) if present and where possible.
3. Introduce the aerosol in a manner that will create a well mixed aerosol upstream of the filter.
4. If a specific introduction location is needed to achieve a well mixed aerosol, that location should be documented by the device manufacturer.
5. Sample or calculate the upstream challenge and verify that a 10-90 µg per liter has been introduced.
6. Adjust the photometer to 100% based on the challenge levels used.
7. With the nozzle of the probe held not more than 1.0 inch (2.5 cm) from the area being tested, scan the entire downstream side of the HEPA filter(s), the perimeter of each filter pack and mounting frame by passing the photometer probe in slightly overlapping strokes at a traverse rate of not more than 2 inches (5.1 cm) per second when using a rectangular probe.
8. For filters that cannot be scanned, the manufacturer shall develop a test procedure that allows for probe testing at a location where adequate mixing and safety to the certifier can be achieved.

> **INFORMATIONAL NOTE**: *The manufacturer shall verify both temporal and spatial uniformity of challenge as outlined in IEST-RP-CC034* [8].

Acceptance Criteria:

For filters that can be scanned:

- Sustained aerosol penetration shall not exceed 0.01% of the upstream concentration.

For filters that cannot be scanned:

- Sustained aerosol penetration shall not exceed 0.005% of the upstream concentration.

Filter patch size shall not exceed 3% of the effective filter area of the side being patched. The maximum width of any one patch shall not exceed 1.5 inches (3.8 cm).

2.06 Particle Containment Integrity and Enclosure Leak Test:

Purpose:
This test is performed on Compounding Aseptic Containment Isolators only. This test can aid in determining the particle integrity of the cabinet construction joints, seams, access panels and seals, glove ports and entry/exit points into the main chamber or where elevated particle levels have been detected at or near the work surface and where other potential leak sources have been eliminated (e.g. damaged HEPA filters, damaged glove/gauntlet, etc.).

> **NOTE:** A suitable alternative test method to 2.06 is the AGS-G001–2007 Guideline for Gloveboxes [9] section # 9.6.2 Leak Detection. Acceptance criteria is less than or equal to 0.5% of the device volume per hour.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm.

Procedure –Compounding Aseptic Containment Isolators:

1. The isolator shall be operated at operational airflow.
2. Verify the background count in the testing room is at least 3,520,000 particles per cubic meter (ppcm) or 100,000 particles per cubic foot (ppcf). If the count is too low, elevate the background levels using an aerosol generator or smoke generator.
3. Scan interior of main chamber within 1 inch (2.5 cm) of surfaces using a scan rate of no more than 2 inches (5.1 cm) per second.
4. Areas of interest include:
    a) all welded or gasketed seams
    b) side glass gasket/seams
    c) pass-through chamber door seals
    d) glove ports perimeters and gloves
    e) front view screen gasket seals
    f) trash or sharps exit ports/chutes
    g) lights installed inside the main chamber
    h) any penetrations into the main chamber

Acceptance:

- Any detected leaks do not exceed ISO class 5 conditions of 3,520 particles per cubic meter (ppcm) at 0.5µm size particles and larger when the probe is held stationary within 1" (2.5 cm) of the leak.

> **INFORMATIONAL NOTE**:
> Elevating operating pressures during this test may aid in locating leak sources.
>
> This test is most effective when performed in uncontrolled environments (>3,520,000ppcm or >100,000ppcf).

2.07 Recovery Time Determination Test:

Purpose:
This test is performed to determine the amount of time it takes the main chamber to recover to ISO Class 5 particle levels after an event such as an open door or a surge of process generated contamination.

Apparatus:

- Laskin Nozzle aerosol generator or equivalent.
- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm and variable sample times.
- Time keeping device capable of reading in minutes and seconds.
- Particle sample probe cover.

Procedure:

1. Set the particle counter sample time to 6 second sample periods with a 14 second hold time in "Concentration" mode to report in particles per cubic meter or foot.
2. With the Compounding Isolator running, measure particle levels at the center of the work-surface of the main chamber.
3. Collect multiple samples to determine average baseline particle levels using 6 second samples.
4. Three consecutive baseline particle level samples should be established and noted.
5. Turn off particle counter sample pump and cover the particle counter sampling probe.
6. Turn off Compounding Isolator and fill the chamber with particulate using a Laskin nozzle generator set at 1 Laskin nozzle at 20 psi (138 kPa) for five seconds per cubic foot (per 0.028 cubic meter) of chamber interior space.
7. Turn on the Compounding Isolator and start timer.
8. To prevent sampling above the particle counter's coincidence loss rate or damaging the device, wait until the smoke is visibly cleared from the chamber and remove particle counter probe cover and begin sampling.
9. Maintained particle levels are achieved when three consecutive counts are at or below the originally determined baseline particle level.
10. Total recovery time is considered from Compounding Isolator blower turn-on time to the first particle count where maintained particle levels were achieved.

Acceptance criteria:

- The manufacturer will determine the appropriate acceptance criteria for their particular design. Recovery time will be expressed in minutes and seconds to recover to baseline from excursion.

2.08 Airflow Smoke Pattern Test:

Purpose:

This test determines that the airflow within the compounding chamber conforms to the manufacturer's design criteria.

- Airflow within the Direct Compounding Area is downward with no dead spots or refluxing in the Critical Site, that ambient air does not enter the chamber other than through the supply HEPA filter, and that once the air enters the Direct Compounding Area, it is removed to the returns without reentry.

Apparatus:

- A source of visible smoke that is generally neutrally buoyant

> **INFORMATIONAL NOTE:** *Chemical smoke tubes or glycol-based smoke generators are examples of acceptable smoke sources.*

Procedure:

1. Pass the smoke along the work area beginning 1 inch (2.5 cm) from all main chamber walls and view screens at a height determined to authenticate the purpose of test.

2. Pass smoke over gloves, gauntlets, IV bars, interior lights, or other extruding features that may be installed within the main chamber.

3. For Compounding Aseptic Containment Isolators, pay particular attention to all penetrations, pass-through door, trash disposal tubes and gloves where turbulence may occur or may indicate significant penetration of the Compounding Isolator.

Acceptance criteria:

- The smoke shall show smooth downflow with a minimum of dead spots or reflux (upward flow) at obstructions and across the critical work zone and it is removed to the returns without reentry.

2.09 Preparation Ingress and Egress Test:

Purpose:

This test is performed to determine if the Compounding Isolator pass-through system is capable of supporting material transfer while maintaining the designated cleanliness classification during the transfer.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm.
- Aerosol generator or smoke tubes.
- Empty perforated transfer tray.
- Time keeping device capable of reading in seconds.

Procedure:

1. Verify the background count in the testing room is at least 3,532,000 particles per cubic meter (ppcm) (100,000 particles per cubic foot (ppcf)).
2. If the count is too low, elevate the background levels using an aerosol generator or smoke generator.
3. Place the particle counter probe in the Main Chamber approximately 6 to 8 inches (15.2 to 20.3 cm) off the isolator floor surface, approximately 2 inches (5.1 cm) outside the normally used path of the inner pass-through chamber door swing and within the area that would be affected by the airflow caused by the movement of the door. Probe placement should be so that the operator's arms will not pass directly over the probe when removing material from the pass-through.
4. Verify the particle counts meet ISO Class 5 levels before beginning the test cycle.
5. Set the particle counter for a one minute count with no more than a one second hold time.
6. Open the outside pass-through door.
7. Place a perforated empty transfer tray into the pass-through and close the outer door.
8. Wait for the manufacturer's recommended purge time or start the purge cycle.
9. After completion of the purge cycle, open the inside pass-through door and move the transfer tray from the pass-through to the work area.
10. Close the inside pass-through door.
11. Document the particle counts during the transfer process and for a period of one minute after the transfer.

Acceptance Criteria:

- The particle counts shall not exceed the ISO Class 5 @ 0.5 µm and larger class limit at any time during this test.

2.10 Particle Count Tests:

Purpose:

This is a two part test and is performed to verify that the Compounding Isolator main chamber operates within ISO class 5 conditions at 0.5 µm and larger during Static (At-Rest) and Dynamic Operating (Operational) conditions to determine that air within the isolator and the immediate proximity of exposed sterilized preparation operations would be of appropriate particle quality during compounding operations. Air shall be sampled in a manner that characterizes the true level of extrinsic particle contamination to which the product is exposed. Classified pass-though chambers shall be tested in the Static (At Rest) state.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm.
- Clean surrogate materials and transfer tray

2.10A Procedure- Static Particle Level:

1. Sample ports compatible with particle counting equipment should be used to facilitate accurate and repeatable testing.
2. Determine particle locations per ISO 14644-1:1999. Note that a reasonable sample plan is one that addresses the entire work surface and may result in more than minimum sample locations allowed by ISO 14644-1:1999. An example of a reasonable plan for the Main Chamber is one where the locations are in each of the four corners (6" (15.2 cm) from interior walls) and one at the geometric center of the work-area. A reasonable sample plan for the Pass-through would be one location at the geometric center with a minimum of 3 samples.
3. Determine that particle sampling tube has been appropriately purged of particles.
4. Perform the particle counter background noise count rate (zero count) test prior to sampling.
5. The Compounding Isolator should be empty, clean, and safe for access when tested.
6. Position the particle counter isokinetic probe at the 1st location to sample the air as it reaches the clean zone, the probe height being typically no more than 12" (30.5 cm) above the work surface.
7. Operate the Compounding Isolator for a period of time appropriate for the design to clean up the work area.
8. Sample the assigned locations within the space.
9. Note the particle levels at the specified locations.

2.10B Procedure- Dynamic Operating Test (Monitoring):

1. Sample ports compatible with particle counting equipment should be used to facilitate accurate and repeatable testing.
2. Determine that particle sampling tube has been appropriately purged of particles.
3. Perform the particle counter background noise count rate (zero count) test prior to sampling.
4. Compounding Isolator should contain all of the cleaned surrogate compounding components that would support surrogate manipulation operation during the test.
5. Particle counter isokinetic probe location(s) should be placed near the direct compounding area where there is most potential risk to the exposed sterile preparation, containers, and closures. The particle counting probe should be placed in an orientation demonstrated to obtain a meaningful sample.
    a. Position the particle counter isokinetic probe within the airflow not more than 12 inches (30.5 cm) away from the location of the Critical Site within the Direct Compounding Area.
6. Purge the compounding isolator as specified in the operating procedures prior to conducting the particle count survey. If not specified in the operating procedures, allow the isolator to purge for 5 minutes.
7. To simulate actual preparation, perform surrogate manipulation using both gloves during particle testing to determine whether activity affects particle levels at the sample point.
8. Document the particle levels.

Acceptance Criteria:

- ISO 14644-1:1999 Class 5 at 0.5 µm and larger At Rest and Operational.

INFORMATIONAL NOTE:

- *Generally, conditions are met when none of the individual counts exceed the class limit or equivalent of 3,520 particles per cubic meter (ppcm) at 0.5µm size particles and larger.*
- *Where between 2 and 9 locations are sampled, a statistical analysis of the upper 95% confidence level (UCL) must confirm that sample levels fall within the acceptance criteria per ISO 14644-1:1999*

INFORMATIONAL NOTE:
When selecting a Discrete Particle Counter (DPC), the instrument should have the ability of displaying and recording the count and size of discrete particles in air with a size discrimination capability to detect the total particle concentration in the appropriate particle size ranges for the class under consideration. [5]

2.11A Volatile Hazardous Drug Containment Test -Total Exhaust Compounding Isolator:

Purpose:

This test [10] is to verify that Compounding Aseptic Containment Isolator properly connected to building exhaust provides worker protection from the escape of volatilized hazardous drugs during all aspects of compounding operations.

Apparatus:

- A calibrated Infrared Portable Ambient Air Analyzer, Electron Capture Device, or equivalent. Instrument shall be a continuous reading instrument for the tracer gas of choice. Range of detection shall be at least from 0.01 ppm (parts per million) to 100 ppm. The accuracy of the instrument shall be ± 10% of the reading for concentrations above 0.1 ppm and ± 25% for concentrations between 0.01 ppm and 0.1 ppm. The repeatability of the instrument shall be ± 1% of the reading at 50 ppm tracer gas concentration. The response time shall not exceed 10 seconds for 90% indication of actual concentration. The instrument shall not exhaust more than 50 lpm (liters per minute). The detectors shall be calibrated with a known concentration of tracer gas within 24 hours preceding a test. The method for calibration shall be those furnished or specified by the detector manufacturer and shall use the tracer gas that was selected as a standard. The analyzer shall have a strip chart recorder or data logger.
- Tracer Gas – Sulfur Hexafluoride (SF_6), (or a gas of similar molecular weight and stability, supplied from a cylinder capable of maintaining 30 psig (207 kPa) at the test release rate for at least one hour). The tracer gas release rate shall be 4.0 lpm. The tracer gas shall be commercial grade or reagent grade. Since the detection instrument is calibrated by the actual tracer gas, a 100% pure gas is not required. Low-grade mixtures are inappropriate since they significantly reduce the limit of detection for the test.
- Tracer Gas Ejector System - The tracer gas is piped to the ejector. The trace gas passes through a critical orifice, entrains air through the holes in the side of the ejector tube, and is distributed through a wire mesh outlet diffuser.
- Critical Orifice - the flow rate of the tracer gas is determined by the upstream pressure and size of the orifice. The size for the orifice using sulfur hexafluoride as tracer gas, at a flow rate of 4.0 lpm and a nominal upstream pressure of 30 psig (207 kPa) is 0.025 inches (0.635 mm). The orifice size and pressure will give the approximate flow rate of tracer gas; however, the actual flow rate must be measured. Convert the measured value to standard conditions: 70°F (21.1°C) at one atmosphere. The ejector system release rate shall be calibrated within 24 hours preceding a test and each time the orifice plate is changed.
- Flow meter - capability of reading 4 lpm, accuracy of ± 3% of full scale or better calibrated per manufacturer's specifications.
- Pressure Gauge - capability of reading 30 psig (207 kPa), accuracy of ± 2% of full scale calibrated per manufacturer's specifications.
- Surrogate materials and transfer tray.

INFORMATIONAL NOTE: For compounding of volatile drugs, Compounding Aseptic Containment Isolators which use negative pressure plenums and ducts are preferred. For those compounding isolators with positive pressure plenums or ducts, the seam leak test of step #6 should also be performed along all duct connections and plenum seams.

Procedure:

1. Place surrogate materials into main chamber via pass-through chamber.
2. Record room background levels of SF_6 (or tracer gas).
3. Activate SF_6 gas flow and verify 4 LPM flow rate through ejector within isolator.
4. Perform surrogate manipulations.
5. Upon conclusion of surrogate manipulation, stop SF_6 gas flow and place surrogate materials in pass-through chamber.
6. Seal inner door and follow established purge time.
7. Upon completion of established purge time, open exterior pass-through door and retrieve surrogate preparation.
8. Tester takes SF_6 samples at the least favorable position within 1" (2.5 cm) of exterior pass-through chamber door based on Isolator design (i.e. measure just below door on static pass-through or measure just above door on integral vertical flow pass-through).
9. Remove materials from pass-through chamber.
10. Document results.

Acceptance Criteria:

- Tracer gas concentration level shall not exceed 0.01 ppm at any time during these tests.

2.11B Volatile Hazardous Drug Containment Test-Partial-Recirculating Compounding Isolator:

Purpose:
This test [10] is to verify that the partial-recirculating Compounding Aseptic Containment Isolator that is properly connected to building exhaust system provides personnel protection from the escape of volatilized hazardous drugs during all aspects of compounding operations. Due to its design, any volatiles released in the workzone will partially recirculate and partially exhaust from the building.

Apparatus:

- A calibrated Infrared Portable Ambient Air Analyzer, Electron Capture Device, or equivalent. Instrument shall be a continuous reading instrument for the tracer gas of choice. Range of detection shall be at least from 0.01 ppm (parts per million) to 100 ppm. The accuracy of the instrument shall be ± 10% of the reading for concentrations above 0.1 ppm and ± 25% for concentrations between 0.01 ppm and 0.1 ppm. The repeatability of the instrument shall be ± 1% of the reading at 50 ppm tracer gas concentration. The response time shall not exceed 10 seconds for 90% indication of actual concentration. The instrument shall not exhaust more than 50 lpm (liters per minute). The detectors shall be calibrated with a known concentration of tracer gas within 24 hours preceding a test. The method for calibration shall be those furnished or specified by the detector manufacturer and shall use the tracer gas that was selected as a standard. The analyzer shall have a strip chart recorder or data logger.
- Tracer Gas – Sulfur Hexafluoride (SF_6), (or a gas of similar molecular weight and stability, supplied from a cylinder capable of maintaining 30 psig (207 kPa) at the test release rate for at least one hour). The tracer gas release rate shall be 4.0 lpm. The tracer gas shall be commercial grade or reagent grade. Since the detection instrument is calibrated by the actual tracer gas, a 100% pure gas is not required. Low-grade mixtures are inappropriate since they significantly reduce the limit of detection for the test.

- Tracer Gas Ejector System - The tracer gas is piped to the ejector. The trace gas passes through a critical orifice, entrains air through the holes in the side of the ejector tube, and is distributed through a wire mesh outlet diffuser.
- Critical Orifice - the flow rate of the tracer gas is determined by the upstream pressure and size of the orifice. The size for the orifice using sulfur hexafluoride as tracer gas, at a flow rate of 4.0 lpm and a nominal upstream pressure of 30 psig (207 kPa) is 0.025 inches (0.635 mm). The orifice size and pressure will give the approximate flow rate of tracer gas; however, the actual flow rate must be measured. Convert the measured value to standard conditions: 70°F (21.1°C) at one atmosphere. The ejector system release rate shall be calibrated within 24 hours preceding a test and each time the orifice plate is changed.
- Flow meter - capability of reading 4 lpm, accuracy of ± 3% of full scale or better calibrated per manufacturer's specifications.
- Pressure Gauge - capability of reading 30 psig (207 kPa), accuracy of ± 2% of full scale calibrated per manufacturer's specifications.
- 60 mL syringe filled with tracer gas Sulfur Hexafluoride (SF_6) (or a gas of similar molecular weight and stability) and placed within a sealed plastic bag.

Procedures:

1. Place sealed plastic bag containing SF_6 gas-filled 60 mL syringe in main chamber.
2. Record room background levels of SF_6.
3. Perform surrogate manipulation by opening bag and releasing 60 mL of tracer gas into workzone. Start timer upon release of tracer gas. Place syringe back into bag and seal. Place sealed bag into pass-through chamber, then open outer pass-through door and remove bag.
4. Operator places analyzer detector in least favorable position within 1" (2.5 cm) of exterior pass-through chamber door based on Isolator design. (i.e. measure just below door on static pass-through or measure just above door on integral vertical flow pass-through).

> NOTE: Either a main chamber or pass-through chamber purge or delay time may be required to meet acceptance criteria. Repeat Phase 2 with adequate purge or delay time until acceptance criteria is met.

Acceptance Criteria:

- SF_6 concentration level shall not exceed 0.01 ppm at any time during these tests.

INFORMATIONAL NOTE:
With the test results, a risk analysis can be performed for the hazardous drug preparation process equating amount of volatiles generated by the hazardous drug compounding process to purge time required for the safe removal of compounded materials.

To assure personnel protection, the test uses a known quantity of volatile tracer gas (SF_6), released into the main chamber airstream, while monitoring the material transfer process for tracer gas just outside the external interchange door. The test is designed to determine the volatile purge time based on the known release volume.

The NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings (2004) [11] recommends against the use of recirculating cabinets for the manipulation of volatile hazardous drugs. This test procedure should not be misconstrued as an endorsement of recirculating isolators with volatile drugs.

2.12 Hazardous Particle Containment Test:

Purpose: This test is to verify that Compounding Aseptic Containment Isolator provides worker protection from the escape of hazardous drug particles during all aspects of compounding operations.

NOTE: This test is not required if Section 2.11A or 11B is successfully completed.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm.
- A calibrated aerosol photometer capable of indicating 100% upstream concentration with an aerosol of between 10 and 90 µg per liter of polydispersed dioctylphthalate (DOP), polyalphaolefin (PAO) or an equivalent fluid. Unit must have a threshold sensitivity of at least 10^{-3} micrograms per liter and be capable of measuring concentrations over a range of 10^5 times the threshold sensitivity. The sampling rate shall be 1 CFM (28.3 lpm) (±10%) with an inlet probe having sufficient area (1.7 square inches) (11.0 cm^2) as to maintain a probe inlet velocity of 90 fpm (0.46 m/s) or slightly higher.
- Laskin Nozzle aerosol generator or equivalent.
- Aerosol diffuser (shown in Figure 1 below)
- Particle diluter.
- Time keeping device capable of reading in minutes and seconds.
- Cleaned preparation transfer tray and safe surrogate compounding manipulation materials.

Figure 1

INFORMATIONAL NOTE:
The aerosol diffuser is used to reduce turbulence caused by the aerosol generator within the isolator chamber.

The diffuser should be centered between the glove ports and centered between the back wall and the view screen.

Procedure:

Operational test – material transfer test:

1. This test should be performed in a controlled atmosphere such as a cleanroom. The interior of isolator main and pass-through chambers should be clean.
2. Place the aerosol diffuser in the isolator main chamber and connect to the aerosol generator.
3. Operate the isolator normally.
4. Place cleaned preparations transfer tray and safe surrogate materials via the pass-through into the main chamber.
5. Activate aerosol supply.
6. Perform surrogate manipulations.

7. Upon conclusion of surrogate manipulations, stop aerosol generator.
8. Place surrogate materials and tray into pass-through chamber and follow established purge time using time keeping device to verify.
9. With the particle counter (with installed particle diluter), and photometer test probes, 2.5" (6.4 cm) directly under the center of the door swing of the exterior pass-through door, monitor particle levels, remove materials and transfer tray from pass-through chamber via exterior door.
10. Record the particle counts at 0.5 µm and larger (calculate actual particle levels based upon diluter rating) and photometer readings as the materials are removed from the pass-through chamber and for a period of 30 seconds after the door is closed. Verify that arm movement in opening the door does not create a particle stream.

> INFORMATIONAL NOTE: To avoid the impact of arm movement creating a particle stream when opening the door, a non-shedding remote handle or door handle actuator should be considered.

Acceptance Criteria:

- No elevation in particle level during completion of transfer process.

2.13 Pass-through Particle Purge Time Determination Test:

Purpose:

This test is to determine the appropriate purge cycle time to be used after placing materials in the pass-through prior to transferring them into or out of the main chamber.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm.
- A source of visible smoke that is generally neutrally buoyant or aerosol particulate detectible by the particle counter. Source is to be determined by the manufacturer.

Procedure for non-unidirectional "Purge" and static pass-through designs:

1. Place the particle counter probe at the geometric center of the pass-through work surface at a height of 6" (15.2 cm).
2. Place a transfer basket on the pass-through work surface.
3. Measure the ambient particle count concentration in the pass-through.

> **NOTE:** If the ambient count at 0.5 µm and larger is not above the equivalent of 3,520,000 ppcm, elevate the counts using smoke or particulate source to achieve at least this level.

4. Initiate purge and particle count cycles simultaneously.
5. Three second particle count samples in concentration mode (normalized to particles per cubic meter) with a one second delay to be taken until counts are at manufacturer's recommended levels for material transfer into the main chamber. This will usually be less than the equivalent of 3,520 ppcm at 0.5 µm and larger particle sizes.
6. Document the time required to get to the manufacturer's recommended levels. This time period will be communicated to the end user in the owner's manual.

Procedure for "constant operation" unidirectional and non-unidirectional pass-through designs:

1. Establish a background room ambient particle concentration at least equivalent to 3,520,000 ppcm at 0.5 µm and larger. Document the background count.
2. Place the particle counter probe at the geometric center of the pass-through work surface at a height of 6" (15.2 cm).
3. Open the outer pass-through door and place a transfer basket on the pass-through work surface.
4. Initiate particle count cycle immediately after closing the outer pass-through door.
5. Three second particle count samples in concentration mode (normalized to particles per cubic meter) with a one second delay to be taken until counts are at manufacturer's recommended levels for material transfer into the main chamber. This will usually be less than the equivalent of 3,520 ppcm at 0.5 µm and larger particle sizes.
6. Document the time required to get to the manufacturer's recommended levels. This time period will be communicated to the end user in the owner's manual.

Acceptance Criteria:

- The maximum acceptable purge time shall be determined by the manufacturer and confirmed using this procedure.

3.0 Reference Material:

[1] USP 32-NF27: United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, www.usp.org.

[2] CAG-001-2005 *(revised 12/08/2008*): 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, www.cetainternational.org.

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

[4] MIL-STD-282: MIL/QQ (Military Standard) Standardization Document Order Desk, 700 Robbins Ave, Bldg 4, Section D, Philadelphia, PA 19111-5094, http//.dodssp.daps.dla.mil.

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

[6] NSF/ANSI 49-2008: Class II (laminar flow) Biosafety Cabinetry, NSF International, P.O. Box 130140, Ann Arbor, MI 48113-0140, www.nsf.org.

[7] ANSI/AIHA Z9.5-2003: American Industrial Hygiene Association, 2700 Prosperity Ave., Suite 250, Fairfax, VA 22031, www.aiha.org

[8] 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, USA, www.iest.org.

[9] AGS-G001 – 2007, 2nd Edition: Guideline for Gloveboxes, American Glovebox Society, P.O. Box 9099, Santa Rosa, CA 95405, www.gloveboxsociety.org.

[10] ANSI/ASHRAE 110-1995: Method of Testing Performance of Laboratory Fume Hoods, American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. 1791 Tullie Circle, NE, Atlanta, GA 30329, www.ashrae.org.

[11] NIOSH Alert for Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings, Department of Health and Human Services, CDC, NIOSH, NIOSH – Publications dissemination, 4676 Columbia Parkway, Cincinnati, OH 45226-1998, www.cdc.gov/niosh.

APPENDIX:

The following is an example of surrogate compounding procedures used during Dynamic Particle Counting procedures (2.10B).

Supplies:

- 2 x 10 mL syringe with needle
- 1 x 20 mL Sterile Water for Injection (SWFI) vial
- 1 x 100 mL bag of Dextrose 5% Water (D5W/NS) or 0.9% Sodium Chloride
- 4 Sterile Alcohol wipes
- Isopropyl Alcohol (IPA) or equivalent disinfectant
- 1 blank label (to be affixed to the bag prior to placing into pass-through)

1) All supplies introduced into the isolator environment for immediate compounding, are to be picked from the warehouse or inventory area. All products will be removed from their master cartons (non-laminated or corrugated cardboard), or non-plastic over wrap prior to leaving the warehouse or inventory area.
2) After inspection, the products and/or supplies are transferred into the isolator pass-through in plastic bin or tote.
3) The operator will insert hands into glove ports of the isolator, seat hands in gloves; disinfect the gloves with an appropriate disinfectant (IPA).
4) The operator will disinfect the interior surfaces of the primary compounding chamber with an appropriate disinfectant and allow the surfaces to dry after establishing that it is safe to do so where flammable materials are used.
5) The operator will open the interior pass-through door, retrieve the bin/tote, close the pass-through door and place the bin/tote in corner of isolator, gather supplies out of bin/tote, and place immediately in front of the operator.
    a. Open one syringe by separating the two halves of the packaging, by slowly peeling the paper half, from the plastic outer wrap, laying the syringe onto the work surface (place packaging in the bin/tote).
    b. Remove the cap of the SWFI vial and disinfect with IPA pad (place pad and packaging in bin/tote after use).
    c. Pick up the syringe with the free dominant hand.
    d. Utilizing just the pinkie finger of the non-dominant hand, dislodge the needle cap, and pierce the septum of the vial and withdraw 3 mL of SWFI.
    e. Remove needle for vial and transfer the SWFI from the syringe into the 100 mL bag of D5W/NS.
    f. Repeat the transfer from the vial into the bag for a total of 5 injections.
6) Upon completion of transfers, place 100 mL bag onto the work surface.
7) Place the syringe and vial of SWFI in the bin/tote.
8) Peel back label and label 100 mL bag with blank label.
9) Place the labeled bag and label backing into the bin/tote.
10) Pick up the bin/tote and open inner pass-through door and place bin/tote into pass-through.
11) Disinfect the interior surfaces of the isolator with the appropriate disinfecting agent.
12) Place cleaning wipes and waste in the pass-through or trash disposal port.
13) Operator will remove hands from glove ports and retrieve bin/tote from pass-through via the outer pass-through door.

CETA High Efficiency Filter Application Guide
CAG-006-2010
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Purpose

The following are recommended guidelines for the selection, procurement, handling, and replacement of high efficiency filters for biosafety cabinets, isolators and laminar flow cabinets. These guidelines are intended to supplement the filter specification portion of the CETA Specification Guide for HEPA and ULPA filters procured for field replacement applications. The information enclosed is also intended to provide additional information regarding general filter guidelines for field applications.

Successful Application of Filters

High Efficiency filters are not a commodity item and must be carefully selected and handled. It is important to specify and install the *correct* filter for each application

- Understand the filter requirements for every application. If you are not certain consult the CETA Specification Guide for performance specifics. You can also request the assistance, and obtain the necessary information from the equipment manufacturer or a filter distributor.
- Factors needing to be met include correct type, size, proper efficiency, leak criteria, volumetric flow, resistance, and the ability to maintain performance required within environments that may include corrosive elements, high temperature, excessive moisture or other elements within the specific environment.
- Correct specification, ordering, receiving, handling, storage, returning (if required), installation and proper validation is a critical part of the service you perform.

Knowledge is power when it concerns correct filter installation. Know the customers requirements and the equipment manufacturers' specifications and follow the CETA Specification Guide.

Filter Qualification

It is recommended that high efficiency filters supplied for use in NSF qualified cabinets be manufactured and shipped under a quality assurance (QA) program that meets the requirements of ASME-NQA-1 or a registered ISO 9001 quality control system.

General Construction Requirements:

If required, the selected filter should be adequately supported with the use of pack stiffeners at a minimum of every (30) inches of filter length. Excessive weight or other shock pressure on the unsupported frame can cause the frame to bow inward, kinking or tearing the filter media.

- High efficiency filters can become out of square relatively easily through improper support during shipping or handling and may not fit within the cabinet. Filter racking can contribute to breaking the sealant from the filter frame and corners and potentially tearing the media due to the outside stress.

- Filter frames should be of the appropriate material thickness as outlined in IEST-RP-CC001, Section 6 Allowable Materials so it is sufficiently rigid for the application based on the filter overall size. Frame bowing and flexing from insufficient frame support will cause stress on the pleated media, causing it to tear away from the adhesive or create a hole or tear in the media itself.
- Assure the applicable flammability rating requirements are met for the filter and its components as appropriate for each cabinet listing.
- Refer to IEST-RP-CC001, HEPA and ULPA Filter reference standard for recommended filter performance level, type, grade, design, performance, construction requirements, testing and appropriate labeling data.
- Ability to maintain performance within the intended environment without compromising the filter integrity required. Environmental factors may include corrosive fumes or compounds, prolonged high temperature or excessive moisture within the airstream which may attack the filter media, gasket material, adhesive sealants or frame material. Understand the filter limitations for each environment.

Factory Filter Testing and Labeling:

Each filter obtained and designated for use should be 100% tested for penetration and resistance using the test methods as described in Section 9 Testing in IEST RP-CC001 standard. In addition, scan testing of each filter for leaks for filter types C,D,E,F,G,H,I, K and K must be performed per IEST-RP-CC034 standard as in the chart below.

	Penetration Test		Scan Test (see note)			Minimum
Filter type	Method	Aerosol	Method	Aerosol	Comments	efficiency rating
HEPA (Type A)	MIL-STD-282	Thermal DOP	None	None		99.97%
HEPA (Type B)	MIL-STD-282	Thermal DOP	None	None	Two-flow leak test	99.97%
HEPA (Type C)	MIL-STD-282	Thermal DOP	Photometer	Polydisperse DOP/PAO		99.99%
HEPA (Type D)	MIL-STD-282	Thermal DOP	Photometer	Polydisperse DOP/PAO		99.999% at 0.3 µm
HEPA (Type E)	MIL-STD-282	Thermal DOP	None	None	Two-flow leak test	99.97%
ULPA (Type F)	IEST-RP-CC007	Open	Particle counter or photometer*	Open		99.999% at 0.1–0.2 or 0.2–0.3 µm
Super ULPA (Type G)	IEST-RP-CC021**	Open	Particle counter	Open		99.9999% at 0.1–0.2 or 0.2–0.3 µm
HEPA (Type H)	IEST-RP-CC007	Open	Photometer	Polydisperse DOP/PAO		99.97% at 0.1–0.2 or 0.2–0.3 µm
HEPA (Type I)	IEST-RP-CC007	Open	None	Open	Two-flow leak test	99.97% at 0.1–0.2 or 0.2–0.3 µm
HEPA (Type J)	IEST-RP-CC007	Open	Particle counter or photometer	Polydisperse DOP/PAO		99.99% at 0.1–0.2 or 0.2–0.3 µm
ULPA (Type K)	IEST-RP-CC007	Open	Particle counter or photometer	Polydisperse DOP/PAO		99.995% at 0.1–0.2 or 0.2–0.3 µm

* This filter (Type F) may be leak-tested with either photometers or particle counters. When hand-scanning in the field, extra attention should be given to the dilution and count statistics.

** Filter medium tested at most penetrating particle size (MPPS) prior to filter assembly. These filters are not tested for overall penetration.
NOTE: Either of the two scan test methods or an alternative method may be used for filter Types C, D, F and G if agreed.

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

It is recommended that all filters be encapsulated within the factory test rig for both scan and penetration testing so the media to frame, frame corner joints, gasket joints and gasket to frame seal are all tested and inspected for potential leaks. At a minimum, the filter shall be encapsulated with the factory penetration test rig.

It is recommended that the appropriate IEST filter performance level classification from the table above is defined and listed on the filter label for field application.

HEPA/ULPA filter labels should contain the following information:

- Filter manufacturers part number
- Manufacturer's serial number and date of manufacture
- Filter size in exact dimensions
- Efficiency on aerosol size or MPPS as applicable, or penetration in % at rated flow.
- Resistance at filter rated flow (SCFM)
- Directional arrow for air flow and proper orientation at installation
- Applicable industry standards required as IEST Type, U.L. classification, etc.

Field Replacement Filter Guidelines

It is important to note that a filter that is currently installed within the equipment does not assure it is the correct one that was originally specified for the equipment or application. Check the manufacturer's specifications or original cabinet test report. This is usually located on the inside of a cabinet dress panel, but can also be requested from the equipment manufacturer, or referenced from the manufacturer's specification data within the CETA Specification Guide.

The arrow also indicates the direction for proper installation within the cabinet. The position of the media pack within the filter frame may be relative to performance and often intentionally positioned to allow plenum mixing space between the pack and the motor/ blower, allowing air to be dispersed downstream in a uniform manner. Installation of the filter must follow the direction of the filter airflow arrow on the filter label. The filter label must be visible from the front of the cabinet. The air directional arrow on the filter label should be in the same orientation when installing as the filter was tested at the factory.

Patching and Repairing Filters

Industry guidelines have been established for reference when filter patching or repair is required. Follow the recommended patch size guidelines below when attempting any filter repair.

ANSI /NSF49	IEST RP-034	IEST RP-001
3% max. of face area per side or 1.50" max. single patch width	Factory Repair 1% of the face area being patched 2 sq/in. max. per single repair area	Factory Repair 1% of the face area being patched or 2 sq/in.max. single repair area
	Field Repair 3% of face area per side or 1.50" width max. for single patch	

1. *ANSI/NSF 49 Biohazard Cabinetry: Design, Construction, Performance and Field Certification. www.nsf.org.*
2. *IEST-RP-CC001: HEPA and ULPA Filters, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008-3841, USA, www.iest.org*
3. *IEST-RP-CC034: 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*

Recommended Filter Repair Adhesives

- ANSI/NSF 49, Annex H.6 Sealants, recommends one part silicone base sealant compound, such as Dow Corning RTV 732 Adhesive Sealant, Dow Corning 781 Building Sealant, Dow Corning RTV 734 or RTV 112 self leveling sealants or equivalent is acceptable when used according to the manufacturer's recommendations.
- IEST-RP-CC001 notes filters may be patched with filter medium or adhesive. Some available sealants and adhesives that may be used to splice the filter medium or repair the filter, attach the gasket to the frame or seal the pack to the frame include polyurethane, epoxy, silicone or acrylic. Others may be used as agreed upon by customer and supplier.
- IEST-RP-CC034 notes that a repair material that is acceptable to the owner of the application should be used. Also recommending that suitable cure time be allowed for any adhesive used due to equipment measurement inaccuracy from potential adhesive off-gassing. Always followed by a re-scan of the area patched.

Filter Shipping and Storage Recommendations

Shipping Guidelines

- Filters should only be stored in their original cartons within a protective sleeve or with other adequate face protection.
- Store filters at ambient environmental conditions without a wide range of fluctuation in temperature or humidity. It is recommended that filters be stored in clean, dry locations at temperature range between 50 and100deg. F. and at humidity levels that does not exceed 95% relative humidity.
- Filters should always be packaged, shipped and stored in an orientation where the pleated media tips are vertical. Cartons should be well marked with a 'This End Up' arrow to insure that proper direction is maintained. Cartons should never, under any circumstances, be stored on their sides with the filter face down or on end with the pleats in a horizontal directional plane where it is possible for the media to sag over time, especially in a span over 30" in width. Inattention to these details may result in damage to the filter making it vulnerable to damage from additional stacking of filters or other items on it.
- If you are responsible for the return of a defective or incorrect filter, always use the same filter carton as was received with the filter. Do not try to pack and ship a filter in a box that is oversized from another application, or wrapping cardboard sheet around the filter, etc. No other container or method of packaging was designed for the specific purpose of protecting the specific filter size received and will most likely result in damage in shipping. If precautions are not taken when returning a filter, the manufacturer or distributor may not be able to either determine the cause of damage or restock the incorrect filter and issue a credit or replacement filter due to the damage that may have occurred.
- Never allow filters to hang over the edge of a skid or storage rack if stored for any period of time within a temporary storage or staging area. Get the filters to a safe storage area or placed within the equipment itself as soon as possible.
- As a general rule of good storage practice, filters 24" height and under should only be stacked three high due to safe weight restrictions on the frame. Filters 25" height and over should only be stacked only two high or damage may occur from excessive weight, especially over time.

Storage Guidelines

- Do not expose to dampness over 95% relative humidity, excessive heat > 120° F, rapid temperatures fluctuations. Never leave filters unattended, out-of-doors, or in an open area surrounded by high traffic or activity. Get the filters to the safest place possible as quickly as possible.
- If a filter has been stored for a prolonged period, carefully inspect both faces of the filter for small cracks, kinks or tears within the media, also for separation of the media at the adhesive and media or frame. Take a close look for cracking or fissures in the adhesive at the frame that may denote chemical or other physical interaction with the adhesive over time.

Receiving HEPA/ULPA Filters:

Carefully compare the filter received with the purchase order specifications

- Are there any labeled differences between the products received vs. what is within the purchase order callout? This can be things as filter type, classification, efficiency, resistance and flow rate, etc.
- Sign for the filter skids or pallets with the carrier, noting any visual damage on the bill of lading. Digital photos of the damaged area and filter label itself are highly recommended for quick product disposition and records.
- If a filter has arrived in damaged condition, contact the filter distributor or manufacturer and provide them with a thorough description, with as many details as are possible to describe the issue or problem. This greatly speeds up the filter disposition process by accelerating communications and allowing things to be processed more efficiently and effectively. Always obtain a return authorization number before proceeding.
- Do not leave filters unattended before properly storing in a safe area, or installing the filter within the cabinet for protection.

Removing HEPA/ULPA Filters from Pallets and Cartons

- When removing the filter from the box, open the top of the box and bend the flaps back. Gently turn the box upside down with the opening on the floor. Lift the box off the filter and remove any packaging material from the filter. Do not lift the filter from the carton; you may damage the media with your fingers.
- If a filter is equipped with a removal strap, you may carefully use this to lift the filter from the box, or slide the filter out from a side opening orientation, being careful to grasp the frame only.
- When handling, grasp the filter only on outside surface of the frame, never touch the fragile filter glass media.

Inspecting the Filter Prior to Installation:

- Review both faces of the high efficiency filter carefully for punctures, tears and scuffs across the media face.
- Closely review where the media is sealed to the frame on all four sides of both faces for tears or small cracks in the adhesive.

- Inspect the pleated media tips carefully for cracks, drag or scuff marks, as this is the most vulnerable area of the media due to exposure.
- By using a powerful fluorescent or incandescent trouble light placed on the opposing side of the filter media in a darkened area, you can easily observe small cracks, tears and deformities to repair. A light table works very well, if one is available.
- Carefully inspect the gasket around the filter frame to make sure it is continuous and unbroken. Also check for gasket adhesion, cracking, or fissures that could occur from age. Inspect the gasket surface for tears or missing pieces that may have occurred when removing the filter out of the carton or in subsequent handling.

Installation of High Efficiency Filters within the Equipment:

- Use two people to move or install if the size is greater than 30”x36”. There can easily be too many obstacles present in ones path to avoid when trying to move the filter with limited visibility when trying to move the filter and still handle it protectively.
- Handle the filter only by the outside of the frame itself. Never allow your fingers, parts of your body or your clothing to brush against the media when handling.
- Inspect the cabinet clamping or sealing mechanisms used in retaining and sealing the filter for any damage before installing the filter and risking additional filter damage in multiple handling.
- Never exert pressure on the center area of a filter frame when lifting, sliding or positioning the filter into the cabinet or grid. You may kink and collapse the media. When installing in equipment where horizontal application is required, always push at the rigid frame corners to slide the filter into the sealing and containment mechanism.

Recommended Shelf-life and Replacement for High Efficiency Filters:

The initial filter efficiency will be its lowest. Particulate loading allows the filter to become more efficient as it is used within the cabinet. Generally cabinet balance, increased decibel level and cost of operation will dictate when a filter change is likely required.

- High Efficiency filters will gradually accumulate airborne particulate matter from the room and from work performed in the enclosure. The rate of accumulation will depend upon the cleanliness of the room air, the amount of time the enclosure is operating, and the nature of work being done. When in a normal lab service area, with proper handling and maintenance, the HEPA filters will conservatively last three to five years before requiring replacement or if the cabinet is moved per ANSI/NSF recommendations.
- In most cases, it is an individual matter for each certifier and their customers to establish their specific recommended practices and to use common sense when reviewing procedures and practices regarding the filters in use within each facility. Filters should always be periodically reviewed and re-tested as part of a quality initiative to check the condition of the filter components as well as the filter’s performance on a regularly scheduled basis. This is generally at a time when the filter is accessible during re-certification of the cabinet.
- High humidity and moisture will increase the overall resistance of a HEPA/ULPA filter when water droplets or spray form within the airstream and collect to a point of saturation on the filter media. Moisture will block the effectiveness of the airflow and eventually disintegrate the media structure by breaking down the latex based adhesives used to provide structure for the media fibers. If the high efficiency filter accidentally becomes wet through water spray or other source,

it should be taken out of service and allowed to dry. It should always be re-scanned and carefully reviewed before being returned to service.

- HEPA and ULPA filters are monitored for pressure drop across the filter media. Once the filter resistance becomes unacceptable, the filter must be replaced. On models equipped with a pressure gauge, HEPA or ULPA filter replacement may be necessary if the pressure drop across the HEPA or ULPA filter increases 100% above the initial value, with clean pre-filters in place and the cabinet speed control set at the maximum level as noted in IEST-RP-CC002, Unidirectional Flow Clean Air Devices in Appendix C2.

Extending High Efficiency Filter Life:

Life expectancy of the HEPA/ULPA depends on several important factors, these being careful handling, controlled environmental conditions within the equipment or the room environment.

- Environmental conditions of critical importance are application temperature, humidity, chemical resistance and particle concentration
- Protective grill screen(s) on filters protect the fragile media during handling, installation and operation. These screens also add a great deal of stiffness and rigidity to the overall filter assembly.
- The addition of lower efficiency pre-filters upstream of the HEPA/ULPA filter extends the life of the HEPA/ULPA filter. Always replace the pre-filters if used as required or at regular intervals.
- HEPA/ULPA filters cannot be cleaned by washing or back flushing with compressed air due to their delicate fiber structure of the media. Once the filter becomes too restrictive (pressure drop to great) due to particulate loading and proper flow adjustment of the equipment cannot be obtained, it must be replaced.

Acknowledgements

1. *ANSI/NSF 49-2009 Biohazard Cabinetry: Design, Construction, Performance and Field Certification. www.nsf.org.*
2. *IEST-RP-CC001: HEPA and ULPA Filters, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008-3841, USA, www.iest.org*
3. *IEST-RP-CC034: 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*
4. *ASME NQA-1 American Society of Mechanical Engineers, Three Park Avenue, New York, New York 10016*

CETA Application Guide for the use of Surface Decontaminants in Biosafety Cabinets
CAG-004-2007
January 30, 2007

1.0 Background

When presented with the task of surface decontaminating a Biosafety Cabinet (BSC), the certifier faces a wide variety of biological agents, and a number of chemical solutions to inactivate them. Further information on the different biological agents can be found in the *References* section of this Applications Guide.

2.0 Agents

The following list represents the significant types of agents that may be found in Biosafety Cabinets. They are listed as the most resistant to chemical decontaminants first, to the most sensitive agent at the bottom.

2.1 Prions – Prions are a type of infectious agent composed only of proteins, and are extremely resistant to most chemicals.

2.2 Bacterial endospores - Thick-walled dormant form of some bacteria. They are more resistant than vegetative bacteria to chemicals, UV light, drying and heat.

2.3 Protozoan cysts (oocysts) - *Cryptosporidium* and *Giardia* are two genera of protozoa that infect the intestinal epithelial cells. They are shed in the feces as a resistant cyst (oocyst). Both are resistant to many disinfectants.

2.4 Mycobacteria - A genus of bacteria that contains higher concentrations of lipids (fats) in their cell wall. This makes them more resistant to many disinfectants. The most notorious member of this genus is *M. tuberculosis*.

2.5 Non-enveloped (naked) viruses - Are composed of a protein coat and genetic material, such as Adenovirus or Polio. These viruses are generally more resistant to disinfectants and dessication (drying) than viruses that have a lipid envelope.

2.6 Fungi and fungal spores - Fungi are plant-like organisms that lack chlorophyll and do not photosynthesize. In nature, fungi usually live on dead tissue, but some can also infect living organisms. Examples include mushrooms, yeast or filamentous (mold). Many fungi also generate spores, but they are not as resistant as bacterial endospores.

2.7 Vegetative bacteria - Metabolically active bacteria are called vegetative. A major classification of bacterial is based on the structure of the cell wall. Two major groups, Gram positive and Gram negative are identified by a staining procedure. Their different cell walls affect their sensitivity to disinfectants, with gram negative bacteria slightly more resistant to most disinfectants.

2.8 Enveloped viruses - Viruses that are have a lipid membrane around their protein coat, such as HIV or influenza. These viruses are generally less resistant to disinfectants and dessication than naked viruses-destroy the lipid membrane, and the virus is no longer infectious.

3.0 Definitions

Sterilants can kill all microbes, spores and viruses, given enough time.
High-Level disinfectants kill all viruses and vegetative cells, but they may not kill endospores reliably.
Intermediate-Level disinfectants destroy all vegetative cells including Mycobacteria, fungi, and most, but not all viruses. They cannot kill endospores.
Low-Level (General Purpose) disinfectants destroy vegetative bacteria, except Mycobacteria, fungi and non-enveloped viruses

4.0 Types of Disinfectants commonly used in BSCs

4.1 Gluteraldehyde
4.2 Peroxide/Peracetic acid
4.3 Chlorine dioxide
4.4 Halogens
4.5 Chlorine (sodium hypochlorite)
4.6 Iodine
4.7 Alcohols (Isopropyl or ethanol)
4.8 Phenolics
4.9 Quaternary ammonium compounds

5.0 Precautions

When handling, using, or disposing of chemical decontaminants, always follow the instructions on the product label

6.0 Applications Matrix

The attached matrix outlines the properties, efficacy and characteristics of the decontaminants listed in Part 7.0.

Controlled Environment Testing Association
1500 Sunday Drive, Suite 102, Raleigh, NC 27607
Phone: 919-861-5576 • Fax: 919-787-4916 Email: info@cetainternational.org

7.0 Properties of Common Liquid Surface Decontaminants

Decontaminant	Gluteraldehyde	Peroxide/ Peracetic acid/ Acetic acid	Chlorine Dioxide	Chlorine	Iodophor	Alcohol	Phenolic	Quaternary Ammonium Compounds
Classification	Sterilant	Sterilant	Sterilant	High Level	Intermediate	Intermediate	Intermediate	Low Level
Parameters for use:								
Concentration	2%	1%	1:5:1 / 100-1000 ppm	0.01-5%	0.5-2.5%	70-85%	0.2-3%	0.1-2%
Contact time (min.)	10-600	10-720	10-600	10-30	10-30	10-30	10-30	10-30
Stability > 1 week[1]	+		+		+	+	+	+
Agents:								
Bacterial Endospores	+	+	+	+/-				
Naked Viruses	+	+	+	+	+/- [2]	+/- [2]	+/- [2]	
Mycobacterium	+	+	+	+	+	+	+	
Vegetative Bacteria	+	+	+	+	+	+	+	+
Enveloped Viruses	+	+	+	+	+	+	+	+
Characteristics:								
Inactivated by Organics		+		+	+	+	+/-	+
Residual	+	+	+	+/-	+		+	
Corrosive		+		+	+		+	
Flammable						+		
Skin Irritant	+	+	+	+	+		+	
Eye Irritant	+	+	+	+	+	+	+	
Respiratory Irritant	+	+	+	+	+	+	+/-	
Toxic	+	+	+	+	+	+	+	+
Use in BSCs:								
Routine Surface Decon				+/-	+	+		+
Biohazardous Spill		+/-	+	+/-	+		+	+/-

1- Protected from light and air
2- Results vary depending on the virus

The information contained herein is for the use of appropriately trained certifiers. Although the information, opinions and recommendations contained herein are compiled from sources believed to be reliable, CETA, its officers, and its members accept no responsibility for the accuracy, sufficiency, or reliability or for any loss or injury resulting from the use of the information. Newly discovered hazards are frequent and this information may not be completely up to date.

Controlled Environment Testing Association
1500 Sunday Drive, Suite 102, Raleigh, NC 27607
Phone: 919-861-5576 • Fax: 919-787-4916 Email: info@cetainternational.org

7.1 Liquid Surface Decontaminant Resources

Hydrogen peroxide/Peracetic acid/Acetic acid
Spor-Klenz® – Available from Steris Corporation. On the web at: www.steris.com
Decon-Spore 200 Plus® - Available from Veltek Associates Inc. 15 Lee Boulevard Malvern, PA 19355 Phone: 610-644-8335 On the web at: http://www.sterile.com
Chlorine Dioxide
2-part liquid-
Clidox-S® – Available from Pharmacal Research Laboratories, P.O.Box 369 Naugatuck, CT. 06770 Phone: 1-800-243-5350 On the web at: www.pharmacal.com
Tablets/Powders-
Virkon-S – Available from Pharmacal
Exterm – Available from Clordisys Solutions, Inc. P.O. Box 549 Lebanon, NJ 08833 Phone: (908) 236-4100 On the web at: http://www.clordisys.com
Gluteraldehyde
Cidex® Johnson & Johnson, Advanced Sterilization Products. On the web at: http://www.jnjgateway.com/index.jhtml?_requestid=883947
Sodium Hypochlorite
In prepackaged spray - Bleach-Rite® by Current Technologies 1-800-456-4022 In prepackaged towelettes – Hype–Wipe® by Current Technologies
Iodophors
Wescodyne® – Available from Steris Corporation.
Alcohol
Ethanol - Liquid Sanihol 70® – Decon Laboratories, Inc. 460 Glennie Circle King of Prussia, PA 19406 (800) 332-6647
Isopropyl - Liquid- CiDehol 70®- *Decon Laboratories, Inc.*
Towelettes-
CiDehol® 70 Wipes - *Decon Laboratories, Inc.*
Phenolics
Vesphene® - Available from Steris Corporation
Hil-Phene® - Hillyard, Inc. 302 North 4th Street P.O. Box 909 St. Joseph, Missouri 64501 800-365-1555 On the web at: **http://www.hillyard.com**
Quaternary Ammonium Compounds
Liquid - Conflikt® - *Decon Laboratories, Inc.*
Aerosol - End-Bac II® - Johnson Diversey Inc. On the web at: **http://www.johnsondiversey.com/Cultures/en/default.htm**

References
Disinfection, Sterilization, and Preservation (Hardcover)
by Seymour S. Block (editor) 5th edition, Lippincott, Williams & Wilkins 2001

Biological Safety: Principles and Practices (Hardcover)
by Diane O. Fleming (Editor), Debra Long Hunt (Editor) 3rd edition, ASM Press 2000

The Foundations of Laboratory Safety: A Guide for the Biomedical Laboratory (Brock/Springer Series in Contemporary Bioscience) Stephen R. Rayburn 1990

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Clinical Laboratory Improvement Amendments (CLIA)

How to Obtain a CLIA Certificate

When is a CLIA Certificate Required?

NOTE: Congress passed the Clinical Laboratory Improvement Amendments (CLIA) in 1988 establishing quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed. The final CLIA regulations were published in the Federal Register on February 28, 1992. The requirements are based on the complexity of the test and not the type of laboratory where the testing is performed. On January 24, 2003, the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare & Medicaid Services (CMS) published final CLIA Quality Systems laboratory regulations that became effective April, 24, 2003.

DO I NEED TO HAVE A CLIA CERTIFICATE?

CLIA requires all facilities that perform even one test, including waived tests, on "materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" to meet certain Federal requirements. If a facility performs tests for these purposes, it is considered a laboratory under CLIA and must apply and obtain a certificate from the CLIA program that corresponds to the complexity of tests performed.

WHAT ARE THE DIFFERENT TYPES OF CLIA CERTIFICATES AND HOW LONG ARE THEY EFFECTIVE?

All types of certificates are effective for two years and the different types of certificates are:

- **Certificate of Waiver (COW):**
  Issued to a laboratory that performs only waived tests.
- **Certificate for Provider Performed Microscopy (PPM) procedures:**
  Issued to a laboratory in which a physician, midlevel practitioner or dentist performs specific microscopy procedures during the course of a patient's visit. A limited list of microscopy procedures is included under this certificate type and these are categorized as moderate complexity.
- **Certificate of Registration:**
  Issued to a laboratory to allow the laboratory to conduct nonwaived (moderate and/or high complexity) testing until the laboratory is surveyed (inspected) to determine its compliance with the CLIA regulations. Only laboratories applying for a certificate of compliance or a certificate of accreditation will receive a certificate of registration.
- **Certificate of Compliance (COC):**
  Issued to a laboratory once the State Department of Health conducts a survey (inspection) and determines that the laboratory is compliant with all applicable CLIA requirements. This type of certificate is issued to a laboratory that performs nonwaived (moderate and/or high complexity) testing.

OPEN MINUTES
Missouri Board of Pharmacy
Sterile Compounding Sub-Committee
Telephone Conference Call
November 10, 2015

Members of the Missouri Board of Pharmacy Sterile Compounding Sub-Committee met via conference call during the times and dates stated in the following minutes. A quorum of the Board was not present or anticipated for the meeting. However, public notice of the meeting was provided to ensure full compliance with Chapter 610, RSMo. The meeting was called to order by Executive Director Kimberly Grinston at 5:07 p.m. on November 10, 2015.

Board Members Present
Christian Tadrus, PharmD, Vice-President
Barbara Bilek, PharmD, Member
Douglas Lang, R.Ph., Member
Pam Marshall, R.Ph., Member

Staff Present
Kimberly Grinston, Executive Director
Tom Glenski, Chief Inspector
Tammy Siebert, Administrative Coordinator

DISCUSSION: Kimberly Grinston reported this meeting was called to discuss whether the committee prefers to pursue changes to Missouri Regulation 20 CSR 2220-2.200 now or wait until finalization of USP 797. Ms. Grinston reported recent USP 797 revisions addressed many concerns about the prior version. Christian Tadrus commented the Department of Health and Senior Services' rule revisions should be considered as the Board moves forward. Tom Glenski reported hospitals will be required to comply with three different regulations if the Board creates a separate regulation different from USP 797. Barbara Bilek suggested the Board continue to work on a revised draft, keeping USP 797 revisions in mind. It was consensus of the committee to continue working on the current review draft and to incorporate relevant changes from the latest USP 797 into the Board's draft. The committee agreed to circulate the draft changes for public comment but to hold filing an official rule until after USP 797 changes are finalized which may be late 2016 or early 2017.

Kimberly Grinston suggested circulating a draft Missouri rule by April 2016 to allow for public comment and to review at the July 2016 Board meeting. Ms. Grinston suggested monthly meetings of the committee be scheduled to work on drafting the Board's proposed rule. The following dates were planned:

- December 18, 2015, had previously been scheduled as an in-person meeting in Jefferson City;
- January 12, 2016, at 2:00 pm in Jefferson City;
- February 18, 2016, conference call or in conjunction with the Board's February 24, 2016, conference call; and
- March 17 or 24, 2016, by conference call.

The Sterile Compounding Sub-committee meeting was adjourned at 5:39 p.m.

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KIMBERLY A. GRINSTON
EXECUTIVE DIRECTOR
Date Approved:

#A5 <u>Approval of Sterile Compounding Group Minutes</u>

- August 26, 2015 Sterile Compounding Minutes
- September 23, 2015 Sterile Compounding Minutes

Note: These only need to be approved by Christian Tadrus and Doug Lang.

OPEN MINUTES
Missouri Board of Pharmacy
Sterile Compounding Sub-Committee
August 26, 2015

Members of the Missouri Board of Pharmacy met in open session during the times and dates stated in the following minutes. A quorum of the Board was not present or anticipated for the meeting. However, public notice of the meeting was provided to ensure full compliance with Chapter 610, RSMo. The meeting was called to order by Executive Director Kimberly Grinston at 9:00 a.m. on August 26, 2015.

Board Members Present
Douglas Lang, R.Ph.,
Christian Tadrus, PharmD, Vice-President

Staff Present
Kimberly Grinston, Executive Director
Tom Glenski, Chief Inspector

Others Present
Kevin Kinkade, R.Ph.

DISCUSSION: Kimberly Grinston reported available Board members were asked to review the current sterile compounding rule draft (20 CSR 2220-2.200) and to prepare a suggested draft for full Board review. Ms. Grinston reported that board members previously indicated they did not have recent sterile compounding or USP 797 experience, with the exception of Barbara Bilek. Kimberly Grinston reported the Board agreed by consensus to retain Kevin Kinkade to assist the Board's review due to his sterile compounding and regulatory background. Ms. Grinston expressed concerns regarding the length of the rule and the potential impact on small business. Christian Tadrus and Kevin Kinkade also expressed concerns regarding the impact on small business and indicated the rule should be understandable.

Staff and participating board members proceeded to review the draft rule. Substantive comments and suggested changes discussed during the meeting are included in the attached revised draft. Kimberly Grinston indicated the draft would be revised and returned to participating board members for finalization. Participating Board members agreed by consensus to review the next draft by conference call.

The meeting was adjourned at approximately 3:43 p.m.

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KIMBERLY A. GRINSTON
EXECUTIVE DIRECTOR

Date Approved:

Title 20—DEPARTMENT OF INSURANCE, FINANCIAL INSTITUTIONS AND PROFESSIONAL REGISTRATION

Division 2220—State Board of Pharmacy
Chapter 2—General Rules

20 CSR 2220-2.200 Sterile Compounding

PURPOSE: This rule establishes standards for the preparation, labeling, dispensing and distribution of compounded sterile preparations (CSPs).

(1) **General Applicability.** Except as otherwise provided herein, the provisions of this rule shall be applicable to licensees, registrants or permit holders of the Board engaged in, or offering to engage in, compounding sterile preparations (CSPs). The provisions of this rule are divided as follows:

(1) General Applicability
(2) Definitions
(3) Risk Levels
(4) Low Risk Preparations with 12-Hour or Less Beyond-Use Date
(5) General Compounding Requirements
(6) Policies and Procedures
(7) Facility Design Requirements
(8) Segregated Compounding Areas
(9) ISO Certification
(10) Equipment
(11) Primary Engineering Controls
(12) Ingredients & Supplies
(13) Standard Operating Procedures
(14) Cleansing and Garbing
(15) Aseptic Processing
(16) Additional Aseptic Technique Requirements for High Risk Preparations
(17) End Preparation Testing
(18) Labeling
(19) Final Verification
(20) Beyond-Use Dating
(21) Point-of-Care Activated Systems
(22) Storage
(23) Packaging and Delivery
(24) Compounding Log
(25) Aseptic Manipulation Training & Assessment
(26) Glove Fingerprint Sampling
(27) Media-Fill Testing
(28) General Cleaning and Disinfection Requirements
(29) Quality Assurance
(30) Recalls
(31) Record Keeping
(32) Hazardous Drugs and Radiopharmaceuticals
(33) Preemption

(2) **Definitions**.

(A) **Action Level:** A situation in which action must be taken in order to maintain compliance with this rule, USP Chapter 797 or both.

(B) **Adverse Event:** Any incident related to or resulting from the compounding process that did or may have resulted in an adverse patient outcome.

(C) **Ante-Area**: An area in which the concentration of airborne particles is controlled to meet ISO Class 8 or better air quality and that provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas.

(D) **Aseptic processing**: A mode of processing pharmaceutical and medical preparations in an ISO Class 5 area that involves procedures designed to produce a sterile drug preparation that meets a predetermined sterility assurance level and to preclude or prevent contamination by microorganisms during processing or preparation.

(E) **Batch**: Batch compounding includes: (1) compounding multiple sterile preparation units in a single discrete process, by the same individual(s), carried out during one limited time period, (2) compounding in advance of receiving a prescription and (3) compounding a quantity in excess of the filling of an individual prescription or medication order.

(F) **Beyond-Use Date**: For purposes of this rule, the date or time after which a compounded preparation should not be dispensed, stored or transported.

(G) **Biological Safety Cabinet**: A ventilated cabinet for compounding sterile preparations (CSPs) and for staff, preparation and environmental protection that has an open front with inward airflow for staff protection, downward high-efficiency particulate air (HEPA) filtered laminar airflow for preparation protection, and HEPA-filtered exhausted air for environmental protection.

(H) **Buffer Area**: An ISO 7 area where a primary engineering control is physically located.

(I) **CFU**: Colony forming units.

(J) **Cold Temperature**: A temperature that is cold as defined by USP.

Comment [A1]:
USP defines "Cold" in 10.30.20. as:
Any temperature not exceeding 8°(46°F) is "cold." A "refrigerator" is a cold place in wh the temperature is maintained thermostatic between 2°and 8°(36°and 46°F).

The definition of "controlled cold temperature" includes the 2° and 8° language that the group discussed referencing to distinguish "cold temperature" from "freezing" which one shoul incorporated here?

(K) **Compounding**: The preparation, incorporation, mixing, packaging or labeling of a drug or device: (1) as the result of a prescriber's prescription or prescription drug order based on the prescriber/patient/pharmacist relationship in the course of professional practice, or (2) in anticipation of a prescription drug or medication order as provided herein, or (3) for or incident to research, teaching or chemical analysis and not for sale or dispensing purposes.

(L) **Compounding Area**: The area designated for preparing sterile preparations and includes the ante-area and buffer area.

(M) **Compounding Aseptic Containment Isolator (CACI)**: A compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations.

(N) **Compounding Aseptic Isolator (CAI)**: A form of isolator specifically designed for compounding pharmaceutical ingredients or preparations and to maintain an

aseptic compounding environment within the isolator throughout the compounding and material transfer processes.

(O) **Compounding Equipment**: Equipment, instruments, apparatuses, and devices used to compound sterile preparations

(P) **Compounding Staff:** Any person who engages or participates in any aspect of sterile compounding regardless of employment status.

(Q) **Compounded Sterile Preparation (CSP)**: Any low risk, medium risk or high risk compounded sterile preparation, including:

a. Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that must or are required to be sterile when they are administered to patients, including, but not limited to the following dosage forms: aqueous bronchial and inhaled nasal preparations intended for deposition in the lung, baths and soaks for live organs and tissues, epidural and intrathecal solutions, bladder/wound solutions, injectables, implantable devices and dosage forms, inhalation solutions, intravenous solutions, irrigation solutions, ophthalmic preparations, parenteral nutrition solutions, and repackaged sterile preparations. Nasal sprays and irrigations intended for deposit in the nasal passages may be prepared as nonsterile compounds;

b. An FDA approved manufactured sterile product that is either prepared according to the manufacturers' approved labeling/recommendations or prepared differently than published in such labeling; and

c. Assembling point-of-care activated systems.

(R) **Controlled Room Temperature**: A controlled room temperature as defined by USP.

(S) **Critical Area**: An ISO Class 5 area where products, preparations, surfaces or containers are exposed to the environment.

(T) **Critical Site:** Any surface, pathway or opening (i.e., vial septa, injection ports, beakers, needle hubs) that provides a direct pathway between a sterile preparation or other ingredient used to compound a sterile preparation and the air, environment or moisture or that poses a risk of touch contamination.

(U) **Direct Compounding Area (DCA)**: A critical area within an ISO Class 5 primary engineering control where critical sites are exposed to unidirectional HEPA-filtered air also known as first air.

(V) **Disinfectant**: An agent applied to inanimate objects that frees from infection and destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores.

(W) **Experiential Training**: Training based on experience and observation.

(X) **First Air**: The air exiting a HEPA filter in a unidirectional air stream that is essentially particle free.

(Y) **Frozen**: A “frozen” temperature as defined by USP.

(Z) **Hazardous Drugs**: A drug that exhibits one or more of the following characteristics in humans or animals: (1) carcinogenicity, (2) teratogenicity or other developmental toxicity, (3) reproductive toxicity, (4) serious organ toxicity at low doses, (5) genotoxicity or (6) structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the previous criteria/characteristics.

(AA) **High-Efficiency Particulate Air (HEPA) filter**: A particulate filter that directs the flow of air forced through the filter in a uniform parallel flow and that is: (1) capable of retaining airborne particles and microorganisms while allowing gases to pass freely through and, (2) a minimum of 99.97% efficient when tested using 0.3-µm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.

(BB) **ISO Class 5:** An area with less than 3,520 particles (0.5 µm) per cubic meter.

(CC) **ISO Class 7:** An area with less than 352,000 particles (0.5 µm) per cubic meter.

(DD) **ISO Class 8:** An area with less than 3,520,000 particles (0.5 µm) per cubic meter.

(EE) **Line of Demarcation:** A visible line or barrier on the floor that separates a room into distinct and identifiable separate areas for the performance of sterile compounding from general pharmacy activities.

(FF) **Media Fill Test**: A test using a growth medium to verify aseptic compounding techniques or processes are able to produce a compounded sterile preparation without microbial contamination.

(GG) **Multiple-Dose Container**: A multiple-unit container for articles or preparations that contains more than one dose of medication.

(HH) **Parenteral**: A drug preparation intended for injection through one (1) or more layers of skin.

(II) **Peer-Reviewed Literature:** Literature that has been evaluated by other qualified scientific, academic or qualified professionals for quality or accuracy and has been nationally published in a pharmaceutical, scientific, compendial or other medical publication.

(JJ) **Point of Care Activated System**: A closed system device that creates a physical barrier between diluents, fluids or other drug components and is designed to be activated by the end user by allowing the components to mix prior to administration.

(KK) **Preparation**: A preparation, or a compounded sterile preparation, that is a sterile drug or nutrient compounded in a licensed pharmacy pursuant to a lawful prescription or medication order. The article may or may not contain sterile products.

(LL) **Primary Engineering Control (PEC)**: A device that provides an ISO Class 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but may not be limited to, laminar airflow

workbenches, biological safety cabinets, compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs).

(MM) **Refrigerator**: A "refrigerator" temperature as defined by USP.

(NN) **Segregated Compounding Area**: A designated area or room within the pharmacy that is restricted to preparing Low Risk or Medium Risk sterile preparations as allowed by section 8 of this rule.

(OO) **Single-Dose/Single-Unit Container/vial**: A container/vial of liquid medication intended for parenteral administration that is meant for use in a single patient for a single case, procedure or injection.

(PP) **Sterile Alcohol:** Alcohol that contains 70% by volume USP grade Isopropanol (isopropyl alcohol) and 30% USP purified water.

(QQ) **Sterilization:** A validated USP recognized process used to render a preparation free of viable organisms.

(RR) **Terminal Sterilization**: The application of a lethal process (i.e., steam under pressure or autoclaving) to sealed containers for the purpose of achieving a predetermined sterility assurance level of less than 10^{-6}, or a probability of less than one nonsterile unit in one million units.

(SS) **USP**: The United States Pharmacopeia and the National Formulary (USP-NF) as adopted and published by the United States Pharmacopeial Convention, effective May 2013. Copies of the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway, Rockville, MD 20852-1790 or online at http://www.usp.org/. The USP-NF is incorporated herein by reference. This rule does not include any later amendments or additions to the USP-NF.

(TT) **Unidirectional Flow**: An airflow moving in a single direction in a robust and uniform manner and at a sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

(3) **Risk Levels**. The following contamination risk levels shall be established for compounded sterile preparations:

A. **Low Risk**: Sterile preparations compounded under the following conditions:

1. Sterile preparations compounded with aseptic manipulations entirely within an ISO Class 5 or better air quality using only sterile ingredients, products, components and devices;
2. Compounding involving the transfer, measuring, mixing or manipulation of no more than three commercially manufactured packages of sterile products and no more than two entries into any one sterile container or package (i.e., bag, vial) of sterile product or administration container/device;

3. Compounding manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles/syringes, and transferring sterile liquids in sterile syringes to sterile administration devices or package containers of other sterile products/containers for storage and dispensing;
4. Preparations prepared by closed-system aseptic transfer of sterile, non-pyrogenic finished pharmaceuticals obtained from licensed manufacturers into sterile final containers obtained from licensed manufacturers, or;
5. Assembly of point-of-care activated systems.

B. **Medium Risk:** Sterile preparations compounded under any of the following conditions:

1. Compounding involving the transfer, measuring, or mixing manipulations of more than three commercially manufactured packages/vials of sterile products or involving more than two entries into any one sterile container or package (i.e., bag, vial) of sterile product or administration container/device;
2. Multiple individual or small doses of sterile products are combined or pooled to prepare a compounded sterile preparation that will be administered either to multiple patients or to one patient on multiple occasions;
3. Preparations compounded with a medium risk product/preparation, or
4. The compounding process includes complex aseptic manipulations other than single-volume transfer and the preparation does not otherwise meet the definition of a high risk sterile preparation.
5. Medium Risk preparations shall remain medium risk for the life of the preparation.

C. **High Risk**: Sterile preparations compounded under any of the following conditions:

1. Preparations compounded from nonsterile ingredients including, but not limited to, manufactured products not intended for sterile routes of administration (i.e., oral);
2. Compounding using nonsterile components, containers, devices or equipment before terminal sterilization. If any nonsterile components are used to make a sterile preparation, the preparation shall be deemed high risk;

3. Confirmed or suspected exposure of any of the following to worse than ISO Class 5 air quality for more than one (1) hour: (1) sterile contents of commercially manufactured products, (2) compounded sterile preparations that lack effective antimicrobial preservatives or (3) any sterile surface of a device or container used for the preparation, transfer, sterilization or packaging of compounded sterile preparations;
4. Preparations prepared by using an open-system transfer or open reservoir before terminal sterilization;
5. Preparations compounded with other high risk products/preparations, or;
6. Nonsterile water-containing preparations that are stored for more than 6 hours before being sterilized.
7. High Risk preparations shall remain high risk for the life of the preparation.

(4) **Low-Risk or Medium Risk preparations with a 12-Hour or Less Beyond-use Date**: A Low Risk or Medium Risk preparation may be compounded in a segregated compounding area if:

(A) The preparation is compounded in a PEC that complies with section (11) of this rule;

(B) The preparation is assigned the lesser of a 12-hour beyond-use date or the beyond-use date recommended in the manufacturers' package insert. The preparation may not be dispensed or distributed after the assigned beyond-use date;

(C) Individuals engaged in, or assisting with, sterile compounding follow proper hand hygiene, garbing and aseptic technique in the segregated compounding area as required by this rule; and

(D) Routine disinfection of the direct compounding area (DCA) is conducted to minimize microbial surface contamination and maintain ISO Class 5 air quality. At a minimum, the DCA shall be cleaned and disinfected prior to compounding, between batches and whenever contamination is suspected using sterile alcohol or an equivalent or superior agent which is allowed to dry immediately prior to compounding.

(5) **General Compounding Requirements.** Sterile preparations shall be correctly packaged, handled, transported, stored, dispensed and distributed. Appropriate quality control methods shall be maintained over compounding methods at all times to ensure proper aseptic technique and compliance with all applicable state and federal law.

A. Pharmacists shall only compound drugs pursuant to a valid prescription, prescription drug order or medication order. However, drugs may be compounded in limited quantities in anticipation of a valid prescription/order based on a history of receiving valid prescriptions/orders that have been generated solely with an established pharmacist/patient/prescriber relationship. "Limited quantities" is defined as an amount of a batched preparation that does not exceed a one (1) month supply.

B. Compounding in anticipation of receiving a prescription, prescription drug order or medication order without an appropriate history of such prescriptions/orders on file shall be considered manufacturing instead of compounding.

C. Any alteration, change or modification to the contents of a commercially manufactured over-the-counter medication shall require a valid prescription, prescription drug order or medication order from an authorized prescriber.

D. Pharmacists shall not offer compounded drug preparations to other pharmacies, practitioners or commercial entities for subsequent resale or administration, except pursuant to a patient specific prescription or as authorized by a Class J pharmacy permit.

E. A pharmacist or pharmacy may advertise or otherwise provide information concerning the provision of compounding services, however, no pharmacist or pharmacy shall attempt to solicit business by making specific claims about compounded preparations without specific testing of the preparation as compounded by the pharmacy to validate such claim.

F. Compounding of drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA approved drug products is prohibited. This prohibition shall not apply if the drug is not commercially available due to circumstances beyond the licensee's control (i.e., a drug shortage) or a specific medical need for a particular variation of a commercially available compound exists. Documentation of drug unavailability or the specific medical need for compounding a commercially available product shall be maintained in the pharmacy's records.

G. The pharmacy shall maintain current drug reference materials related to sterile preparations that shall be electronically or physically available in the pharmacy for use and inspection by pharmacy staff.

H. A third-party may be used to perform any testing or sampling required by this rule, provided the pharmacy and pharmacist-in-charge shall remain responsible for compliance with this rule and all applicable state/federal law.

I. Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or testing required by this rule repeatedly demonstrates CFU counts that exceed USP Chapter 797 recommended action levels for the type of sampling/testing or (2) any sampling or testing demonstrates the presence of a highly pathogenic microorganism (i.e., Gram-negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

1. Compounded preparations and any ingredients used within the compounding process that are part of the remedial investigation shall be quarantined until the results of the investigation are known. All affected areas shall be resampled to ensure a suitable state of microbial control prior to further compounding. The pharmacy shall ensure that no misbranded, contaminated or adulterated product is administered or dispensed for patient use.
2. If highly pathogenic microorganisms are detected, the investigation shall be initiated with the assistance of a competent microbiologist, infection control professional, industrial hygienist or other competent staff and the source of contamination remedied, regardless of CFU count. The presence of a highly pathogenic microorganism shall be reported to the Board within seven (7) days after detection.
3. Investigation procedures and any corrective/remediation methods taken shall be documented in the pharmacy's records.

(6) **Policies and Procedures**. Pharmacies shall establish and follow a written sterile compounding policy and procedure manual. The manual shall be current and shall be electronically or physically accessible to pharmacy staff. The pharmacist-in-charge shall annually review the manual for compliance and document the date of the required annual review in the pharmacy's records. The required policy and procedure manual shall encompass all aspects of sterile compounding performed by the pharmacy and must include policies/procedures for:

1. Compounding, labeling, sterilizing and dispensing sterile preparations;
2. Storing, transporting and delivering sterile preparations;
3. Cleaning and disinfection. Policies and procedures shall identify authorized cleaning/disinfecting agents and materials, schedules of use and methods of application;
4. Maintaining, verifying and testing the accuracy and functioning of compounding equipment, including, time frames for calibration, testing, equipment monitoring and both annual and routine maintenance;
5. Beyond-use-dating;
6. Approved methods of sterilization and purification;
7. Environmental sampling, including, specified time frames and locations;
8. End-preparation testing, including, sampling plans;

9. Staff training and monitoring competency;
10. Reporting and investigating environmental deficiencies and conducting remedial investigations;
11. Media-fill testing. Policies and procedures shall address/identify media-fill procedures, media selection, fill volume, incubation requirements, time and temperature requirements, testing documentation, analyzing results, and any corrective action guidelines or procedures;
12. Measures for preventing cross-contamination when compounding activities require the manipulation of a patient's blood-derived or other biological material (i.e., radiolabeling a patient's or donor's white blood cells);
13. Recall procedures which must include procedures for identifying and notifying affected patients, prescribers and regulators when applicable;
14. Handling and reporting accidental exposures or spills of hazardous sterile preparations, including, reporting methods and timeframes;
15. Reporting and investigating any real or suspected adverse event or any real or suspected contaminated, non-sterile or defective final preparation, and;
16. Educating patients and/or caregivers concerning the appropriate storage, use and control of sterile compounded preparations when applicable.

(7) **Facility Design Requirements**. Sterile preparations shall be prepared in a compounding area that includes an ante area and buffer area(s) or in a segregated compounding area that complies with section 8 of this rule.

A. **Compounding Area Design Requirements:** Compounding areas and surfaces shall be designed, maintained and controlled to minimize the risk of preparation contamination and the introduction, generation, accumulation and retention of particles. Compounding areas must be clean, well lit and designed in a manner that will allow effective cleaning and disinfection for the activities performed.

1. ~~Areas and surfaces within the compounding area shall be constructed and maintained in a manner that will minimize spaces in which microorganisms and other contaminants may accumulate. The **Compounding areas and** surfaces shall be resistant to damage by disinfectant agents.~~ Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels shall be impregnated with a polymer to render them impervious and hydrophobic, and they shall be caulked around each perimeter to seal them to the support frame
2. Dust-collecting overhangs must be avoided, such as ceiling utility pipes, ledges or windowsills.

3. Work surfaces and the surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, cleanable, non-shedding and resistant to damage by disinfectants.
4. Adequate provision for antiseptic hand cleansing shall be provided after entry into the ante area.
5. The buffer area shall not contain sources of water or floor drains. A sink with hot and cold water must be near, but not in, the buffer area.
6. The exterior lens surface of ceiling lighting fixtures shall be smooth, mounted flush or mounted/installed to promote easy cleaning.
7. Furniture in the compounding area shall be nonporous, smooth, non-shedding, impermeable, cleanable, and resistant to damage by disinfectants.
8. Temperature, humidity and pressure in the compounding area shall be controlled as necessary to ensure compliance with this rule.
9. Compounding areas and compounded preparation storage areas (i.e., refrigerators and freezers) must have an effective temperature control device. At a minimum, temperatures shall be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous temperature monitoring system may be maintained if the system maintains ongoing documentation of temperature recordings that are reviewed daily by pharmacy staff. The required daily staff review shall be documented in the pharmacy's records.
10. Segregated compounding areas shall comply with section (8) of this rule.

B. **Environmental Quality & Controls:** The pharmacy shall establish and follow proper controls to ensure environmental quality and to prevent environmental contamination.

1. Ante-areas shall be maintained in an ISO Class 8 or better air quality under dynamic conditions. Buffer areas shall be maintained in an ISO Class 7 or better air quality under dynamic conditions. Critical areas shall be maintained in an ISO Class 5 or better air quality under dynamic conditions.
2. The supply of HEPA-filtered air shall be adequate to maintain the required air quality classification. HEPA-filtered air shall be introduced in compounding areas at the ceiling and returns shall be mounted low on the wall, creating a general top-down dilution of area air with HEPA-filtered make-up air. Pharmacies licensed on the effective date of this rule with ceiling mounted returns shall be authorized to continue operations if the pharmacy maintains documentation that it is able to maintain the required ISO class conditions and environmental quality, provided that compliance with this subsection shall be required if the compounding or segregated compounding area is moved/relocated.

3. An accurate device shall be installed to monitor the pressure differential between the buffer area and ante-area, and between the ante-area and the general environment outside the compounding area. The cascading pressure between the ISO Class 7 buffer area and the ISO Class 7/8 ante area and the general pharmacy area shall not be less than 5 pascals (0.02 inch water column) each for a total of not less than .05-inch water column from the buffer area all the way to the general pharmacy area. Results shall be reviewed and documented on a log at least daily. Alternatively, a continuous recording device may be used to document pressure differential, provided the results are reviewed at least daily.

C. Relocation of the compounding area or segregated compounding area shall constitute a pharmacy remodel and require compliance with 20 CSR 2220-2.020.

(8) **Segregated Compounding Areas:** In lieu of a compounding area that includes an ante area and buffer area, Low Risk and Medium Risk sterile preparations may be compounded in a segregated compounding area that complies with the following:

A. Segregated compounding areas shall be designed, maintained and controlled to minimize the risk of preparation contamination and the introduction, generation and retention of particles inside the PEC. A segregated compounding area must be clean and well lit and designed in a manner that will allow effective cleaning and disinfection for the activities performed.

B. A line of demarcation must be established that defines and separates the segregated compounding area from other pharmacy activities/areas. The segregated compounding area shall be dedicated solely to activities directly related to sterile compounding. Segregated compounding areas shall not be used for non-sterile compounding.

C. Segregated compounding areas shall not include carpet or unsealed windows or doors that connect to the outdoors or be located in high traffic flow areas or areas in or adjacent to construction sites, warehouses, or food preparation or in any area with environmental air disturbances that may affect the PEC.

D. Areas and surfaces within the segregated compounding area shall be constructed and maintained in a manner that will minimize spaces in which microorganisms and other contaminants may accumulate. All surfaces ~~inside the line of demarcation~~ shall be smooth, impervious, cleanable, nonshedding and resistant to damage by disinfectants, including, but not limited to, fixtures, shelving, counters, ceilings, walls and floors.

E. A sink with hot and cold water must be available outside of the segregated compounding area. Sinks must be a minimum of three (3) feet but no farther than twenty-five (25) feet away from the PEC.

F. Adequate provision for performing antiseptic hand hygiene shall be provided before entry into the PEC.

G. Low and medium risk preparations compounded in a segregated compounding area must be assigned a beyond-use date in compliance with section (21). The assigned beyond-use date must be 12-hours or less unless the preparation is compounded in a CAI or CACI that meets the following:

1. The CAI/CACI must provide isolation from the room and maintain ISO Class 5 air quality during dynamic operating conditions;
2. The manufacturer documents or verifies that the CAI/CACI will meet the requirements of this subsection when located in environments where the background particle counts exceed ISO Class 8 for 0.5 µm and larger particles; and
3. Documentation of compliance and the manufacturer's verification is maintained in the pharmacy's records.

H. Segregated compounding areas shall comply with all other applicable provisions of this rule, including, all applicable testing, cleaning and disinfection requirements.

I. High Risk preparations may not be compounded in a segregated compounding area.

(9) **ISO Certification.** All ISO classified areas and each PEC shall be certified to ensure compliance with requirements of this rule. Certification shall be performed by qualified individuals using recognized and appropriate certification and testing equipment:

A. Certification shall be performed before initially beginning sterile compounding activities and every six (6) months thereafter. Recertification shall be completed whenever the physical structure of the buffer area or ante-area has been altered or any other facility changes or any changes to the PEC occur that may affect airflow or pressure differential. PECs shall also be recertified when the device is relocated or altered or major service to the PEC is performed.

B. Certification/re-certification shall be conducted in accordance with the Controlled Environment Testing Association Certification Guide for Sterile Compounding Facilities (2008), which is incorporated herein by reference. Copies of the Certification Guide for Sterile Compounding Facilities (2008) are published by, and available from, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607 or online at http://www.cetainternational.org/. This rule does not include any later amendments or additions to the Certification Guide. The pharmacy shall maintain an attestation or statement from the certifier verifying that certification/recertification was performed in compliance with Certification Guide guidelines.

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Comment [A2]: I think we still need to cla
what is required in an SCA.

C. Certification/recertification results shall be reviewed by a pharmacist once the completed results are received to ensure compliance with this rule. Deficiencies or failures shall be investigated and corrected prior to further compounding. Corrections may include, but are not limited to, changes in the use of the affected PEC or the ongoing use/recall of compounded preparations. The identity of the pharmacist conducting the required review and the review date shall be documented in the pharmacy's records.

D. An in situ air pattern analysis (i.e. smoke study) shall be required prior to initial compounding and whenever maintenance, repairs or changes to the PEC or compounding area occur that may affect the airflow pattern. The in situ air pattern analysis shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the preparation under dynamic conditions. For purposes of this section, maintenance does not include routine pre-filter changes.

(10) **Equipment**. Compounding equipment shall be clean, accurate, and effective for their intended use and shall be consistently capable of operating properly and within acceptable limits.

A. Equipment or other supplies shall be used, maintained, calibrated and verified for accuracy according to manufacturer recommendations, unless otherwise provided by Board rules.

B. Surfaces of compounding equipment that contact ingredients, in-process materials or drug products shall not be reactive, additive or absorptive so as to alter the ~~safety, identity,~~ strength, quality or purity of the drug product/preparation beyond that desired.

C. Automated compounding devices shall be tested for content, volume and weight accuracy prior to both initial and daily use. Test results shall be promptly reviewed by a pharmacist to ensure compliance. The identity of the reviewing pharmacist and the review date shall be documented in the pharmacy's records.

Comment [A3]: "Promptly" isn't defined. Suggestions? Should it be included here?

D. In the event of improper or inaccurate functioning, the equipment/device shall not be used until the deficiency has been remedied.

E. If drug products/preparations with special precautions for contamination are involved (i.e., penicillin), appropriate measures must be utilized in order to prevent cross-contamination (i.e., restricting equipment use for other operations/compounding or proper cleaning).

(11) **Primary Engineering Controls (PEC):** PECs shall be properly located, operated and maintained and shall comply with the following:

A. PECs must be located in a restricted access ISO Class 7 buffer area or in a segregated compounding area that complies with this rule and shall be placed in a manner to avoid conditions that could adversely affect their operation. PECs shall be located out of traffic patterns and away from ~~room air currents~~ conditions that could disrupt the intended airflow patterns (i.e., ventilation systems or cross-drafts).

B. PECs shall maintain ISO Class 5 or better conditions during dynamic operating conditions and while compounding sterile preparations, including, when transferring ingredients into and out of the isolator and during exposure of critical sites;

C. PECs shall provide unidirectional (laminar flow) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites.

D. Compounding Aseptic Isolators (CAI): Air exchange into the isolator from the surrounding environment shall not occur unless the air has first passed through a microbial retentive HEPA filter.

E. Compounding Aseptic Containment Isolators (CACI): Air exchange with the surrounding environment shall not occur unless the air is first passed through a microbial retentive HEPA filter system capable of containing airborne concentrations of the physical size and state of the drug being compounded. When volatile hazardous drugs are prepared, the exhaust air from the isolator shall be removed by properly designed building ventilation.

F. If an isolator is used, the recovery time to achieve ISO Class 5 air quality shall be identified in the pharmacy's policies and procedures and internal procedures developed to ensure adequate recovery time is allowed after material transfer and before or during compounding operations.

(12) **Ingredients and Supplies**. Compounding ingredients, supplies and containers shall be properly stored and secured in a clean, dry area to prevent contamination and to maintain preparation strength, quality and purity. Ingredients, drugs and supplies must be stored according to manufacturer or USP requirements and conditions.

A. Except as otherwise provided by the board by rule, pharmacists/pharmacies shall only receive, store or use drugs or active ingredients for compounding that have been received from a Missouri licensed pharmacy or drug distributor. Active ingredients must be manufactured in an FDA registered facility. Expired, misbranded, adulterated or contaminated products shall not be used in compounding.

B. Active ingredients and added substances or excipients for CSPs shall be compendial grade articles or shall be accompanied by a certificate of analysis from their supplier which shall be retained in the pharmacy's records. Tom will research if all are compendial grade.

C. Upon receipt of each lot of sterile compounding ingredients and prior to compounding, a visual inspection of the lot shall be conducted for evidence of unacceptable condition or quality.

D. Drugs, ingredients and supplies shall be shelved off the floor. Bulk or unformulated drug substances and added substances or excipients shall be stored in adequately labeled and tightly closed containers under temperature, humidity, and lighting conditions that are either indicated in official monographs or approved by the manufacturer.

E. Products or ingredients that lack a supplier's expiration date cannot be used after one (1) year after receipt. The receipt date shall be recorded on the container of the product/ingredient.

F. Ingredient containers and container closures shall not be reactive, additive or absorptive so as to alter the ~~safety, identity,~~ strength, quality or purity of the compounded drug beyond the desired result. Container systems shall provide adequate protection against foreseeable external factors that can cause deterioration or contamination of the compounded preparation.

G. **Single-Dose and Multiple Dose Containers**. Single and multiple-dose containers shall be labeled to indicate the date and time of initial entering or opening. A beyond-use date must be assigned for the use of single-dose and multiple-dose containers after initial entering or opening.

1. Single-dose vials exposed to ISO Class 5 or cleaner air may be used up to six (6) hours after initial needle puncture. Opened single-dose ampules shall not be stored for any time period.
2. Multiple-dose containers may be used up to twenty-eight (28) days after initially entering or opening (i.e., needle-puncture) unless otherwise specified by the manufacturer.

(13) **Standard Operating Procedures.** The following standard operating procedures shall be applicable to and observed in both compounding areas and segregated compounding areas:

A. Traffic flow in or around the compounding and segregated compounding areas shall be minimized and controlled.

B. Food items, chewing gum, eating, drinking and smoking are prohibited.

C. Nonessential objects that shed particles shall not be brought into the areas, including, but not limited to, pencils, cardboard cartons, paper towels, and cotton items (i.e., gauze pads).

D. Furniture, carts, supplies and equipment shall be removed from shipping cartons/containers and properly cleaned and disinfected before entering the compounding area or segregated compounding area. No shipping or other external cartons may be taken into the areas.

E. Packaged compounding supplies and components (i.e.-, needles, syringes and tubing sets) shall be opened and wiped down with a non-residue generating disinfecting agent before being passed into the buffer area or segregated compounding area. Supplies and equipment shall be decontaminated once again before entering the ISO 5 PEC by wiping the outer surface with sterile alcohol or an equivalent or superior disinfectant that does not leave residue.

F. Only supplies essential for compounding shall be stored in the buffer area. Supplies or other equipment shall not be stored in the PEC.

(14) **Cleansing and Garbing.** Individuals engaged in, or assisting with, compounding sterile preparations shall be trained and demonstrate competence in proper cleansing, garbing and gloving procedures. Competence must be documented and assessed through direct observation.

1. Except as otherwise provided herein, cleansing and garbing shall comply with USP Chapter 797.
2. In lieu of full garbing, compounding personnel using a CAI or CACI to compound non-hazardous drugs shall at a minimum don facial masks, non-shedding gowns and sterile gloves over the isolator gloves during compounding. Non-shedding gowns and gloves shall also be used during material handling. This section shall only be applicable if the CAI/CACI provides isolation from the room and is certified to maintain ISO Class 5 air quality during dynamic operating conditions.

(15) **Aseptic Processing**. Sterile preparations shall be prepared in a manner that maintains sterility and minimizes contamination and the introduction of particulate matter. Appropriate aseptic technique shall be utilized at all times.

A. Aseptic processing must be performed in at least ISO Class 5 conditions. Critical sites shall not be exposed to touch/contact contamination or worse than ISO Class 5 air.

B. Prior to use, drug products, ingredients and packaging shall undergo a visual unit-by-unit inspection to verify the components are free from defects and otherwise suitable for their intended use. Products or ingredients shall not be used if: (1) evidence of deterioration or contamination exists or is suspected, (2) an unauthorized break in any container, closure or seal is detected, (3) the contents do not have the expected appearance, aroma, or texture or (4) the beyond-use date or expiration date has been exceeded.

C. Only materials and equipment essential for aseptic compounding shall be placed in the primary engineering control. Materials and equipment shall be arranged in the DCA to allow a clear, uninterrupted path of HEPA-filtered air over critical sites at all times during compounding. Compounding staff shall not interrupt, impede, or divert flow of first-air from HEPA filters to critical sites. ~~No objects may be placed between the first-air from HEPA filters and an exposed critical site.~~

D. All critical sites shall be wiped vigorously in one direction with sterile alcohol and allowed to dry before being punctured or used.

E. Wetted gauze pads or other particle-generating material shall not be used to disinfect sterile entry points. If sterile, single-use alcohol prep pads are used, the surface of the pad shall not contact any other object before contacting the surface of the entry point.

F. When sterile supplies are received in sealed pouches designed to keep them sterile until opening, the sterile item may be removed from the covering pouches as the supplies are introduced into the ISO Class 5 PEC without disinfecting the individual sterile supply items. However, syringes, needles, and tubing with an outer wrap shall remain in their individual packaging and shall only be opened in an ISO Class 5 work area.

G. Before compounding, staff shall visually confirm that ingredients used and measured in syringes match the prescription or medication order being compounded. Density or specific gravity values programmed in automated compounding devices shall be confirmed to be correct before and after delivering volumes of the liquids assigned to each channel or port.

(16) **<u>Additional Aseptic Technique Requirements for High Risk Preparations.</u>** In addition to section (15), the following requirements for high risk preparations are applicable:

A. Presterilization procedures for High Risk preparations, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 environment.

B. All non-sterile equipment that is to come in contact with the sterilized final high risk preparation shall be sterilized before introduction into the buffer area. Additionally, all nonsterile measuring, mixing and purifying devices shall be rinsed thoroughly with sterile water for irrigation, disinfected and thoroughly drained or dried before being used to compound.

C. All high risk preparations must be sterilized before dispensing or distribution via a method recognized for the preparation type by USP Chapter 1211.

1. Water-containing CSPs that are nonsterile during any phase of the compounding procedure shall be sterilized within 6 hours after completing the preparation.

2. Filters used for sterilization shall be tested for integrity (i.e., bubble point testing) after use. Testing shall comply with manufacturer recommendations. Testing dates and results must be documented in the pharmacy's records and reviewed by a pharmacist prior to preparation release.
3. Commercially available filters shall be approved for human use applications in sterilizing pharmaceutical fluids. Sterile filters used to sterilize CSPs shall be pyrogen free and a pore size of 0.20 to 0.22 microns. They shall be certified by the manufacturer to retain at least 10 to the seventh microorganisms of a strain of Brevundimonas (pseudomonas) diminute. The pharmacy must maintain this documentation for each filter utilized in the sterilization of CSPs.

D. Final containers used for high risk preparations must be sterile and capable of maintaining preparation integrity until the beyond-use date. Sterilization methods must be based on the properties of the preparation.

(17) **End Preparation Testing**. End preparation testing for sterile CSPs shall be conducted as required by this section. Finished preparations must be quarantined pending results of any required testing. Except as otherwise allowed by this rule, CSPs shall not be dispensed until all end-preparation testing results are final and meet required results. Quarantine dates and time periods must be documented in the pharmacy's records. The results of any end preparation testing (i.e., sterility, endotoxin and potency) shall be reviewed by a pharmacist

A. **Low & Medium Risk**: Except as otherwise provided herein, low and medium risk preparations shall undergo sterility testing if the beyond-use date is extended beyond the storage limits in section (22).

B. **High Risk**: At a minimum, the following testing shall be required for high risk preparations:

1. **Sterility Testing:** All High Risk preparations must be tested for sterility without exception in accordance with a method recommended or required by USP Chapter 71. Samples for sterility testing shall be collected immediately after preparation completion. The sampling plan shall comply with USP Chapter 71, Tables 2 and 3.
2. **Bacterial Endotoxin (Pyrogen) Testing:** All high risk parenteral sterile preparations or compounded sterile preparations administered via epidural or intrathecal route shall be tested for bacterial endotoxins using a USP Chapter 85 recognized method for bacterial endotoxin testing.

3. **Potency Testing:** Final potency shall be confirmed by validated instrumental analysis for each sterile preparation that has been assigned a beyond-use date of more than thirty (30) days. Testing of each preparation/batch is not required once potency has been established for the specific preparation if no modifications have been made to the compounding procedure, process or formula (i.e., ingredient sources, batch size or equipment).
4. **Antimicrobial Effectiveness Testing**: Antimicrobial effectiveness must be demonstrated for aqueous-based, multiple-dose topical and oral dosage forms and for other dosage forms such as ophthalmic, otic, nasal, irrigation and dialysis fluids. For purposes of this section, aqueous is defined as a water activity of more than 0.6. Testing must comply with USP Chapter 51. [My notes say Tom will provide language: "reference USP w/ potency for multidose." I added this language from Chapter 51.]

C. **Emergency Dispensing**: Sterile preparations may be dispensed for immediate administration to a patient prior to receiving the results of the testing required by this rule if:

1. No alternative product/preparation is available and the patient will be exposed to negative risks if therapy is delayed. The reason for the emergency dispensing shall be documented in the pharmacy's records; and
2. The prescriber/ordering health care provider is informed the preparation will be dispensed prior to receiving test results and approves the dispensing. Prescriber/provider approval shall be documented in the pharmacy's records. A separate authorization from the prescriber/provider is required for each emergency dispensing.
3. This section shall not be construed to exempt any person or entity from performing any testing required by this rule.

(18) **Labeling**. Except as otherwise provided herein, sterile preparations dispensed to patients shall be labeled in accordance with section 338.059, RSMo, and with the following supplemental information affixed to the preparation:

A. Beyond-use date;
B. Date of preparation
C. The actual name of each active or therapeutic ingredient;
D. The amounts or concentration of active or therapeutic ingredients. For injectables, the amounts or concentration of all active ingredients;
E. Total volume;
F. Storage requirements;

G. Any preparation or device specific instructions for use including the route of administration and the rate of administration, and;

H. Auxiliary labels when applicable.

I. When a preparation is packaged in individual containers and dispensed to the patient in a labeled outer container as required above, the individual containers must be labeled with the preparation name, lot number and beyond use date.

(19) **Final Verification**. Prior to dispensing, a pharmacist shall physically verify that the compounded preparation has been properly prepared, sterilized, packaged and labeled and that all required end preparation testing has been performed and documented. The following quality assurance measures shall be performed by a pharmacist before a sterile preparation is dispensed or distributed:

1. Compounding records shall be reviewed to verify that the correct measurements, volumes, quantities, calculations and sterilization procedures were used. If an automated compounding device was used, a pharmacist must verify that data entered into the device was correct and accurate, including, but not limited to, density or specific gravity values.
2. The final preparation must be visually inspected for physical integrity, clarity and expected appearance. Additionally, each compounded unit shall be inspected against lighted white or black background or both for evidence of visible particulates or other foreign matter. Visual inspection shall not be required for hazardous drugs if the inspection may be harmful.

(20) **Beyond-Use Dating**. All sterile preparations must be assigned a beyond-use date. Beyond-use dates shall be determined from the date or time the preparation is compounded. The nature of the drug and its degradation mechanism, drug stability, sterility considerations, container packaging, storage conditions and the intended duration of therapy shall be considered.

A. For Low and Medium Risk preparations, beyond-use dates shall be assigned based on any of the following resources: USP Chapter 797, the manufacturer's labeling, direct testing using validated testing methods, compendial references or peer-reviewed literature based on preparation-specific experimental studies/testing.

Comment [A4]: I checked the DQSA for additional labeling requirements. It appear 503(b) outsourcers have to include "this is compounded drug" and "not for resale" on labels. *See 503(b)* *http://uscode.house.gov/view.xhtml?req=gr eid:USC-prelim-title21-section353b&num=0&edition=prelim*

I didn't find any labeling changes for pharmacies operating under 503(a). Do we need to add anything else here?

B. High Risk preparations: Beyond-use dates not specifically referenced in the manufacturer's approved labeling or not established by preparation specific instrumental analysis shall be limited to thirty (30) days after compounding. High risk preparations with beyond-use dates greater than thirty (30) days shall undergo laboratory testing using validated methods prior to release to verify stability (sterility and potency) for the maximum beyond-use date. Testing of each preparation/batch is not required once stability has been established for the specific preparation as required by this subsection and no modifications have been made to the compounding procedure, process or formula.

(21) **Point-of-Care Activated Systems .** In addition to other applicable requirements:

A. Point-of-Care activated systems shall be assembled within an ISO Class 5 environment and assigned a beyond-use date in accordance with the manufacturer's recommendations or labeling.

B. The beyond-use date of an assembled non-activated system shall be limited to a maximum of fifteen (15) days unless the pharmacy has documentation from the system's manufacturer that a longer date is acceptable. When dispensed, an assembled non-activated system shall be labeled with beyond-use dates for both activated and non-activated states. The compounding record must document both dates.

C. Point of care activated systems shall be stored in accordance with the manufacturer's labeling and recommendations.

(22) **Storage.** Sterile preparations shall be properly stored and maintained. Preparations shall be stored strictly in accordance with the conditions stated on the ingredient label, if applicable. Adulterated, misbranded, expired or contaminated preparations shall be segregated and quarantined from the compounding area and other drug inventory. In the absence of passing a sterility test, compounded sterile preparations shall be stored as follows:

A. Low Risk: Shall be stored for no more than 48 hours at controlled room temperature, 14 days at cold temperature, and 45 days in solid frozen state at -25° to -10° Celsius or colder.

B. Medium Risk: Shall be stored for no more than 30 hours at controlled room temperature, 9 days at cold temperature, and 45 days in solid frozen state at - 25° to -10° Celsius or colder.

C. High Risk: Shall be stored for no more than 24 hours at controlled room temperature, 3 days at cold temperature, and 45 days in solid frozen state at -25° to -10° Celsius or colder.

D. If storage at controlled room temperature is directed, an article may alternatively be stored and distributed in a cool place as defined by USP, unless otherwise specified in the individual USP monograph or on the label.

E. Temperature excursions shall be allowed as permitted or recognized by USP.

F. Any excess compounded preparation shall be stored and accounted for under conditions dictated by the preparation's composition and stability characteristics to ensure its strength, quality and purity. Excess preparations shall be labeled with the name and strength of the drug(s), an in-house lot number, date of preparation, volume and beyond-use date.

(23) **Packaging and Delivery**. Compounded sterile preparations shall be packaged, stored, transported and delivered in a manner that will preserve the physical integrity, sterility, stability, and purity of the preparation. Packaging shall be selected that simultaneously protects CSPs from damage, leakage, contamination, and degradation and protects individuals transporting packed CSPs from harm. The final preparation shall maintain a potency of +\- 10% within monograph limits for USP articles. Prescription delivery shall comply with applicable provisions of 20 CSR 22202.013. The pharmacy shall establish a mechanism for patient reporting of packaging or transporting concerns to the pharmacy and documenting any reports received.

(24) **Compounding Log**: A compounding log shall be maintained that records/documents each sterile preparation made. The compounding log shall be maintained at the pharmacy separate from the prescription record, either electronically or in writing, and shall be immediately available upon request. Each compounding entry shall be verified and manually or electronically signed or initialed by the verifying pharmacist. The following information shall be recorded in the compounding log for each sterile preparation:

1. Compounding date;
2. The identity of the compounder and the final verification pharmacist, if different;
3. A list of ingredients and their amounts by weight or volume;
4. Description of the compounding process and, if necessary for proper compounding, the order of adding drug products and ingredients. The method, formula or recipe for compounding, provided this information may be separately maintained in the pharmacy's records if immediately upon request;
5. The identity of the source, lot number and the expiration or beyond-use date of each ingredient, as well as an in-house lot number and a beyond-use date for batch bulk CSPs;
6. An identifying prescription number or a readily retrievable unique identifier;

7. The beyond-use date assigned to the preparation and placed on the label;
8. For High Risk preparations, the type of container and container lot number, if applicable; and
9. Any preparation storage conditions included on the patient label or in materials provided to the patient.

(25) **Aseptic Manipulation Training and Assessment**. Compounding staff shall be skilled and trained to accurately and competently perform the duties assigned and to operate any equipment used. At a minimum, compounding staff must undergo Aseptic Competency Training and an Aseptic Technique Skill Assessment as follows:

A. Aseptic Competency Training: Aseptic competency training shall include both didactic and experiential training and may be tailored to the pharmacy's activities. Didactic training must include an instructional component along with a testing or evaluation method to verify competency. Staff shall be trained to perform the duties assigned when the level of sterile activity or sterile compounding methods change. Aseptic competency training must be completed for all risk levels prior to initial compounding and every twelve (12) months thereafter.

B. Aseptic Technique Skill Assessment: A practical aseptic technique skill assessment shall be completed for all individuals compounding sterile preparations to verify aseptic competency. The assessment must include glove fingertip sampling, media fill testing and a direct visual evaluation of the individual's competency. The visual observation shall assess:

1. Proper aseptic technique, manipulations and work practices, including, but not limited to, avoiding touch contamination, proper use of first air and if applicable, sterilizing high risk preparations;
2. Sanitation and disinfection;
3. Hand hygiene, gloving and garbing;
4. Identifying, weighing, and measuring of ingredients;
5. Maintaining and achieving sterility in ISO Class 5 areas and within primary engineering controls, and;
6. Labeling and inspecting CSPs for quality.

C. The required Aseptic Technique Skill Assessment must be completed for staff compounding low or medium risk preparations prior to initial compounding and every twelve (12) months thereafter. For staff compounding high risk preparations, the assessment must be completed prior to initial compounding and every six (6) months thereafter.

D. Compounding staff shall successfully pass all training and assessments. Staff who fail to demonstrate competency or whose glove fingertip sampling or media-fill tests demonstrate one or more units of visible microbial contamination shall be reinstructed and re-evaluated to ensure correction of all deficiencies prior to beginning or continuing any further compounding. The reinstruction and revaluation shall be documented in the pharmacy's records.

E. Training and assessment dates along with the results of the required practical aseptic technique skill assessment, glove fingertip sampling and media fill testing shall be documented and maintained in the pharmacy's records and reviewed by the pharmacist-in-charge to ensure compliance.

(26) **Glove Fingertip Sampling.** Compounding staff shall undergo and successfully complete both initial and ongoing glove fingertip sampling to assess compliance with gloving and aseptic processing. Initial and ongoing fingertip sampling shall be completed in accordance with USP Chapter 797 procedures, timeframes and methods. Sampling shall be conducted following each required media fill test as part of the practical aseptic technique skill assessment. In addition to USP requirements, samples must be tested for mold, yeast, bacteria and fungus.

(27) **Media-Fill Testing**. Pharmacies shall establish and follow policies and procedures for conducting media-fill testing to assess the quality of aseptic skills/techniques of compounding staff. Media fill tests shall be conducted as part of the required aseptic technique skill assessment and shall include a minimum of three media fill units using the same container or closure. Initial and ongoing media-fill testing shall be completed in accordance with USP Chapter 797 recommended procedures and methods for the risk level(s) of sterile compounding performed.

(28) **Environmental Sampling.** Environmental sampling shall be routinely conducted in all ISO classified areas to evaluate air quality compliance and microbial bio burden levels. Sampling shall be conducted during dynamic operating conditions in accordance with USP Chapter 797. Surface samples and viable airborne particle samples shall be tested for mold, yeast, bacteria and fungus. Sampling shall occur as follows:

A. **Surface Sampling**: Surface sampling shall be conducted in accordance with USP Chapter 797 using both general growth media and fungal specific media. Surface sampling for pharmacies engaged in Low Risk and Medium Risk must be performed every 30-days. For High Risk compounding, surface sampling shall be performed every fourteen (14) days.

B. **Viable Airborne Particle Testing**: Volumetric viable air sampling by impaction shall be conducted in all ISO classified environments. Each viable air sample shall sample 1,000 liters for all ISO Class 5 areas and 500 liters for other ISO classified areas. Each sample location shall be tested with both general growth media (i.e., tryptic soy agar) and fungal specific media (i.e., malt extract agar or saboraud dextrose agar) on plates of at least 55mm in size. Use of settling plates alone shall not be sufficient. Viable Airborne Particle Testing must be conducted prior to initial compounding and every six (6) months thereafter. Testing shall also occur:

1. As part of the initial certification of new facilities and equipment;
2. Whenever the physical structure of the compounding area has been altered;
3. As part of the recertification of facilities and equipment;
4. In response to identified problems with sterile preparations or end-preparation testing failure; and
5. Whenever maintenance, repairs or changes to the primary engineering control(s) or compounding area may affect the airflow pattern. The date and type of maintenance, repair or change shall be documented in the pharmacy's records;

C. **Non-Viable Airborne Particle Testing**. Non-viable air sampling shall be performed using a volumetric device in compliance with USP Chapter 797. Non-Viable Airborne Particle Testing must be conducted prior to initial compounding and every six (6) months thereafter.

D. **Pressure Differential**: Pressure differential monitoring shall be required for all sterile compounding areas to ensure compliance with section (7)(B) of this rule. Pressure differential monitoring results shall be documented in writing and reviewed daily.

(29) **General Cleaning and Disinfection Requirements**. The pharmacy shall establish and follow written policies and procedures governing all aspects of cleaning and disinfection. Except as otherwise provided herein, the following requirements shall be applicable:

A. Compounding areas and segregated compounding areas shall be free of infestation by insects, rodents and other vermin. Trash shall be disposed of in a timely and sanitary manner.

B. Cleaning and disinfection shall be performed and conducted in accordance with USP Chapter 797 timeframes and procedures, except as otherwise provided herein.

C. Individuals responsible for cleaning and disinfecting shall be trained in proper cleaning and disinfection procedures and mechanisms prior to performing cleaning/disinfection activities. Training shall include direct visual observation of the individual's cleaning and disinfecting process by qualified staff. The individual shall be annually reassessed for competency through direct visual observation. Documentation of the required training and training dates shall be maintained in the pharmacy's records. Individuals who fail to demonstrate competency shall be reinstructed and successfully reevaluated prior to cleaning or disinfecting the compounding or segregated compounding area.

D. Cleaning, disinfection and mopping activities shall be performed using approved agents and procedures described in the pharmacy's written policies and procedures. Cleaning and disinfecting agents shall be selected based on compatibility, effectiveness and the absence of inappropriate or toxic residues. Manufacturers' directions or published peer-reviewed literature for minimum contact time shall be followed.

E. Primary engineering controls shall be cleaned with a germicidal detergent followed by sterile alcohol. Sterile water for irrigation shall be used to dilute germicidal agents used inside the PEC that require dilution.

F. ***Segregated Compounding Areas***: Floors and work surfaces within the line of demarcation shall be cleaned and disinfected daily or immediately prior to compounding if not used daily. Shelving and storage areas shall be cleaned and disinfected monthly.

(30) **Quality Assurance**. Sterile compounding pharmacies shall establish and follow a written quality assurance program for monitoring and evaluating the quality of compounding activities.

A. At a minimum, the quality assurance program shall include procedures for monitoring and tracking infection rates, adverse drug events, preparation recalls and complaints from prescribers, patients or other individuals or entities.

B. The quality assurance plan shall delineate the individuals responsible for each aspect of the quality assurance program either by name or position title.

C. The quality assurance plan shall be maintained at the pharmacy or readily retrievable upon request. The pharmacist-in-charge shall annually review the quality assurance program and document the review in the pharmacy's records.

(31) **Recalls**. A recall must be initiated when a dispensed or distributed preparation is deemed to be misbranded, adulterated or non-sterile or if end-preparation testing results are out of specification. The pharmacy shall notify the prescriber of the nature of the recall, the problem(s) identified and any recommended actions to ensure public health and safety. In cases where the compounded preparation has the potential to harm the patient, the same notification shall be provided to all patients that received the recalled preparation(s).

A. Patient and prescriber notifications required by this section shall be made as soon as reasonably practicable but in no event later than one (1) business day of the recall. The date and manner of notification shall be documented in the pharmacy's records.

B. If a patient recall notification is unsuccessful, the pharmacy shall mail notification to the patient within the required one (1) business day timeframe.

C. Recalls initiated pursuant to this section shall be reported to the board in writing within three (3) business days, in a form approved by the Board.

D. If recall notification cannot be conducted as required herein, the pharmacy may submit to the Board a written plan to extend the notification period. The request must include a description of the nature of the recall, the potential number of patients affected, the reason(s) supporting the extension request and a proposed timeframe for completing the required notifications.

Comment [A5]: I revised this section to m closely match 2220-2.040(8)(C). My notes didn't have a firm recommendation on the timeframe. What should be included here?

(32) **Record Keeping**. The pharmacy shall maintain the following records:

A. Aseptic competency training and aseptic technique skill assessment dates and results;

B. Testing dates and results for glove fingertip sampling, media-fill tests and end-preparation testing;

C. Environmental sampling dates and results, including, any corrective efforts taken;

D. Cleaning and disinfection evaluation dates and results;

E. Required refrigerator and temperature logs;

F. Cleaning and disinfection records that document compliance with this rule;

G. Equipment calibration dates and results and maintenance reports;

H. Certificates of analysis for compounding ingredients;

I. Certification records for PECs and sterile compounding areas;

J. Copies of any manufacturer equipment standards that are relied upon to maintain compliance with this rule;

K. Batch preparation files;

L. For high risk preparations, sterilization, quarantine and ingredient validation records;

M. Emergency dispensing records as required by subsection (17), including, documentation of prescriber authorization and the dates of such authorization;

N. Preparation recall records, including, dates, patients affected and any investigation, corrective actions or recall notifications made; and

O. All other records required by this rule or governing law.

P. Except as otherwise provided herein, records and reports required by this rule shall be either electronically or physically maintained for two (2) years. Records shall be readily retrievable and subject to inspection by the Board of Pharmacy or its agents upon request. At a minimum, records shall be physically or electronically produced immediately or within two (2) hours of a request from the Board or the Board's authorized designee.

Q. Prescription records shall be maintained in compliance with Missouri law and the rules of the Board.

(33) **Hazardous Drugs and Radiopharmaceuticals**. Hazardous CSPs and radiopharmaceuticals shall be prepared, stored and compounded in accordance with USP 797. Compounding staff engaged in handling, preparing or compounding hazardous drugs or radiopharmaceuticals shall be trained as required by USP Chapter 797. The following additional requirements shall be implemented to insure the protection of the staff involved:

A. Hazardous drugs/preparations shall be stored, handled and prepared under conditions that protect workers and other staff.

B. Appropriate disposal containers shall be available for used needles, syringes, and if applicable, hazardous waste from the preparation of chemotherapy agents and infectious waste. Disposal of hazardous waste shall comply with all applicable local, state and federal requirements;

C. Written procedures for handling major and minor spills and generated waste of hazardous agents must be developed and must be included in the policy and procedure manual, and;

D. Prepared doses of hazardous drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

E. Notwithstanding any provision of this rule or USP Chapter 797, low risk radiopharmaceutical preparations prepared in a segregated compounding area may be assigned an eighteen (18) hour or lesser beyond-use date.

(34) **Applicability.** If a conflict between this rule and the applicable provisions of USP exists, the requirements of this rule shall apply unless otherwise indicated herein.

OPEN MINUTES
Missouri Board of Pharmacy
Sterile Compounding Sub-Committee
Telephone Conference Call
September 23, 2015

Members of the Missouri Board of Pharmacy met via conference call during the times and dates stated in the following minutes. A quorum of the Board was not present or anticipated for the meeting. However, public notice of the meeting was provided to ensure full compliance with Chapter 610, RSMo. The meeting was called to order by Executive Director Kimberly Grinston at 4:03 p.m. on September 23, 2015.

Board Members Present
Douglas Lang, R.Ph.,
Christian Tadrus, PharmD, Vice-President

Staff Present
Kimberly Grinston, Executive Director
Tom Glenski, Chief Inspector

DISCUSSION: Kimberly Grinston reported that revisions from the 8/26/15 rule review meeting have been incorporated into the current proposed draft as well as additional changes by Ms. Grinston and Tom Glenski. Discussion was held. Substantive comments and suggested changes discussed during the meeting are included in the attached revised draft. Participating Board members agreed to submit the proposed draft for full Board review but noted several provisions were included for Board discussion purposes only and would likely be revised based on public/board comments.

The meeting was adjourned at approximately 8:07 p.m.

_____
KIMBERLY A. GRINSTON
EXECUTIVE DIRECTOR

Date Approved:

Title 20—DEPARTMENT OF INSURANCE, FINANCIAL INSTITUTIONS AND PROFESSIONAL REGISTRATION

Division 2220—State Board of Pharmacy
Chapter 2—General Rules

20 CSR 2220-2.200 Sterile Compounding

PURPOSE: This rule establishes standards for the preparation, labeling, dispensing and distribution of compounded sterile preparations (CSPs).

(1) **General Applicability.** In lieu of 20 CSR 2220-2.400, t~~T~~he provisions of this rule shall be applicable to licensees, registrants or permit holders of the Board engaged in, or offering to engage in, compounding sterile preparations (CSPs). The provisions of this rule are divided as follows:

(1) General Applicability
(2) Definitions
(3) Risk Levels
(4) Low Risk CSPs with 12-Hour or Less Beyond-Use Date
(5) General Compounding Requirements
(6) Policies and Procedures
(7) Facility Design Requirements
(8) Segregated Compounding Areas
(9) ISO Certification
(10) Equipment
(11) Primary Engineering Controls
(12) Ingredients & Supplies
(13) Standard Operating Procedures
(14) Personal Cleansing and Garbing
(15) Aseptic Processing
(16) Additional Aseptic Technique Requirements for High Risk CSPs
(17) End Preparation Testing
(18) Labeling
(19) Final Verification
(20) Beyond-Use Dating
(21) Point-of-Care Activated Systems
(22) Storage
(23) Packaging and Delivery
(24) Compounding Log
(25) Aseptic Manipulation Training & Assessment
(26) Glove Fingertip Sampling
(27) Media-Fill Testing
(28) Environmental Sampling
(29) Facility Cleaning and Disinfection Requirements
(30) Quality Assurance
(31) Recalls
(32) Record Keeping
(33) Hazardous Drugs
(34) Applicability

(2) **Definitions**.

(A) **Action Level:** A situation in which action must be taken in order to maintain compliance with this rule, USP Chapter 797 or both.

(B) **Adverse Event:** Any incident related to or resulting from the compounding process that did or may have resulted in an adverse patient outcome.

(C) **Ante-Area**: An area in which the concentration of airborne particles is controlled to meet ISO Class 8 or better air quality and that provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas.

(D) **Aseptic processing**: A mode of processing pharmaceutical and medical CSPs in an ISO Class 5 area that involves procedures designed to produce a CSP that meets a predetermined sterility assurance level and to preclude or prevent contamination by microorganisms during processing or preparation.

(E) **Batch**: Batch compounding includes: (1) compounding multiple CSP units in a single discrete process, by the same individual(s), carried out during one limited time period, (2) compounding in advance of receiving a prescription and (3) compounding a quantity in excess of the filling of an individual prescription or medication order.

(F) **Beyond-Use Date**: For purposes of this rule, the date or time after which a CSP should not be ~~dispensed, stored or transported~~ used.

(G) **Biological Safety Cabinet**: A ventilated cabinet for CSPs and for staff, preparation and environmental protection that has an open front with inward airflow for staff protection, downward high-efficiency particulate air (HEPA) filtered laminar airflow for CSP protection, and HEPA-filtered exhausted air for environmental protection.

(H) **Buffer Area**: An ISO 7 area where a primary engineering control is physically located.

(I) **CFU**: Colony forming units.

~~(J) **Cold Temperature**: A temperature that is cold as defined by USP.~~

~~(K)~~(J) **Compounding**: The preparation, incorporation, mixing, packaging or labeling of a drug or drug containing device: (1) as the result of a prescriber's prescription or prescription drug order based on the prescriber/patient/pharmacist relationship in the course of professional practice, or (2) in anticipation of a prescription drug or medication order as provided herein, or (3) for or incident to research, teaching or chemical analysis and not for sale or dispensing purposes.

~~(L)~~(K) **Compounding Area**: The area designated for preparing CSPs and includes the ante-area and buffer area.

~~(M)~~(L) **Compounding Aseptic Containment Isolator (CACI)**: A compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drugs throughout the compounding and material transfer processes and to provide an aseptic environment for CSPs.

~~(N)~~(M) **Compounding Aseptic Isolator (CAI)**: A form of isolator specifically designed for compounding pharmaceutical ingredients or CSPs and to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes.

~~(O)~~(N) **Compounding Equipment**: Equipment, instruments, apparatuses, and devices used to compound CSPs.

~~(P)~~(O) **Compounding Staff:** Any person who engages or participates in any aspect of sterile compounding regardless of employment status.

~~(Q)~~(P) **Compounded Sterile Preparation (CSP)**: Any low risk, medium risk or high risk CSP prepared by a pharmacy, including:

a. Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that must or are required to be sterile when they are administered to patients, including, but not limited to the following dosage forms: bronchial and inhaled nasal preparations intended for deposition in the lung, baths and soaks for live organs and tissues, epidural and intrathecal solutions, bladder/wound solutions, injectables, implantable devices and dosage forms, inhalation solutions, intravenous solutions, irrigation solutions, ophthalmic preparations, parenteral nutrition solutions, and repackaged sterile preparations. Nasal sprays and irrigations intended for deposit in the nasal passages may be prepared as nonsterile compounds;

b. An FDA approved manufactured sterile product that is either prepared according to the manufacturers' approved labeling/recommendations or prepared differently than published in such labeling; and

c. Assembling point-of-care activated systems.

~~(R)~~(Q) **Controlled Room Temperature**: A controlled room temperature as defined by USP.

~~(S)~~(R) **Critical Area**: An ISO Class 5 area where products, CSPs, surfaces or containers are exposed to the environment.

~~(T)~~(S) **Critical Site:** Any surface, pathway or opening (i.e., vial septa, injection ports, beakers, needle hubs) that provides a direct pathway between a CSP or other ingredient used to compound a CSP and the air, environment or moisture or that poses a risk of touch contamination.

~~(U)~~(T) **Direct Compounding Area (DCA)**: A critical area within an ISO Class 5 primary engineering control where critical sites are exposed to unidirectional HEPA-filtered air also known as first air.

~~(V)~~(U) **Disinfectant**: An agent applied to inanimate objects that frees from infection and destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial and fungal spores.

~~(W)~~(V) **Experiential Training**: Training based on experience and observation.

~~(X)~~(W) **First Air**: The air exiting a HEPA filter in a unidirectional air stream that is essentially particle free.

~~(Y)~~(X) **Frozen**: The temperature range for a freezer as defined by USP.

~~(Z)~~(Y) **Hazardous Drugs**: A hazardous drug as indicated on the National Institute for Occupational Safety and Health's (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings.

~~(AA)~~(Z) **High-Efficiency Particulate Air (HEPA) filter**: A particulate filter that directs the flow of air forced through the filter in a uniform parallel flow and that is: (1) capable of retaining airborne particles and microorganisms while allowing gases to pass freely through and, (2) a minimum of 99.97% efficient when tested using 0.3-µm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.

~~(BB)~~(AA) **ISO Class 5:** An area with less than 3,520 particles (0.5 µm and larger in size) per cubic meter.

~~(CC)~~(BB) **ISO Class 7:** An area with less than 352,000 particles (0.5 µm and larger in size) per cubic meter.

~~(DD)~~(CC) **ISO Class 8:** An area with less than 3,520,000 particles (0.5 µm and larger in size) per cubic meter.

~~(EE)~~(DD) **Line of Demarcation:** A visible line or barrier on the floor that separates a room into distinct and identifiable separate areas for the performance of sterile compounding from general pharmacy activities.

~~(FF)~~(EE) **Media-Fill Test**: A test using a growth medium to verify aseptic compounding techniques or processes that are able to produce a CSP without microbial contamination.

~~(GG)~~(FF) **Multiple-Dose Container**: A multiple-unit container for articles or CSPs that contains more than one dose of medication.

~~(HH)~~(GG) **Parenteral**: A CSP intended for injection through one (1) or more layers of skin.

~~(II)~~(HH) **Peer-Reviewed Literature:** Literature that has been evaluated by other qualified scientific, academic or qualified professionals for quality or accuracy and has been nationally published in a pharmaceutical, scientific, compendial or other medical publication.

~~(JJ)~~(II) **Point of Care Activated System**: A closed system device that creates a physical barrier between diluents, fluids or other drug components and is designed to be activated by the end user by allowing the components to mix prior to administration.

~~(KK) **Preparation**: A compounded sterile preparation prepared by a pharmacy.~~

(JJ) **Primary Engineering Control (PEC)**: A device that provides an ISO Class 5 environment for the exposure of critical sites when compounding sterile preparations. PECs include, but may not be limited to, laminar airflow workbenches, biological safety cabinets, compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs).

~~(LL)~~(KK) **Drug Product**: A commercially manufactured drug or nutrient that has been evaluated for safety and efficacy by the United States Food and Drug Administration (FDA).

~~(MM)~~(LL) **Refrigerated**. A cold place in which the temperature is maintained thermostatically between 2° and 8° (36°C and 46°F).

~~(NN)~~(MM) **Segregated Compounding Area**: A designated area or room within the pharmacy that is restricted to preparing Low Risk or Medium Risk CSPs as allowed by section 8 of this rule.

~~(OO)~~(NN) **Single-Dose/Single-Unit Container/vial**: A container/vial of ~~liquid~~ medication intended for ~~parenteral~~ administration that is meant for use in a single patient for a single case, procedure or injection.

~~(PP)~~(OO) **Sterile Alcohol:** Alcohol that contains 70% by volume USP grade Isopropanol (isopropyl alcohol) and 30% USP purified water and is free of viable organisms.

~~(QQ)~~(PP) **Sterilization:** A validated USP recognized process used to render a CSP free of viable organisms.

~~(RR)~~(QQ) **Terminal Sterilization**: The application of a lethal process for the purpose of achieving a predetermined sterility assurance level of less than 10^{-6}, or a probability of less than one nonsterile unit in one million units.

~~(SS)~~(RR) **USP**: The United States Pharmacopeia and the National Formulary (USP-NF) as adopted and published by the United States Pharmacopeial Convention, effective May 2013. Copies of the USP-NF are published by, and available from, USP, 12601 Twinbrook Parkway, Rockville, MD 20852-1790 or online at http://www.usp.org/. The USP-NF is incorporated herein by reference. This rule does not include any later amendments or additions to the USP-NF.

~~(TT)~~(SS) **Unidirectional Flow**: An airflow moving in a single direction in a robust and uniform manner and at a sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

(3) **Risk Levels**. The following contamination risk levels shall be established for CSPs:

A. **Low Risk**: CSPs compounded under the following conditions:

1. CSPs compounded with aseptic manipulations entirely within an ISO Class 5 or better air quality using only sterile ingredients, products, components and devices;
2. Compounding involving the transfer, measuring, mixing or manipulation of no more than three commercially manufactured packages of sterile products and no more than two entries into any one sterile container or package (i.e., bag, vial) of sterile product or administration container/device;

3. Compounding manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles/syringes, and transferring sterile liquids in sterile syringes to sterile administration devices or package containers of other sterile products/containers for storage and dispensing;
4. CSPs prepared by closed-system aseptic transfer of sterile, non-pyrogenic finished pharmaceuticals obtained from licensed manufacturers into sterile final containers obtained from licensed manufacturers, or;
5. Assembly of point-of-care activated systems.

B. **Medium Risk:** CSPs compounded under any of the following conditions:

1. Compounding involving the transfer, measuring, or mixing manipulations of more than three commercially manufactured packages/vials of sterile products or involving more than two entries into any one sterile container or package (i.e., bag, vial) of sterile product or administration container/device;
2. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions;
3. CSPs compounded with a medium risk ~~product/~~CSP, or
4. The compounding process includes complex aseptic manipulations other than single-volume transfer and the CSP does not otherwise meet the definition of a high risk sterile CSP.
5. Medium Risk CSPs shall remain medium risk for the life of the CSP.

C. **High Risk**: CSPs compounded under any of the following conditions:

1. CSPs compounded from nonsterile ingredients including, but not limited to, manufactured products not intended for sterile routes of administration (i.e., oral);
2. Compounding using nonsterile components, containers, devices or equipment before terminal sterilization. If any nonsterile components are used to make a CSP, the CSP shall be deemed high risk;
3. Confirmed or suspected exposure of any of the following to worse than ISO Class 5 air quality for more than one (1) hour: (1) sterile contents of commercially manufactured products, (2) CSPs that lack effective antimicrobial preservatives or (3) any sterile surface of a device or container used for the preparation, transfer, sterilization or packaging of CSPs;
4. CSPs prepared by using an open-system transfer or open reservoir before terminal sterilization;
5. CSPs compounded with a high risk ~~products/~~CSP, or;

6. Nonsterile water-containing CSPs that are stored for more than 6 hours before being sterilized.
7. High Risk CSPs shall remain high risk for the life of the CSP.

(4) **Low-Risk or Medium Risk CSP with a 12-Hour or Less Beyond-use Date**: A Low Risk or Medium Risk CSP may be compounded in a segregated compounding area if:

(A) The CSP is compounded in a PEC that complies with section (11) of this rule;

(B) The CSP is assigned the lesser of a 12-hour beyond-use date or the beyond-use date recommended in the manufacturers' package insert. The CSP may not be dispensed or distributed after the assigned beyond-use date;

(C) Individuals engaged in, or assisting with, sterile compounding follow proper hand hygiene, garbing and aseptic technique in the segregated compounding area as required by this rule; and

(D) The PEC shall be cleaned and disinfected as required by this rule.

(5) **General Compounding Requirements.** CSPs shall be correctly packaged, handled, transported, stored, dispensed and distributed. Appropriate quality control methods shall be maintained over compounding methods at all times to ensure proper aseptic technique and compliance with all applicable state and federal law.

A. CSPs shall only be compounded pursuant to a valid patient-specific prescription, prescription drug order or medication order. However, drugs may be compounded ~~in limited quantities~~ in anticipation of a valid prescription/order based on a history of receiving valid prescriptions/orders that have been generated solely with an established pharmacist/patient/prescriber relationship and in an amount that does not exceed a one (1) month supply for dispensing purposes. ~~"Limited quantities" is defined as an amount of a batched preparation that does not exceed a one (1) month supply needed for dispensing purposes.~~

B. Compounding in anticipation of receiving a prescription, prescription drug order or medication order without an appropriate history of such prescriptions/orders on file shall be considered manufacturing instead of compounding.

C. Any alteration, change or modification to the contents of a commercially manufactured over-the-counter medication shall require a valid prescription, prescription drug order or medication order from an authorized prescriber.

D. Pharmacists shall not offer CSPs to other pharmacies, practitioners or commercial entities for subsequent resale or administration, except pursuant to a patient specific prescription/order or as authorized by a Class J pharmacy permit.

E. A pharmacist or pharmacy may advertise or otherwise provide information concerning the provision of compounding services, however, no pharmacist or pharmacy shall attempt to solicit business by making specific claims about CSPs without specific testing of the CSP as compounded by the pharmacy to validate such claim.

F. Compounding of ~~drug products~~ CSPs that are commercially available in the marketplace or that are essentially copies of commercially available FDA approved drug products is prohibited. This prohibition shall not apply if the drug is not commercially available due to circumstances beyond the licensee's control (i.e., a drug shortage) or a specific medical need for a particular variation of a commercially available compound exists. Documentation of drug unavailability or the specific medical need for compounding a commercially available product shall be maintained in the pharmacy's records.

G. The pharmacy shall maintain current drug reference materials related to CSPs that shall be electronically or physically available in the pharmacy for use and inspection by pharmacy staff.

H. A third-party may be used to perform any testing or sampling required by this rule, provided the pharmacy and pharmacist-in-charge shall remain responsible for compliance with this rule and all applicable state/federal law.

I. Remedial Investigations: A remedial investigation shall be required if: (1) any sampling or testing required by this rule repeatedly demonstrates CFU counts that exceed USP Chapter 797 recommended action levels for the type of sampling/testing or (2) any sampling or testing demonstrates the presence of a highly pathogenic microorganism (i.e., Gram-negative rods, coagulase positive staphylococcus, molds, fungus or yeasts).

1. CSPs and any ingredients used within the compounding process that are part of the remedial investigation shall be quarantined until the results of the investigation are known. All affected areas shall be resampled to ensure a suitable state of microbial control prior to further compounding. The pharmacy shall ensure that no misbranded, contaminated or adulterated product is administered or dispensed for patient use.
2. If highly pathogenic microorganisms are detected, the investigation shall be initiated with the assistance of a competent microbiologist, infection control professional, industrial hygienist or other competent staff and the source of contamination remedied, regardless of CFU count. The presence of a highly pathogenic microorganism shall be reported to the Board within seven (7) days after detection.
3. Investigation procedures and any corrective/remediation methods taken shall be documented in the pharmacy's records.

(6) **Policies and Procedures**. Pharmacies shall establish and follow a written sterile compounding policy and procedure manual. The manual shall be current and shall be electronically or physically accessible to pharmacy staff. The pharmacist-in-charge shall annually review the manual for compliance and document the date of the required annual review in the pharmacy's records. The required policy and procedure manual shall encompass all aspects of sterile compounding performed by the pharmacy and must include policies/procedures for:

1. Compounding, labeling~~, sterilizing~~ and dispensing CSPs;
2. Storing, transporting and delivering CSPs;
3. Cleaning and disinfection. Policies and procedures shall identify authorized cleaning/disinfecting agents and materials, schedules of use and methods of application;
4. Maintaining, verifying and testing the accuracy and functioning of compounding equipment, including, time frames for calibration, testing, equipment monitoring and both annual and routine maintenance;
5. Beyond-use-dating;
6. Approved methods of sterilization and purification;
7. Environmental sampling, including, specified time frames and locations;
8. End-preparation testing, including, sampling plans;
9. Staff training and monitoring competency;
10. Reporting and investigating environmental deficiencies~~ and conducting remedial investigations~~;
11. Media-fill testing. Policies and procedures shall address/identify media-fill procedures, media selection, fill volume, incubation requirements, time and temperature requirements, testing documentation, analyzing results, and any corrective action guidelines or procedures;
12. Measures for preventing cross-contamination when compounding activities require the manipulation of a patient's blood-derived or other biological material (i.e., radiolabeling a patient's or donor's white blood cells);
13. Recall procedures which must include procedures for identifying and notifying affected patients, prescribers and regulators when applicable;
14. Handling and reporting accidental exposures or spills of hazardous CSPs, including, reporting methods and timeframes;
15. Reporting and investigating any real or suspected adverse event or any real or suspected contaminated, non-sterile or defective final CSP, and;
16. Educating patients and/or caregivers concerning the appropriate storage, use and control of CSPs, when applicable.

(7) **Facility Design Requirements**. Except as otherwise provided in section (8), CSPs shall be prepared in a compounding area that includes an ante area and buffer area(s).

A. **Compounding Area Design Requirements:** Compounding areas and surfaces shall be designed, maintained and controlled to minimize the risk of preparation contamination and the introduction, generation, accumulation and retention of particles. Compounding areas must be clean, well lit and designed in a manner that will allow effective cleaning and disinfection for the activities performed.

1. Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels shall be impregnated with a polymer to render them impervious and hydrophobic, and they shall be caulked around each perimeter to seal them to the support frame.
2. Dust-collecting overhangs must be avoided, such as ceiling utility pipes, ledges or windowsills.
3. Work surfaces and the surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, cleanable, non-shedding and resistant to damage by disinfectants.
4. Adequate provision for antiseptic hand cleansing shall be provided after entry into the ante area.
5. The buffer area shall not contain sources of water or floor drains. A sink with hot and cold water must be near, but not in, the buffer area.
6. The exterior lens surface of ceiling lighting fixtures shall be smooth, mounted flush or mounted/installed to promote easy cleaning.
7. Furniture in the compounding area shall be nonporous, smooth, non-shedding, impermeable, cleanable, and resistant to damage by disinfectants.
8. Temperature, humidity and pressure in the compounding area shall be controlled as necessary to ensure compliance with this rule.
9. Compounding areas and CSP storage areas (i.e., refrigerators and freezers) must have an effective temperature measuring device. At a minimum, temperatures shall be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous temperature monitoring system may be maintained if the system maintains ongoing documentation of temperature recordings or, if applicable, temperature alerts that are reviewed daily ~~by pharmacy staff~~. ~~The required daily staff review shall be documented and maintained in the pharmacy's records or accessible to the pharmacy~~. Documentations of the required review shall be maintained in the pharmacy's records or otherwise accessible to the pharmacy.

B. **Environmental Quality & Controls:** The pharmacy shall establish and follow proper controls to ensure environmental quality and to prevent environmental contamination.

1. Ante-areas shall be maintained in an ISO Class 8 or better air quality under dynamic conditions. Buffer areas shall be maintained in an ISO Class 7 or better air quality under dynamic conditions. Critical areas shall be maintained in an ISO Class 5 or better air quality under dynamic conditions.
2. The supply of HEPA-filtered air shall be adequate to maintain the required air quality classification. HEPA-filtered air shall be introduced in compounding areas at the ceiling and returns shall be mounted low on the wall, creating a general top-down dilution of area air with HEPA-filtered make-up air. Pharmacies licensed on the effective date of this rule with ceiling mounted returns shall be authorized to continue operations if the pharmacy maintains documentation that it is able to maintain the required ISO class conditions and environmental quality, provided that compliance with this subsection shall be required if the compounding area ~~or segregated compounding area~~ is moved/relocated.
3. An accurate device shall be installed to monitor the pressure differential between the buffer area and ante-area, and between the ante-area and the general environment outside the compounding area. The cascading pressure between the ISO Class 7 buffer area and the ISO Class 7/8 ante area and the general pharmacy area shall not be less than 5 pascals (0.02 inch water column) each for a total of not less than .05-inch water column from the buffer area all the way to the general pharmacy area. Results shall be reviewed and documented on a log at least daily. Alternatively, a continuous recording device may be used to document pressure differential, provided the results are reviewed at least daily.

C. Relocation of or revisions to the compounding area shall constitute a pharmacy remodel and require compliance with 20 CSR 2220-2.020 remodeling requirements. Revisions include any structural changes to or replacement of the ante/buffer area walls/ceilings, sink, HEPA filtration system or heating/ventilating/air conditioning system.

(8) **Segregated Compounding Areas:** In lieu of a compounding area that includes an ante area and buffer area, Low Risk and Medium Risk CSPs may be compounded in a segregated compounding area that complies with the following:

A. Segregated compounding areas shall be designed, maintained and controlled to minimize the risk of preparation contamination and the introduction, generation and retention of particles inside the PEC. A segregated compounding area must be clean and well lit and designed in a manner that will allow effective cleaning and disinfection for the activities performed.

B. A line of demarcation must be established that defines and separates the segregated compounding area from other pharmacy activities/areas. The segregated compounding area shall be dedicated solely to activities directly related to sterile compounding. Segregated compounding areas shall not be used for non-sterile compounding.

C. Segregated compounding areas shall not include carpet or unsealed windows or doors that connect to the outdoors or be located in high traffic flow areas or areas in or adjacent to construction sites, warehouses, or food preparation or in any area with environmental air disturbances that may affect the PEC.

D. Areas and surfaces within the segregated compounding area shall be constructed and maintained in a manner that will minimize spaces in which microorganisms and other contaminants may accumulate. All surfaces ~~inside the line of demarcation~~ shall be smooth, impervious, cleanable, nonshedding and resistant to damage by disinfectants, including, but not limited to, fixtures, shelving, counters, ceilings, walls and floors.

E. The segregated compounding area shall not contain sources of water or floor drains. A sink with hot and cold water must be available outside of the segregated compounding area. Sinks must be a minimum of three (3) feet but no farther than twenty-five (25) feet away from the PEC.

F. Adequate provision for performing antiseptic hand hygiene shall be provided before entry into the PEC.

G. CSP storage areas (i.e., refrigerators and freezers) must have an effective temperature measuring device. At a minimum, temperatures shall be recorded and documented each day that the pharmacy is open for pharmacy activities. Alternatively, a continuous temperature monitoring system may be maintained if the system maintains ongoing documentation of temperature recordings that are reviewed daily by pharmacy staff. The required daily staff review shall be documented in the pharmacy's records.

H. Low and medium risk CSPs compounded in a segregated compounding area must be assigned a beyond-use date in compliance with section (21). The assigned beyond-use date must be 12-hours or less unless the CSP is compounded in a CAI or CACI that meets the following:

1. The CAI/CACI must provide isolation from the room and maintain ISO Class 5 air quality during dynamic operating conditions;
2. The manufacturer documents or verifies that the CAI/CACI will meet the requirements of this subsection when located in environments where the background particle counts exceed ISO Class 8 for 0.5 µm and larger particles; and
3. Documentation of compliance and the manufacturer's verification is maintained in the pharmacy's records.

I. Except as otherwise provided in this subsection (8), segregated compounding areas shall comply with all other applicable provisions of this rule.

J. High Risk CSPs may not be compounded in a segregated compounding area.

K. Relocation of the ~~compounding area or~~ segregated compounding area shall constitute a pharmacy remodel and require compliance with 20 CSR 2220-2.020.

(9) **ISO Certification.** All ISO classified areas and each PEC shall be certified to ensure compliance with requirements of this rule. Certification shall be performed by qualified individuals using recognized and appropriate certification and testing equipment:

A. Certification shall be performed ~~before initially~~ prior to beginning sterile compounding activities and every six (6) months thereafter. Recertification shall be completed whenever the physical structure of the buffer area or ante-area has been altered or any other facility changes or any changes to the PEC occur that may affect airflow or pressure differential. PECs shall also be recertified when the device is relocated or altered or major service to the PEC is performed.

B. Certification/re-certification shall be conducted in accordance with the Controlled Environment Testing Association Certification Guide for Sterile Compounding Facilities (2008), which is incorporated herein by reference. Copies of the Certification Guide for Sterile Compounding Facilities (2008) are published by, and available from, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607 or online at http://www.cetainternational.org/. This rule does not include any later amendments or additions to the Certification Guide. The pharmacy shall maintain an attestation or statement from the certifier verifying that certification/recertification was performed in compliance with Certification Guide guidelines.

C. Certification/recertification results shall be reviewed by a pharmacist once the completed results are received ~~to ensure compliance with this rule~~. Deficiencies or failures shall be investigated and corrected prior to further compounding. Corrections may include, but are not limited to, changes in the use of the affected PEC or the ongoing use/recall of CSPs. The identity of the pharmacist conducting the required review and the review date shall be documented in the pharmacy's records.

D. An in situ air pattern analysis (i.e. smoke study) shall be required prior to initial compounding and whenever maintenance, repairs or changes to the PEC or compounding area occur that may affect the airflow pattern. The in situ air pattern analysis shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the CSP under dynamic conditions. For purposes of this section, maintenance does not include routine pre-filter changes.

(10) **Equipment**. Compounding equipment shall be clean, properly functioning and effective for their intended use and shall be consistently capable of operating properly and within acceptable limits.

A. Equipment or other supplies shall be used, maintained, calibrated and verified for accuracy according to manufacturer recommendations, unless otherwise provided by Board rules.

B. Surfaces of compounding equipment that contact ingredients, in-process materials or drug products shall not be reactive~~, additive, adsorptive or absorptive~~ so as to alter the strength, stability, quality or purity of the drug product/CSP beyond that desired.

C. Automated compounding devices shall be tested for content, volume and weight accuracy prior to both initial and daily use. Test results shall be reviewed by a pharmacist to ensure compliance. The identity of the reviewing pharmacist and the review date shall be documented in the pharmacy's records.

D. In the event of improper or inaccurate functioning, the equipment/device shall not be used until the deficiency has been remedied.

E. If drug products/CSPs with special precautions for contamination are involved (i.e., penicillin), appropriate measures must be utilized in order to prevent cross-contamination (i.e., restricting equipment use for other operations/compounding or proper cleaning).

(11) **Primary Engineering Controls (PEC):** PECs shall be properly located, operated and maintained and shall comply with the following:

A. PECs must be located in a restricted access ISO Class 7 buffer area or in a segregated compounding area that complies with this rule and shall be placed in a manner to avoid conditions that could adversely affect their operation. PECs shall be located out of traffic patterns and away from conditions that could disrupt the intended airflow patterns (i.e., ventilation systems or cross-drafts).

B. PECs shall maintain ISO Class 5 or better conditions during dynamic operating conditions and while compounding sterile preparations, including, when transferring ingredients into and out of the isolator and during exposure of critical sites;

C. PECs shall provide unidirectional (laminar flow) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites.

D. Compounding Aseptic Isolators (CAI): Air exchange into the isolator from the surrounding environment shall not occur unless the air has first passed through a microbial retentive HEPA filter.

E. Compounding Aseptic Containment Isolators (CACI): Air exchange with the surrounding environment shall not occur unless the air is first passed through a microbial retentive HEPA filter system capable of containing airborne concentrations of the physical size and state of the drug being compounded. When volatile hazardous drugs are prepared, the exhaust air from the isolator shall be removed by properly designed building ventilation.

F. If an isolator is used, the recovery time to achieve ISO Class 5 air quality shall be identified in the pharmacy's policies and procedures and internal procedures developed to ensure adequate recovery time is allowed after material transfer and before or during compounding operations.

(12) **Ingredients and Supplies**. Compounding ingredients, supplies and containers shall be properly stored and secured in a clean, dry area to prevent contamination and to maintain the CSP's strength, quality and purity. Ingredients, drugs and supplies must be stored according to manufacturer or USP requirements and conditions.

A. Except as otherwise provided by the board by rule, pharmacists/pharmacies shall only receive, store or use drugs or active ingredients for compounding that have been received from a Missouri licensed pharmacy or drug distributor. Active ingredients must be manufactured in an FDA registered facility. Expired, misbranded, adulterated or contaminated products shall not be used in compounding.

B. Active ingredients and added substances or excipients for CSPs shall be compendial grade articles or shall be accompanied by a certificate of analysis from their supplier which shall be retained in the pharmacy's records.

~~C. Upon receipt of each lot of sterile compounding ingredients and prior to compounding, a visual inspection of the lot shall be conducted for evidence of unacceptable condition or quality.~~

~~D.~~C. Drugs, ingredients and supplies shall be shelved off the floor. Bulk or unformulated drug substances and added substances or excipients shall be stored in adequately labeled and tightly closed containers under temperature, humidity, and lighting conditions that are either indicated in official monographs or approved by the manufacturer.

~~E.~~D. ~~Products or i~~Ingredients that lack a supplier's expiration date cannot be used after one (1) year after receipt. The receipt date shall be recorded on the container of the product/ingredient.

~~F.~~E. Ingredient containers and container closures shall not be reactive, ~~additive, adsorptive or absorptive~~ so as to alter the strength, stability, quality or purity of the compounded drug beyond the desired result. Container systems shall provide adequate protection against foreseeable external factors that can cause deterioration or contamination of the CSP.

~~G.~~F. **Single-Dose and Multiple Dose Vials/Containers**. Single and multiple-dose vials/containers used in compounding shall be labeled with the date and time of initial entering or opening and a beyond-use date after which the product shall not be used.

1. Single-dose vials/containers exposed to ISO Class 5 or cleaner air may be used until the assigned beyond-use date which shall not exceed six (6) hours after initial needle puncture, unless otherwise specified by the manufacturer. Opened single-dose ampules shall not be stored for any time period.
2. Unless otherwise specified by the manufacturer, multiple-dose~~/use~~ vials/containers may be used until the assigned beyond-use date which shall not exceed twenty-eight (28) days after initially entering or opening (i.e., needle-puncture).

(13) **Standard Operating Procedures.** The following standard operating procedures shall be applicable to and observed in both compounding areas and segregated compounding areas:

A. Traffic flow in or around the compounding and segregated compounding areas shall be minimized and controlled.

B. Food items, chewing gum, eating, drinking and smoking are prohibited.

C. Nonessential objects that shed particles shall not be brought into the areas, including, but not limited to, pencils, cardboard cartons, paper towels, and cotton items (i.e., gauze pads).

D. Furniture, carts, supplies and equipment shall be removed from shipping cartons/containers and properly cleaned and disinfected before entering the compounding area or segregated compounding area. No shipping or other external cartons may be taken into the areas.

~~D.~~E. Carts/conveyances must be cleaned and disinfected before entering or returning to the ante area or buffer area.

~~E.~~F. Supplies and equipment shall be ~~decontaminated~~ disinfected before entering the ISO 5 PEC by wiping the outer surface with sterile alcohol or an equivalent or superior non-residue generating disinfectant.

~~F.~~G. Only supplies essential for compounding shall be stored in the buffer area. Supplies or ~~other~~ non-essential equipment shall not be stored in the PEC.

(14) **Personal Cleansing and Garbing.** Individuals engaged in, or assisting with, CSPs shall be trained and demonstrate competence in proper personal cleansing, garbing and gloving procedures. Competence must be documented and assessed through direct observation.

1. Except as otherwise provided herein, personal cleansing and garbing shall comply with USP Chapter 797.
2. In lieu of full garbing, compounding personnel using a CAI or CACI to compound non-hazardous drugs shall at a minimum don facial masks, non-shedding gowns and sterile gloves over the isolator gloves during compounding. Non-shedding gowns and gloves shall also be used during material handling. This section shall only be applicable if the CAI/CACI provides isolation from the room and is certified to maintain ISO Class 5 air quality during dynamic operating conditions as defined in 8 (G).

(15) **Aseptic Processing**. CSPs shall be prepared in a manner that maintains sterility and minimizes contamination and the introduction of particulate matter. Appropriate aseptic technique shall be utilized at all times.

A. Aseptic processing must be performed in at least ISO Class 5 conditions. Critical sites shall not be exposed to touch/contact contamination or worse than ISO Class 5 air.
B. Prior to ~~use~~compounding, drug products, ingredients and packaging shall undergo a visual unit-by-unit inspection to verify the components are free from defects and otherwise suitable for their intended use. Products or ingredients shall not be used if: (1) evidence of deterioration or contamination exists or is suspected, (2) an unauthorized break in any container, closure or seal is detected, (3) the contents do not have the expected appearance, aroma, or texture or (4) the beyond-use date or expiration date has been exceeded.
C. Only materials and equipment essential for aseptic compounding shall be placed in the primary engineering control. Materials and equipment shall be arranged in the DCA to allow a clear, uninterrupted path of HEPA-filtered air over critical sites at all times during compounding. Compounding staff shall not interrupt, impede, or divert flow of first-air from HEPA filters to critical sites.
D. All critical sites shall be wiped vigorously in one direction with sterile alcohol and allowed to air dry before being punctured or used.
E. Wetted gauze pads or other particle-generating material shall not be used to disinfect sterile entry points. If sterile, single-use alcohol prep pads are used, the surface of the pad shall not contact any other object before contacting the surface of the entry point.

F. When sterile supplies are received in sealed pouches designed to keep them sterile until opening, ~~the sterile item may be removed from the covering pouches as the supplies are introduced into the ISO Class 5 PEC without disinfecting the individual sterile supply items~~ the outer wrap must be disinfected before placement in the PEC. ~~However, s~~Syringes, needles, and tubing with an outer wrap shall remain in their individual packaging and shall only be opened in an ISO Class 5 work area.

G. Before compounding, staff shall visually confirm that ingredients used and measured in syringes match the prescription or medication order being compounded. Density or specific gravity values programmed in automated compounding devices shall be confirmed to be correct before and after delivering volumes of the liquids assigned to each channel or port.

(16) **Additional Aseptic Technique Requirements for High Risk CSPs.** In addition to section (15), the following requirements for high risk CSPs are applicable:

A. Presterilization procedures for High Risk CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 environment.

B. All non-sterile equipment that is to come in contact with the sterilized final high risk CSP shall be sterilized before introduction into the buffer area. Additionally, all nonsterile measuring, mixing and purifying devices shall be rinsed thoroughly with sterile water for irrigation, disinfected and thoroughly drained or dried before being used to compound.

C. All high risk CSPs must be sterilized before dispensing or distribution via a method recognized for the CSP type by USP Chapter 1211.

1. Water-containing CSPs that are nonsterile during any phase of the compounding procedure shall be sterilized within 6 hours after completing the CSP.
2. Filters used for sterilization shall be tested for integrity (i.e., bubble point testing) after use. Testing shall comply with manufacturer recommendations. Testing dates and results must be documented in the pharmacy's records and reviewed by a pharmacist prior to releasing the CSP.
3. Commercially available filters shall be approved for human use applications in sterilizing pharmaceutical fluids. Sterile filters used to sterilize CSPs shall be pyrogen free and a pore size of 0.20 to 0.22 microns. They shall be certified by the manufacturer to retain at least 10 to the seventh microorganisms of a strain of Brevundimonas (pseudomonas) diminute. The pharmacy must maintain this documentation for each filter utilized in the sterilization of CSPs.

D. Final containers used for high risk CSPs must be sterile and capable of maintaining CSP integrity until the beyond-use date. Sterilization methods must be based on the properties of the CSP.

(17) **End Preparation Testing**. End preparation testing for CSPs shall be conducted as required by this section. Finished CSPs must be quarantined pending results of any required testing. Except as otherwise allowed by this rule, CSPs shall not be dispensed until all end-preparation testing results are final and meet required results. Quarantine dates and time periods must be documented in the pharmacy's records. The results of any end preparation testing (i.e., sterility, endotoxin and potency) shall be reviewed by a pharmacist

A. **Low Risk**: Low Risk CSPs shall undergo sterility testing if ~~the preparation is stored for more than~~ the beyond-use date exceeds 48 hours at controlled room temperature, 14 days at ~~cold~~ refrigerated temperature, and 45 days in solid frozen state at -25° to -10° Celsius or colder.

B. **Medium Risk:** Medium Risk CSPs shall undergo sterility testing if the ~~CSP is stored for~~ beyond-use date exceeds more than 30 hours at controlled room temperature, 9 days at ~~cold~~ refrigerated temperature, and 45 days in solid frozen state at - 25° to -10° Celsius or colder.

C. **High Risk**: At a minimum, the following testing shall be required for high risk CSPs:

1. **Sterility Testing:** All High Risk CSPs must be tested for sterility without exception in accordance with a method recommended or required by USP Chapter 71. Samples for sterility testing shall be collected immediately after CSP completion. The sampling plan shall comply with USP Chapter 71, Tables 2 and 3.

2. **Bacterial Endotoxin (Pyrogen) Testing:** All high risk parenteral, epidural or intrathecal ~~sterile preparations or administered via epidural or intrathecal route~~ CSPs shall be tested for bacterial endotoxins using a USP Chapter 85 recognized method for bacterial endotoxin testing.

3. **Potency Testing:** Final potency shall be confirmed by validated instrumental analysis for each CSP that has been assigned a beyond-use date of more than thirty (30) days. The final CSP shall maintain a potency within monograph limits for USP articles or, in the absence of a monograph, of +\- 10%. Testing of each CSP/batch is not required once potency has been established for the specific CSP if no modifications have been made to the compounding procedure, process or formula (i.e., ingredient sources, batch size or equipment).

4. **Antimicrobial Effectiveness Testing**: All high risk multiple dose CSPs must be ~~dose~~ tested for antimicrobial effectiveness. Testing must comply with USP Chapter 51. Testing of each CSP/batch is not required once antimicrobial effectiveness has been established for the specific CSP if no modifications have been made to the compounding procedure, process or formula (i.e., ingredient sources, batch size or equipment).

D. **Emergency Dispensing**: CSPs may be dispensed for immediate administration to a patient prior to receiving the results of the testing required by this rule if:

1. No alternative product/CSP is available and the patient will be exposed to negative risks if therapy is delayed. The reason for the emergency dispensing shall be documented in the pharmacy's records; and
2. The prescriber/ordering health care provider is informed the CSP will be dispensed prior to receiving test results and approves the dispensing. Prescriber/provider approval shall be documented in the pharmacy's records. A separate authorization from the prescriber/provider is required for each emergency dispensing.
3. This section shall not be construed to exempt any person or entity from performing any testing required by this rule.

(18) **Labeling**. Except as otherwise provided herein, CSPs dispensed to patients shall be labeled in accordance with section 338.059, RSMo, and with the following supplemental information affixed to the CSP:

A. Beyond-use date;

B. ~~Date of preparation~~~~compounding~~ Compounding date, if different from the date the prescription is filled;

C. The actual name of each active or therapeutic ingredient;

D. The amounts or concentration of all active or therapeutic ingredients;

E. Total volume;

~~E.~~F. The pharmacy's phone number;

G. Storage requirements;

~~F.~~H. If given to a patient, a statement indicating "This is a compounded preparation";

~~G.~~I. Any CSP or device specific instructions for use including the route of administration and the rate of administration, and;

~~H.~~J. Auxiliary labels when applicable.

~~I.~~K. When a CSP is packaged in individual containers and dispensed to the patient in a labeled outer container as required above, the individual containers must be labeled with the CSP name, lot number and beyond use date.

(19) **Final Verification**. Prior to dispensing, a pharmacist shall physically verify that the CSP has been properly prepared, sterilized, packaged and labeled and that all required end-preparation testing has been performed and documented. The following quality assurance measures shall be performed by a pharmacist before a CSP is dispensed or distributed:

1. Compounding records shall be reviewed to verify that the correct measurements, volumes, quantities, calculations and sterilization procedures were used. If an automated compounding device was used, a pharmacist must verify proper calibration and verify that data entered into the device was correct and accurate, including, but not limited to, density or specific gravity values.
2. The final CSP must be visually inspected for physical integrity, clarity and expected appearance. Additionally, each compounded unit shall be inspected against lighted white or black background or both for evidence of visible particulates or other foreign matter. Visual inspection shall not be required for hazardous drugs if the inspection may be harmful.

(20) **Beyond-Use Dating**. All CSPs must be assigned a beyond-use date. Beyond-use dates shall be determined from the date or time the CSP is compounded. The nature of the drug and its degradation mechanism, drug stability, sterility considerations, antimicrobial effective testing results, container packaging, storage conditions and the intended duration of therapy shall be considered. CSPs shall not be dispensed past the assigned beyond-use date.

A. For Low and Medium Risk CSPs, beyond-use dates shall be assigned based on any of the following resources: USP Chapter 797, the manufacturer's labeling, direct testing using validated testing methods, compendial references or peer-reviewed literature based on CSP-specific experimental studies/testing.
B. High Risk CSPs: Beyond-use dates not specifically referenced in the manufacturer's approved labeling or in a USP monograph or not established by CSP specific instrumental analysis shall be limited to thirty (30) days after compounding. High risk CSPs with beyond-use dates greater than thirty (30) days shall undergo laboratory testing using validated methods prior to release to verify stability (sterility and potency) for the maximum beyond-use date. Testing of each CSP/batch is not required once stability has been established for the specific CSP as required by this subsection and no modifications have been made to the compounding procedure, process or formula.

(21) **Point-of-Care Activated Systems .** In addition to other applicable requirements:

A. Point-of-Care activated systems shall be assembled within an ISO Class 5 environment and assigned a beyond-use date in accordance with the manufacturer's recommendations or labeling.

B. The beyond-use date of an assembled non-activated system shall be limited to a maximum of fifteen (15) days unless the pharmacy has documentation from the system's manufacturer that a longer date is acceptable. When dispensed, an assembled non-activated system shall be labeled with beyond-use dates for both activated and non-activated states. The compounding record must document both dates.

C. Point of care activated systems shall be stored in accordance with the manufacturer's labeling and recommendations.

(22) **Storage**. ~~Sterile preparations shall be properly stored and maintained. Preparations~~ CSPs shall be stored strictly in accordance with the conditions stated on the ingredient label, if applicable. Adulterated, misbranded, expired or contaminated CSPs shall be segregated and quarantined from the compounding area and other drug inventory and properly disposed of.

A. If storage at controlled room temperature is directed, an article may alternatively be stored and distributed in a cool place as defined by USP, unless otherwise specified in the individual USP monograph or on the label.

B. Temperature excursions shall be allowed as permitted or recognized by USP.

C. Any excess CSP shall be stored and accounted for under conditions dictated by the CSP's composition and stability characteristics to ensure its strength, quality and purity. Excess CSPs shall be labeled with the name and strength of the drug(s), an in-house lot number, date of ~~preparation~~ compounding, volume and beyond-use date.

(23) **Packaging and Delivery**. CSPs shall be packaged, stored, transported and delivered in a manner that will preserve the physical integrity, sterility, stability, and purity of the CSP. Packaging shall be selected that simultaneously protects CSPs from damage, leakage, contamination, and degradation and protects individuals transporting packed CSPs from harm. Prescription delivery shall comply with applicable provisions of 20 CSR 2220-2.013. The pharmacy shall establish a mechanism for the patient/ultimate user to report packaging or transporting concerns to the pharmacy and documenting any reports received.

(24) **Compounding Log**: A compounding log shall be maintained that records/documents each CSP made. The compounding log shall be maintained at the pharmacy separate from the prescription record, either electronically or in writing, and shall be immediately available upon request. Each compounding entry shall be verified and manually or electronically signed or initialed by the verifying pharmacist. The following information shall be recorded in the compounding log for each CSP:

(A) Compounding date;

(B) The identity of the compounder and the pharmacist performing the final verification required by section (19) of this rule ~~pharmacist~~, if different;

(C) A list of ingredients and their amounts by weight or volume;

(D) Description of the compounding process, including, the compounding method, formula or recipe and, if necessary for proper compounding, the order of adding drug products and ingredients. For High Risk CSPs, the log must also include sterilization and testing methods. The information required by this subsection may be separately maintained in the pharmacy's records if immediately available on request;

(E) The identity of the source, lot number and the expiration or beyond-use date of each ingredient, as well as an in-house lot number and a beyond-use date for batch bulk CSPs;

(F) An identifying prescription number or a readily retrievable unique identifier;

(G) The beyond-use date assigned to the CSP and placed on the label;

(H) For High Risk CSPs, the type of container and container lot number, if applicable; and

(I) Any CSP storage conditions included on the CSP label or in materials provided to the patient.

(25) **Aseptic Manipulation Training and Assessment**. Compounding staff shall be skilled and trained to accurately and competently perform the duties assigned and to operate any equipment used. At a minimum, compounding staff must undergo Aseptic Competency Training and an Aseptic Technique Skill Assessment as follows:

A. Aseptic Competency Training: Aseptic competency training shall include both didactic and experiential training and may be tailored to the pharmacy's activities. Didactic training must include an instructional component along with a testing or evaluation method to verify competency. Staff shall be trained to perform the duties assigned when the level of sterile activity or sterile compounding methods change. Aseptic competency training must be completed for all risk levels prior to initial compounding and every twelve (12) months thereafter.

B. Aseptic Technique Skill Assessment: A practical aseptic technique skill assessment shall be completed for all individuals compounding sterile preparations to verify aseptic competency. The assessment must include glove fingertip sampling, media-fill testing and a direct visual evaluation of the individual's competency. The visual observation shall assess:

1. Proper aseptic technique, manipulations and work practices, including, but not limited to, avoiding touch contamination, proper use of first air and if applicable, sterilizing high risk CSPs;
2. Sanitation and disinfection;
3. Hand hygiene, gloving and garbing;
4. Identifying, weighing, and measuring of ingredients;
5. Maintaining and achieving sterility in ISO Class 5 areas and within primary engineering controls, and;
6. Labeling and inspecting CSPs for quality.

C. The required Aseptic Technique Skill Assessment must be completed for staff compounding low or medium risk CSPs prior to initial compounding and every twelve (12) months thereafter. For staff compounding high risk CSPs, the assessment must be completed prior to initial compounding and every six (6) months thereafter.

D. Compounding staff shall successfully pass all training and assessments. Staff who fail to demonstrate competency or whose glove fingertip sampling or media-fill tests demonstrate one or more units of visible microbial contamination shall be reinstructed and re-evaluated to ensure correction of all deficiencies prior to beginning or continuing any further compounding. The reinstruction and revaluation shall be documented in the pharmacy's records.

E. Training and assessment dates along with the results of the required practical aseptic technique skill assessment, glove fingertip sampling and media-fill testing shall be reviewed and documented ~~and maintained in the pharmacy's records and reviewed~~ by the pharmacist-in-charge ~~to ensure compliance~~ or his/her~~their~~ designee.

(26) **Glove Fingertip Sampling.**

Compounding staff shall undergo and successfully complete both initial and ongoing glove fingertip sampling to assess compliance with gloving and aseptic processing. Initial and ongoing fingertip sampling shall be completed in accordance with USP Chapter 797 procedures, timeframes and methods. Glove fingertip sampling ~~Ongoing sampling~~ shall be conducted following each required media-fill test. ~~In addition to USP requirements, samples must be tested for mold, yeast, bacteria and fungus.~~

(27) **Media-Fill Testing**. Pharmacies shall establish and follow policies and procedures for conducting media-fill testing to assess the quality of aseptic skills/techniques of compounding staff. Media-Fill tests shall be conducted as part of the required aseptic technique skill assessment and shall include a minimum of three media-fill units using the same container or closure. Media-fill tests shall represent the most challenging or stressful conditions actually encountered by the personnel being evaluated Initial and ongoing media-fill testing shall be completed in accordance with USP Chapter 797 recommended procedures and methods for the applicable risk level(s). ~~In addition to USP requirements, samples must be tested for mold, yeast, bacteria and fungus.~~

(28) **Environmental Sampling.** Environmental sampling shall be routinely conducted in all ISO classified areas to evaluate air quality compliance and microbial bio burden levels. Sampling shall be conducted during dynamic operating conditions in accordance with USP Chapter 797. Surface samples and viable airborne particle samples shall be tested for bacteria, fungus, mold and yeast. Sampling shall occur as follows:

A. **Surface Sampling**: Surface sampling shall be conducted in accordance with USP Chapter 797 using both general growth media and fungal specific media. Surface sampling for pharmacies engaged in Low Risk and Medium Risk must be performed every 30-days. For High Risk compounding, surface sampling shall be performed every fourteen (14) days.

B. **Viable Airborne Particle Testing**: Volumetric viable air sampling by impaction shall be conducted in all ISO classified environments. Each viable air sample shall sample 1,000 liters for all ISO areas ~~Class 5 areas and 500 liters for other ISO classified areas.~~ Each sample location shall be tested with both general growth media (i.e., tryptic soy agar) and fungal specific media (i.e., malt extract agar or saboraud dextrose agar) on plates of at least 55mm in size. Use of settling plates alone shall not be sufficient. Viable Airborne Particle Testing must be conducted prior to initial compounding and every six (6) months thereafter. Testing shall also occur:

1. As part of the initial certification of new facilities and equipment;
2. Whenever the physical structure of the compounding area has been altered;
3. As part of the recertification of facilities and equipment;
4. In response to identified problems with CSPs or end-preparation testing failure; and
5. Whenever maintenance, repairs or changes to the primary engineering control(s) or compounding area may affect the airflow pattern. The date and type of maintenance, repair or change shall be documented in the pharmacy's records;

C. **Non-Viable Airborne Particle Testing**. Non-viable air sampling shall be performed using a volumetric device in compliance with USP Chapter 797. Non-Viable Airborne Particle Testing must be conducted prior to initial compounding and every six (6) months thereafter.

D. **Pressure Differential**: Pressure differential monitoring shall be required for all sterile compounding areas to ensure compliance with section (7)(B) of this rule. Alternatively, a continuous pressure monitoring system may be maintained if the system maintains ongoing documentation of pressure recordings, or if applicable, pressure alerts/notifications that are reviewed daily. ~~Pressure differential monitoring results shall be documented in writing and reviewed daily.~~ Documentation of the required review shall be maintained in the pharmacy's records or otherwise accessible to the pharmacy.

(29) **General Cleaning and Disinfection Requirements**. The pharmacy shall establish and follow written policies and procedures governing all aspects of cleaning and disinfection. Except as otherwise provided herein, the following requirements shall be applicable:

A. Compounding areas and segregated compounding areas shall be free of infestation by insects, rodents and other vermin. Trash shall be disposed of in a timely and sanitary manner.

B. Cleaning and disinfection shall be performed and conducted in accordance with USP Chapter 797 timeframes and procedures, except as otherwise provided herein.

C. Individuals responsible for cleaning and disinfecting shall be trained in proper cleaning and disinfection procedures and mechanisms prior to performing cleaning/disinfection activities. Training shall include direct visual observation of the individual's cleaning and disinfecting process by qualified staff. The individual shall be annually reassessed for competency through direct visual observation. Documentation of the required training and training dates shall be maintained in the pharmacy's records. Individuals who fail to demonstrate competency shall be reinstructed and successfully reevaluated prior to cleaning or disinfecting the compounding or segregated compounding area.

D. Cleaning, disinfection and mopping activities shall be performed using approved agents and procedures described in the pharmacy's written policies and procedures. Cleaning and disinfecting agents shall be selected based on compatibility, effectiveness and the absence of inappropriate or toxic residues. Manufacturers' directions or published peer-reviewed literature for minimum contact time shall be followed.

E. Primary engineering controls shall be cleaned with a germicidal ~~detergent~~ agent followed by sterile alcohol. Sterile water for irrigation shall be used to dilute germicidal agents used inside the PEC that require dilution.

F. Routine disinfection of the direct compounding area (DCA) is conducted to minimize microbial surface contamination and maintain ISO Class 5 air quality. At a minimum, the DCA shall be cleaned and disinfected prior to compounding, between batches and whenever contamination is suspected using sterile alcohol or an equivalent or superior agent which is allowed to dry immediately prior to compounding.

G. ***Segregated Compounding Areas***: Floors and work surfaces within the line of demarcation shall be cleaned and disinfected daily or immediately prior to compounding if not used daily. Shelving and storage areas shall be cleaned and disinfected monthly.

(30) **Quality Assurance**. Sterile compounding pharmacies shall establish and follow a written quality assurance program for monitoring and evaluating the quality of compounding activities.

A. At a minimum, the quality assurance program shall include procedures for monitoring and tracking infection rates, adverse drug events, CSP recalls and complaints from prescribers, patients or other individuals or entities.

B. The quality assurance plan shall delineate the individuals responsible for each aspect of the quality assurance program either by name or position title.

C. The quality assurance plan shall be maintained at the pharmacy or readily retrievable upon request. The pharmacist-in-charge shall annually review the quality assurance program and document the review in the pharmacy's records.

(31) **Recalls**. A recall must be initiated when a ~~dispensed or distributed~~ CSP is deemed to be misbranded, adulterated or non-sterile or if end-preparation testing results are out of specification. The pharmacy shall notify the prescriber of the nature of the recall, the problem(s) identified and any recommended actions to ensure public health and safety. In cases where the CSP has the potential to harm the patient, the same notification shall be provided to all patients that received the recalled CSP(s).

A. Patient and prescriber notifications required by this section shall be made as soon as reasonably practicable but in no event later than one (1) business day of the recall. The date and manner of notification shall be documented in the pharmacy's records.

B. If a patient recall notification is unsuccessful, the pharmacy shall mail notification to the patient within the required one (1) business day timeframe.

C. Recalls initiated pursuant to this section shall be reported to the board in writing within three (3) business days.

D. If recall notification cannot be conducted as required herein, the pharmacy may submit to the Board a written plan to extend the notification period. The request must include a description of the nature of the recall, the potential number of patients affected, the reason(s) supporting the extension request and a proposed timeframe for completing the required notifications.

(32) **Record Keeping**. The pharmacy shall maintain the following records:

A. Aseptic competency training and aseptic technique skill assessment dates and results;
B. Testing dates and results for glove fingertip sampling, media-fill tests and end-CSP testing;
C. Environmental sampling dates and results, including, any corrective efforts taken;
D. Cleaning and disinfection evaluation dates and results;
E. Required refrigerator and temperature logs;
F. Cleaning and disinfection records that document compliance with this rule;
G. Equipment calibration dates and results and maintenance reports;
H. Certificates of analysis for compounding ingredients, if applicable;
I. Certification records for PECs and sterile compounding areas;
J. Copies of any manufacturer equipment standards that are relied upon to maintain compliance with this rule;
K. Batch CSP files;
L. For high risk CSPs, sterilization, quarantine and ingredient validation records;
M. Emergency dispensing records as required by subsection (17), including, documentation of prescriber authorization and the dates of such authorization;
N. CSP recall records, including, dates, patients affected and any investigation, corrective actions or recall notifications made; and
O. All other records required by this rule or governing law.
P. Except as otherwise provided herein, records and reports required by this rule shall be either electronically or physically maintained for two (2) years. Records shall be readily retrievable and subject to inspection by the Board of Pharmacy or its agents upon request. At a minimum, records shall be physically or electronically produced immediately or within two (2) hours of a request from the Board or the Board's authorized designee.
Q. Prescription records shall be maintained in compliance with Missouri law and the rules of the Board.

(33) **Hazardous Drugs.** Hazardous drugs shall be prepared, stored and compounded in accordance with the USP-NF. Compounding staff engaged in handling, preparing or compounding hazardous drugs shall be trained as required by USP-NF and the rules of the Board. The following additional requirements shall be implemented to insure the protection of the staff involved:

A. Hazardous drugs/CSPs shall be stored, handled and prepared under conditions that protect workers and other staff.

B. Appropriate disposal containers shall be available for used needles, syringes, and if applicable, hazardous waste from the CSP of chemotherapy agents and infectious waste. Disposal of hazardous waste shall comply with all applicable local, state and federal requirements;

C. Written procedures for handling major and minor spills and generated waste of hazardous agents must be developed and must be included in the policy and procedure manual, and;

D. Prepared doses of hazardous drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

(34) **Applicability.** If a conflict between this rule and the applicable provisions of USP exists, the requirements of this rule shall apply unless otherwise indicated herein. In the interest of public protection, the use of an alternative technology, technique, material or procedure not specifically included in this rule or USP shall only be authorized if an exemption is approved by the Board. The exemption request must be in writing and must include:

(A) A description of the exemption requested and the reasons supporting the request;

(B) Testing or other scientific evidence demonstrating the technology, technique, material or procedure is equivalent or superior with statistical significance to those included in this rule or USP. Peer-reviewed literature shall be insufficient without actual proof of the testing or other scientific evidence methods and results supporting the request;

(C) A detailed statement of any hardship or public harm that will occur if the exemption is not granted, and;

(D) Any other evidence requested by the Board.

(35) Effective Date. Compliance with this rule shall be required within six (6) months after this rule becomes effective. Pharmacies that hold a current and active pharmacy permit on the effective date of this rule shall be granted an additional one (1) year after such effective date to comply with the provisions of section (7) or (8) of this rule that require physical or structural changes to the pharmacy to be compliant. The one (1) year exemption shall not apply to pharmacies that undergo a change of ownership or change of location.