Draft Compounding Regulation: Full Committee Compiled Draft as of 5/30/2025

99-48. Compounding Generally.

A. These regulations are applicable to all individuals and facilities engaged in the compounding, administration, sale, transfer, distribution, or dispensing of compounded preparations for use by humans or animals, including but not limited to compounding by practitioners who may otherwise be exempted from facility permitting by the Board.

B. Engaging in the practice of compounding constitutes the practice of Pharmacy, and upon receipt of a complaint by the South Carolina Board of Medical Examiners, the South Carolina Board of Nursing, the South Carolina Board of Veterinary Medical Examiners, or any other licensing board against a licensed practitioner related to pharmaceutical compounding, the Board of Pharmacy has the jurisdiction to inspect the location where the compounding occurred and to otherwise fully investigate the complaint to the extent the practice of Pharmacy is reasonably implicated. If a violation of the Pharmacy Practice Act is found, the Board may, as it deems appropriate, refer the completed investigation to the relevant licensing board for discipline along with a recommendation for appropriate sanctions.

C. The Board acknowledges that the compounding standards published by the private nonprofit organization known as the United States Pharmacopeia (USP) are utilized by federal authorities and regulatory bodies in many other states. However, the Board has determined that in furtherance of South Carolina's citizens' access to compounded preparations, as deemed appropriate by licensed prescribers in the context of a patient-prescriber relationship, South Carolina is well-served by not adopting the USP-NF standards outright.

D. If a facility or individual engaged in compounding is held to the higher standard of another governmental agency or body, such as an accrediting body, the facility or individual should comply with the more stringent standard.

E. Bulk drug substances may only be used in compounding when such bulk drug substances:

(1) Comply with the standards of an applicable United States Pharmacopoeia or National Formulary ("USP-NF") monograph, if such monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding; or are drug substances that are components of drugs approved by the FDA for use in the United States; or are otherwise approved by the FDA; or are manufactured by an establishment that is registered by the FDA; and

(2) Are distributed by a licensed wholesale distributor or registered nonresident wholesale distributor, or are distributed by a supplier otherwise approved by the Board and the FDA to distribute bulk drug substances if the compounder can establish purity and safety by reasonable means, such as lot analysis, manufacturer reputation, or reliability of the source. Documentation of this determination and any supporting documents must be maintained with the compounding record.

F. Compounding may be conducted using ingredients that are not considered drug products in accordance with the USP-NF standards and guidance on pharmacy compounding.

G. The compounding of inordinate amounts of any preparation in cases in which there is no observed historical pattern of prescriptions and dispensing to support an expectation of receiving a valid prescription for the preparation. The compounding of an inordinate amount of a preparation in such cases constitutes the manufacturing of drugs and appropriate federal and State permits are required. Such compounding conducted without the appropriate Board-issued permit constitutes unpermitted practice of Pharmacy.

H. Facility design must be appropriate for the risk level of compounded preparations prepared by the facility.

I. Pharmacy technicians, both state certified and non-state certified, with the appropriate training and demonstrated competency may compound under the direct, in-person supervision of a South Carolina-licensed pharmacist at a South Carolina-permitted facility. Pharmacy technicians may not compound under the supervision of a physician, physician assistant, nurse, or any other practitioner.

99-49. Compounding Definitions.

A. Compounding is defined as the preparation, mixing, assembling, packaging, or labeling of a drug or device:

(1) as the result of a practitioner's prescription drug or medication order based on the practitioner-patient-pharmacist relationship in the course of professional practice;

(2) for administration to a patient by a practitioner as the result of a practitioner's initiative based on the practitioner-patient-pharmacist relationship in the course of professional practice;

(3) in anticipation of prescription drug or medication orders based on routine, regularly observed prescribing patterns; or

(4) for or as an incident to research, teaching, or chemical analysis and not for sale or dispensing, except as permitted by law.

B. The following words and terms, when used in this section, shall have the following meanings, unless the
context clearly indicates otherwise.

(1) ACPE--Accreditation Council for Pharmacy Education.

(2) Airborne particulate cleanliness class--The level of cleanliness specified by the maximum allowable number of particles per cubic meter of air as specified in the International Organization of Standardization (ISO) Classification Air Cleanliness (ISO 14644-1). For example:

(a) ISO Class 5 (formerly Class 100) is an atmospheric environment that contains less than 3,520 particles 0.5 microns in diameter per cubic meter of air (formerly stated as 100 particles 0.5 microns in diameter per cubic foot of air);

(b) ISO Class 7 (formerly Class 10,000) is an atmospheric environment that contains less than 352,000 particles 0.5 microns in diameter per cubic meter of air (formerly stated as 10,000 particles 0.5 microns in diameter per cubic foot of air); and

(c) ISO Class 8 (formerly Class 100,000) is an atmospheric environment that contains less than 3,520,000 particles 0.5 microns in diameter per cubic meter of air (formerly stated as 100,000 particles 0.5 microns in diameter per cubic foot of air).

(3) Ancillary supplies--Supplies necessary for the preparation and administration of compounded sterile preparations.

(4) Anteroom--An ISO Class 8 or better area where personnel may perform hand hygiene and garbing procedures, staging of components, order entry, labeling, and other high particulate generating activities. It is also a transition area that:

(a) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas; and

(b) reduces the need for the heating, ventilating and air conditioning (HVAC) control system to respond to large disturbances.

(5) Aseptic Processing--The technique involving procedures designed to preclude contamination of drugs, packaging, equipment, or supplies by microorganisms during preparation.

(6) Automated compounding device--An automated device that compounds, measures, and/or packages a specified quantity of individual components in a predetermined sequence for a designated sterile preparation.

(7) Batch--A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced during a single preparation cycle.

(8) Batch preparation compounding--Compounding of multiple sterile preparation units, in a single discrete process, by the same individual(s), carried out during one limited time period. Batch preparation/compounding does not include the preparation of multiple sterile preparation units pursuant to patient specific medication orders.

(9) Beyond-use date--The date or time after which the compounded sterile preparation shall not be stored or transported or begin to be administered to a patient. The beyond-use date is determined from the date or time the preparation is compounded.

(10) Biological Safety Cabinet, Class II--A ventilated cabinet for personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA filtered laminar airflow for product protection, and HEPA filtered exhausted air for environmental protection.

(11) Buffer Area, Buffer or Core Room, Buffer or Clean Room Areas, Buffer Room Area, Buffer or Clean Area, or Buffer Zone--An ISO Class 7 area where the primary engineering control area is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding sterile preparations.

(12) Clean room or controlled area--A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.

(13) Competency--Demonstrated capability of personnel to perform their job duties safely and effectively, particularly in the realm of sterile compounding. This includes possessing the necessary knowledge, skills, and abilities to maintain a safe environment and ensure patient safety.

(14) Component--Any ingredient intended for use in the compounding of a drug preparation, including those that may not appear in such preparation.

(15) Compounding Aseptic Isolator--A form of barrier 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 shall not occur unless it has first passed through a microbial retentive filter (HEPA minimum).

(16) Critical Area--A critical area is an ISO Class 5 environment.

(17) Critical Sites--Sterile ingredients of compounded sterile preparations and locations on devices and components used to prepare, package, and transfer compounded sterile preparations that provide opportunity for exposure to contamination.

(18) Cytotoxic--A pharmaceutical that has the capability of killing living cells.

(19) Device--An instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent, or other similar or related article, including any component part or accessory, that is required under federal or State law to be ordered or prescribed by a practitioner.

(20) Disinfectant--A disinfectant is an agent that frees from infection, usually a chemical agent but sometimes a physical one, and that destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial spores. It refers to substances applied to inanimate objects.

(21) Hot water--The temperature of water from the pharmacy's sink maintained at a minimum of 105 degrees F (41 degrees C).

(22) HVAC--Heating, ventilation, and air conditioning.

(23) Immediate use—A sterile preparation for immediate use may be appropriate in situations where delaying the administration by preparing the necessary CSPs in a more suitable environment would pose risks to the patient's health or well-being. See R.99-50(F) for relevant requirements.

(24) IPA--Isopropyl alcohol (2-propanol).

(25) Media-Fill Test--A media-fill test is used to qualify aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce sterile preparation without microbial contamination. During this test, a microbiological growth medium such as Soybean--Casein Digest Medium (SCDM) is substituted for the actual drug product to simulate admixture compounding. The issues to consider in the development of a media-fill test are the following: media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required.

(26) Multiple-Dose Container--A multiple-unit container for articles or preparations intended for potential administration only and usually contains antimicrobial preservatives. The beyond-use date for an opened or entered (e.g., needle-punctured) multiple-dose container with antimicrobial preservatives is 28 days, unless otherwise specified by the manufacturer.

(27) Negative Pressure Room--A room that is at a lower pressure compared to adjacent spaces and, therefore, the net flow of air is into the room.

(28) Office use--The administration of a compounded drug to a patient by a practitioner in the practitioner's office or by the practitioner in a health care facility or treatment setting, including a hospital, ambulatory surgical center, or pharmacy in accordance with State and federal law.

(29) Pharmacy Bulk Package--A container of a sterile preparation for potential use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. The pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

(30) Prepackaging--The act of repackaging and relabeling quantities of drug products from a manufacturer's original container into unit dose packaging or a multiple dose container for distribution within a facility licensed as a Class C pharmacy or to other pharmacies under common ownership for distribution within those facilities. The term as defined does not prohibit the prepackaging of drug products for use within other pharmacy classes.

(31) Preparation or Compounded Sterile Preparation--A sterile admixture compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber.

(32) Primary Engineering Control--A device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding sterile preparations. Such devices include, but may not be limited to, laminar airflow workbenches, biological safety cabinets, and compounding aseptic isolators.

(33) Product--A product is a commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the U.S. Food and Drug Administration (FDA). Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or product package insert.

(34) Positive Control--A quality assurance sample prepared to test positive for microbial growth.

(35) Positive Pressure Room--A room that is at a higher pressure compared to adjacent spaces and, therefore, the net airflow is out of the room.

(36) Quality assurance--The set of activities used to ensure that the process used in the preparation of sterile drug preparations lead to preparations that meet predetermined standards of quality.

(37) Quality control--The set of testing activities used to determine that the ingredients, components (e.g., containers), and final compounded sterile preparations prepared meet predetermined requirements with respect to identity, purity, non-pyrogenicity, and sterility.

(38) Reasonable quantity--An amount of a compounded drug that:

(a) does not exceed the amount a practitioner anticipates may be used in the practitioner's office or facility before the beyond use date of the drug;

(b) is reasonable considering the intended use of the compounded drug and the nature of the practitioner's practice; and

(c) for any practitioner and all practitioners as a whole, is not greater than an amount the pharmacy is capable of compounding in compliance with pharmaceutical standards for identity, strength, quality, and purity of the compounded drug that are consistent with United States Pharmacopoeia guidelines and accreditation practices.

(39) Single-dose container--A container intended for a single use, other than single-dose vials and single-dose large volume potential solutions. Examples of single-dose containers include pre-filled syringes, cartridges, and fusion-sealed containers without preservatives.

(40) Single-dose vial--A vial intended for a single use. Exceptions to this definition would be single dose vials routinely used to compound total potential nutrition (TPN) preparations (e.g., sodium chloride, sodium acetate, sodium phosphate, potassium chloride, potassium acetate, potassium phosphate, calcium glucontae, magnesium sulfate, multivitamin for injection, multi-trace elements, ascorbic acid, folic acid, heparin, phytonadione, l-carnitine, cysteine, selenium, injectable zinc).

(41) Single-dose large volume parenteral (LVP) solution--LVP solutions (i.e., containers of solution of at least 1000 mL) routinely used for compounding sterile TPN preparations or for batch compounding (e.g., sterile water for injection (SWFI); 5%, 10%, and 70% dextrose in SWFI; 0.9% sodium chloride; 0.45% sodium chloride; 5% dextrose/0.9% sodium chloride; 5% dextrose/0.45% sodium chloride).

(42) SOPs--Standard operating procedures.

(43) Terminal Sterilization--The application of a lethal process, e.g., steam under pressure or autoclaving, to sealed final preparation containers for the purpose of achieving a predetermined sterility assurance level of usually less than 106, i.e., or a probability of less than one in one million of a non-sterile unit.

(44) USP/NF--The current edition of the United States Pharmacopeia/National Formulary.

99-50. Sterile Compounding Regulations Applicability

A. These regulations are applicable to any permit or license holder that engages in the preparation of compounding sterile preparations (CSPs) for human and/or animal drugs that will be dispensed pursuant to a legitimate prescription or will be provided to a healthcare provider solely for them to administer within their clinical practice setting within their respective scope of practice.

B. A 503A compounding pharmacy permitted by the Board may prepare, but is not limited to, the following preparations:

(1) injections, including infusions;
(2) irrigations for internal body cavities excluding the mouth, rectum, or sinus cavity;
(3) ophthalmic dosage forms;
(4) pulmonary inhalations;
(5) baths or soaks for live organs or tissues;
(6) implants; and
(7) additional patient-specific preparations authorized by the Board.

C. Category 1 Compounds.

(1) May be prepared in a Segregated Compounding Area (SCA) or a cleanroom suite
(2) Must be prepared using aseptic technique
(3) Do not require terminal sterilization
(4) Do not require sterility testing
(5) May be provided a beyond used date (BUD) according to Table 1

Table 1 : Beyond Use Dates for Category 1 CSP's	
Controlled Room Temperature (20-25 degrees Celsius)	**Refrigerator (2-8 degrees Celsius)**
≤ 12 hours	≤ 24 hours

D. Category 2 Compounds.

(1) Must be prepared in a cleanroom suite
(2) Must be prepared using aseptic technique
(3) May require terminal sterilization, if appropriate, in order to be assigned an extended BUD
(4) May require successful sterility testing supplemented by endotoxin testing as appropriate, that meets the requirements of USP <71> or a validated, noninferior, alternative method, in order to be assigned an extended BUD

(5) May be provided a beyond used date according to Table 2

Table 2: Beyond Use Dates for Category 2 CSP's			
WITHOUT Terminal Sterilization or Sterility Testing			
Prepared from ≤ 1 non-sterile starting components		**Prepared from sterile starting components**	
Controlled Room Temp	1 day	Controlled Room Temp	4 days
Refrigerator	4 days	Refrigerator	10 days
Freezer	45 days	Freezer	45 days
WITHOUT Terminal Sterilization but WITH Sterility Testing			
Controlled Room Temp		30 days	
Refrigerator		45 days	
Freezer`		60 days	
WITH Terminal Sterilization but WITHOUT Sterility Testing			
Controlled Room Temp		14 days	
Refrigerator		28 days	
Freezer		45 days	
WITH Terminal Sterilization and Sterility Testing			
Controlled Room Temp		45 days	
Refrigerator		60 days	
Freezer		90 days	

*Controlled Room Temp = 20 to 25° C; Refrigerator = 2 to 8° C; Freezer = -25 to -10° C

E. Category 3 Compounds:

(1) Must be prepared in a cleanroom suite

(2) Must be prepared using aseptic technique

(3) May require terminal sterilization, if appropriate, in order to be assigned an extended BUD

(4) Require Release Testing of each batch or lot: sterility testing supplemented by endotoxin testing as appropriate, that meets the requirements of USP <71> or a validated, noninferior, alternative method

(5) Additional testing, personnel competency, environmental monitoring and sporicidal disinfectant applications are recommended for assignment of extended BUD, as described in Section […], due to increased risk of microbial proliferation, chemical degradation, physical incompatibilities, and compromised container closure.

(a) Recommended once per formulation:

(i) Stability testing obtained using stability-indicating analytical method (ex: forced degradation studies).

(ii) Particulate-matter testing for injections and ophthalmic preparations

(iii) Package integrity/Container Closure Evaluation for each formulation and each container closure system

(6) May be provided a beyond used date according to Table 3

Table 3: Beyond Use Date for Category 3 CSP's			
WITH Sterility Testing but WITHOUT Terminal Sterilization		**WITH Sterility Testing and Terminal Sterilization**	
Controlled Room Temp	60 days	Controlled Room Temp	90 days
Refrigerator	90 days	Refrigerator	120 days
Freezer	120 days	Freezer	180 days

(7) Testing

(a) Stability Test: the analytical method must be validated based on characteristics described in USP <1225>;

(b) Process Delineation: The CSP must be prepared according to the same formulation from which the stability data was derived;

(c) Container Closure: The Category 3 CSP must be packaged and stored in a container closure that is comprised of the same materials that was used in the stability study noted above;

d) Particulate matter testing for injections and ophthalmic solutions: conducted once per formulation with an acceptable result

e) Package Integrity Evaluation: Conducted once per formulation and container closure system combination, the container closure system used must be evaluated for conformance via the container closure integrity test to the end of the BUD as per USP <1207>

F. Immediate-Use CSPs

(1) Compounding sterile preparations for immediate use may be appropriate in situations where delaying the administration by preparing the necessary CSPs in a more suitable environment would pose risks to the patient's health or well-being.

(2) When all of the below conditions are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, 2, or 3 CSPs:

(a) Aseptic techniques, processes, and procedures are followed;

(b) Personnel are trained and demonstrate competency at least annually in aseptic processes in question;

(c) The preparation is performed in accordance with available literature regarding the drugs physical and chemical compatibility;

(i) The preparation involves not more than three (3) unique or distinct sterile products. For purpose of clarity, if using multiple vials of a given product (i.e. same NDC), this would count as one (1) distinct product.

(ii) Any unused starting component must be disposed of after preparation, and all single-dose containers must be used for no more than one (1) patient; and

(iii) Administration begins within one (1) hour following the start of preparation

(d) Docking and activation of proprietary bag and vial systems in accordance with the manufacturer's labeling for immediate administration to an individual or patient is not considered compounding and may be performed in unclassified space. Docking of a proprietary bag and vial systems for future administration (i.e. more than one hour after docking) is compounding and should follow all applicable standards regarding compounding aside from the products BUD. The assigned BUD should be established based on the systems instruction for use (IFU) provided by the manufacturer.

G. Multi-dose CSPs are CSPs formulated to contain multiple doses that will be dispensed in a single container.

(1) Multi-dose CSPs must be prepared as a Category 2 or Category 3 CSP as delineated in sections D and E above.

(2) If these formulations are aqueous in nature and the compounder provides a BUD of greater than 4 days room temperature storage, 10 days with refrigerated storage or 45 days with frozen storage, they must pass antimicrobial effectiveness testing in accordance with USP Chapter 51. The compounder may rely on antimicrobial effectiveness testing:

(a) Conducted once for each formulation in the respective container closure system in which it will be dispensed; or

(b) Results from an FDA-registered facility or published in a peer reviewed literature source so long as the CSP formulation and container closure system are an exact match to the publication unless a bracketing study is performed.

(3) After a multi-dose container is opened or utilized initially, it must not be used for longer than the BUD or twenty-eight (28) days, whichever is shorter.

99-51. Sterile Compounding: Facility Design.

A. Sterile compounding facilities must be designed, outfitted, and maintained properly to maintain the required air quality classification through primary engineering controls (PECs) and secondary engineering controls (SECs). The ISO Air Quality Standards below must be followed.

Table 1. ISO Air Quality Standards

ISO Class	Particle Count per Cubic Meter
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

B. A cleanroom suite consisting of an anteroom and buffer room, or a segregated compounding area (SCA) may be used depending on the type of compounding being performed. These areas must be separated from areas not directly related to compounding.

(1) The cleanroom suite must be separated from the surrounding unclassified areas of the facility by fixed walls and doors.

(2) The anteroom must have a line of demarcation or other suitable delineation to separate the clean side from the dirty side, with the clean side being closest to the buffer room.

(3) If using a cleanroom suite, PEC's must be placed within the buffer room

(4) A PEC may be placed in an unclassified SCA for use in compounding only Category 1 CSP's

(a) The area within one (1) meter of the PEC must be defined by a visible line of demarcation and should be dedicated only for sterile compounding.

(b) The SCA must be located away from unsealed windows, doors that connect to the outside, and high traffic flow areas that may adversely affect the air quality of the PEC within the SCA

5) Access to the compounding areas must be restricted to authorized personnel and required materials.

C. Facilities used for compounding CSPs must be designed so that air quality improves with movement through the separate operational areas (anterooms, buffer rooms) to the PEC.

(1) Anterooms providing access only to positive pressure buffer rooms must meet at least ISO Class 8 classifications.

(2) Anterooms providing access to negative-pressure buffer rooms must meet at least ISO Class 7 classification.

(3) A buffer room must meet at least ISO Class 7 air quality.

(4) PEC's placed within a buffer room must maintain ISO Class 5 or better air quality during dynamic operating conditions

D. Temperature and humidity in the cleanroom suite must be controlled through a heating, ventilation, and air conditioning (HVAC) system.

(1) Free-standing air conditioners, humidifiers, and dehumidifiers must not be used within the classified area or the SCA.

(2) The cleanroom suite should be well-lit and maintained at a temperature of 20 degrees Celsius or cooler and a relative humidity of 60% or below to minimize the risk of microbial proliferation and to provide comfortable conditions for compounding personnel attired in required garb.

(3) The temperature and humidity must be monitored either manually or by a continuous recording device in each cleanroom suite and documented at least once daily or stored in the continuous recording device on days compounding is performed. These logs must be readily retrievable.

(4) Temperature and humidity monitoring devices must be verified as accurate at least every twelve (12) months or as required by the manufacturer.

E. All classified rooms must be equipped with a pressure-differential monitoring system

F. Air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer room and anteroom.

G. Air returns in the cleanroom suite must be low on the wall unless smoke studies demonstrate the lack of stagnant airflow with the facilities equipment and HVAC return and supply configuration

H. If a pass-through chamber is used, both doors must never be opened at the same time, and doors should be interlocking.

I. Seals and sweeps should not be installed at doors between buffer rooms and anterooms.

J. Tacky mats must not be placed within ISO-classified areas.

K. If compounding both sterile and nonsterile preparations, the respective PECs must be placed in separate rooms if the single room cannot maintain ISO Class 7 classification.

(1) If the PECs for sterile and nonsterile compounding are placed in the same room, they must be at least one (1) meter apart, and particle generating activity must not be performed when sterile compounding is in process.

L. Types of permissible PECs are laminar airflow system (LAFS), restricted-access barrier system (RABS), and pharmaceutical isolator.

(1) LAFS, RABS, and pharmaceutical isolators must have a dynamic airflow smoke pattern test performed initially and at least every six (6) months. This also applies if a robotic enclosure is used as the PEC or placed within the PEC.

(2) The LAFS must provide unidirectional HEPA-filtered airflow and should be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns inside the PEC.

(3) Antineoplastic and/or hazardous drug compounding may be conducted in a Class II Biological Safety Cabinet (BSC) or a Compounding aseptic containment isolator (CACI). Exhaust air from a BSC must be externally vented. External venting is not required if a containment ventilated enclosure (CVE) is configured with multiple (i.e. 2 or more) HEPA filters in series.

(4) Minimum Requirements for Placement of PECs for Compounding Non-HD CSPs:

(a) Laminar Airflow Workbench (LAFW), Class II Biological Safety Cabinet (BSC), Compounding Aseptic Isolators (CAI or CACI), and Pharmaceutical Isolator can be located in Unclassified SCA if used for Category 1 CSPs or ISO Class 7 buffer rooms with ISO Class 8 Positive-Pressure anteroom if used for Category 2 and/or 3 CSPs.

(b) Integrated Vertical Laminar Flow Zone (IVLFZ) is only allowed for placement in ISO Class 7 buffer rooms with ISO Class 8 Positive-Pressure anteroom

M. Total air exchange requirements for cleanroom suites, measured in terms of the number of air changes per hour (ACPH) for Non-HD Sterile Compounding Areas:

(1) At least fifteen (15) ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling.

(2) The total ACPH must be documented on the certification report.

N. Continuous Pressure differentials should be maintained to minimize airflow for an area with lower air-quality classification to an area of higher air-quality classification.

(1) A minimum differential positive pressure of 0.020-inch water column is required between ISO-classified areas of the buffer room and anteroom for non-hazardous CSPs.

(2) A minimum differential positive pressure of 0.020-inch water column is required between the anteroom and unclassified area.

(3) A minimum differential negative pressure between 0.01 to 0.03 -inch water column is required between the buffer room and anteroom for hazardous CSPs

(4) No pressure differential is required between the SCA and the surrounding area.

(5) A pressure differential monitoring device must be used to continuously monitor the pressure differentials and the results must be reviewed and documented at least daily on days when compounding is occurring.

O. Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components must complete presterilization procedures, such as weighing and mixing, in an ISO Class 8 or better containment ventilated enclosures (CVEs), BSCs, or CACIs to minimize the risk of airborne containment. CVEs, BSCs, or CACIs used for presterilization procedures must be certified at least every twelve (12) months.

P. Easily cleanable conditions must exist in the cleanroom suite.

(1) The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and nonshedding so they can be cleaned and disinfected and to minimize spaces in which microorganisms and other contaminates can accumulate.

(2) Surfaces must be resistant to damage by cleaning agents, sporicidal and other types of disinfectants and the tools used to clean.

(3) Junctures between the ceiling and the walls and between walls and the floor must be sealed to eliminate cracks and crevices where dirt can accumulate.

(4) Ceilings with inlaid panels must be caulked around each panel to seal them to the support frame or clipped in place.

(5) Walls must be constructed of or otherwise must be covered with durable material such as epoxy paint or heavy-gauge polymer and the integrity of the surface must be maintained.

(6) Panels must be joined together and sealed to each other and the support structure.

(7) Floors must include coving to the sidewall, or the juncture between the floor and the wall must be caulked.

(8) Classified areas should minimize dust collecting overhangs (such as utility pipes) and ledges (such as windowsills). If overhangs are present, they must be easily cleanable.

(9) The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed.

(10) Any other penetrations through the ceiling or walls not named in this section must be sealed.

(11) The requirements in this section also apply to SCAs and all surfaces therein.

Q. In facilities with a cleanroom suite, the sink used for hand hygiene may be placed either inside or outside of the anteroom.

(1) If the sink is located outside of the anteroom, it must be located in a clean space to minimize the risk of bringing contaminants into the anteroom.

(2) If the sink is located inside the anteroom, it may be placed on either the clean side or the dirty side of the anteroom and the order of washing and garbing should be defined in the facilities SOPs based on this placement.

R. The buffer room must not contain plumbed water sources.

S. The anteroom must not contain floor drains.

T. If installed, sprinkler systems should be recessed and covered, and the covers should be easily cleanable.

U. If using an SCA, a hand washing sink must not be placed closer than one (1) meter to the PEC and may be either inside the SCA or in close proximity to the SCA.

V. Surfaces of the sink must be cleaned and disinfected each day of use and a sporicidal disinfectant must be applied at least monthly.

W. Only furniture, equipment, and other materials necessary for performing compounding activities are permitted in a classified area or SCA unless an accommodation is made in the facilities policies and procedures for additional items or equipment in the compounding space.

(1) The materials must be low-shedding, easily cleaned and disinfected, not impact environmental air quality and must be in place during dynamic airflow smoke pattern test to demonstrate minimal disruption in airflow.

(2) Equipment and other items used in a classified area or SCA should not be removed except for calibration, servicing, cleaning, or other activities associated with maintenance and if removed must be cleaned and wiped with sterile 70% isopropyl alcohol (IPA) or a suitable disinfectant before they are returned to the classified area or SCA.

(3) Carts used to transport components or equipment into classified areas must be constructed from nonporous materials with cleanable casters and wheels to promote mobility and ensure ease of cleaning and disinfection.

(4) Carts should not be moved from an area of lower sterility to an area of higher sterility unless the entire cart, including casters, is cleaned and disinfected.

(5) No shipping cartons or other corrugated or uncoated cardboard are allowed in a classified area or SCA.

(6) Materials for performing compounding activities that have been exposed in patient care and treatment areas must not enter anterooms, buffer rooms, or segregated compounding areas unless thoroughly cleaned and disinfected.

99-52. Sterile Compounding: Certification.

A. All classified areas and PECs must be independently certified before being used to confirm that they are meeting the ISO air quality standards required.

B. Testing for certification must include:

(1) airflow testing;

(2) HEPA filter integrity testing;

(3) total airborne particle count testing; and

(4) dynamic (e.g. under normal operation conditions or conditions that simulate normal operations) airflow smoke pattern testing.

C. Measurements of total airborne particle samples in classified areas and PECs should be at locations that reflect the quality of air in the room and locations where there is greatest risk of exposed CSPs.

D. Recertification should occur at least every six (6) months.

E. Classified areas additionally must be recertified if there are changes to the area such as redesign, construction, replacement or relocation of any PEC, or alteration in the configuration of the room that could affect airflow or air quality.

F. A corrective action plan must be implemented and documented in response to any out-of-range results.

99-53. Sterile Compounding: Personnel Training and Evaluation.

A. All personnel engaging in compounding or who have direct oversight of compounding personnel or verify finished CSPs must be initially trained and qualified by demonstrating knowledge and competency in compounding CSPs before being allowed to perform their job functions independently.

B. The designated person is responsible for creating, implementing, maintaining, and updating a training program for all personnel involved in the compounding facilities operations.

(1) This training program must be outlined in the facilities policies and procedures and must include detail on:

(a) the required training by role (i.e. staff overseeing compounding, compounding staff, checking pharmacist, etc.)

(b) the required training frequency;

(c) the process for evaluation competency for individual involved in compounding; and

(d) the oversight of compounding, including those who complete in-process or final checks of CSPs.

(2) All training and competency assessment documentation must be retained on site upon completion and for a period of at least two (2) years thereafter.

(3) Training must be completed initially and then at least annually thereafter for all compounding personnel.

(a) Competency assessments for gowning, garbing, glove fingertip sampling and aseptic manipulation must be completed initially, then compounding staff compounding Category 1 and 2 CSPs must successfully recomplete the competency every six (6) months, compounding staff compounding Category 3 CSPs must successfully recomplete the competency every three (3) months and staff who

oversee compounding or those involved in the facility operations but not involved in compounding must successfully recomplete the competency annually.

(4) At minimum, training must include:

(a) hand hygiene;

(b) garbing;

(c) cleaning and disinfection of both the PEC and SEC;

(d) calculations and measuring and mixing as applicable to the organizations compounding processes;

(e) aseptic technique and principles of HEPA airflow within ISO 5 Area;

(f) proper use of PECs and any other applicable equipment; and

(g) principles of movement of materials and personnel within the compounding area.

C. The following specific training and assessment procedures must be completed and documented as part of the training program:

(1) Gowning and Garbing

(a) Prior to compounding Category 1, 2, or 3 CSPs or having oversight of compounding personnel in any form or fashion, compounding staff must complete initial garbing competency.

(b) This competency must be passed in three consecutive independent successful iterations.

(c) The assessment includes visual observation and evaluation of the personnel's garbing as well as successful gloved fingertip and thumb sampling following garbing.

(d) Gloved fingertip sampling must be completed prior to any sterile 70% IPA is applied to the gloves and must be performed on donned sterile gloves on both hands within a classified area or segregated compounding area (SCA). This assessment is considered to be failed if improper gowning technique is observed or any CFUs (> 0 CFU) are noted on any media utilized for the gloved fingertip sampling. The following sampling procedures must be utilized.

(i) When sampling, use one media device per hand and ensure that media contains general microbial growth agar supplemented with neutralizing additives.

(ii) Label the media after collection and incubate the media in an incubator at 30 to 35 degrees Celsius for no less than forty-eight (48) hours followed by 20 to 25 degrees Celsius for no less than five (5) additional days.

(iii) Results must be documented and an action plan must be developed for any failures. The log must include name of personnel evaluated and evaluating, evaluation date and time, media and components used, including manufacturer, LOT and expiration date, temperature ranges for incubation, dates of incubation and temperatures on those respective dates, results and identification of observer of final results.

(2) Aseptic Manipulation Competency

(a) After successfully completing the initial gowning and garbing competencies and prior to compounding independently or having oversight of compounding personnel these individuals must complete an aseptic manipulation competency evaluation including:

(i) visual observation of aseptic technique

(ii) Media fill testing

(iii) (Gloved finger tip & thumb sampling on each hand

(iv) surface sampling of the direct compounding area (DCA)

(b) The aseptic manipulation portion of the challenge must mimic the most challenging compounding activity that staff routinely complete while replacing the components with soybean-casein digest media.

(c) If using commercial growth media, a certificate of analysis must be obtained and included with the results that demonstrate that the media supports the growth of microorganisms.

(d) If preparing media in house, the growth promotion must be demonstrated for each batch

(e) All media must be appropriately stored as per labeling prior to utilization.

(f) Following completion of the media fill challenge, it is to be incubated in an incubator at 20 to 25 degrees Celsius for a minimum of seven (7) days as well as 30 to 35 degrees Celsius for a minimum of seven (7) days in the sequence as delineated in the facilities policies and procedures

(g) Failure of the media fill test occurs if any samples show turbidity or other visual manifestations of growth in the media on or prior to the final (i.e. fourteenth) day of incubation.

(h) Immediately following the media fill challenge, gloved fingertip and thumb sampling must be performed on both hands and the direct compounding area in the ISO Class 5 PEC. Sterile 70% IPA shall not be applied immediately prior to these samplings.

(i) Successful completion of the gloved fingertip sampling is no more than three (3) CFU cumulative between both hands.

(ii) Surface sampling of the direct compounding area is successful if no more than three (3) CFU are noted on the sample.

(i) Any failing results require a corrective action plan to investigate and remediate the results.

99-54. Sterile Compounding: Cleaning and Disinfection.

A. Definitions. For purposes of this subsection, the following definitions apply:

(1) "Cleaning" is the process of removing materials from the surfaces using a combination of mechanical processes and a cleaning agent

(2) "Cleaning agents" are typically surfactants, used for the removal of substances from surfaces

(3) "Disinfection agents" are chemical or physical agents used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria

(4) "Sporicidal agents" are chemical or physical agents that destroy bacterial and fungal spores when used at a sufficient concentration for a specified contact time. Sporicidal agents are expected to kill all vegetative microogranisms.

B. Cleaning Process and Agents

(1) All cleaning activities must be completed by trained personnel.

(2) When cleaning, personnel must be appropriately gowned and garbed.

(3) Each facility's standard operating procedures must outline the cleaning process, the cleaning agents to be used, and the days/frequencies that each respective agent is utilized.

(4) Published data must be followed in respect to the appropriate contact time for each of the cleaning, disinfecting, and sporicidal agents used.

D. Cleaning Frequencies

(1) Surfaces in areas used to prepare CSPs must be cleaned, disinfected, and have sporicidal disinfectants applied according the frequencies outlined below:

Table 1. Cleaning, Disinfecting, and Sporicidal Disinfecting Frequency

Area/Location	Cleaning	Disinfection	Application of Sporicidal Disinfectant
Removable work tray of the PEC, if applicable	• Work surfaces of the tray daily when compounding occurs • All surfaces and the area under the tray monthly	• Work surface of the tray on days when compounding occurs • All surfaces and the area under the tray monthly	• Work surfaces of the tray monthly • All surfaces and the area under the tray monthly
Pass-through chambers	• Daily on days when	• Daily on days when	• Monthly for facilities

	compounding occurs	compounding occurs	compounding Category 1 and or Category 2 CSP • Weekly for facilities compounding any Category 3 CSPs
Work surface(s) outside of the PEC	• Daily on days when compounding occurs	• Daily on days when compounding occurs	
Floors	• Daily on days when compounding occurs	• Daily on days when compounding occurs	
Wall(s), Door(s), and Door Frame(s)	• Monthly	• Monthly	• Monthly
Ceiling(s)[A]			
Storage Shelve(s) and Bin(s)			
Equipment outside the PEC(s)			
Sink(s)	• Daily on days when compounding occurs	• Daily on days when compounding occurs	• Monthly

[A] Ceilings of the SCA are only required to be cleaned, disinfected, and applied with sporicidal disinfectants when visible soiled or when surface contamination is known or suspected

(2) Additionally, in a PEC, sterile 70% IPA must be applied after cleaning and disinfection, or after the application of a one-step disinfectant or sporicidal disinfectant. Sterile 70% IPA must also be applied immediately before compounding.

(3) During the compounding process, sterile 70% IPA must be applied to the horizontal work surface, including any removable work trays, of the PEC at least every thirty (30) minutes or at the conclusion of the compounding session if it takes greater than thirty (30) minutes.

99-55. Sterile Compounding: Environmental Monitoring.

A. Sterile compounding facilities must develop and implement written SOPs for microbiological air and surface monitoring.

B. A facility's microbiological air and surface monitoring program must include:

(1) viable impact airborne particulate sampling; and

(2) surface sampling

C. The microbiological air and surface monitoring program must also include the collection and evaluation of samples from various air and surface locations to detect airborne and surface contaminants.

D. Corrective action in response to any adverse findings is required to maintain the necessary environmental quality for preparation of CSPs.

E. Microbiological air and/or surface monitoring must be conducted in all classified areas during dynamic operating conditions and PECs to confirm that the required environmental quality is maintained. Sampling must be performed at the following frequency and in the below circumstances:

(1) Initially for sterile compounding facilities;
(2) Viable air sampling every six (6) months for entities compounding Category 1 and 2 CSPs;
(3) Viable air sampling at least monthly for entities compounding Category 3 CSPs;
(4) Surface sampling at least monthly for entities compounding Category 1 and 2 CSPs;
(5) Surface sampling at least weekly for entities compounding Category 3 CSPs;
(6) In conjunction with the certification of new facilities and equipment;
(7) After any servicing of facilities or equipment;
(8) In response to identified problems (positive growth in sterile tests of CSPs);
(9) In response to identified trends (repeated positive fingertip results or failed media testing); and
(10) In response to changes that could impact the sterile compounding environment (change in cleaning agent).

F. Personnel must be trained and competent in surface sampling procedures to ensure accuracy. If viable air samples are collected by facility personnel, this must be delineated in policy and the personnel completing this activity must be trained and competent to ensure accuracy.

G. All impaction air samplers must be serviced and calibrated as recommended by the manufacture.

H. A general microbiological growth media that supports the growth of bacteria and fungi must be used

I. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device.

J. The incubator must be placed in a location outside the sterile compounding area.

K. Active air sampling procedures for viable airborne monitoring must include the following steps:
(1) Using the impaction air sampler, test at least one (1) cubic meter or 1000 L of air from each location sampled;
(2) Incubate the media device at 30 to 35 degrees Celsius for no less than forty-eight (48) hours;
(3) Examine growth, and record the total number of discrete colonies of microorganisms on each media device as CFU per cubic meter of air on an environmental sampling form based on sample type, sample location, and sample date;
(4) Then, incubate the media device at 20 to 25 degrees Celsius for no less than five (5) additional days;
(5) Examine growth, and record the total number of discrete colonies of microorganisms on each media device as CFU per cubic meter of air on an environmental sampling form based on sample type, sample location, and sample date.

L. In the alternative to the procedures in section K above, to shorten the overall incubation period, the following active air sampling procedures for viable airborne monitoring may be utilized:
(1) Two samples may be collected for each sample location incubated concurrently. Both media devices may be TSA or one media device may be TSA and the other fungal media (e.g., malt extract agar or sabouraud dextrose agar);
(2) Incubate each media device in a separate incubator, incubating one media device at 30 to 35 degrees Celsius for no less than forty-eight (48) hours and incubating the other media device at 20 to 25 degrees Celsius for no less than five (5) days;
(3) If fungal media are used as one of the samples, incubate the fungal media sample at 20 to 25 degrees Celsius for no less than five (5) days;
(4) Count the total number of discrete colonies of microorganisms on each media device and record these results.

M. Action levels for viable airborne particle sampling are:

Table 1. Viable Airborne Particle Sampling Action Levels

ISO Class	Air Sampling Action Levels [cfu/cubic meter (1000 liters) of air/media device]
5	>1
7	>10
8	>100

N. Surface sampling procedures must include the following steps:

(1) Collect surface samples within the PEC per the facility SOP at locations delineated in the facility SOP

(2) Cover and invert the plates;

(3) Incubate the media device at 30 to 35 degrees Celsius for no less than (48) forty-eight hours;

(4) Examine growth, and record the total number of discrete colonies of microorganisms on each media device on an environmental sampling form based on sample type, sample location, and sample date;

(5) Then, incubate the media device at 20 to 25 degrees Celsius for no less than five (5) additional days;

(6) Examine growth, and record the total number of discrete colonies of microorganisms on each media device on an environmental sampling form based on sample type, sample location, and sample date.

O. In the alternative to the procedures in section N above, to shorten the overall incubation period, the following surface sampling procedures may be utilized:

(1) Two (2) samples may be collected for each sample location incubated concurrently. Both media devices may be TSA or one media device may be TSA and the other fungal media (e.g. malt extract agar or sabouraud dextrose agar);

(2) Incubate each media device in a separate incubator, incubating one media device at 30 to 35 degrees Celsius for no less than forty-eight (48) hours and incubating the other media device at 20 to 25 degrees Celsius for no less than five (5) days;

(3) If fungal media are used as one of the samples, incubate the fungal media sample at 20 to 25 degrees Celsius for no less than five (5) days;

(4) Count the total number of discrete colonies of microorganisms on each media device and record these results; and

(5) Record the results of the sample on an environmental sampling form based on sample type and include the sample location and sample date.

P. Action levels for viable surface sampling are:

ISO Class	Surface Sampling Action Levels (cfu/media device)
5	>3
7	>5
8	>50

(1) If two (2) sampling media devices are collected at a single location, all recovered growth on each must be documented and action levels applied to each sampling media device separately.

(2) If levels measured during the monitoring program exceed the levels, the cause must be investigated, and corrective actions taken. The corrective action plan must be documented and should include resampling of failed areas to confirm corrective action was successful.

(3) An attempt must be made to identify any microorganisms recovered to the genus level, if the action level is exceeded

99-56. Sterile Compounding: Cleanroom Activities and Workflows.

A. Personnel Preparation. All personnel entering a compounding area where Category 1, 2, or 3 CSPs are prepared must take appropriate steps to minimize contamination of the environment and of CSPs.

(1) Individuals with a higher risk of contaminating the environment or CSPs include those with visible rashes, recent tattoos, oozing sores, conjunctivitis, and active respiratory infections. These individuals must report these conditions to the Designated Individual and obtain approval to enter the compounding area prior to doing so.

(2) Food and drinks shall not enter any classified compounding space or segregated compounding area.

(3) Prior to entering the compounding area, at a minimum, personnel must:

(a) Remove unnecessary outer garments or accessories (e.g. bandanas, coats, hats, jackets, vests, sweaters, headphones, ear buds, etc.);

(b) Remove all cosmetic products (i.e. makeup, artificial eyelashes, etc.);

(c) Remove all visible jewelry including hand, wrist, and other visible jewelry that impedes the form or function of the PPE as determined by the designated individual's assessment ;

(d) Ensure that nails are kept clean and neatly trimmed to minimize particle shedding and avoid glove punctures. Nail products (i.e. polish, artificial nails, and extenders) must not be worn; and

(e) Wipe eyeglasses, if worn.

(f) Necessary electronic devices that are introduced into the classified area(s) must be disinfected as delineated by policy in regards to both process and frequency

B. Hand Hygiene. Any person entering a compounding area where Category 1, 2, or 3 CSPs are compounded must wash their hands and forearms, up to the elbows, with soap and warm water before initiating compounding activities.

(1) Brushes must not be used for hand hygiene.

(2) Hand dryers must not be used.

(3) To minimize the risk of contamination, disposable soap containers must not be refilled or topped off.

(4) While performing hand hygiene, personnel must:

(a) clean underneath their fingernails using a nail pick;

(b) ensure that handwashing last for at least thirty (30) seconds; and

(c) dry their hands and forearms fully using a low-lint disposable towel or wiper.

(5) Prior to donning sterile gloves, but after completing hand hygiene, personnel must sanitize their hands with alcohol-based hand rub and allow it to fully dry.

(6) Sterile gloves must be donned in classified room or segregated compounding area, but other aspects of hand hygiene can be performed in different stages of the gowning process depending on the facility's layout.

(7) The appropriate sequence of hand hygiene steps for each facility must be delineated in SOPs.

C. Garbing. Any person entering a compounding area where Category 1, 2, or 3 CSPs are compounded must be properly garbed.

(1) Garb must be donned and doffed in a sequence that reduces the risk of contamination to both personnel and the area.

(2) The required garb, manner of storage, and order of garbing must be outlined in the facilities standard operating procedures.

(3) If a facility is preparing Category 2 or Category 3 CSPs:

(a) All garb must be donned in a classified area prior to entering the buffer room;

(b) If hand hygiene is completed outside of a classified area, alcohol-based hand rub must be used immediately prior to donning garb;

(c) Bare skin must not be exposed inside the ISO Class 5 PEC, accordingly gloves must not be donned or doffed in the ISO Class 5 PEC to expose bare hands; and

(d) Donning and doffing of PPE by different personnel should not occur simultaneously.

(4) The minimum garbing requirements for Category 1 and 2 CSPs include the following:

(a) low-lint garment with sleeves that fit snugly around the wrist and an enclosed neck (i.e. gown or coverall);

(b) low-lint covers for shoes;

(c) low-lint headcover(s) that covers the all hair and ears;

(d) low-lint cover for facial hair, if applicable;

(e) low-lint face mask; and

(f) sterile, powder-free gloves (If using a RABS, disposable gloves should be worn inside the gloves attached to the RABS's sleeves and sterile gloves must be worn over the gloves attached to the RABS's sleeve.).

(5) Garb must be replaced immediately if it becomes visible soiled, its integrity is compromised, or if it is removed from the classified environment.

(6) If compounding Category 1 and 2 CSPs, gowns can be reused on a single compounding day as long as they are not soiled or dirty and are hung in an area within anteroom or SCA and in a manner that minimizes contamination when not in use.

(7) If a facility compounds Category 3 CSPs, additional garbing requirements must be continuously met in the buffer room in which any Category 3 CSPs are prepared. The following additional garbing requirements must be followed in the buffer room where Category 3 CSPs are prepared at all times, regardless as to whether Category 3 CSPs are being prepared on that given day or not:

(a) Do not allow any exposed skin in the buffer room;

(b) All low-lint outer garb must be sterile;

(c) If a RABS is used, sterile gloves must be worn over gauntlet gloves

(d) Disposable garbing items must not be reused;

(e) Laundered garb must not be reused without being re-laundered and re-sterilized with a validated cycle; and

(f) The facilities SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

D. Donning Gloves. Gloves must be donned in a classified room or segregated compounding area after hand hygiene has been completed and after an alcohol-based hand rub has been applied and allowed to dry.

(1) Gloves must be sterile and powder free.

(2) After gloves are donned (except in the case of gloved fingertip sampling), they must be immediately sprayed with sterile 70% IPA. This application must be repeated immediately prior to compounding and regularly throughout the compounding process.

(3) Gloves must be inspected for holes, punctures, or tears immediately after being donned and routinely during the compounding process. If such defects are detected, the gloves must be replaced immediately.

(4) RABS sleeves and gloves and or pharmaceutical isolator sleeves and gloves must be changed as per the manufacturers recommendations and as defined in the facilities standard operating procedures.

99-57. Sterile Compounding: Compounding Activities.

A. Introducing Items into the SEC.

(1) Before an item is placed into the clean side of an anteroom, placed into a pass-through chamber, or brought into a SCA, it must be wiped with a sporicidal disinfectant, EPA registered disinfectant, or sterile 70% IPA using a low lint wiper by personnel who should be donning gloves.

(a) If an EPA registered disinfectant or sporicidal disinfectant is utilized it must be allowed to dwell for a period of time that meets or exceeds the manufacturers minimum contact time.

(b) If sterile 70% IPA is used, it must be allowed to dry.

(2) The wiping process must not compromise the package integrity or render the label unreadable.

(3) If the wiping process renders package integrity or renders a label unreadable, other steps must be taken to ensure the cleanliness of the compounding area is maintained and monitored.

(4) All such steps must be documented in the facility's SOPs.

B. Introducing Items into the PEC.

(1) Prior to any item being introduced into the PEC, it must be wiped with sterile 70% IPA using low lint wipers and allowed to dry prior to use unless the item is received in sealed containers designed to keep them sterile until such container is opened.

(2) When a sealed container renders the inner components sterile, these components may be removed from the container just prior to being placed in the PEC and are not required to be wiped with sterile 70% IPA.

C. Use of Sterile 70% IPA on Critical Sites.

(1) Critical site(s) must be wiped with sterile 70% IPA in the PEC to provide both chemical and mechanical actions to remove contaminants.

(2) The sterile 70% IPA must be allowed to dry before compounding personnel enter or puncture stoppers and septums or break ampule necks.

D. Compounding Equipment.

(1) Equipment used in compounding CSPs, and equipment that will be in classified areas, must be of suitable composition such that the surfaces are not reactive to the various cleaning agents in which they will come in contact with nor are they sorptive.

(2) All equipment must be disinfected prior to being placed in the SEC and or PEC as outlined previously.

(3) Once placed, equipment must be positioned in a manner that facilitates compounding operations.

(4) Equipment must follow the equipment manufacturers' established SOPs for calibration, maintenance, cleaning, and use of the equipment.

(5) Activities, including calibration, verification, and maintenance, must be documented as per the facility's SOPs, and records of these activities must be maintained for at least two (2) years.

(6) Prior to using automated compounding devices or other such compounding equipment, compounding personnel must be trained and demonstrate competency on using the equipment.

(a) After initial training occurs and competency is demonstrated, on the start of each compounding day, trained and competent compounding personnel must verify equipment for accuracy prior to using the equipment to compound any CSPs.

(b) Compounding personnel must maintain a daily record of these reviews on the days that compounding occurs, and these logs must be maintained for a period of at least two (2) years.

E. Compounding with Powders.

(1) If a facility's process requires weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles, the facility must have SOPs in place detailing the specific locations where these activities occur and whether these activities must be completed in a PEC or other closed system processing device. These procedures must ensure that the compounding staff and or other CSPs are not contaminated by exposure to these airborne particles.

(2) When it is determined that the facility's process could generate airborne chemical particles, during each certification, non-viable particle counting must be completed during the completion of each activity in the facility's process capable of such particle generation to ensure that the cleanroom's design maintains ISO criteria when these processes are underway.

99-58. Sterile Compounding: Compounding Components.

A. Standard Operating Procedures.

(1) Each facility must have SOPs that address the type of components and type of compounding completed at the facility.

(2) Each facility's SOPs must address the selection, receipt, evaluation, handling, storage, and documentation of each CSP components as well finished CSPs.

B. Component Selection.

(1) Conventionally manufactured sterile products should be used when available and appropriate for the intended CSP.

(2) When APIs are used:

(a) Must comply with the criteria in the USP-NF monograph, if one exists;

(b) Must have a COA that includes the specifications and that the test results for the component show that the API meets expected quality; and

(c) Must be manufactured by an FDA-registered facility.

(3) For all components other than APIs:

(a) Must comply with the criteria in the USP-NF monograph, if one exists;

(b) Must have a COA that includes the specifications and that the test results for the component show that the API meets expected quality; and

(c) Must be manufactured by an FDA-registered facility, or if a component cannot be obtained from such a facility, the Designated Individual must select an acceptable and reliable source. The compounding facility must establish the identify, strength, purity, and quality of the ingredients.

(4) API and other Components:

(a) All input APIs and other components used to prepare the respective CSP must be evaluated for suitability for use in sterile drug preparation.

(b) Components labeled with "not for pharmaceutical use," "not for injectable use," "not for human use," or an equivalent statement must not be used to compound CSPs for human use; however, components labeled with "not for human use" may be used in non-human related compounding (i.e. veterinary compounding) if /as appropriate.

(c) If a single dose CSP or stock solution is used as a component to compound additional CSPs, it must be stored based on its label for the provided BUD prior to manipulation and any manipulations must occur within an ISO Class 5. After initial entry into the above input, it can be used for compounding for no more than 12 hours or its assigned BUD, whichever is shorter.

C. Component Receipt.

(1) Upon receipt of each lot of a component, the packaging must be assessed for evidence of deterioration or other indications of unacceptable quality or unsuitable prior storage.

(2) Facility personnel must verify the labeling and condition of all components.

(3) Any component found to be of unsuitable quality must be promptly removed from active stock as delineated in applicable facility policy.

(4) The date of receipt by the compounding facility must be clearly marked on each API or added substance package that lacks a vendor expiration. Such packages must be provided a conservative expiration date, not to exceed one (1) year after receipt.

D. Component Storage and Handling.

(1) All components must be handled and stored in a manner that prevents contamination, mix-ups, and deterioration.

(2) Components must be stored in closed containers in areas with suitable temperature, humidity, and lighting conditions consistent with the parameters in their official monographs, instructions for use, or supplier and/or manufacturer instructions.

(a) Personnel must monitor temperature and humidity (excluding humidity in refrigerators or freezers) in area(s) where components are stored either manually at least once per day on each day the facility is open or continuously using a continuous temperature recording device.

(b) Temperatures and humidity (excluding humidity in refrigerators or freezers) must be logged daily and these record(s) must be retained for at least two (2) years.

(c) Any noted excursions in temperature or humidity must documented on the log, including sufficient details on the root causes and corrective action.

(d) All temperature and humidity monitoring devices must be calibrated or verified for accuracy at least every twelve (12) months.

E. Component Evaluation.

(1) Prior to using any component, compounding personnel must ascertain that the inputs are of the identity, appropriate quality, within expiry date, and have been stored under suitable conditions.

(2) All components must be re-inspected before use.

(a) All packages must be evaluated to detect container breaks, inadequacy of the closure, and/or deviation from the expected appearance, aroma, and/or texture of the components that may have occurred during storage.

(b) Sterile container closures must be visually re-inspected to ensure that they are free from defects that could compromise sterility and that they are otherwise suitable for their intended user.

(c) Any component found to be of unacceptable quality must be immediately rejected

(d) Each lot of commercially available sterile, depyrogenated containers, and container closure systems must be accompanied by a certificate of analysis (COA) or other documentation showing conformance with established specifications. Additionally, if sterilization and depyrogenation of supplies, containers, or container closure systems is performed at a respective facility, the efficacy of such process must be established and documented in SOPs.

99-59. Sterile Compounding: Sterilization.

A. If a facility is compounding sterile CSPs from non-sterile supplies or inputs, they must take into consideration the nature of the components utilized, including their properties and the properties of the container closure system. These aspects must be considered along with the sterilization method to ensure that sterilization is achieved while also ensuring that the physical or chemical properties of the CSP and or container closure system are not adversely impacted (i.e. degraded). The appropriate sterilization method must be selected based on this and included in the master formulation record (MFR) for each CSP a facility compounds.

B. Sterilization must be completed within 6 hours after completing the compounding of the preparation

C. All relevant details (i.e. temperature, pressure, duration, load, use of indicators, etc.) about the sterilization process must be included in the MFR or other suitable SOPs to ensure that the process is completed consistently. Similarly, all relevant details for each batch must be documented on the respective batches compounding record(s).

D. SOPs must be in place that outline key steps to the sterilization process, utilization of equipment (i.e. cleaning, maintenance, calibration, effectiveness evaluation, etc.), and training and competency of staff involved in sterilization process.

E. Any glassware or other such product used in the compounding process must be pyrogen free. SOPs must be in place to ensure this equipment is suitable for usage in the compounding process.

F. Sterilization by Filtration.

(1) Filters must be sterile, depyrogenated and have a nominal pore size of 0.22 microns or less.

(2) Filters must be appropriate for pharmaceutical use.

(3) Filters must be certified to retain at least 10^7 microorganisms of a Brevundimonas diminuta per square centimeter of filter surface area under conditions similar to those in which the CSPs will be filtered.

(4) The Designated Individual must ensure that the filters are compatible with all ingredients in the CSP, that the filters are stable at the temperature and pressure at which they will be used; and that they have enough capacity to filter the required volume related to the CSP or batch.

(5) The filter should be adequate to complete the sterilization process for a given CSP or batch without the need to replace the filter during the filtering process.

(6) All filters used must be subjected to suitable integrity testing. If a filter fails integrity testing, the product prepared using that filter must be discarded or re-filtered not more than one time.

(7) If a CSP is known to contain excessive particulate matter, pre-filtration should be considered.

G. Sterilization by Steam Heat.

(1) SOPs must be in place to ensure equipment utilized for sterilization is appropriately maintained, tested, cleaned. Additionally, SOPs must outline specifications for utilization for each batch to ensure that sterilization is achieved consistently as well as the necessary training and competency for personnel engaging in these activities.

(2) The effectiveness of sterilization must be verified and documented with each run or load using the appropriate biological indicators or suitable physiochemical indicators.

(3) Logs must include date and run and load numbers for each CSP sterilized and this information must be included or referenced on each applicable compounding record. Additionally, compounding records should reference equipment used by name or suitable identifier (i.e serial number).

(4) Each piece of equipment must have a calibrated data recorder that monitors each cycle. The data from this device must be reviewed after each run for irregularities (i.e. deviations in pressure or temperature from the respective policy and or procedure) prior to releasing the run for dispensing.

H. Sterilization by Dry Heat. Effectiveness must be verified and documented with each run or load using appropriate biologic indicators or other confirmation methods. The date and run and load numbers as well as a reference number of the equipment used (i.e. oven) must be documented on the compounding record for the respective CSP.

99-60. Sterile Compounding: Sterility Testing.

A. Sterility testing is not required for Category 1 CSPs.

B. For Category 2 CSPs assigned a BUD that requires sterility testing and all Category 3 CSPs, sterility testing must be performed in conformance with USP Chapter 71 or a validated alternative method that is noninferior to the testing outlined in USP Chapter 71.

C. If a sterility test is performed, the minimum quantity of each container to be tested is specified in USP Chapter 71, Table 2, and the number of containers required to be tested in relation to the batch size is specified in USP Chapter 71, Table 3, with the following exceptions:

(1) The maximum batch size for all CSPs required sterility testing must be limited to two hundred fifty (250) final yield units.

(2) If the number of CSPs to be completed in a single batch is less than the number of CSPs needed for testing as outlined in the applicable USP Chapter 71 Table referenced above in section C, additional units must be compounded to perform stability testing as follows:

(a) If one to thirty-nine CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number.

(b) If more than forty CSPs are prepared in a single batch, the sample sizes specified in the applicable USP Chapter 71 Table referenced above in section C must be used.

D. If sterility testing is performed in accordance with USP Chapter 71, the Method Suitability Test described in that Chapter must be performed to ensure that contamination can be recovered.

F. Sterility test resulting in failures must prompt an investigation into the possible causes, must include identification of the microorganism, and must include an evaluation of all related processes and or personnel that may have contributed to the failure.

G. The source of identified contamination must be corrected, and the facility must determine whether the conditions impacted any other CSPs or batches of CSPs.

H. The investigation results and resulting corrective actions must be documented and such records must be retained for a period of at least two (2) years.

99-61. Sterile Compounding: Bacterial Endotoxin Testing

A. Category 2 CSPs compounded from one or more nonsterile components and assigned a BUD that requires sterility testing and Category 3 CSPs compounded from one or more nonsterile component must be tested to ensure that the do not contain excessive bacterial endotoxins.

B. In the absence of a bacterial endotoxin limit in an official US-NF monograph or other suitable formula source, the CSP must not exceed the endotoxin limited calculated and described in USP Chapter 85 based on the CSPs route of administration as well as the intended patient subgroup (i.e. human or animal).

C. CSPs administered via an epidural route should have the same endotoxin limits as CSPs administered via an intrathecal route.

99-62. Sterile Compounding: CSP Storage and Handling.

A. CSPs must be handled in a manner that prevents any negative effects related to quality of the finished dosage form.

B. To ensure appropriate storage, compounding personnel must monitor both temperature and humidity (excluding humidity in refrigerators or freezers) in storage areas and ensure they are appropriate for the respective finished dosage form with their controlled storage area(s).

(1) The measures must be logged each day the facility is opened or continuously using a continuous data monitor.

(2) Logs must be retained for a period of at least two (2) years.

(3) Any temperature monitoring devices must be calibrated or verified for accuracy at least annually or as prescribed by the manufacturer, whichever is more frequently.

C. If deviations or excursions occur, the impacted CSPs must be assessed by the designated individual to determine if they remain suitable for administration as it relates to quality and or integrity. If this cannot be determined, the CSP(s) must be discarded.

D. If CSPs are to be shipped or delivered, packaging materials must be selected that protect the CSP during transportation. Additionally, packaging materials must ensure that the CSP is kept within appropriate storage parameters (i.e. temperature, light exposure, etc.) during transit and ensure that the CSP is protected from other factors (i.e physical agitation, etc.) that could cause the finished dosage form to degrade or be of inferior quality.

99-63. Sterile Compounding: Documentation.

A. Each facility engaged in compounding shall have SOPs for all key elements related to their compounding processes and personnel, including but not limited to:

(1) Compounds, including the category of compounds that are compounded at the facility;

(2) Personnel training, competency assessment(s), and qualification records, including corrective actions for any failures;

(3) Environmental air and surface monitoring procedures and results;

(4) Equipment maintenance and related records (i.e. calibration, verification, maintenance reports, etc.);

(5) Receipt of inventory to include components;

(6) SOPs, MFRs, and compounding records (CRs), as required; and

(7) In-process checks, final checks, and release inspection and or testing results.

B. Each facility must have a master formulation record for each formulation that is compounded that includes:

(1) Name, strength, or activity of the CSP;

(2) Dosage form;

(3) Identifies and amounts of all ingredients;

(4) Details of the container closure system;

(5) Complete instructions for preparing the CSP;

(6) Physical description of finished product (i.e. expected appearance);

(7) BUD and storage requirements based on the final product and container closure as well as the compounding facility's design and SOPs;

(8) Reference to support the stability or the provided BUD; and

(9) Any testing or in-process checks required and their expected results.

C. Each specific compound that is prepared, pursuant to an established patient, provider, and pharmacy relationship shall have a fully completed compounding record (CR). The compounding record shall include the below details for each compound prepared and dispensed:

(1) Name and strength or activity of the CSP;

(2) Dosage form;

(3) Date and time of preparation;

(4) Assigned identification number (i.e. prescription number);

(5) Identities of the individuals involved in the compounding and verification of the CSP;

(6) Vendor, lot, and expiration date for each component utilized;

(7) Weight or volume of each component;

(8) Strength or activity of each component;

(9) Total quantity of dosage forms compounded;

(10) Assigned BUD and storage requirements;

(11) Any calculations made in the preparation of the CSP, if applicable;

(12) Results of any quality control (QC) procedures or documentation of any in-process checks;

D. Each SOP utilized by the facility must be reviewed and updated annually.

E. All compounding staff as well as all staff who supervise compounding (i.e. pharmacists, including the Designated Individual) must be aware of the respective SOPs and be able to recognize problems, deviations, defects, failures, etc. that could adversely impact the compounding environment or a respective CSP. Immediately upon awareness of such a problem, it should be reported to the Designated Individual.

F. All documentation pertaining to compounding, including compounding records, facility logs, certification records, policies, etc. should be maintained for a period of at least two (2) years.

99-64. Sterile Compounding: Labeling.

A. For purposes of this regulation, the term "Labeling" designates all labels and other written, printed, or graphic matter on the immediate container or on or inside any package or wrapper in which it is enclosed, except any outer shipping container. The term "Label" designates the part of the labeling that is on the immediate container.

B. Category 1, 2, and 3 CSPs must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use.

C. All labeling requirements found in SC Code of Laws Section 40-43-83 apply in addition to the labeling requirements found herein.

D. The label on the immediate container of the CSP must, at a minimum, display prominently and legibly the following information:

(1) Internal identification number (e.g. prescription number, order number, etc.)

(2) Active ingredient(s) and their amount(s), activity(ies), or concentrations;

(3) Storage conditions;

(4) Beyond Use Date (BUD);

(5) Dosage form;

(6) Total amount or volume; and

(7) Whether the CSP contained is a multiple dose container, if applicable.

F. The labeling on the CSP must also include (as applicable):

(1) Route of administration;

(2) Special handling instructions;

(3) Warning statements;

(4) Compounding facility name, address and contact information if to be administered outside of the facility in which it was prepared (i.e. hospital);

G. Labeling procedures must be followed as described in the facilities SOPs to prevent labeling errors or mix-ups.

H. The label of the CSP must be visually verified by a pharmacist at the facility in which the CSP was compounded prior to it being dispensed.

99-65. Sterile Compounding: In-Process and Final Checks

A. Any in-process check or test must be completed as outlined in the CSPs MFR and the results of each test must be included and retained on or affixed to the compounding record for the respective CSP.

B. Any out of specification in-process checks must be investigated and remediated under the direction of a licensed pharmacist within the dispensing pharmacy. Patterns or trends related to such findings should be reviewed and documented as a part of the organization's continuous quality improvement program.

C. Upon the completion of compounding and prior to release and dispensing of a CSP, the product must be visually inspected by a licensed pharmacist within the dispensing pharmacy to determine that the physical appearance is as expected. Additionally, this visual inspection must confirm that the CSPs labeling matches the prescription and the compound in question.

D. Any CSP found of unacceptable quality must be rejected and immediately segregated from stock.

E. If a CSP will not be dispensed until a period after preparation, the visual inspection must be conducted immediately prior to the dispensation of the product to ensure that the CSP does not show signs of degradation between compounding and dispensing.

99-66. Sterile Compounding: Specific Compounding Practices.

A. Allergenic Extracts

(1) Allergenic extracts are routinely mixed and diluted to prescription sets for subsequent administration to patients. A set is a vial or set of vials of premixed extracts for subcutaneous immunotherapy that have been diluted with appropriate diluent for an individual patient. Because of certain considerations related to allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in this chapter that are applicable to other CSPs. These limited requirements are applicable, only when:

(a) The compounding process involves transfer via sterile needle(s) and syringe(s) of a conventionally manufactured sterile allergen product(s) and appropriate conventionally manufacturer sterile added substances; and

(b) Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

(2) If the above conditions are met, the below limited requirements are suitable for this subset of compounds:

(a) Compounding must occur in a certified ISO Class 5 PEC or within a suitable and dedicated allergenic extract compounding area (AECA). The AECA must be away from unsealed doors, windows, areas of high traffic or other aspects that may cause unfavorable environmental control challenges (i.e. restrooms, warehouses, food preparation areas, etc.).

(b) If an AECA is utilized, the following design criteria must be met:

(i) The PEC and or work surfaces within the AECA must be one (1) meter or more from any water sources (i.e. sink);

(ii) The AECA must be defined/outlined via a visible perimeter/demarcation;

(iii) Access to the AECA must be restricted to authorized personnel by SOPs;

(iv) During compounding, no other activities can occur in the AECA;

(v) The surfaces of all areas in the AECA must be smooth, impermeable, wipeable, and cleanable. Additionally, these surfaces should be compatible with commonly utilized cleaning and disinfection agents;

(vi) The AECA must be designed with suitable light and also have appropriate engineering controls to facilitate temperature and humidity management at all times; and

(vii) The AECA must be cleaned and disinfected at least monthly and or when contamination is suspected.

(b) BUDs for prescription sets should not exceed the earliest expiration date of any allergenic extract or input component that is included in the set. Additionally, the BUD should not exceed one (1) year from the date the prescription set is prepared.

(c) Each vial of an allergenic prescription set must display clearly and prominently:

(i) patient name;

(ii) type and fractional dilution of each vial with corresponding vial number;

(iii) BUD; and

(iv) storage conditions.

(c) The full set should be contained within an outer container that is appropriately labeled in accordance with all applicable statutes and regulations, including SC Code of Laws Section 40-43-86.

B. Blood-Derived and Other Biologics.

(1) When compounding activities involve the manipulation of blood-derived or other biological material (i.e. serum), the manipulations must be clearly separated from other activities and the equipment used in the activities.

(2) Processes and manipulations must be controlled by SOPs that prevent any cross contamination.

C. Hazardous Drugs or Substances. Handling of sterile hazardous drugs (HDs) must comply with applicable statutes and regulations protecting both the preparer (i.e. compounding staff), patient, and other healthcare staff from incidental exposure or adverse effects from these drugs or agents.

99-67. Sterile Compounding: Designated Individual.

A. Permitted facilities engaged in compounding should have a designated individual who is responsible for and otherwise accountable for the management of compounding operations and activities at the permitted site(s). If this individual is not the pharmacist-in-charge, the facility's SOPs should detail the designated individual and the delineation of responsibilities between this individual and the PIC

B. The Designated Individual must hold an active South Carolina pharmacist license unless this requirement is waived by the Board.

C. The responsibilities of the Designated Individual include ensuring the facility operates in conformance with these regulations related to sterile compounding and that all CSPs dispensed or provided to clinicians for administration are safe for their intended utilization.

99-70. Non-Sterile Compounding: Scope

A. This section describes the standards to be followed for the preparation of compounded nonsterile preparations (CNSPs) for humans and animals. It is divided into two (2) primary types of non-sterile compounding: simple and complex.

(1) Simple non-sterile compounding includes the following practices:

(a) Flavoring: A flavoring agent may be added to a drug at the discretion of the pharmacist or upon the request of the prescriber, the patient, or the patient's agent. The pharmacist may add flavoring agents not to exceed five (5) percent of the total volume of the drug to which the flavoring agents are added.

(b) Simple Compounding: Compounding of an oral liquid or topical dosage utilizing non-particle producing, non-hazardous commercially available ingredients. Such preparations may include, but are not limited to, the following dosage forms: mouthwashes, ointments, and creams.

(2) Complex Non-Sterile Compounded preparations include, but are not limited to, the following dosage forms:

(a) Solid oral preparations
(b) Liquid oral preparations
(c) Rectal preparations
(d) Vaginal preparations
(e) Topical preparations (i.e., creams, gels, and ointments)
(f) Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
(g) Otic preparations (excluding use in perforated eardrums)

B. The following practices are not considered non-sterile compounding, will not trigger a non-sterile compounding inspection, and are not required to meet the requirements for non-sterile compounding.

(1) Nonsterile radiopharmaceuticals: Compounding of nonsterile radiopharmaceuticals is subject to the requirements of Section ???

(2) Reconstitution: Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling

(3) Repackaging: Repackaging of conventionally manufactured drug products

(4) Splitting tablets: Breaking or cutting a tablet into smaller portions

(5) Administration: Preparation of a single dose for a single patient when administration will begin within four (4) hours. This includes crushing a tablet(s) or opening a capsule(s) to mix with food or liquids to facilitate patient dosing.

C. Section ??? requirements apply to all persons who prepare or oversee the preparation of CNSPs and all places where CNSPs are prepared.

99-71: Non-Sterile Compounding: Simple Compounding

A. Flavoring: A flavor additive may be incorporated into a non-sterile prescription drug. This practice is exempt from the requirements of sections pertaining to complex non-sterile compounding under the following conditions:

(1) The patient, patient's caregiver, or practitioner who authorized the original prescription shall authorize the flavoring of each new and, if applicable, refilled prescription;

(2) The pharmacist has done their due diligence to ensure that the flavor additive shall in no way compromise the stability, safety, or efficacy of the dispensed drug.

(3) No expired flavor additive shall be incorporated into a prescription. No flavor additive shall be incorporated which will expire prior to utilization by the patient, based on the practitioner's directions for use.

(4) For flavoring additives that do not have expiration dates assigned by the manufacturer or supplier, a pharmacist shall clearly and legibly label the container with the date of receipt and assign a conservative expiration date, not to exceed three years after receipt.

(5) The following information shall be recorded and maintained in a suitable hard-copy or electronic dispensing record for a period of two years from the date of flavoring the corresponding new or refilled prescription. This record shall be made available, in printed form, for the Board or its representatives immediately upon the request of the Board or its representatives.

(a) Additive's flavor;

(b) Flavor additive's manufacturer

(c) Flavor additive's lot number (if available); and

(d) Flavor additive's expiration date.

B. Simple non-sterile compounded preparations shall be exempt from the requirements in sections pertaining to complex non-sterile compounding under the following conditions:

(1) Non-particle producing, non-hazardous commercially available ingredients, that have not been manipulated, are used

(2) Compounding is done pursuant to an active prescription and not done in anticipation of medication orders

(3) Must follow beyond use dates (BUDs) of:

(a) 14 days refrigerated if not preserved (ingested orally)

(b) 35 days refrigerated if a preservative is contained (ingested orally)

(c) 35 days at room temperature for topical preparations or preparations for mucosal membrane application.

(4) A compounding record must be maintained for a minimum duration of 2 years.

(a) A valid prescription may shall serve as the compounding record with additional documentation of the following information at a minimum for the initial fill and all subsequent refills:

(i) Identity of all components and their corresponding amounts, concentrations, and or volumes

(ii) Lot number and expiration date of each component

(iii) Component manufacturer/distributor or suitable identifying number

(iv) Unique lot or control number for the compounded preparation

(v) Beyond use date assigned to the compounded preparation

(vi) Date of preparation

(vii) Name, initials, or electronic signature of the person(s) involved in the preparation of the compound

(viii) Name, initials, or electronic signature of the checking pharmacist.

(5) An area must be designated for nonsterile compounding activities. Other activities must not be occurring in the compounding area at the same time as compounding.

(a) The compounding area must be well lit and must be maintained in a clean, orderly, sanitary condition and in a good state of repair.

(b) There should not be carpet in the compounding area.

(c) The compounding area must provide for the orderly placement of equipment and materials to prevent mix-ups among components, containers, labels, in-process materials, and finished CNSPs. The area should be designed, arranged, and used in a way that minimizes cross contamination from non-compounding areas.

(6) The facility that houses the compounding area must comply with all other facility requirements of a retail pharmacy in the state of South Carolina according to S.C. Code of Laws Section 40-43-86.

(7) Where water is an ingredient in a compound; purified, distilled water, or sterile water shall be used

C. Personnel shall clean or wipe down compounding area after all spills and as needed before and after compounding.

D. Personnel shall wash their hands prior to preparing a simple compound.

E. Pharmacists are trained in the art of simple compounding as part of their formal pharmacy education and may train technicians to perform practices related to simple compounding and are expected to ensure that all procedures are being followed.

99-72. Non-Sterile Compounding: Complex Compounding

A. The Pharmacist-in-Charge or a designated person is responsible for creating and implementing a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel.

B. All personnel who compound or have direct oversight of compounding CNSPs must be initially trained and qualified by demonstrating knowledge and competency according to the requirements in this before being allowed to perform their job functions independently. Training should be thorough enough to ensure accurate compounding at the required level.

(1) Training should be verifiable and documented specific to the type of compounding being performed.

(2) General compounding skills (i.e. trituration of tablets to make a suspension, using geometric dilution to mix topical preparations together on an ointment slab, etc.) are part of the curriculum in pharmacy school, therefore the degree serves as evidence of initial training for the pharmacist.

(3) More advanced compounding requires additional training, either through a course offered by a reputable compounding education platform, or via documented onsite training by professional who has already completed a course or who has 5+ years of experience working with the advanced dosage forms.

C. Personnel who compound or have direct oversight of compounding personnel must complete at least four (4) hours of documented ongoing training every twelve (12) months relating to compounding principles and practices in order to stay up to date with new developments in the field. The four (4) hours of ongoing training may be completed in house in accordance with facility SOP's or via accredited continuing education platform.

D. Other personnel, who do not compound and only perform functions such as in-process checks, final verification, or dispensing of CNSPs, must undergo training as required by the facility's SOPs.

E. In addition to the initial and annual competency training and evaluation described in this section, the designated person(s) should monitor and observe compounding activities and must take immediate corrective action if deficient practices are observed.

F. If the facility has only one person in the compounding operation, that person must document that they have obtained training and demonstrated competency, and they must comply with the other requirements of State compounding law and regulation.

99-73. Non-Sterile Compounding: Personal Hygiene and Garbing.

A. Any person with a communicable illness or open lesion that may adversely affect the safety or quality of a drug product being compounded shall report these conditions to the designated person(s). The

designated person(s) shall determine whether the person must be excluded from compounding areas until the person's conditions have resolved.

B. Personnel engaged in the compounding of medications must:

(1) wear clean clothing appropriate to the operation being performed.

(2) wear gloves and protective apparel as necessary to protect personnel from chemical exposure and medication or chemical contamination. Garbing requirements and the frequency of changing the garb shall be included in the facility's SOPs.

(3) Perform proper hand hygiene as defined in the facility's SOP prior to engaging in compounding activities.

C. The facility's SOP(s) should at least detail:

(1) Appropriate personal protective equipment (PPE needed for the type of compounding to be done

(2) Hand hygiene procedures

(3) Frequency of PPE replacement

(4) Procedure for disposal of soiled PPE

(5) Required training and frequency of training if applicable

99-74. Non-Sterile Compounding: Buildings and Facilities

A.Compounding Area

(1) An area must be designated for nonsterile compounding. Other activities must not be occurring in the compounding area at the same time as compounding.

(2) The compounding area must be well lit and must be maintained in a clean, orderly, sanitary condition and in a good state of repair.

(3) Surfaces should be resistant to damage by cleaning and sanitizing agents. Floors in the compounding area should be easily cleanable and should not be porous or particle generating. There should not be carpet in the compounding area.

(4) The compounding area must be maintained in a manner to prevent mix-ups among components, containers, labels, in-process materials, and finished CNSPs. The area should be designed, arranged, and used in a way that minimizes cross contamination from non-compounding areas.

B. Storage Area

(1) Compounding personnel must monitor temperature and room relative humidity in the storage area(s) either manually at least once daily on days that the facility is open, or continuously with a temperature and humidity recording device to ensure the temperature and humidity remain within the appropriate range for the CNSPs and components.

(a) Temperature in the compounding area should be maintained to provide controlled room temperature storage of 20°C to 25°C (68°F to 77°F), or more restrictive if warranted by specific drug product storage requirements.

(b) Relative Humidity should be maintained at or below 60% in the storage area. Relative Humidity inside the refrigerator(s) must be logged if a refrigerator is maintained in an area that does not maintain the environment as defined by controlled room temperature.

(c) The results of the temperature and humidity readings must be documented on a log or stored in the continuous recording device and must be retrievable.

(2) Bulk or unformulated drug substances and added substances or excipients must be stored in tightly closed containers under temperature, humidity, and lighting conditions that are either indicated in official monographs or approved by suppliers.

(3) If no storage requirements are established for a drug, the drug may be held at "controlled" room temperature.

(4) Refrigerators used for storage must maintain a temperature range of 36°F to 46°F. Freezers used for storage must maintain a temperature range of -13°F to 14°F.

(5) If a CNSP or component experiences a temperature excursion outside of its recommended storage requirements, personnel must determine whether the CNSP or component integrity or quality has been compromised, and, if so, the CNSP or component must be discarded.

(6) All temperature monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

(7) All CNSPs, components, equipment, and containers must be stored off the floor and in an orderly manner free of dust, insects, vermin, or any other type of contaminant.

(8) The storage of equipment, bulk substances, components or any other items used during any part of the compounding and dispensing process in the restroom of the pharmacy is prohibited.

(9) All outdated, damaged, defaced, or unlabeled drugs, pharmaceuticals, biologicals, and chemicals must be removed from active stock.

C. Water Sources

(1) A source of hot and cold water supplied under continuous positive pressure in a plumbing system free from defects that could contribute to contamination of any compounded drug preparation must be provided.

(2) The facility must provide adequate and easily accessible washing facilities near the compounding areas that include a sink, hot and cold water, soap or detergent, and single-use towels. The sink must be kept free of any items unrelated to compounding and must be cleaned if visibly soiled before being used to clean any equipment involved in nonsterile compounding.

99-75. Non-Sterile Compounding: Cleaning and Sanitizing

A. Cleaning and sanitizing the surfaces in the nonsterile compounding area(s) must occur on a regular basis at the minimum frequencies specified in Table 1 or, if compounding is not performed daily, cleaning and sanitizing must be completed on days when compounding takes place before initiating compounding. Cleaning and sanitizing must be repeated when spills occur and when surfaces are visibly soiled. Applicable cleaning and sanitizing must be documented daily on days when compounding occurs.

B. Cleaning and sanitizing agents must be selected and used with consideration of compatibility, effectiveness, and minimal potential to leave residues.

C. If cleaning and sanitizing are performed as separate steps, cleaning must be performed first.

Table 1. Minimum Frequency for Cleaning and Sanitizing in Nonsterile Compounding Area(s)—Surfaces

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Between compounding CNSPs with different components
Equipment Used	• Daily, after use • Between compounding CNSPs with different components
Floors	• Sweeping Daily on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Mopping weekly, after spills, and when surface contamination (e.g. from splashes) is known or suspected
Walls	• When visibly soiled, after spills, and when surface contamination (e.g., from splashes) is known or suspected

Ceilings	• When visibly soiled and when surface contamination (e.g., from splashes) is known or suspected
Open Storage shelving	• Every 3 months, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Closed Cabinets	• Exterior every 3 months • Interior As needed, after spills, and when surface contamination (e.g., from splashes) is known or suspected
Waste Removal	• Daily, or more frequently as needed

99-76. Non-Sterile Compounding: Equipment and Components

A. Equipment

(1) Equipment must be stored in a manner that minimizes the risk of contamination and should be located to facilitate equipment use, maintenance, and cleaning.

(2) Equipment and devices used in the compounding or testing of compounded preparations must be inspected prior to use and, if appropriate, should be calibrated or verified for accuracy as recommended by the manufacturer at the frequency recommended by the manufacturer or at least every twelve (12) months, if not specified by the manufacturer.

B. Components

(1) The compounding facility should have a SOP for the evaluation of suppliers of components used in compounding non-sterile preparations.

(2) A compounder shall first attempt to use components manufactured in an FDA-registered facility. When components cannot be obtained from an FDA-registered facility, a compounder shall use his professional judgment in selecting an acceptable and reliable source and shall establish purity and safety by reasonable means, to include Certificate of Analysis, manufacturer reputation, and reliability of source.

(3) The compounding facility must have a written SOP for the selection of components used in compounding non-sterile preparations.

(4) APIs should meet one of the following criteria for use in CNSPs:

(a) Be part of an FDA approved product

(b) Have a USP or NF monograph

(c) Be included on the FDA's list of "Bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act."

(5) Should an API fail to meet any of the aforementioned criteria, the pharmacist must exercise professional judgment in determining whether to use it as a component of a compounded non-sterile preparation. In making this determination, the pharmacist should consider, at a minimum, the availability of a Certificate of Analysis (CofA), the specific information contained within the CofA, and the potential need for independent third-party testing to verify the quality and purity of the API.

(6) Where water is an ingredient in a CNSP; purified, distilled water, or sterile water is used.

(7) Upon receipt of components other than conventionally manufactured products, the COA, if provided, must be reviewed to ensure that the component has met the acceptance criteria in an appropriate USP–NF monograph, if one exists.

(8) Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal or return to the supplier.

(9) Before use, compounding personnel must visually re-inspect all components for container breakage, or deviation from the expected appearance or texture of the contents that might have occurred during storage.

(10) Compounding personnel must ascertain before use, that components are of the correct identity based on the labeling and have been stored under required conditions in the facility. If the identity, strength, purity, and quality of components intended for preparation of CNSPs cannot be verified (e.g., containers with damaged or incomplete labeling), the components must be immediately rejected. Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal.

(11) The handling of components must minimize the risk of contamination, mix-ups, and deterioration (e.g., loss of identity, strength, purity, or quality).

(12) The facility must maintain physical or digital access to current chemical safety data sheets (SDSs). SDSs must be readily accessible to all personnel working with components located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information. The management and disposal of component spills must be described in the facility's SOPs and must be in accordance with laws and regulation of the applicable regulatory jurisdiction.

99-77. Non-Sterile Compounding: Master Formulation and Compounding Records

A. A Master Formulation record must be developed by qualified personnel and approved by a pharmacist for all compounded preparations. Once approved, a Compounding Record must be used to document the preparation of the compound. The Compounding Record must contain all aspects of the Master Formula with additional specific details related to the specific batch being prepared.

B. The Master Formulation record shall contain at a minimum:

(1) The name, strength, and dosage form of the compounded product

(2) The components

(3) The compounding directions

(4) Evaluation and testing requirements

(5) Specific equipment used during preparation

(6) The type of containers that may be used for dispensing

(7) Storage requirements and any special requirements that should be noted in the record as well as on the container for dispensing. This may include but not limited to: shake well, refrigerate or freeze, protect from light etc.

(8) Documentation, or a reference to the location to documentation which may be maintained with other records, related to quality control for determining:

(9) The criteria used to determine the beyond-use date; and

(10) The type of final checks required including, but not limited to: expected physical appearance of the final product, calculations performed, determination of final vs expected results.

(11) Documentation of parameters applicable to the CNSP. These may include, but are not limited to: pH, color, smell, and clarity.

B. Compounding Record:

(1) A duplicate of the master formulation record may be used as the compound record each time the compound is prepared on which all documentation for that specific compound occurs.

(2) The compounding record for each preparation shall document requirements of the Master Formulation as well as:

(a) Identity of all components and their corresponding amounts, concentrations, or volumes

(b) Lot number and expiration date of each component

(c) Component manufacturer/distributor or suitable identifying number

(d) Unique lot or control number

(e) Beyond use date

(f) Date of preparation

(g) Name, initials, or electronic signature of the person(s) involved in the preparation

(h) Name, initials, or electronic signature of the responsible pharmacist

(i) Finished preparation evaluation and testing specifications, if applicable; and

(j) Documentation of performance of final checks as applicable

99-78. Non-Sterile Compounding: Release Inspections and Testing

A. The following items, at a minimum, shall be inspected for accuracy before the non-sterile preparations are dispensed:

(1) Correct identities, expiration dates, and amounts of ingredients
(2) Packaging
(3) Labeling
(4) The prescription drug or medication order
(5) The compounding record
(6) The materials or equipment used in the preparation
(7) The written compounding procedure
(8) Expected physical appearance and properties
(9) Documentation of applicable parameters. Ex: pH, color, smell, clarity
(10) Expected versus actual yield of final product
(11) Pharmaceutical elegance

B. Such final checks should be documented either on the compounding record, attached to the compounding record, or the document is referenced and readily available for review.

C. At a minimum, the initials and the date should be indicated on the record of the person performing the final checks.

99-79. Non-Sterile Compounding: Labeling

A. Every CNSP must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use. Labels on compounds should include all components required on a regular prescription per S.C. Code of Laws Section 40-43-86, and, at a minimum, must display prominently and legibly the following information:

(1) Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
(2) Unabbreviated or clearly defined names of all active ingredient(s), and their amount(s), activity(ies), or concentration(s)
(3) Storage conditions if other than controlled room temperature
(4) BUD
(5) Dosage form
(6) Total amount or volume if it is not obvious from the container
(7) Route of administration
(8) Indication that the preparation is compounded
(9) Any applicable special handling instructions
(10) Any applicable warning statements
(11) Pharmacy/Compounding facility name, and contact information if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded

B. Any excess compounded preparation to be stored must be labeled so as to reference it to the formula used and the assigned identification number and the beyond-use date. The preparation must be stored appropriately.

C. The date of receipt by the compounding facility must be clearly marked or labeled on each component.

(1) For components that do not have expiration dates assigned by the manufacturer or supplier, a compounder must assign a conservative expiration date, not to exceed three years after receipt of the component based on the nature of the component and its degradation mechanism, the container in which it is packaged, and the storage conditions. This date must be marked or labeled on the container.

(2) Any chemical or component transferred to a new container from the original container must be labeled with information that identifies the specific component. This information must be the same as the information on the original container. This label may include, but is not limited to:

(a) name of component
(b) lot number
(c) expiration date
(d) manufacturer
(e) supplier
(f) date of transfer to new container

99-80. Non-Sterile Compounding: Establishing Beyond Use Dates

A. Each CNSP label must state the date, or the hour and date, beyond which the preparation should not be used and should be discarded (i.e., the BUD). BUDs for CNSPs are calculated in terms of hours, days, or months.

B. Parameters to Consider in Establishing a BUD

(1) BUDs for CNSPs should be established conservatively in an effort to ensure that the preparation maintains its required characteristics and to minimize the risk of contamination or degradation.

(2) In the absence of stability information applicable to the specific compound, the maximum BUD must be determined by:

(a) The type of formulation, such as nonaqueous, water containing, oral or topical; and
(b) Professional judgment

(3) When warranted, the pharmacist's professional judgment shall be based on the criteria used to determine a beyond-use date outlined in this subsection.

(a) Physical and chemical properties of active ingredients;
(b) Potential for microbial proliferation in the CNSP and the use of preservatives and/or stabilizing agents;
(c) Dosage form;
(d) Storage containers and conditions; and
(e) Scientific, laboratory, or reference data from a peer reviewed source. The reference data should follow the same preparation instructions for combining components and should be packaged in a container with similar properties. The facility must maintain access to any reference material used to establish BUDs physically or digitally.

(4) The BUD for any CNSP must not exceed 180 days.

(5) Water Activity

(a) The aqueous and nonaqueous dosage forms in Table 4 are defined based on the water activity (aw) of the most similar drug preparations described in Table 3
(b) Compounders are not required to measure aw for CNSPs.

Table 1. Water Activity of Common Compounded Nonsterile Dosage Forms

Nonaqueous Dosage Forms: a_w **< 0.6**			**Aqueous Dosage Forms:** $a_w \geq 0.6$		
Dosage Form	**Description**	a_w	**Dosage Form**	**Description**	a_w
Animal treat	Animal treat (oil flavor)	0.507	Animal treat	Animal treat with 15%– 18% aqueous flavor	0.716

Capsule (oil filled)	Olive oil encapsulated	0.468	Cream	Cream vehicle (oil in water emulsion, petrolatum free)	0.968
Capsule (powder filled)	Powder base encapsulated	0.435	Cream	Emollient cream (petrolatum and mineral oil)	0.984
Gel (glycol based)	Propylene glycol, ethoxy diglycol, hydroxypropyl cellulose gel	0.056	Cream	Cream (oil in water emulsion with natural oils)	0.989
Lollipop (sorbitol based)	Sorbitol-based lollipop	0.460	Foam	Foaming surfactant solu- tion	0.983
Ointment	Hydrophilic petrolatum	0.396	Gel (water based)	Alcohol-free aqueous gel	0.990
Ointment	Polyethylene and mineral oil gel base	0.459	Gel (water based)	Hydroxypropyl methyl- cellulose (HPMC) gel	1.000
Oral solution (glycol based)	20% Polyethylene glycol and 80% propylene glycol	0.009	Lotion	Lotion (oil in water emulsion)	0.986
Oral solution (oil based)	Medium chain triglycerides oil	0.338	Nasal spray	Nasal spray	0.991
Oral suspension (fixed oil)	Fixed oil with thickener	0.403	Oral solution (water based)	Low-sucrose syrup vehicle	0.906
Powder for inhalation	Encapsulated powder for inhalation	0.402	Oral solution (water based)	90% Water and 10% glycerin	0.958
Stick	Lip balm	0.181	Oral suspension (water based)	Oral suspension base	0.992
Suppository	Polyethylene glycol base	0.374	Rinse	Polymer gel with 30% water	0.960
Suppository	Fatty acid base	0.385	Shampoo	Shampoo	0.976
Tablet (compressed)	Compressed tablet	0.465	Simple syrup	Simple syrup	0.831
Tablet (triturate)	Tablet triturate (lactose and/or sucrose)	0.427	—	—	—

Troche or lozenge (gela- tin based)	Gelatin troche or lozenge with NMT 3% aqueous flavor	0.332	—	—	—
Troche or lozenge (gly- col based)	Polyethylene glycol tro- che or lozenge with NMT 3% aqueous flavor	0.571	—	—	—

a: The measured aw values in Table 1 for the different dosage forms are intended to be representative examples. The descriptions listed are details about the tested formulation and are provided to assist personnel in determining whether their CNSPs are aqueous or nonaqueous. Compounded preparations in Table 1 below are not exhaustive, they provide examples of dosage forms that have an aw < 0.6 and those that have an aw ≥ 0.6 and can assist in determination of appropriate BUDs.

Table 2. BUDs

Type of Preparation	**BUD (days)**	**Storage Temperature**
Aqueous Dosage Forms ($a_w \geq 0.60$)		
Nonpreserved aqueous dosage forms[c]	14	Refrigerator
Preserved aqueous dosage forms[c]	35	Controlled room temperature or refrigerator
Nonaqueous Dosage Forms ($a_w < 0.60$)		
Oral liquids (nonaqueous)[d]	180	Controlled room temperature or refrigerator
Other nonaqueous dosage forms[e]	180	Controlled room temperature or refrigerator

The BUDs in Table 2 are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. These BUDs represent the limit for CNSPs that are packaged in tight, light-resistant containers unless conditions for CNSPs Requiring Shorter BUDs (ie. narrow therapeutic index drugs) or Extended BUDs for CNSPs apply.

a: A shorter BUD must be assigned when the physical and chemical stability of the CNSP is less than the BUD limit stated in the table.
b: See Packaging and Storage Requirements (USP 659).
c: An aqueous preparation is one that has an aw ≥ 0.6 (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).
d: A nonaqueous oral liquid is one that has an aw < 0.6.
e: Other nonaqueous dosage forms that have an aw < 0.6 (e.g., capsules, tablets, granules, powders, nonaqueous topicals, suppositories, and troches or lozenges).

D. CNSPs Requiring Shorter BUDs

(1) The BUDs in Table 4 are recommended BUD limits for CNSPs in the absence of specific stability information. They do not absolve the pharmacist or designated person(s) from performing due diligence to determine if there is existing stability data that would require a shorter BUD.

(2) The BUD of the CNSP must not exceed the shortest remaining expiration date of any of the commercially available starting components.

(3) For CNSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components. However, there may be acceptable instances when the BUD of the final CNSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CNSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CNSP must not be negatively impacted.

E. Extending BUDs for CNSPs

(1) All CNSPs with an extended BUD must meet the requirements of this section.

(2) CNSPs with a USP–NF monograph:

(a) When compounding from a USP–NF compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.

(3) CNSPs with stability information:

(a) If there is a stability study using a stability-indicating analytical method for the API(s), CNSP formulation, and material of composition of the container closure that will be used, then the BUD indicated by the study may be used in lieu of the BUDs specified in Table 4 for aqueous and nonaqueous dosage forms, up to a maximum of 180 days.

(b) Ingredients used in preparations with referenced stability information may be interchanged, regardless of supplier, as long as the chemical quality grade is achieved for the ingredient (ie. USP or NF, oral, cosmetic, vet etc.).

(4) If the BUD of the CNSP is extended beyond the BUDs in Table 4, in the absence of USP-NF monograph or stability information, an aqueous CNSP must be tested for antimicrobial effectiveness.

(a) Antimicrobial effectiveness testing may be conducted once for each formulation in the same or similar container closure system in which it will be packaged.

(b) Alternatively, antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature may be referenced as long as the CNSP formulation (including any preservative), container closure and materials of composition are the same (ie. chemical quality grade) as those tested (unless a bracketing study is performed).

(c) When a bracketing study is performed, antimicrobial effectiveness testing may be performed on a low concentration and on a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) must fall within the bracketed range.

(d) When preservatives are contraindicated, storage of the preparation in a refrigerator is required if such storage does not change the physical or chemical properties of the CNSP (i.e., precipitation).

99-81. Non-Sterile Compounding: Standard Operating Procedures

A. Facilities preparing CNSPs must develop SOPs on all significant aspects of the compounding operation.

B. These procedures must be developed for the facility, equipment, personnel, preparation, packaging, and storage of compounded preparations and ingredients to ensure accountability, accuracy, quality, safety, and uniformity in compounding as appropriate for the level of compounding performed at the facility.

C. All personnel who conduct or oversee compounding activities must be trained in the facility's SOPs and be responsible for ensuring that they are followed.

D. SOPs must be periodically reviewed and updated as necessary.

E. Required SOP's

(1) Training and safety

(2) Hand Hygiene and garbing

(a) Proper hand hygiene shall be defined in appropriate SOPs as detailed in the SOP section and appropriate for prevention of preparation and facility contamination

(b) Garbing requirements and the frequency of changing garb shall be determined by the pharmacy and documented in appropriate SOPs as detailed in the SOP section of the practice act

(c) Manipulations such as weighing, measuring, or mixing components that could generate airborne chemical particles should be evaluated to determine if specialized PPE is required or if the activities should be performed in a negative pressure space or closed system processing device to reduce the potential for personnel exposure and facility contamination. The process for evaluation must be carried out in accordance with the facility's SOPs.

(3) Compounding procedures and techniques, including describing packaging of CNSPs.

(4) Cleaning/spill kits, including the management and disposal of component spills.

(5) Equipment usage and calibration (Note that all temperature monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.)

(6) Temperature and humidity

(7) Designated personnel/organizational chart

(8) Quality assurance and quality control

(9) Recall / adverse event record keeping and reporting

(10) Shipping/transportation, if applicable (If transporting CNSPs, the facility must have written SOPs to describe the mode of transportation, any special handling instructions, and whether temperature monitoring devices are needed.)

(11) Formulation and record keeping

(12) Component selection and usage (Note that manipulations such as weighing, measuring, or mixing components that could generate airborne chemical particles should be evaluated to determine if specialized PPE is required or if the activities should be performed in a negative pressure space or closed system processing device to reduce the potential for personnel exposure and facility contamination. The process for evaluation must be carried out in accordance with the facility's SOPs.)

(13) An area must be designated for nonsterile compounding (Note that the method of designation must be described in the facility's SOPs)

99-82. Non-Sterile Compounding: Quality Assurance and Quality Control

A. Quality assurance (QA) is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.

B. Quality control (QC) is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP.

C. A facility's QA and QC programs must be formally established and documented in the facility's SOPs.

D. At each step of the compounding process, the pharmacist shall ensure that components used in compounding are accurately weighed, measured, or subdivided as appropriate to conform to the formula being prepared.

E. Quality Assurance:

(1) Initial formula validation. Prior to routine compounding of a non-sterile preparation, a pharmacy shall conduct an evaluation that shows that the pharmacy is capable of compounding a product that contains the stated amount of active ingredient(s).

(2) Finished preparation checks. The prescription drug and medication orders, written compounding procedure, preparation records, and expended materials used to make compounded non-sterile preparations shall be inspected for accuracy of correct identities and amounts of ingredients, packaging, labeling, and expected physical appearance and properties before the non-sterile preparations are dispensed.

F. Quality Control:

(1) The pharmacy shall follow established quality control procedures to monitor the quality of compounded drug preparations for uniformity and consistency such as capsule weight variations, adequacy of mixing, clarity, or pH of solutions. When developing these procedures, pharmacy personnel should consider the provisions of Chapter 795, concerning Pharmacy Compounding Non-Sterile Preparations, Chapter 1075, concerning Good Compounding Practices, and Chapter 1160, concerning Pharmaceutical Calculations in Prescription Compounding contained in the current USP/NF. Such procedures shall be documented and be available for inspection.

(2) Compounding procedures that are routinely performed, including batch compounding, shall be completed and verified according to written procedures. The act of verification of a compounding procedure involves checking to ensure that calculations, weighing and measuring, order of mixing, and compounding techniques were appropriate and accurately performed.

(3) Unless otherwise indicated or appropriate, compounded preparations are to be prepared to ensure that each preparation shall contain not less than 90.0 percent and not more than 110.0 percent of the theoretically calculated and labeled quantity of active ingredient per unit weight or volume and not less than 90.0 percent and not more than 110.0 percent of the theoretically calculated weight or volume per unit of the preparation.

G. Notification About and Recall of Dispensed Compounded Preparations

(1) The pharmacy shall have written procedures for the recall of any compounded preparations provided to a patient, to a practitioner for office use, or a pharmacy for administration. These procedures must address:

(a) When recalls must be initiated, which should include procedures to immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., strength, purity, or other quality attributes)

(b) Procedure to recall any unused dispensed CNSPs and quarantine any stock remaining in the pharmacy

(c) Necessity of investigating if other lots are affected and whether a further recall is necessary

(2) An SOP for recall of dispensed compounded preparations must contain the following procedures:

(a) The pharmacy shall have written procedures for the recall of any compounded non-sterile preparations provided to a patient, to a practitioner for office use, or a pharmacy for administration. Written procedures shall include, but not be limited to, the requirements as specified in paragraph (3) of this subsection.

(b) The pharmacy shall immediately initiate a recall of any non-sterile preparation compounded by the pharmacy upon identification of a potential or confirmed harm to a patient.

(c) In the event of a recall, the pharmacist-in-charge shall ensure that:

(i) each practitioner, facility, and/or pharmacy to which the preparation was distributed is notified, in writing, of the recall;

(ii) each patient to whom the preparation was dispensed is notified, in writing, of the recall;

(iii) the preparation is quarantined; and

(iv) the pharmacy keeps a written record of the recall including all actions taken to notify all parties and steps taken to ensure corrective measures.

(d) If a pharmacy fails to initiate a recall, the board may require a pharmacy to initiate a recall if there is potential for or confirmed harm to a patient.

(e) If a non-sterile compounding facility has three (3) or more recalls within a 12-month period, the recalls must be reported to the South Carolina Board of Pharmacy.

99-83. Non-Sterile Compounding: CNSP Packaging and Transporting

A. The facility's SOPs must describe packaging of CNSPs. Personnel shall select and use packaging materials that will maintain the physical and chemical integrity and stability of the CNSPs. Packaging materials must protect CNSPs from damage, leakage, contamination, and degradation, while simultaneously protecting personnel from exposure.

B. If transporting CNSPs, the facility must have written SOPs to describe the mode of transportation, any special handling instructions, and whether temperature monitoring devices are needed.

(1) hazardous CNSP must be packaged for handling and delivery in a manner that minimizes the risk of rupture of the primary container and ensures the stability, and potency of the preparation.

(2) Transporting includes delivery, either through company delivery service or contracted courier, and shipping.

99-84. Non-Sterile Compounding: Documentation

A. All facilities where CNSPs are prepared must have and maintain written, electronic or readily accessible documentation to demonstrate compliance with applicable laws and regulations. This documentation must include, but is not limited to, the following:

(1) Personnel training, competency assessments
(2) Equipment records (e.g., calibration, verification, and maintenance reports)
(3) COAs
(4) SOPs, Master Formulation Records, and Compounding Records
(5) Records of cleaning the designated compounding area
(6) Temperature and humidity logs for compounding areas as well as refrigerators as applicable
(7) Information related to adverse events including corrective actions taken
(8) Applicable Quality Control results

B. Records must be legible and stored in a manner that prevents their deterioration and/or loss.

C. All required CRs for a particular CNSP must be kept for a period of time as other prescriptions as required by the Board of Pharmacy. These records must be readily available for authorized inspection during the retention period at the establishment. These records are subject to duplication by photocopying or other means of reproduction as part of the inspection.

D. Hazardous Drug Compounding

(1) Manipulations such as weighing, measuring, or mixing components that could generate airborne chemical particles should be evaluated to determine if specialized PPE is required or if the activities should be performed in a negative pressure space or closed system processing device to reduce the potential for personnel exposure and facility contamination. The process for evaluation must be carried out in accordance with the facility's SOPs.
(2) If a closed system processing device such as a CVE or BSC is used, it must be certified at least every 12 months according to manufacturer specifications or other laws and regulations of the applicable regulatory jurisdiction.
(3) If the facility utilizes hazardous components in nonsterile compounding, they must have an appropriate and readily accessible spill kit in the compounding area.

99-90. Nuclear Compounding: Scope

A. The Board of Pharmacy's Nuclear Compounding regulations apply to the practice of the sterile and non-sterile compounding of radiopharmaceuticals or radioactive materials ("RAM") by South Carolina-permitted nuclear pharmacies. This includes pharmacies who prepare, compound, dispense, or repackage radiopharmaceuticals. These regulations also apply to all individuals who prepare, compound, dispense, or repackage radiopharmaceuticals. Individuals bound by these regulations include authorized nuclear pharmacists ("ANPs") as well as licensed pharmacy technicians working under the supervision of an ANP.

B. The receipt, storage, handling, disposal, shipment, and delivery of radiopharmaceuticals and RAM falls under the jurisdiction of the U.S. Nuclear Regulatory Commission ("NRC") or the South Carolina Department of Environmental Services ("SCDES"). Compliance with the regulations set forth by the NRC and/or SCDES are required in addition to all regulations promulgated by the Board.

C. The Board's Nuclear Compounding regulations do not apply to:

(1) Manufacturing of approved radiopharmaceuticals (e.g., NDA, ANDA, BLA) in FDA-registered manufacturing facilities.

(2) Manufacturing of radiopharmaceuticals as investigational agents (e,g, IND, RDRC)

(3) Compounding of radiopharmaceuticals in a registered FDCA 503B outsourcing facility.

(4) Preparation/compounding of positron emission tomography (PET) drugs that are not manufactured as approved drug products (e.g. NDA, ANDA, BLA).

(5) Administration of radiopharmaceuticals to patients.

99-91. Nuclear Compounding: Definitions.

A. "Authorized Nuclear Pharmacist" is defined as an actively licensed pharmacist in good standing with and licensed by the South Carolina Board of Pharmacy, who is certified as a nuclear pharmacist that meets the standards set forth by the U.S. Nuclear Regulatory Commission ("NRC") regulations.

B."Nuclear Compounding" is defined as the combining, mixing, pooling, or otherwise altering (excluding preparation with minor deviations) of a conventionally manufactured radiopharmaceutical or synthesizing/formulating a radiopharmaceutical from bulk drug substances and radionuclides.

C."Dispensing" is defined as the manipulation or labeling of a radiopharmaceutical to render it in its final form for administration, typically obtained from a single-dose or multiple-dose container (e.g., withdrawing a volume of finished product or preparation from a vial into a syringe). Dispensing must be performed under the supervision of a physician or pharmacist and, for radiopharmaceuticals, includes dilution with an appropriate diluent or adjusting the activity in an individual dosage.

D."Internal Test Assessment" is defined as, but is not limited to, conducting those tests of quality assurance necessary to ensure the integrity of the test.

E. "Nuclear Pharmacy/Radiopharmacy" is defined as a pharmacy providing radiopharmaceutical services or an appropriately designated and outfitted area of any institutional facility.

F. "Preparation" is defined as the act of combining a conventionally manufactured kit with a conventionally manufactured radionuclide following manufacturer's recommended instructions. Mixing, reconstituting, combining, diluting, or repackaging of a radiopharmaceutical, or other such acts, performed in accordance with directions contained in the FDA-approved labeling.

G."Preparation with Minor Deviations" is defined as the act of preparing a conventionally manufactured kit with a conventionally manufactured radionuclide with volume, and/or radioactivity, and/or step-by-step deviations from the manufacturers recommended labeling while ensuring that the final preparation maintains appropriate radiochemical and radionuclidic purity for the entirety of the beyond use date ("BUD"). Examples of minor deviations include, but are not limited to, altering the amount of activity or volume added to the vial, changes in step-by-step operations (e.g., dilute Tc-99m solution after, rather than before, addition to the vial, use of a venting needle or filter), using alternative devices or equipment (e.g., a heating block rather than a hot water bath), and using alternative radiochemical purity testing methods.

H. "Qualified Licensed Professional" is defined as a non-pharmacist individual (such as a physician, nurse, or technologist) who possesses a current South Carolina professional license, if applicable, and who has sufficient training and experience to safely handle and dispense radiopharmaceuticals as defined by the respective requirements of the NRC and the South Carolina Department of Environmental Services ("SCDES")

I. "Cleaning" is defined as the process of removing materials from the surfaces using a combination of mechanical processes and a cleaning agent.

J. "Cleaning agents" are defined as surfactants, typically, used for the removal of substances from surfaces

K. "Disinfection agents" are chemical or physical agents used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria

L. "Sporicidal agents" are chemical or physical agents that destroy bacterial and fungal spores when used at a sufficient concentration for a specified contact time. Sporicidal agents are expected to kill all vegetative microogranisms.

M. “Radiopharmaceutical Quality Assurance” means, but is not limited to, the performance of appropriate chemical, biological, and physical tests on potential radiopharmaceuticals and the interpretation of the resulting data to determine their suitability for use in humans and animals, including internal test assessment, authentication of product history, and the keeping of proper records.

N. “Radiopharmaceutical Service” is defined as, but is not limited to, the procurement, storage, handling, preparation, labeling, quality assurance testing, dispensing, delivery, record keeping, and disposal of radiopharmaceuticals and other drugs.

O. “Radiopharmaceuticals” means a finished dosage form that contains a radioactive substance in association with one or more ingredients and that is intended to diagnose, stage a disease, monitor treatment, or provide therapy. A radiopharmaceutical includes any non-radioactive reagent kit or radionuclide generator that is intended to be used in the preparation of any such substance. The terms “radiopharmaceutical” and “radioactive drug” are used interchangeably.

P. “Segregated Radiopharmaceutical Processing Area (“SRPA”) refers to an unclassified area, without an ante-room or buffer area, where only sterile radiopharmaceuticals prepared with minor deviations, dispensing, and repackaging may be performed.

Q. “Repackaging” means the act of removing a conventionally manufactured radiopharmaceutical from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. Repackaging also includes the act of placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients. Radiopharmaceutical manipulation in any other way, including reconstitution, dilution, mixing, or combination with another ingredient, is not considered repackaging.

R. “Non-Direct Infusion Generator” is defined as a device containing a parent radionuclide (e.g., Mo-99 or Ge-68) that decays to produce a daughter radionuclide (e.g., Tc-99m or Ga-68) used in radiopharmaceutical preparation§ not intended for direct patient infusion without additional compounding or labeling.

99-92. Nuclear Compounding: Facilities

A. The balancing of aseptic practices during compounding of radiopharmaceuticals must be balanced with the principles of radiation safety considerations. These include the following principles:

(1) Time: Radiation exposure to personnel is directly proportional to the quantity of radiation handled and the time handling the RAM; minimizing handling time will minimize radiation exposure. Personnel handling radiopharmaceuticals may work quickly in a controlled and safe manner, including multiple hand movements in and out of the ISO class 5 primary engineering control (“PEC”) during aseptic processes.

(2) Distance: Radiation exposure follows the inverse square law increasing the distance between the operator and the RAM will decrease radiation exposure by the square of the distance. Handlers of radiopharmaceuticals may utilize techniques to increase distance, such as remote handling tools, including within an ISO class 5 PEC.

(3) Shielding: Radiation exposure to personnel decreased with use of shielding materials. Therefore, handlers of radiopharmaceuticals may use various shielding materials (e.g., lead, tungsten) in various configurations. The use of shielding, such as L-blocks, tongs, vial, and syringe shields, is usually required throughout the radiopharmaceutical handling process, including within an ISO Class 5 PEC.

B. A permit to operate a pharmacy or facility engaged in the compounding radiopharmaceuticals will only be issued to an authorized nuclear pharmacist (“ANP”) holding a valid South Carolina pharmacist license.

(1) All personnel performing tasks in the preparation and distribution of radioactive drugs must be under the direct supervision of a South Carolina-licensed ANP.

(2) An ANP must be responsible for all operations of the pharmacy and shall be in personal attendance at all times that the pharmacy is open for business. In emergency situations when an authorized nuclear pharmacist is not present, designated qualified professionals may have access to the licensed area as outlined in the facilities standard operating procedures (“SOPs”). These designated qualified professionals

may only prepare single unit doses of radiopharmaceuticals for immediate emergency and must document such activities. A designated qualified professional would include a South Carolina-licensed pharmacist who does not hold an Authorized User ("AU") Certification in Nuclear Pharmacy issued by U.S. Nuclear Regulatory Commission ("NRC").

C. Nuclear pharmacies must have adequate space and equipment, commensurate with the scope of services required and provided, meeting minimal space requirements established for all pharmacies in the state or as otherwise defined by the South Carolina Board of Pharmacy.

D. The nuclear pharmacy area must be secured from unauthorized personnel.

E. Nuclear pharmacies must maintain records of acquisition, inventory, and disposition of all radioactive drugs and other radioactive materials in accordance with South Carolina Department of Environmental Services ("SCDES") and/or the NRC.

F. All pharmacies handling radiopharmaceuticals must provide a radioactive storage and product decay area. Detailed floor plans shall be submitted to the state board of pharmacy and SCDES or NRC before approval of the license.

G. Radiopharmaceuticals must be dispensed only upon a prescription drug order from a practitioner authorized to possess, use, and administer the radiopharmaceutical being prescribed.

H. The permit to operate a nuclear pharmacy/radiopharmacy is conditioned upon an approved South Carolina Department of Environmental Services ("SCDES") and/or NRC license. Copies of the RCA or NRC inspection reports shall be made available upon request for board inspection.

I. Facility Design: The design of a nuclear pharmacy must take into consideration the interdependence of the various areas that make up the compounding of different radiopharmaceuticals.

(1) Types of Secondary Engineering Controls and Design

(a) The primary engineering control ("PEC") must be located in a secondary engineering control ("SEC"), which may be either in an ISO-classified buffer room with ante-room or a segregated radiopharmaceutical processing area ("SRPA") in a manner that minimized conditions that could increase the risk of microbial contamination.

(b) Ante-rooms must be separate from the buffer area and the surrounding unclassified areas of the facility with fixed walls and doors.

(2) Facility designs and controls must be in place to minimize the flow of lower-quality air into the more controlled areas.

(3) Air supplied to areas of the classified area must be introduced through HEPA filters that are located in the ceiling.

(4) Returns must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulates will accumulate.

(5) A smoke study of the PEC must be repeated whenever a change to the placement of the PEC within the area is made.

(6) The classified areas must be equipped with a pressure-differential monitoring system.

(7) The ante-room must have a line of demarcation to separate the clean side from the less-clean side. The ante-room is entered through the less-clean side, and the clean side is the area closest to the buffer area.

(8) Shoe covers or designated shoes must be placed on prior to crossing the line of demarcation; remaining required garb must then be donned prior to entering the buffer area.

(9) Control of movement of materials (supplies and equipment) is critical as they move from classified areas of lower quality to those of higher quality (i.e. ISO Class 8 ante-room to ISO Class 7 buffer area to ISO Class 5 PEC) to prevent the influx of contaminants.

(10) Airlocks and interlocking doors should be used to facilitate better control of air flow between areas of differing ISO classification or between a classified area and an unclassified area. If using a pass-through, both doors should never be opened at the same time which may be achieved using interlocking mechanisms.

J. Segregated Radiopharmaceutical Processing Areas ("SRPAs")

(1) Must have a PEC present for where all compounding activities are performed.

(2) If the SRPA meets ISO Class 8 total airborne particle count specifications, it can also be used for storage and elution of non-direct infusion radionuclide generators (Mo-99/Tc99m generators and Ge-68/Ga-68 generators).

(3) The SRPA must be located away from unsealed windows, doors the connect to the outdoors, and traffic flow which may adversely affect the air quality in the PEC.

(4) A visible perimeter must establish the boundaries of the SRPA. Access to the SRPA must be restricted to authorized personnel and required materials. An SRPA must not be located adjacent to environmental control challenges.

K. Radiopharmaceutical Processing Environments

(1) The PEC must be certified to meet ISO class 5 or better conditions and must be designed to minimize microbial contamination during processing of radiopharmaceuticals under dynamic operating conditions. See R.99-51 for additional requirements regarding ISO classification of particulate matter in area air.

(a) The PEC must be located out of traffic patterns and away from area air currents that could disrupt the intended airflow patterns inside the PEC.

(b) If only used to prepare, prepare with minor deviations, dispense, or repackage sterile radiopharmaceuticals the ISO 5 PEC may be placed in an unclassified SRPA.

(c) If used to compound sterile radiopharmaceuticals, the PEC must be located within an ISO Class 7 or better buffer area with an ISO Class 8 or better ante-room.

(2) The airflow in the PEC must be unidirectional (i.e. laminar flow), and because of the particle collection efficiency of the filter, the "first air" at the face of the filter is, for the purpose of aseptic processing, free from airborne particulate contamination.

(3) HEPA-filtered air must be supplied in the direct processing area ("DPA") at a velocity sufficient to sweep particles away from aseptic processing areas and maintain unidirectional airflow as much as possible during operations, given the limitations added from the radiation shielding in the DPA.

(4) In situ air pattern analysis via smoke studies must be conducted at the critical area to demonstrate unidirectional airflow and sweeping action under dynamic conditions.

(5) The air exchange requirements in R.99-50 must be followed.

M. Classified Areas

(1) Activities carries out within the buffer area must be limited to only those necessary.

(2) Food, drinks, and material exposed in patient care and treatment areas must not enter ante-rooms or buffer areas.

(3) When processing activities require the manipulation of blood-derived or other biological material (e.g., radiolabeling patient's or donor's blood cells), the manipulations must be clearly separated from routine material-handling procedures and equipment used in radiopharmaceutical preparation activities, and they must be controlled by specific SOPs to avoid any cross-contamination.

N. Remote Aseptic Processing Involving a Hot-Cell

(1) A hot-cell device provides an inherent physical segregation for the ISO Class 5 aseptic processing area. If the hot-cell is located in an ISO-classified space, personnel must garb according to requirements listed in USP <895> 4.5, *Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*, In settings where tasks are carried out within the hot-cell enclosure not within an ISO-classified space by remote means (i.e., no direct intervention by personnel into the ISO Class 5 space), it is not necessary for personnel to don the garbing described in USP <895> 4.5, *Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*, to carry out these aseptic manipulations or to perform other routine tasks in the general area where the hot-cell is located.

(2) If hand and arm incursions into the interior of the hot-cell might be necessary for personnel to stage the required materials and supplies, the personnel must garb in relation to the contamination risk associated with the individual hot-cell/ISO Class 5 relationship.

(3) For situations where a PEC device is located within a hot-cell, dynamic airflow smoke pattern tests must show that the staging of supplies and materials in the demarcated PEC area does not allow the influx

of unclassified air into the PEC. Personnel may be garbed in nonsterile gloves and a low-particulate lab coat for interventions that are outside of the PEC.

(4) A failure of the airflow smoke pattern test requires personnel to garb in accordance with USP <895> 4.5, *Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*, in for all incursions into the hot-cell.

(5) For situations where the hot-cell is an integrated HEPA filtration system with a clear demarcated area that is a PEC, dynamic airflow smoke pattern tests must show that the staging of supplies and materials into the demarcated PEC area does not allow the influx of less than ISO Class 5 quality air into the PEC.

(6) Personnel may be garbed in nonsterile gloves and a low particulate lab coat for interventions that are outside of the PEC. A failure of the airflow smoke pattern test requires personnel to garb in accordance with USP <895> 4.5, *Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*, for all incursions into the PEC. Since other hot-cell/PEC configurations and technologies may exist, verification (either by airflow smoke pattern tests or other manufacturer specified methods) must ensure, upon each certification, that the staging of materials and supplies does not allow for the intrusion of less than ISO Class 5 air into the designated ISO Class 5 space. A failure of the airflow smoke pattern test requires personnel to garb in accordance with USP <895> 4.5, *Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area*.

O. Environmental Controls

(1) All radioactive materials ("RAM") users must comply with the conditions specified in their approved RAM license application and regulations, and RAM license conditions may supersede the following requirements for environmental controls described in these regulations.

(2) Passthrough enclosures for transferring radiopharmaceuticals from controlled handling areas (e.g., buffer area) should be designed to provide reasonable balance between maintenance of air quality and other worker safety concerns (e.g., radiation exposure, physical injury from lifting heavy shielded cases). At a minimum, there must be a mechanical system or SOP in place that ensures that both doors cannot be open at the same time.

(3) There may be both positive and negative air pressure within the facility: positive pressure to minimize the potential of microbial contamination in sterile drug preparation areas and negative pressure to minimize potential radioactive contamination from volatile or airborne radiopharmaceuticals.

(4) Positive pressure environments must have a minimum differential positive pressure of 0.02-inch water column between each ISO-classified area (e.g., between the buffer area and ante-room). The pressure differential between the ante-room and the unclassified area must be no less than a positive 0.02-inch water column. Refer to the RAM license for negative pressure requirements.

(5) For preparation of sterile radiopharmaceuticals, consideration of both concerns could be addressed as follows:

(a) Buffer area, if present, must be positive pressure compared to the ante-room

(b) Ante-room, if present, must be positive pressure compared to unclassified portions of the restricted area

(c) Restricted area, in the presence of volatile or airborne radiopharmaceuticals, must be negative pressure compared to the unrestricted area

(d) SRPA must be negative pressure compared to unrestricted areas in the presence of volatile or airborne radiopharmaceuticals (e.g., I-131 sodium iodide and Xenon).

P. Establishing and Maintaining Environmental Controls. A pressure monitoring device must be utilized in accordance with R.99-50.

Q. Ambient Atmosphere for Immediate Use Preparations. The following requirements should be met in ambient atmosphere environments:

(1) Non-patient care space, functionally separate (not necessarily a different area) from the patient care area, such as a radiopharmaceutical handling space, or hot lab, in a hospital, clinic, or mobile coach

(2) A designated area for medication preparation that is clean and free from clutter

(3) Low traffic (i.e., limited number of people going in and out or moving around the area during times that radiopharmaceutical processing is being carried out)

R. SRPA with Vertical Flow ISO Class 5 (PECs) for Radiopharmaceutical Preparations.

(1) An SRPA with vertical ISO Class 5 PECs must meet the following requirements:

(a) Area surrounding the PEC may be ambient (unclassified) atmosphere

(b) Area must be clean, uncluttered, and dedicated to the processing of radiopharmaceuticals

(c) Appropriate for preparation, preparation with minor deviations, repackaging, and dispensing of radiopharmaceuticals

(2) An area that meets ISO Class 8 total airborne particle-count specifications may be used to store and elute non-direct infusion radionuclide generators (e.g., Tc-99m).

S. Certification of the classified areas, including the PEC, must be performed initially and recertification must be performed at least every 6 months using procedures outlined in the current Controlled Environment Testing Association (CETA) certification guide for Sterile Compounding Facilities, or an equivalent guideline, and must include all testing and studies outlined in R.99-50.

(1) Airflow testing: To determine acceptability of the air velocity, the air exchange rate, and area pressure cascade to ensure that air consistently flows from most to least clean areas, and that the appropriate quality of air is maintained under dynamic operating conditions.

(2) HEPA filter integrity testing: HEPA filters must be leak tested after installation and as part of recertification.

(3) Total particle counts testing: Conducted under dynamic operating conditions using calibrated electronic equipment.

(4) Smoke visualization studies: Performed under either simulated or dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the preparation(s).

T. Daily the temperature and humidity must be monitored in the SRPA or area containing a hot-cell, and if in a classified area the pressure must monitored, each day that preparations are made, either manually or by a continuous recording device. These include:

(1) Relative humidity should be kept at 60% or lower

(2) Temperature and relative humidity continuous readings must be confirmed daily to have remained within the acceptable range

(3) Excursions must be documented and, if applicable, appropriate corrective actions taken

(4) Temperature monitoring devices must be verified for accuracy every 12 months or as required by the manufacturer

(5) Monitoring of pressure differentials must be performed

99-93. Nuclear Pharmacy: Training and Qualifications for Authorized Nuclear Pharmacists

A. An Authorized Nuclear Pharmacist is defined as required by Nuclear Regulation Commission ("NRC") Regulations, 10 C.F.R. 35.55.

B. An Authorized Nuclear Pharmacist must have the following minimum qualifications:

(1) Certified by a specialty board whose certification process has been recognized by the Commission or an Agreement State;

(2) Have graduated from a pharmacy program accredited by the Accreditation Council for Pharmacy Education (ACPE) (previously named the American Council on Pharmaceutical Education) or have passed the Foreign Pharmacy Graduate Examination Committee (FPGEC) examination;

(3) Hold a current, active license to practice pharmacy in South Carolina;

(4) Provide evidence of having acquired at least 4000 hours of training/experience in nuclear pharmacy practice. Academic training may be substituted for no more than 2000 hours of the required training and experience; and

(5) Pass an examination in nuclear pharmacy administered by diplomates of the specialty board, that assesses knowledge and competency in procurement, compounding, quality assurance, dispensing, distribution, health and safety, radiation safety, provision of information and consultation, monitoring patient outcomes, research and development.

C. If a pharmacist is unable to meet the requirements in Subsection B, the pharmacist may still obtain authorization as an Authorized Nuclear Pharmacist if the pharmacist has:

(1) Completed 700 hours in a structured educational program consisting of both:

(a) 200 hours of classroom and laboratory training in the following areas—

(i) Radiation physics and instrumentation;

(ii) Radiation protection;

(iii) Mathematics pertaining to the use and measurement of radioactivity;

(iv) Chemistry of byproduct material for medical use;

(v) Radiation biology

(b) 500 hours of supervised practical experience in a nuclear pharmacy involving—

(i) Shipping, receiving, and performing related radiation surveys;

(ii) Using and performing checks for proper operation of instruments used to determine the activity of dosages, survey meters, and, if appropriate, instruments used to measure alpha- or beta-emitting radionuclides;

(iii) Calculating, assaying, and safely preparing dosages for patients or human research subjects;

(iv) Using administrative controls to avoid medical events in the administration of byproduct material; and

(v) Using procedures to prevent or minimize radioactive contamination and using proper decontamination procedures; and

(2) Has obtained written attestation, signed by an appropriately qualified preceptor Authorized Nuclear Pharmacist, that the individual has satisfactorily completed the requirements of this regulation and is able to independently fulfill the radiation safety-related duties as an Authorized Nuclear Pharmacist.

D. Aseptic Training and Validations.

(1) Competency of personnel must be demonstrated and documented related to their job functions. Aseptic technique and cleaning processes must be confirmed in order to assure a quality product is dispensed. Testing of such techniques are similar to those described in R.99-50 with allowances for radiation safety. The following tests must be documented initially for personnel as well as reevaluated every 6 months to assure competencies. Appropriate SOPs should be established to address these requirements:

(a) Garbing and hand hygiene

(b) PEC cleaning and disinfecting

(c) Gloved fingertip, thumb and workstation sampling

(d) Media-fill testing

(2) Requalification After Failure.

(a) Personnel who fail visual observation of hand hygiene, garbing, and aseptic technique, gloved fingertip and thumb sampling, or media-fill testing must successfully pass reevaluations in the deficient area(s) before they can resume processing of sterile preparations. All failures, retraining, and reevaluations must be documented.

99-94. Nuclear Pharmacy: Cleaning and Disinfecting

A. All cleaning activities must be completed by trained personnel.

B. When cleaning, personnel must be appropriately gowned and garbed.

C. Each facility's standard operating procedures must outline the cleaning process, the cleaning agents to be used, and the days/frequencies that each respective agent is utilized.

D. Cleaning must be performed from clean to dirty. For example, if equipment is shared between respective areas, it should always be used to clean from cleanest room to dirtiest and then subsequently be disinfected prior to being reused subsequently.

E. Published data must be followed in respect to the appropriate contact time for each of the cleaning, disinfecting, and sporicidal agents used.

F. All cleaning, disinfection and application of sporicidal disinfectants must be documented according to facility policies and these records must be retained at least two (2) years.

G. When diluting concentrated cleaning and disinfecting agents for use in classified areas, sterile water must be used.

H. Supplies used for cleaning and disinfection must be low lint.

I. Cleaning agents and supplies used in the PEC should be sterile aside from tool handles, which must be cleaned and disinfected prior to being placed in a PEC.

J. Wipers, sponges, pads, and mop heads are to be disposable. Disposable supplies must be discarded after each activity or no less frequent than daily. This should be delineated in the facilities standard operating procedures and supported by the manufacturer's instructions for use.

K. Reusable cleaning tools, including handles, must be made of cleanable materials and cannot be constructed of wood or other porous materials. Tool handles must be cleaned and disinfected prior to being placed in a PEC

L. Once opened, sterile cleaning supplies and cleaning or disinfecting agents or sterile 70% IPA may be reused for the time period as outlined by the manufacturer unless the facilities SOPs provide a shorter time period.

M. Surfaces should be cleaned prior to being disinfected unless an Environmental Protection Agency (EPA)-registered (or equivalent) on-step disinfectant cleaner is used to accomplish both the cleaning and disinfecting in one step.

N. After cleaning and disinfecting or the application of a one-step disinfectant cleaner in a PEC, apply sterile 70% IPA to remove any residue.

O. Cleaning and disinfecting of surfaces should occur at the minimum frequencies specified in the table below.

P. If compounding activities are not performed daily, cleaning and disinfecting must be completed before initiating compounding.

Q. The act of reducing or removing radioactivity (radioactive decontamination) from equipment or a surface must be balanced with the risk of spreading radioactive contamination.

R. Shielding of radioactive contamination, at times, may be necessary to lower the radiation exposure levels prior to cleaning and disinfecting.

S. The PEC should be checked for radioactive contamination

T. Additionally, in a PEC, sterile 70% IPA must be applied after cleaning and disinfection, or after the application of a one-step disinfectant or sporicidal disinfectant. Sterile 70% IPA must also be applied immediately before compounding.

U. During the compounding process, sterile 70% IPA must be applied to the horizontal work surface, including any removable work trays, of the PEC at least every thirty (30) minutes or at the conclusion of the compounding session if it takes greater than thirty (30) minutes.

V. When sterile 70% IPA is used, it must be allowed to dry prior to proceeding to any subsequent step or activity.

W. Cleaning and disinfecting must be completed at minimum in accordance with the table below.

Table 1. Cleaning and Disinfecting Schedule

Site	Cleaning	Disinfecting	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield, and any exposed surface of equipment inside the PEC to the extent possible as specified by	Following cleaning on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent as possible as specified by the manufacturer or the assessment of a qualified individual	Monthly

	the equipment manufacturer or the assessment of a qualifies individual	(e.g., microbiologist or industrial hygienist) and should be specified by SOPs. Remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.	
Surface of sink(s)	Daily	Daily	Monthly
Hot-Cells (all interior surfaces, dependents on design, equipment, and shielding present)	Daily	Daily	Monthly
PEC and the equipment inside the PEC(s) located in a hot-cell	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield, and any exposed surface of equipment inside the PEC to the extent possible as specified by the equipment manufacturer or the assessment of a qualifies individual	Following cleaning on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent as possible as specified by the manufacturer or the assessment of a qualified individual (e.g., microbiologist or industrial hygienist) and should be specified by SOPs. Remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.	Monthly
Work surface(s) outside of the PEC	Daily	Daily	Monthly
Ceiling(s)	Monthly	Monthly	Monthly
Wall(s), door(s), door frame(s), and other fixtures	Monthly	Monthly	Monthly
Floor(s)	Daily	Daily	Monthly
Storage shelving and storage bins	Monthly	Monthly	Monthly

Generator Housing (Mo-99 or Ga-68/Ge-68) and area around generators	Daily	Daily	Monthly

99-95. Nuclear Pharmacy: Microbial Air and Surface Monitoring

A. Radiopharmacies must develop and implement written air and surface monitoring procedures for all sterile radiopharmaceutical classified areas as outlined in R.99-50. The air and surface sampling procedures must include viable impact volumetric airborne particulate sampling and surface sampling.

B. Results and corrective actions must be documented, and records must be readily retrievable.

99-96. Nuclear Pharmacy: Viable Air and Surface Monitoring

A program for monitoring the viable airborne particles in accordance with R.99-50 must be implemented to assess for microbial air quality in all classified areas.

99-97: Nuclear Compounding: Radiopharmaceutical Preparations and Compounding

A. Nonsterile Preparations

(1) A designated area must be defined separate from any aseptic procedures.

(2) Manufacturers preparation instructions must be followed, while taking into account the appropriate safety considerations and environmental controls, if applicable (e.g., negative air pressure area, chemical fume hood, activated charcoal filters when handling a potentially volatile radionuclide).

(3) The area for nonsterile preparation must be cleaned and uncluttered to ensure the overall integrity and quality of the prepared radiopharmaceutical(s).

(4) Documentation of processes for all activities (e.g. cleaning) should occur between the preparation cycles of different nonsterile products, to decrease the likelihood of contamination from other prepared products.

B. Sterile Preparations

(1) For these preparations (including intravascular devices), manufacturers preparation instructions must be followed, while taking into account the appropriate radiation safety considerations, appropriate, environmental controls, and aseptic handling practices to maintain sterility.

(2) The minimum environmental standard for the preparation of sterile radiopharmaceuticals beyond immediate-use is within an ISO Classified area or device.

C. Preparation with Minor Deviations

(1) Radiopharmaceuticals prepared with minor deviations from the manufacturer's instructions are sometimes necessary to accommodate circumstances not contemplated in the FDA-approved labeling.

(2) While allowed, deviations from manufacturer preparation instructions for radiopharmaceuticals must maintain the same ingredients but may differ in their proportions.

(3) Preparation with minor deviations must be performed in a classified area within an ISO5 PEC or within an SRPA.

(4) Prior to preparing with minor deviations, appropriate in-house QC testing, designed to validate the radiochemical purity of the product for the entirety of the BUD or is supported by appropriate peer-reviewed publications for the minor deviation utilized.

(5) Examples of minor deviations include, but are not limited to, the following:

(a) Altering the quantity of radioactivity or volume added to the vial

(b) Changes in step-by-step operations (e.g., dilute Tc-99m sodium pertechnetate after rather than before addition to the vial).

(c) Using alternative devices or equipment (e.g., a heating block rather than a hot water bath, using a different sized needle, different shielding materials)

(d) Using QC test methods other than those described in the product labeling (e.g., radiochemical purity)

(e) Filtered Tc-99m sulfur colloid

(6) Records for Preparation with Minor Deviations

(a) A record for preparation with minor deviations or compounding should include the following:

(i) Name of the radiopharmaceutical

(ii) Physical Form (e.g., capsule or solution)

(iii) Name and quantity of ingredients including calibration time for radioactive ingredients (e.g., 100mCi Tc-99m sodium pertechnetate @1200)

(iv) Total volume

(v) Reference to the MFR

(vi) Any deviation from the MFR, if applicable

(vii) Name of vendor or manufacturer, lot numbers, and expiration dates of all ingredients and components

(viii) Name of the person who prepared and name of the supervising personnel (ANP)

(ix) Date and time of preparation

(x) Assigned internal identification number (e.g, lot number)

(xi) Unique reference [e.g., prescription number]

(xii) Assigned BUD and storage requirements if applicable

(xiii) Documentation of QC results

D. Preparation of Radiolabeled Blood Components

(1) The handling and radiolabeling of blood require special considerations for the biological risks while using aseptic technique to prevent the introduction of new microorganisms into the blood sample.

(2) Preparations utilizing radiolabeled blood samples must be re-administered as soon as possible but no later than 6 hours after the blood sample is obtained or drawn from the patient.

(3) The presence of microorganisms in a blood sample may present a risk to the individual performing the preparation as well as cross-contamination to other blood samples or other non-blood related radiopharmaceuticals. Equipment and supplies should never be shared with other activities unless they are first thoroughly cleaned and disinfected.

(4) Special precautions when radiolabeling of blood components for non-immediate use include:

(a) There must be complete separation (either fixed or non-fixed walls) of areas where blood products are handled from areas where non-blood products are handled.

(b) An ISO Class 5 biological safety cabinet (BSC) located in an ISO Class 7 buffer area is required for blood-labeling processes. If more than one ISO Class 5 PEC is located within the ISO Class 7 buffer area, policies and SOPs must be in place to include certification that the SEC meets conditions or air quality at a maximum occupancy under dynamic operating conditions.

(c) One radiolabeling procedure per PEC at a time. Blood products for more than one patient must never be manipulated at the same workstation at the same time. Each area should have dedicated supplies, equipment, and waste disposal to eliminate sharing of these items or overlap in pathways.

(d) Thorough cleaning and disinfection of the ISO Class 5 BSC and all reusable equipment within, prior to starting another blood component radiolabeling procedure.

(e) If a dedicated dose calibrator is not available, then a means of preventing the blood container(s) from contaminating the dose calibrator must be used or the dose calibrator dipper and liner must be cleaned and disinfected following the radioassay.

(f) Centrifuge should be located within the ISO Class 7 buffer area that is dedicated for blood component radiolabeling processes.

(g) Dedicated (per each radiolabeling procedure) consumable products (e.g., 0.9% sodium chloride injection, diluent, tubes, syringes, and other supplies) necessary for each individual patient radiolabeling procedure.

(h) All tubes and syringes in contact with the patient's blood components must be clearly labeled with the patient's name and at least one identifier (e.g., date of birth, medical record number, barcode).

(i) Dedicated syringe shields and vial shields

(j) Remove and replace any garb that enters the ISO Class 5 BSC before handling anything else not related to performing this procedure.

(k) Removal of all disposable items from the ISO Class 5 BSC utilized in each radiolabeling procedure.

(l) Cleaning and disinfection of all reusable equipment and components (e.g., BSC, centrifuge, dose calibrator, syringe shields, vial shields, syringe transport shields and delivery cases) after each radiolabeling procedure prior to any further use. Polies and SOPs must address cleaning and disinfection processes including the use of an EPC-registered (or equivalent) one-step disinfectant cleaner with activity against blood-borne pathogens followed by sterile 70% IPA. Sterile 70% IPA alone is not sufficient.

(m) After the completion of blood radiolabeling procedures, follow all requirements for hand hygiene and garbing for buffer areas and segregated radiopharmaceutical processing area.

E. Compounding

(1) Each activity that involves compounding must be based on a written procedure and must include maintenance of compounding records.

(2) All sterile compounding must be performed in an ISO Class 5 PEC using aseptic technique.

(3) Compounding of any radiopharmaceutical(s) that have been withdrawn from the market because of safety concerns or lack of effectiveness (unless part of an institutional review board approved investigational study) is not allowed.

(4) Radiopharmaceuticals that are essentially copies of marketed FDA-approved radiopharmaceuticals must not be compounded unless there is a change that produces a clinical difference for an identified individual patient, as determined by a prescriber.

(5) Non-Sterile Radiopharmaceutical Compounding

(a) Non-sterile radiopharmaceutical compounding includes the combining, mixing, diluting, pooling, reconstituting, or otherwise altering a drug or bulk drug substance other than as provided by the manufacturer's package insert to create a nonsterile radiopharmaceutical.

(b) Areas designated for nonsterile compounding must be cleaned and free from clutter and separated from areas designated for sterile radiopharmaceutical compounding.

(c) Compounding should take into account RAM licensing requirements and appropriate radiation safety considerations and utilize appropriate environmental controls. The placement of equipment and materials must take into account a design that prevents cross-contamination.

(d) BUDs must be applied to compounded nonsterile radiopharmaceuticals that takes into account the stability of the ingredients, intermediate containers, the final container, and the storage conditions. A BUD cannot extend past the labeled expiration date of any component in the compound, unless the manufacturer has documentation that after a manipulation, an extended BUD may apply (e.g. I-131 solution compounded into a capsule on the day of expiration, the capsule may expire 5 days later). If the compounded radiopharmaceutical includes ingredients from other preparations or preparations with minor deviations, the BUD of the final compounded radiopharmaceutical must not exceed the shortest remaining BUD of any of those components.

(6) Sterile Radiopharmaceutical Compounding

(a) When determining an appropriate BUD, there must be consideration for the possible interactions between different components of compounded radiopharmaceuticals. These include: radiochemical stability, solubility, changes in pH, chemical stability, and other factors.

(b) In some scenarios, systematic QC testing over time may be required to assign or validate an appropriate BUD.

(c) Kit splitting or fractionation of conventionally marketed FDA approved kits: may be used to meet a patient or multiple patient needs.

(7) Sterile Radiopharmaceutical Compounding Using a Nonsterile Drug Substance or Components

(a) Sterile radiopharmaceutical compounding using a nonsterile drug substances or nonsterile components involves the use of materials other than commercially marketed products (e.g., drug substances

and/or radionuclides). If one of more of the components or ingredients are not considered sterile or pyrogen free, a sterilization procedure (e.g., filtration with bubble point testing) must be performed.

(b) The compounder must be responsible for confirming that the final preparation complies with pre-established standards or acceptance criteria for identity, quality, purity, and must consider all possible interactions between the components, such as altered chemical stability, purity, and must consider all possible interactions between the components, such as altered chemical stability, radiochemical stability, solubility, or other parameters (e.g., osmolarity) related to changes in pH, excipients, or other factors, in determining an appropriate BUD. This may require testing to validate the appropriateness of a particular BUD.

(c) Bulk drug substances: the radiopharmaceutical used in compounding must be a component of an approved drug product. Bulk drug substances include: a radionuclide, a ligand, or other substance, such as a precursor that becomes an active ingredient in the final radiopharmaceutical. Each bulk drug substance is to be manufactured by drug establishments registered with the FDA and be accompanied by a valid CoA or equivalent testing procedures.

(d) If compounding involves excipients or other inactive ingredients, the excipients or other inactive ingredients must comply with standards of an applicable USP or NF monograph, if one exists.

(8) Immediate use of Sterile Radiopharmaceuticals

(a) Radiopharmaceuticals may be compounded as immediate use in an ambient environment that lacks primary and secondary engineering controls only when intended for a single patient. Strict aseptic technique and limited beyond use date (BUD) must be adhered to given the lack of engineering controls.

(b) The following must be followed when preparing and dispensing radiopharmaceuticals in an immediate us setting:

(i) Limited for single patient use

(ii) Preparation (including preparation with minor deviations) components must be sterile, conventionally manufactured drug products.

(iii) Dispensing of drug products produced under an approved IND or RDRC protocol is allowed.

(iv) Manipulations for any unit doses (e.g., decreasing the dosage, needle changes) or dispensing for one patient (e.g., withdrawing a dose) is allowed.

(v) Must be administered within 1 hour of the first container puncture or exposure of any critical site involved (e.g., syringe tup, needle hub or needle) to ambient air, whichever is first.

(vi) All components involved (e.g., Tc-99m sodium pertechnetate syringe or vial, final prepared radiopharmaceutical kit vial, diluent vial) must be discarded within 1 hour of being punctured or after use for a single patient administration, whichever is first.

(vii) Dose pooling (combining doses from two or more syringes to meet one patient's needs) may be performed as immediate use. Any residual that remains must be immediately discarded and not utilized for any other patient.

(viii) Follow proper hand hygiene and garbing protocols.

(ix) Follow proper labeling for radiopharmaceuticals.

(x) The area for sterile preparation and/or dispensing must be functionally separated from any nonsterile compounding areas during the time of use.

(xi) Does not require a segregated radiopharmaceutical processing area (SRPA), classified area, or PEC.

(xii) The number of steps or punctures is not limited.

(xiii) Dose splitting (splitting a unit dose for administration to more than one patient) may not be performed as immediate use; if performed, dose splitting must be done in an ISO class 5 PEC in either an SROA r in an ISO class 8 or better buffer area.

F. Quality Control and Quality Assurance

Radiopharmacies must have documentation related to the quality control standards and ongoing quality assurance protocols for all activities related to products dispensed. This should at least cover:

(1) Source of receipt documentation

(2) Quality control testing of products

(3) Internal test assessments of procedures used for QC tests or related documentation to procedures being used.

(4) Procedures for recall or notifications for out of specifications of products dispensed

G. Assigning Beyond Use Date (BUD) of Radiopharmaceuticals

(1) Beyond Use Date (BUD) is defined as the date, or date and time (if applicable), beyond which a radiopharmaceutical preparation must not be used and must be discarded.

(2) Determination of the BUD begins at the moment of the first sterile vial puncture or exposure of a critical site to ambient air, whichever is first.

(3) The BUD should not limit the time during which the radiopharmaceutical is administered (e.g. infused).

Table 1. BUD of Sterile Radiopharmaceutical Preparations

Preparation Conditions			
Preparation	**PEC**	**SEC**	**BUD (hours)**
Immediate use	-	-	1
Dispensing, repackaging, preparation, and preparation with minor deviations.	ISO Class 5	SRPA	12
Radionuclide generator storage or elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	-	SRPA with ISO Class 8 total airborne particle count	12
Radionuclide generator storage or elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	-	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, and preparation with minor deviations.	ISO Class 5	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, and preparation with minor deviations, and compounding using sterile components.	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	96
Dispensing, repackaging, preparation, preparations with minor deviations, and compounding using a nonsterile component and performing sterilization procedure but without performing sterility testing.	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room.	24
Radiolabeled blood components (e.g., radiolabeled leukocytes)	ISO Class 5 BSC	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room.	6 hours after blood sample is obtained

H. Dispensing and Assaying

(1) Radiopharmacies are allowed to dispense prescriptions from a single-dose or multiple dose container of prepared, prepared with minor deviations, compounded, or manufactured radiopharmaceuticals, and may involve needle changes, affixing a sterile cap, or dilution (e.g., adding 0.9% sodium chloride injection) in the final container.

(2) Prior to dispensing, the final dose or ordered amount must be radioassayed using a dose calibrator. The exception to this would be an unmanipulated dose in the original unopened manufacturer's container.

(3) The measured activity should be mathematically corrected for radioactive decay to the time of scheduled administration or calibration time.

(4) The activity at time of calibration must be within limits set for by the South Carolina Department of Environmental Services ("DES")

I. Labeling and Documentation Requirements

(1) Labeling Requirements

(a) No radiopharmaceutical may be dispensed unless a label is affixed to the immediate container bearing:

(i) A standard radiation safety symbol

(ii) The words, "Caution-Radioactive Material" and

(iii) The prescription number

(b) No radiopharmaceutical may be dispensed unless a label is affixed to the outer or delivery container bearing the:

(i) Standard radiation symbol

(ii) Words "Caution-Radioactive Material"

(iii) Radionuclide and chemical form (generic name)

(iv) Activity and date and time of assay

(v) Volume in liquid form or number of units dispensed, as applicable

(vi) Requested activity and the calibrated activity

(vii) Route of administration

(viii) Prescription number

(ix) Product expiration or BUD, as applicable, and any special storage or handling instructions for non-immediate use (e.g. refrigeration, resuspension).

(x) Patient name or space for patient name. Where the patient's name is not available at the time of dispensing, a seventy-two-hour exemption is allowed to obtain the name of the patient. No later than seventy-two hours after dispensing the radiopharmaceutical, the patient's name shall become a part of the prescription drug order to be retained for two years

(xi) Name and address of the nuclear pharmacy

(xii) The South Carolina Radioactive Material ("RAM') License number of the pharmacy dispensing the prescription

(xiii) Name of the practitioner, and

(xiv) Lot number of the prescription

J. Documentation Requirements

(1) Records must be maintained for all activities taking place in a radiopharmacy. These records must be in physical form, in digital form, or documented in a computer database that can be retrieved.

(2) Documents must include:

(a) Personnel Qualifications for each job title

(b) Personnel and Environmental monitoring and validations

(c) Quality control data

(d) Inventory receipt data

(e) Equipment maintenance and cleaning logs

(3) Documentation related to all preparations must be maintained and retrievable.

(4) This documentation must include:

(a) Name of radiopharmaceutical

(b) Physical form

(c) Name and quantity of ingredients including calibration time for radioactive ingredients
(d) Total volume
(e) Vendor/Manufacturer, lot numbers, and expiration dates of all components
(f) Name of preparer as well as the date and time of preparation
(g) Internal Identification number
(h) All other required documentation related to the dispensing and labeling of the preparation.

K. Master Formulation Record

(1) Documentation related to Preparations with minor deviations, fractionation-compounding, and more complex radiopharmaceutical compounding must follow a Master Formulation Record ("MFR") as detailed in the facility's SOP on such preparations.

(2) The MFR or SOP must detail:
(a) Name of the radiopharmaceutical
(b) Detailed procedure (e.g., heating, components, incubation time)
(c) Range of radioactivity
(d) Range of volume
(e) PEC and SEC to be used, if applicable
(f) QC required
(g) Reference to justification of BUD

(3) Complex radiopharmaceutical compounding must also include:
(a) Procedures related to depyrogenation and sterility procedures and validation, if applicable
(b) Name, identity, strength, purity, quality, and quantity of ingredients with validated documentation (e.g., CoA)
(c) Equipment to be used
(d) Components used in the preparation

(4) Records related to each preparation using minor deviation or other compounding must:
(a) Include all documentation related to preparations, dispensing and labeling
(b) Reference the MFR or preparation SOP
(c) Include any notations or deviation from the MFR/SOP in a note section attached to the preparation record.

99-98. Nuclear Compounding: Generator Requirements

A. This regulation establishes requirements for the possession, handling, and use of non-direct infusion radionuclide generators, such as Molybdenum-99 (Mo-99)/Technetium-99m (Tc-99m) and Germanium-68 (Ge-68)/Gallium-68 (Ga-68) generators, to ensure safe and effective radiopharmaceutical practices under the supervision of a South Carolina licensed authorized nuclear pharmacist.

B. This regulation applies to nuclear pharmacies and facilities in South Carolina possessing or operating non-direct infusion generators for the preparation of radiopharmaceuticals. These generators are used to produce radioisotopes for diagnostic imaging and other nuclear medicine applications, not for direct infusion into patients without further processing.

C. Supervision Requirements

(1) Non-direct infusion generators shall only be possessed, operated, or used under the direct supervision of a South Carolina licensed authorized nuclear pharmacist.

(2) All personnel involved in generator operations must be trained and work under the direct supervision of the authorized nuclear pharmacist.

(3) Facilities are permitted to possess Tc99m generators for emergency use only under the supervision of a licensed physician.

D. Licensing and Permitting

(1) Facilities possessing non-direct infusion generators must hold a valid pharmacy permit issued by the South Carolina Board of Pharmacy and a current radioactive materials license from the South Carolina Department of Environmental Services.

(2) Facilities are permitted to possess Tc99m generators for emergency use only under the supervision of a licensed physician.

E. Facility and Equipment Standards: Non-direct infusion generators (e.g. Tc99m, Ga68 generators) may be eluted only within a Class 7 buffer area or a SRPA that meets the minimum requirements of a Class 8 particle count criteria.

F. Generator Operation and Elution

(1) Mo-99/Tc-99m Generators: Elution protocols must follow manufacturer recommendations. Mo-99 content of each elution must tested for breakthrough and Mo-99 content be <0.15 μCi per mCi Tc-99m at the time of elution.

(2) Ge-68/Ga-68 Generators: Elution standards must follow manufacturer recommendations. Protocols must be established to test for Ge-68 breakthrough to ensure the lowest amounts possible of Ge-68 are present in each elution.

(a) Breakthrough standards must follow manufacturer recommendations.

(b) Breakthrough records must be kept for a minimum of 3 years.

G. Transporting generators between facilities: If transporting generators between facilities, the following standards should be followed:

(1) Transport of either Mo-99 of Ga-68 generators is permitted.

(2) The generator needle/and or ports should be capped with sterile protectors in an ISO Class 8 air or better or in an SRPA that meets ISO Class 8 total airborne particle count specifications.

(3) The generator should be packaged and transported in a manner to maintain the integrity and sterility of the generator system.

(4) Environmental monitoring should be performed during transport to ensure recommended temperature per the manufacturer is maintained.

99-99. Nuclear Compounding: Repackaging

A. Repackaging refers to the act of removing conventionally manufactured radiopharmaceutical(s) from the container in which it was distributed by the manufacturer and placing it into a different container without further manipulations. This may occur with non-sterile or sterile radiopharmaceuticals.

(1) If used for an individual patient, refer to the labeling requirements for individual preparations.

(2) If not for an individual patient:

(a) The inner and outer package must display:

(i) Standard radiation symbol

(ii) The words “Caution-Radioactive Material”

(iii) The radionuclide and chemical form (generic name)

(iv) Radioactivity with units at time of calibration and the calibration time

(b)The outer container must also state:

(i) Number of units

(ii) Product expiration or BUD

(iii) Special storage and handling instructions.

99-100. Outsourcing Facility Compounding

A. All outsourcing facilities must be inspected for cGMP compliance.

B. Compounded Drugs obtained from an outsourcing facility for further patient specific dispensing may only be obtained from facilities appropriately permitted by the South Carolina Board of Pharmacy.

C. Finished products purchased from an outsourcing facility may not be further manipulated.

D. Labeling of finished products must comply with applicable federal requirements.

E. Outsourcing facilities are required to report adverse events to the FDA. If a patient reports an adverse event related to a 503B compounded product to the dispensing pharmacy, the pharmacist must refer the

patient to the outsourcing facility or report to the outsourcing facility on behalf of the patient. Failure to make this report is considered misconduct and may subject the pharmacist to discipline by the Board.

F. Pharmacists must report any product quality concerns directly to the outsourcing facility. Failure to make this report is considered misconduct and may subject the pharmacist to discipline by the Board. The outsourcing facility must stipulate this expectation and any other expectation to any entity purchasing products for dispensing.

G. The outsourcing facility must handle complaints in accordance with cGMP.

H. For any recalled product, the pharmacy should follow the procedures provided by the outsourcing facility.

I. The pharmacist-in-charge ("PIC") of a non-resident outsourcing facility must be permitted for such operations in the state where it is located. The PIC is not required to be licensed in South Carolina but must attest to familiarity with all South Carolina pharmacy laws and regulations and agree to be subject to the South Carolina Board of Pharmacy's jurisdiction for any purpose related to disciplinary actions or investigations, including but not limited to, agreeing to timely and fully reply to any subpoena issued by the Board.

J. Outsourcing facilities must notify the Board of any changes in PIC, ownership, address, or closure within 30 days of the change.

K. Outsourcing facilities must report compliance and enforcement actions taken against it by the FDA—and, for non-resident outsourcing facilities, any adverse action taken by other state boards of pharmacy or similar permitting entity—within 30 days of such action.

(1) For purposes of this subsection, FDA Form 483s and Inspection reports are not considered compliance or enforcement actions. Therefore, the following actions may be, but are not required to be reported to the Board:

(a) Untitled letters
(b) Inspection reports or findings
(c) FDA Form 483s

(2) The following compliance and enforcement actions must be reported to the Board:

(a) Warning letters
(b) Recalls
(c) Debarment or Disqualification
(d) Product Seizures
(e) Injections
(f) Criminal Prosecution

(3) If an outsourcing facility is unsure if reporting a specific FDA action to the Board is required, it must report the action.