DRAFT Standards for Sterile Compounding by Pharmacy Permits and Practitioners

99-50. Sterile Compounding Standards Applicability

A. These standards 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. The following patient-specific preparations may be prepared by a 503A compounding pharmacy permitted by the Board:

(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 One Compounds. CSPs can be provided the below beyond use dates (BUDs) when all applicable requirements have been achieved:

(1) Twelve (12) hours or less when stored at room temperature of 20 to 25 degrees Celsius

(2) Twenty-Four (24) hours or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

D. Category Two Compounds. Category Two CSPs should be assigned BUDs based on the following criteria:

(1) Aseptically Processed CSPs

(a) CSPs underwent and passed sterility testing:

(i) Thirty (30) days or less when stored at room temperature of 20 to 25 degrees Celsius

(ii) Forty-five (45) days or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

(iii) Sixty (60) days or less when frozen at -25 to -10 degrees Celsius

(b) CSPs that did not undergo sterility testing and are prepared from only sterile components:

(i) Four (4) days or less when stored at room temperature of 20 to 25 degrees Celsius

(ii) Ten (10) days or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

(iii) Ninety (45) days or less when frozen at -25 to -10 degrees Celsius

(c) CSPs that did not undergo sterility testing and are prepared from one (1) or more non-sterile components:

(i) One (1) day or less when stored at room temperature of 20 to 25 degrees Celsius

(ii) Four (4) days or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

(iii) Forty-five (45) days or less when frozen at -25 to -10 degrees Celsius

(2) CSPs Undergoing Terminal Sterilization

(a) CSPs underwent and passed sterility testing:

(i) Forty-Five (45) days or less when stored at room temperature of 20 to 25 degrees Celsius

(ii) Sixty (60) days or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

(iii) Ninety (90) days or less when frozen at -25 to -10 degrees Celsius

(b) CSPs that did not undergo sterility testing:

(i) Fourteen (14) days or less when stored at room temperature of 20 to 25 degrees Celsius

(ii) Twenty-eight (28) days or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

(iii) Forty-five (45) days or less when frozen at -25 to -10 degrees Celsius

E. Category Three Compounds

(1) Facilities preparing Category Three CSPs must meet the following requirements in addition to all other applicable requirements:

(a) All personnel, including compounding personnel and those who monitor, manage, or supervise compounding personnel, must complete all personnel competency requirements;

(b) Garbing requirements apply to anyone entering the facilities classified areas at any time, whether aseptic processing is underway or not;

(c) Environmental monitoring must occur at least daily, if not continuously, whether compounding is completed on a given day or not; and

(d) Sporicidal cleaning agents must be used in all classified areas based on the defined frequency, whether compounds are being prepared or not.

(2) The following tests must be completed and passed to utilize the below Category Three CSP BUD dates, otherwise, the BUDs for Category Two compounds in section D above must be utilized:

(a) Stability Test: The BUD assigned must be supported by stability data utilizing an analytical method that distinguishes the active ingredient from degradants and impurities and can quantity the amount of active ingredient. The analytical method must be validated based on characteristics described in USP Chapter 1225;

(b) Process Delineation: The Category Three CSP must be prepared according to the exact same formulation, including both procedurally and ingredients/inputs, from which the stability data was derived;

(c) Container Closure: The Category Three 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 in item E(2)(a) above;

(d) If the CSP is an injection or it is an ophthalmic solution, particulate matter testing must be conducted once per formulation with an acceptable result. The methodology of the test should apply to the appropriate USP chapter for the respective test;

(e) Package Integrity Evaluation: Once for each 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 Chapter 1207; and

(f) Release Testing: Each time a Category Three CSP is prepared, it shall be sterility tested. The sterility test should meet the requirements of USP Chapter 71 or a validated alternative method that is noninferior to these requirements.

(3) Category Three CSPs should be assigned BUDs based on the following criteria:

(a) Aseptically processed, sterility tested, and passed all other applicable testing:

(i) Sixty (60) days or less when stored at room temperature of 20 to 25 degrees Celsius

(ii) Ninety (90) days or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

(iii) One hundred twenty (120) days or less when frozen at -25 to -10 degrees Celsius

(b) Terminally sterilized, sterility tested, and passed all other applicable testing:

(i) Ninety (90) days or less when stored at room temperature of 20 to 25 degrees Celsius

(ii) One hundred twenty (120) days or less when stored at refrigerated temperature of 2 to 8 degrees Celsius

(iii) One hundred eighty (180) days or less when frozen at -25 to -10 degrees Celsius

(4) Immediate-Use CSPs

(a) When all of the below conditions are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category One, Two, or Three CSPs:

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

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

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

(iv) 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.

(v) 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;

(vi) Administration begins within one (1) hour following the start of preparation; and

(vii) Delaying the administration by preparing the necessary CSPs in a more suitable environment would pose risks to the patients' health or well-being

(b) 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.

F. 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 Two or Category Three 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.

(4) The container closure system of a multi-dose CSP must be evaluated for and conform to container closure integrity testing as delineated in USP Chapter 1207 if the compounder provides a BUD of greater than 4 days room temperature or 10 days with refrigerated storage.

(5) For aqueous topical and topical ophthalmic multi-dose CSPs for which antimicrobial effectiveness testing is not passed or not completed, the CSP must be prepared as Category Two or Three and dispensed for use by a single patient with labeling that indicates they are to be discarded twenty-four (24) hours after opening/use if stored at room temperature or seventy-two (72) hours if refrigerated once opened for initial use. Formulations of vancomycin or tobramycin eye drops that are formulated entirely from sterile ingredients are exempt from this specific requirement, so long as all other requirements related to their preparation comply with the applicable standards.

99-55. Facility Design.

A. Sterile compounding facilities must be designed, outfitted, and maintained properly to minimize the risk of contamination of CSPs.

(1) The required air quality must be achieved and maintained through primary engineering controls (PECs) and secondary engineering controls (SECs).

(2) The anteroom, buffer room, and segregated compounding area (SCA) must be separated from areas not directly related to compounding.

(3) The anteroom and buffer room must be appropriately controlled to achieve and maintain the required air quality classifications.

(4) Facility design and environmental control procedures must be implemented in a manner to minimize airborne contamination from contacting critical sites

B. 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

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) Garbing procedures, staging of components, and other activities that potentially generate higher levels of particulates are performed in the anteroom.

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

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

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

(5) All Category One, Two, and Three CSPs must be compounded in an ISO Class 5 or better PEC. If compounding only Category One CSPs, the PEC may be placed in an unclassified SCA.

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-lighted 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.

(4) The temperature and humidity readings must be retrievable and reviewed as described in the facilities SOPs.

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

E. The types of SECs that may be utilized are a cleanroom suite or a segregated compounding area (SCA).

(1) Access to these areas must be restricted to authorized personnel and required materials.

(2) The cleanroom suite has an ISO-classified anteroom and buffer room that must be separated from the surrounding unclassified areas of the facility by fixed walls and doors.

(3) The classified rooms must be equipped with a pressure-differential monitoring system and air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer room and anteroom.

(4) 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

(5) The PEC must be located in the buffer room.

(6) 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.

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

(8) Seals and sweeps should not be installed at doors between buffer rooms and anterooms.

(9) Tacky mats must not be placed within ISO-classified areas.

(10) 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.

(11) 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.

(12) The SCA design is when a PEC is located within an unclassified area without an anteroom or buffer room.

A. The area within one (1) meter of the PEC should be dedicated only for sterile compounding.

B. Only Category One CSPs may be compounded in an SCA, which 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.

C. A visible line of demarcation must define the compounding area of a SCA

(14) The PEC must be certified to meet ISO Class 5 or better conditions during dynamic operating conditions.

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

(1) Laminar Airflow System (LAFS). A LAFS must provide an ISO 5 or better environment for sterile compounding.

(a) The LAFS must provide unidirectional HEPA-filtered airflow that is designed to minimize the risk of contamination of a sterile compounding environment and should be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns inside the PEC.

(b) Examples of LAFS are Laminar airflow workbench (LAFW), integrated vertical laminar flow zone (IVLFZ), and Class II biological safety cabinet (BSC). Only a suitably designedBSC should be used for preparation of antineoplastic and/or active pharmaceutical ingredient hazardous drugs (API HDs), and the exhaust air 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.

(2) Restricted Access Barrier System (RABS). A RABS is an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air. It allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of environmental air contamination and are generally not to be opened during compounding operations.

(a) Examples of RABS are compounding aseptic isolator (CAI) and compounding aseptic containment isolator (CACI).

(b) Only the CACI may be used for compounding sterile hazardous drug (HD) preparations.

(3) A pharmaceutical isolator provides isolation form the surrounding area and maintains ISO Class 5 air quality during dynamic operating conditions.

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

PEC Type	Device type	Placement for Compounding Only Category 1 CSPs	Placement for Compounding Category 2 and 3 CSPs
LAFS	LAFW	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 Positive-pressure anteroom
LAFS	IVLFZ	N/A	ISO Class 7 positive-pressure buffer room with an ISO Class 8 Positive-pressure anteroom
LAFS	BSC	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 Positive-pressure anteroom
RABS	CAI or CACI	Unclassified SCA	ISO Class 7 positive-pressure buffer room with an ISO Class 8 Positive-pressure anteroom
Pharmaceutical isolator	Pharmaceutical isolator	Unclassified SCA	ISO Class 8 positive-pressure room

G. Air exchange requirements for cleanroom suites are measured in terms of the number of air changes per hour (ACPH). This measurement of adequate HEPA-filtered airflow to the buffer rooms(s) and anteroom(s) is required to maintain the appropriate ISO classification during compounding activities.

(1) ACPH Requirements for Non-HD Sterile Compounding Areas:

Compounding Area	ACPH Requirement
Unclassified SCA	No requirement
ISO Class 7 room(s)	= or >30 ACPH
ISO Class 8 room(s)	= or >20 ACPH

(2) 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.

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

H. Pressure differentials should be continuous positive pressure to minimize airflow for an area with lower air-quality classification to an area of higher air-quality classification.

(1) In a cleanroom suite, a minimum differential positive pressure of 0.020-inch water column is required between ISO-classified areas of the buffer room and anteroom.

(2) The pressure differential between the anteroom and the unclassified area must not be less than 0.02-inch water column.

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

(4) 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.

I. Facilities preparing Category Two or Category Three 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.

J. 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.

K. 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.

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

M. The anteroom must not contain floor drains.

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

O. 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.

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

R. 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.

99-60. 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.

99-65. 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 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.

(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;

(f) use of equipment;

(g) documentation of the compounding process;

(h) principles of HEPA airflow within the ISO 5 Area;

(i) proper user of PECs; and

(j) 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 One, Two, or Three 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) If a competency is failed, additional instances must be completed such that three consecutive successful iterations are completed.

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

(e) 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.

(f) After the initial assessment, compounding staff compounding Category One and Two CSPs must successfully recomplete the competency every six (6) months, compounding staff compounding Category Three 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.

(2) Aseptic Manipulation Competency

(a) Prior to compounding Category One, Two, or Three CSPs or having oversight (i.e. designated individual(s)) of compounding personnel in any form or fashion, compounding staff must successfully complete three (3) successive gowning and garbing competency evaluations each concurrent with glove finger tip sampling.

(b) After successfully completing the above 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)

(iv) surface sampling of the direct compounding area

(b) After initial assessment, staff compounding Category One or Two CSPs must successfully repeat the assessment every six (6) months, staff compounding Category Three CSPs must successfully repeat the assessment every three (3) months, and those who oversee compounding operations but do not compound must successfully repeat the assessment annually.

(c) 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. Additionally, the challenge must represent elements within the facilities operations that could impact stability such as length of compounding operations, number of additions or transfers, number, type and complexity of manipulations, and number of other personnel in the compounding area.

(d) 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.

(e) If preparing media in house, the growth promotion must be demonstrated for each batch and documented in accordance with USP Chapter 71

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

(g) 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

(h) 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.

(i) 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.

(j) Results of these aseptic manipulation competency activities must be retained on file for a period of at least two (2) years.

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

99-70. 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) 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.

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

(6) 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.

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

(8) Supplies used for cleaning and disinfection, with an exception for tool handles, must be low lint.

(9) 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.

(10) 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 manufacturers instructions for use.

(11) 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

(12) 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.

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:

Area/Location	Cleaning	Disinfection	Application of Sporicidal Disinfectant
Removable work tray of the PEC, if applicable	• **Work surfaces of the tray daily when**	• **Work surface of the tray on days when**	• **Work surfaces of the tray monthly**

	• compounding occurs • All surfaces and the area under the tray monthly	• compounding occurs • All surfaces and the area under the tray monthly	• All surfaces and the area under the tray monthly
Pass-through chambers	• Daily on days when compounding occurs	• Daily on days when compounding occurs	• Monthly for facilities 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.

(4) When sterile 70% IPA is used, it must be allowed to dry prior to proceeding to any subsequent step or activity.

99-75. 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 One and Two CSPs;

(3) Viable air sampling at least monthly for entities compounding Category Three CSPs;

(4) Surface sampling at least monthly for entities compounding Category One and Two CSPs;

(5) Surface sampling at least weekly for entities compounding Category Three 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:

(2) Using the impaction air sampler, test at least one (1) cubic meter or 1000 L of air from each location sampled;

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

(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;

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

(7) 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; and

M. Action levels for viable airborne particle sampling are:

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

(4) Cover and invert the plates;

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

(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;

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

(8) 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 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

Q. For both air and surface samples, evaluate CFU counts against the action levels, and examine counts in relation to previous data.

(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

99-80. Cleanroom Activities and Workflows.

A. Personnel Preparation. All personnel entering a compounding area where Category One, Two, or Three 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 ;

(e) 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

(f) Wipe eyeglasses, if worn.

(g) 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 One, Two, or Three 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:

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

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

(iii) 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 One, Two, or Three 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 Two or Category Three 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 One and Two 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 One and Two 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 Three CSPs, additional garbing requirements must be continuously met in the buffer room in which any Category Three CSPs are prepared. The following additional garbing requirements must be followed in the buffer room where Category Three CSPs are prepared at all times, regardless as to whether Category Three 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 sapling), they must 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.

99-85. 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. 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 sterile 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 personal 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.

99-90. 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. vetinary 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 reviewed monthly by the Designated Individual. Following review, 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.

99-95. 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. Clear 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, etc. 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.

99-100. Sterility Testing.

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

B. For Category Two CSPs assigned a BUD that requires sterility testing and all Category Three 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 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.

99-110. Bacterial Endotoxin Testing

A. Category Two CSPs compounded from one or more nonsterile components and assigned a BUD that requires sterility testing and Category Three 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.

99-115. 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.

99-120. 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.

99-125. 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 One, Two, and Three CSPs must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use.

C. All labeling requirements found in [CITE PRACTICE ACT] 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 immediate contained is a multiple dose container.

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 be dispensed. Thereafter, the CSP cannot be re-dispensed by another pharmacy or pharmacist; however, it can be administered within a hospital, clinic, or procedural area as ordered by a practitioner.

99-130. 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.

99-135. 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 standards 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 standards 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;

(

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

(ix) 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 [PRACTICE ACT CITATION].

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. Specific standards regarding HDs are located in relevant standard.

99-140. 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-XX [TBD]. Applicability, Legal Effect, and Severability of Regulations.

A. The regulations of the Board are intended to be consistent with the applicable Federal and State law and shall be so construed, whenever necessary, to achieve such consistency.

B. In the event that any provision of these regulations is declared unconstitutional or invalid or that the application of them to any person or circumstance is held invalid, the applicability of the provision to other persons and circumstances, and the constitutionality or validity of every other provision of these regulations shall not be eaffected.

D. These regulations shall not eaffect pending actions or proceedings, civil or criminal, which may be prosecuted or defended in the same manner and with the same effect as though these regulations had not been promulgated.

Non-Sterile Draft - 5/21/2025

1. INTRODUCTION AND SCOPE
   - 1.1. This chapter describes the standards to be followed for the preparation of compounded nonsterile preparations (CNSPs) for humans and animals.
   - 1.2. This chapter is divided into 2 primary types of non-sterile compounding: SIMPLE and COMPLEX
     - 1.2.1. SIMPLE non-sterile compounding includes the following practices
       - 1.2.1.1. *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 5 percent of the total volume of the drug to which the flavoring agents are added.
       - 1.2.1.2. *Simple Compounding:* Compounding of an oral liquid or topical dosage utilizing non-particle producing, non-hazardous commercially available ingredients.
         - *1.2.1.2.1.* Preparations may include, but are not limited to, the following dosage forms:
           - *1.2.1.2.1.1.* Mouthwashes
           - *1.2.1.2.1.2.* Ointments
           - *1.2.1.2.1.3.* Creams
     - 1.2.2. COMPLEX Non-Sterile Compounded preparations include, but are not limited to, the following dosage forms:
       - 1.2.2.1.1. Solid oral preparations
       - 1.2.2.1.2. Liquid oral preparations
       - 1.2.2.1.3. Rectal preparations
       - 1.2.2.1.4. Vaginal preparations
       - 1.2.2.1.5. Topical preparations (i.e., creams, gels, and ointments)
       - 1.2.2.1.6. Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
       - 1.2.2.1.7. Otic preparations (excluding use in perforated eardrums)
   - 1.3. 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 of this section.

1.3.1. *Nonsterile radiopharmaceuticals:* Compounding of nonsterile radiopharmaceuticals is subject to the requirements in [...]

1.3.2. *Reconstitution:* Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling

1.3.3. *Repackaging:* Repackaging of conventionally manufactured drug products

1.3.4. *Splitting tablets:* Breaking or cutting a tablet into smaller portions

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

1.4. This chapter applies to all persons who prepare or oversee the preparation of CNSPs and all places where CNSPs are prepared.

2. SIMPLE NON-STERILE COMPOUNDING

2.1. Flavoring: A flavor additive may be incorporated into a non-sterile prescription drug shall be exempt from the requirements of subsequent sections under the following conditions:

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

2.1.2. 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.

2.1.3. 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.

2.1.4. 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, to the flavoring additive shall clearly and legibly be labeled on the container. In no event shall the labeled date of receipt or assigned expiration date be later altered after originally labeling the container.

2.1.5. 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.

2.1.5.1. Additive's flavor;

2.1.5.2. Flavor additive's manufacturer

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

2.1.5.4. Flavor additive's expiration date.

2.1.6. The pharmacist responsible for conducting the final evaluation of a new or refilled prescription shall also be responsible for the flavoring of the prescription as specified in subsections a., b., and c. of this section.

2.1.7. The pharmacist manager shall be responsible for subsection d. of this section and the maintenance of records as specified in subsection e. of this section.

2.2. Simple non-sterile compounded preparations shall be exempt from the requirements subsequent sections under the following conditions:

2.2.1. Non-particle producing, non-hazardous commercially available ingredients, that have not been manipulated, are used

2.2.2. Compounding is done pursuant to an active prescription and not done in anticipation of medication orders;

2.2.3.Must follow beyond use dates (BUDs) of:
- 2.2.3.1. 14 days refrigerated if not preserved (ingested orally)
- 2.2.3.2. 35 days refrigerated if a preservative is contained (ingested orally)
- 2.2.3.3. 35 days at room temperature for topical preparations or preparations for mucosal membrane application

2.2.4. A compounding record must be maintained for a duration of [..]
- 2.2.4.1. 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:
  - 2.2.4.1.1. Identity of all components and their corresponding amounts, concentrations, and or volumes
  - 2.2.4.1.2. Lot number and expiration date of each component
  - 2.2.4.1.3. Component manufacturer/distributor or suitable identifying number
  - 2.2.4.1.4. Unique lot or control number for the compounded preparation
  - 2.2.4.1.5. Beyond use date assigned to the compounded preparation
  - 2.2.4.1.6. Date of preparation
  - 2.2.4.1.7. Name, initials, or electronic signature of the person(s) involved in the preparation of the compound
  - 2.2.4.1.8. Name, initials, or electronic signature of the checking pharmacist. responsible pharmacist
  - 2.2.4.1.9. Finished preparation final check and visual evaluation

2.2.5. 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. The compounding area must be well lit and must be maintained in a clean, orderly, sanitary condition and in a good state of repair. There should not be carpet in the compounding area.
- 2.2.5.1. 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.

2.2.6. 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 section […] of the Pharmacy Practice Act

2.2.7. Where water is an ingredient in a compound; purified, distilled water, or sterile water shall be used

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

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

2.5. 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.

3. COMPLEX NON-STERILE COMPOUNDING

4. PERSONNEL TRAINING AND EVALUATION

4.1. 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.

4.1.1. Training should be verifiable and documented specific to the type of compounding being performed.

4.1.2. General compounding skills (ie: 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.

4.1.3. 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.

4.2. The Pharmacist in Charge or 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. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks.

4.3. Personnel who compound or have direct oversight of compounding personnel must complete training initially that prepares them for the most complex dosage form they may encounter and complete at least 4 hours of documented ongoing training every 12 months relating to compounding principles and practices in order to stay up to date with new developments in the field. The 4 hours of ongoing training may be completed in house in accordance with facility SOP's or via accredited continuing education platform.

4.3.1. Prior to compounding or directly overseeing compounding activities, personnel must complete training and be able to demonstrate knowledge of principles and competency of skills for performing nonsterile manipulations as applicable to their assigned tasks. Knowledge and competency must be demonstrated initially and at least every 12 months in at least the following core areas:

4.3.1.1. Hand hygiene

4.3.1.2. Donning personal protective equipment

4.3.1.3. Cleaning, sanitizing, and decontaminating as applicable

4.3.1.4. Handling and transporting components and CNSPs

4.3.1.5. Measuring and mixing

4.3.1.6. Proper use of equipment and devices selected to compound CNSPs

4.3.1.7. Documentation of the compounding process and the required components of the Master Formulation and Compounding Records

4.3.1.8. Understand and interpret safety data sheets (SDSs) and certificates of analysis (COA) as applicable

4.3.1.9. Read and understand procedures related to their compounding duties

4.4. 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.

4.5. Training and competency of personnel must be documented as described in accordance with section […]

4.6. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel must be observed and guided throughout the training process.

4.7. The personnel should repeat the procedures independently while under the direct supervision of the designated person(s) and/or assigned trainer. Personnel should be

permitted to perform the procedure without direct supervision only after independently demonstrating understanding and competency.

4.8. 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.

4.9. 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 this chapter.

5. Personal Hygiene and Garbing

5.1. 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.

5.2. Personnel engaged in the compounding of medications shall wear clean clothing appropriate to the operation being performed. Protective apparel must be worn as necessary to protect personnel from chemical exposure and medication or chemical contamination.

5.3. Personnel engaged in the compounding of drug preparations shall perform proper hand hygiene prior to engaging in compounding activities. Proper hand hygiene shall be defined in appropriate SOPs as detailed in the SOP section and appropriate for prevention of preparation and facility contamination.

5.4. 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.

5.5. The garbing requirements under the pharmacy's SOPs must be appropriate for the type of compounding performed. Gloves shall be worn for the prevention of preparation and facility contamination.

5.5.1. SOP(s) should at least detail:

5.5.1.1. What is appropriate attire for the compounding environment what is appropriate garb needed for the type of compounding to be done (ie. Basic vs complex compounding)

5.5.1.2. A list of garb to be used depending on what compounding is required such as: gloves, gowns, hair net, face mask, shoe covers etc.

5.5.1.3. Hand hygiene: appropriate soap and disinfectants and their use

5.5.1.4. How and when to glove and when to replace gloves and garb

5.5.1.5. A requirement to demonstrate effective techniques so as to prevent contamination to the lab and products dispensed

5.5.1.6. Frequency of training

6. BUILDINGS AND FACILITIES

6.1. Compounding Area

6.1.1. An area must be designated for nonsterile compounding. The method of designation must be described in the facility's SOPs. Other activities must not be occurring in the compounding area at the same time as compounding. The compounding area must be

well lit and must be maintained in a clean, orderly, sanitary condition and in a good state of repair. There should not be carpet in the compounding area.

6.1.2. 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.

6.2. Storage Area

6.2.1. 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.

6.2.2. 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.

6.2.3. 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.

6.2.4. If no storage requirements are established for a drug, the drug may be held at "controlled" room temperature, as defined in an official compendium, to help ensure that its identity, strength, quality, and purity are not adversely affected.

6.2.5. 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. Refrigerator temperature shall be maintained at the range of 36°F to 46°F.

6.2.6. 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.

6.2.7. When it is known that a CNSP or component has been exposed to temperatures either below or above the storage temperature limits for the CNSP or component, personnel must determine whether the CNSP or component integrity or quality has been compromised, and, if so, the CNSP or component must be discarded.

6.2.8. 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.

6.2.9. All CNSPs, components, equipment, and containers must be stored off the floor in a manner that prevents contamination and permits inspection and cleaning of the storage area(s). The storage of drugs, medicines, pharmaceuticals, or consumable materials used in compounding and dispensing prescriptions and pharmaceutical preparations in the washroom or toilet of the pharmacy is prohibited.

6.2.10. Drugs, pharmaceuticals, and chemicals must be arranged in a neat, orderly manner, free from dust, insects, rodents, or any type of contamination.

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

6.3. Water Sources

6.3.1. 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.

6.3.2. 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.

7. CLEANING AND SANITIZING

7.1. 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 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.

7.2. 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. (ie locking laminate flooring)

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

7.4. 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
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

8. EQUIPMENT AND COMPONENTS

8.1. Equipment

8.1.1. The equipment and components used for compounding a CNSP must be suitable for the specific compounding process.

8.1.2. Equipment surfaces that contact components must not be reactive, additive, or sorptive, and must not alter the quality of the CNSP. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross contamination.

8.1.3. Equipment must be stored in a manner that minimizes the risk of contamination and should be located to facilitate equipment use, maintenance, and cleaning. 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 12 months, if not specified by the manufacturer. After compounding, the equipment must be cleaned to prevent cross contamination of the next preparation.

8.1.4. 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.

8.1.5. 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.

8.2. Components

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

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

8.2.3.APIs should meet one of the following criteria for use in CNSPs:

8.2.3.1. Be part of an FDA approved product

8.2.3.2. Have a USP or NF monograph

8.2.3.3. 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."

8.2.4. 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.

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

8.2.6.Component receipt

8.2.6.1. 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.

8.2.6.2. 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. Any other lots of that component from the same vendor must should be examined to determine whether the other lots have the same defect.

8.2.7.Component evaluation before use:

8.2.7.1. 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.

8.2.7.2. 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.

8.2.8.Component handling

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

8.2.9. Component spill and disposal

8.2.9.1. The facility must maintain access to current chemical hazard and disposal information (e.g., SDSs). SDSs may be stored physically or digitally on site or may be digitally accessible via supplier website. 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

8.2.9.2. If the facility utilizes hazardous components in nonsterile compounding, they must have an appropriate and readily accessible spill kit in the compounding area.

8.2.9.3. 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.

9. Master Formulation and Compounding Records

9.1. Master Formulation Record:

9.1.1. A Master Formulation Record is a detailed document that states the identity of a compounded product and all aspects of how it is to be prepared.

9.1.2. A Master Formulation record shall 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 compound being prepared.

9.1.3. 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.

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

9.1.4.1. The name, strength, and dosage form of the compounded product

9.1.4.2. The components

9.1.4.3. The compounding directions

9.1.4.4. Evaluation and testing requirements

9.1.4.5. Specific equipment used during preparation

9.1.4.6. The type of containers that may be used for dispensing

9.1.4.7. 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.

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

9.1.4.9. The criteria used to determine the beyond-use date; and

9.1.4.10. 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.

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

9.2. Compounding Record:

9.2.1. The record for each preparation shall document requirements of the Master Formulation as well as:

9.2.1.1. Identity of all components and their corresponding amounts, concentrations, or volumes
9.2.1.2. Lot number and expiration date of each component
9.2.1.3. Component manufacturer/distributor or suitable identifying number
9.2.1.4. Unique lot or control number
9.2.1.5. Beyond use date
9.2.1.6. Date of preparation
9.2.1.7. Name, initials, or electronic signature of the person(s) involved in the preparation
9.2.1.8. Name, initials, or electronic signature of the responsible pharmacist
9.2.1.9. Finished preparation evaluation and testing specifications, if applicable; and
9.2.1.10. Documentation of performance of final checks as applicable including, but not limited to: expected physical appearance of the final product, pH measurement, calculations performed, determination of final vs expected results.

10. Release Inspections and Testing (Quality Controls, Quality Assurance, Finished preparation checks)
    10.1. The following items, at a minimum, shall be inspected for accuracy before the non-sterile preparations are dispensed:
        10.1.1. Correct identities and amounts of ingredients
        10.1.2. Packaging
        10.1.3. Labeling
        10.1.4. The prescription drug or medication order
        10.1.5. The compounding record
        10.1.6. The materials used in the preparation
        10.1.7. The written compounding procedure
        10.1.8. Expected physical appearance and properties
        10.1.9. Documentation of applicable parameters. Ex: pH, color, smell, clarity
        10.1.10. Final weights and variations
        10.1.11. Pharmaceutical elegance
    10.2. 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.
    10.3. At a minimum, the initials and the date should be indicated on the record of the person performing the final checks.

11. LABELING
    11.1. Compounded preparations:
        11.1.1. 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 section [...] of the South Carolina Pharmacy Practice Act.
        11.1.2. The label on each container of the dispensed CNSP must, at a minimum, display prominently and legibly the following information:

11.1.2.1. Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
11.1.2.2. Unabbreviated or clearly defined names of all active ingredient(s), and their amount(s), activity(ies), or concentration(s)
11.1.2.3. Storage conditions if other than controlled room temperature
11.1.2.4. BUD
11.1.2.5. Dosage form
11.1.2.6. Total amount or volume if it is not obvious from the container
11.1.2.7. Route of administration
11.1.2.8. Indication that the preparation is compounded
11.1.2.9. Any applicable special handling instructions
11.1.2.10. Any applicable warning statements
11.1.2.11. 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

11.1.3. Any excess compounded preparation 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.

11.1.4. After completion of the compounding process and prior to dispensing any CSNP, the pharmacist shall examine the preparation for correct labeling. The label of the CNSP must be verified to ensure that it conforms with the following:
11.1.4.1. Prescription or medication order;
11.1.4.2. Master formulation record;
11.1.4.3. Compounding record.

11.2. Chemicals and components:

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

11.2.2. For components that do not have expiration dates assigned by the manufacturer or supplier, a compounder shall label the container with the date of receipt and 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.

11.2.3. Any chemical or component transferred to a new container from the original container must be labeled with the same information as on the original container and the date of transfer placed on the label.

12. Establishing Beyond Use Dates

12.1. Terminology

12.1.1. 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.

12.1.2. BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured product, API, or added substance can be expected to meet the requirements of a compendial monograph, if one exists, or

maintain expected quality, provided it is kept under the prescribed storage conditions.

12.2. Parameters to Consider in Establishing a BUD

12.2.1. BUDs for CNSPs should be established conservatively to ensure that the preparation maintains its required characteristics to minimize the risk of contamination or degradation.

12.2.2. In the absence of stability information applicable to the specific compound, the maximum BUD must be determined by:

12.2.2.1. The type of formulation, such as nonaqueous, water containing, or topical; and

12.2.2.2. Professional judgment

12.2.3. The pharmacist's professional judgment shall be based on the criteria used to determine a beyond-use date outlined in this subsection.

12.2.3.1. Physical and chemical properties of active ingredients;

12.2.3.2. Potential for microbial proliferation in the cnsp and the use of preservatives and/or stabilizing agents;

12.2.3.3. Dosage form;

12.2.3.4. Storage containers and conditions; and

12.2.3.5. Scientific, laboratory, or reference data from a peer reviewed source and retained in the pharmacy. The reference data should follow the same preparation instructions for combining components and packaged in a container with similar properties.

12.2.4. The BUD for any CNSP must not exceed 180 days.

12.2.5. Water Activity

12.2.5.1. The aqueous and nonaqueous dosage forms in *Table 4* are defined based on the water activity (a_w) of the most similar drug preparations described in *Table 3* or *Application of Water Activity Determination to Nonsterile Pharmaceutical Products*

12.2.5.2. In general, the use of a_w aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. The a_w is different from the water content and may be considered as the available water to support microbial growth and hydrolytic reactions. Nonaqueous dosage forms will not support spore germination or microbial growth due to their low a_w. Reduced a_w greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs.

12.2.5.3. Compounders are not required to measure a_w for CNSPs.

12.2.5.4. Compounded preparations in *Table 3* below are not exhaustive, they provide examples of dosage forms that have an $a_w < 0.6$ and those that have an $a_w \geq 0.6$ and can assist in determination of appropriate BUD's.

Table 3. 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 wa- ter emulsion, petrola- tum free)	0.968
Capsule (powder filled)	Powder base encapsulat- ed	0.435	Cream	Emollient cream (petro- latum and mineral oil)	0.984
Gel (glycol based)	Propylene glycol, ethoxy diglycol, hydroxypropyl cellulose gel	0.056	Cream	Cream (oil in water emul- sion 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 miner- al 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 gly- col	0.009	Lotion	Lotion (oil in water emul- sion)	0.986
Oral solution (oil based)	Medium chain triglycer- ides 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 vehi- cle	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 3 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.

12.2.5.5. The BUDs in *Table 4* 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.

Table 4. BUD Limit by Type of Preparation in the Absence of a *USP–NF* Compounded Preparation Monograph or CNSP-Specific Stability Information

Type of Preparation	BUD (days)	Storage Temperature[b]
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

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 (see *10.4 CNSPs Requiring Shorter BUDs*).
b See *Packaging and Storage Requirements* (659).
c An aqueous preparation is one that has an $a_w \geq 0.6$ (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).
d A nonaqueous oral liquid is one that has an $a_w < 0.6$.
e Other nonaqueous dosage forms that have an $a_w < 0.6$ (e.g., capsules, tablets, granules, powders, nonaqueous topicals, suppositories, and troches or lozenges).

12.3. CNSPs Requiring Shorter BUDs

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

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

12.3.3. 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.

12.4. Extending BUDs for CNSPs

12.4.1. All CNSPs with an extended BUD must meet the requirements of this section. Careful consideration should be taken when selecting a preservative to ensure microbiological effectiveness and stability. When antimicrobial preservatives are contraindicated in a CNSP, 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).

12.4.2. CNSPs with a USP–NF monograph:

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

12.4.3. CNSPs with stability information:

12.4.3.1. 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.

12.4.3.1.1. 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.).

12.4.4. 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.

12.4.4.1. The designated person(s) may rely on antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container closure system—including materials of composition of the container closure system—in which it will be packaged.

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

12.4.4.2.1. 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.

13. Standard Operating Procedures

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

13.2. 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.

13.3. 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.

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

13.5. Required SOP's
- 13.5.1. Training and safety
- 13.5.2. Hand Hygiene and garbing
  - 13.5.2.1. Proper hand hygiene shall be defined in appropriate SOPs as detailed in the SOP section and appropriate for prevention of preparation and facility contamination
  - 13.5.2.2. 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
  - 13.5.2.3. 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.
- 13.5.3. Compounding Procedures and Technique
  - 13.5.3.1. The facility's SOPs must describe packaging of CNSPs.
- 13.5.4. Cleaning / spill kits
  - 13.5.4.1. The management and disposal of component spills must be described in the facility's SOPs.
- 13.5.5. Equipment usage and calibration
  - 13.5.5.1. "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."
- 13.5.6. Temp and humidity
- 13.5.7. Designated personnel/organizational chart
- 13.5.8. Qa and qc
- 13.5.9. Recall / adverse event record keeping and reporting
- 13.5.10. Shipping/transportation if applicable
  - 13.5.10.1. 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.
- 13.5.11. Formulation and record keeping
- 13.5.12. Component selection and usage
  - 13.5.12.1. "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."
- 13.5.13. "An area must be designated for nonsterile compounding. The method of designation must be described in the facility's SOPs"

14. QUALITY ASSURANCE AND QUALITY CONTROL
- 14.1. Quality assurance (QA) is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. 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.

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

14.3. 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.

14.4. Quality Assurance:

14.4.1. 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).

14.4.2. 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.

14.5. Quality Control:

14.5.1. 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.

14.5.2. 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.

14.5.3. 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.

14.6. Notification About and Recall of Dispensed CNSPs

14.6.1. 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. These procedures must address:

14.6.1.1. 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)

14.6.1.2. Procedure to recall any unused dispensed CNSPs and quarantine any stock remaining in the pharmacy

14.6.1.3. Necessity of investigating if other lots are affected and whether a further recall is necessary

14.6.2. An SOP for recall of dispensed CNSPs must contain the following procedures:

14.6.2.1. 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.

14.6.2.2. 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.

14.6.2.3. In the event of a recall, the pharmacist-in-charge shall ensure that:

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

14.6.2.3.2. each patient to whom the preparation was dispensed is notified, in writing, of the recall;

14.6.2.3.3. the preparation is quarantined; and

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

14.6.2.4. 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.

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

15. CNSP PACKAGING AND TRANSPORTING

15.1. Packaging of CNSPs

15.1.1. 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.

15.2. Transporting of CNSPs

15.2.1. 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. A 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. Transporting includes delivery, either through company delivery service or contracted courier, and shipping.

15.2.2. Delivery of Prescription Drugs:

15.2.3. This section applies to the delivery of prescription drugs by a pharmacy licensed by the board.

15.2.4. Delivery by common carrier:

15.2.4.1. A pharmacy may deliver prescription drugs by use of a common carrier (e.g., U.S. Mail) on request of the patient or patient's agent. Common carrier means

a person or entity who holds out to the general public a willingness to provide transportation of property from place to place for compensation in the normal course of business. A pharmacy that delivers prescription drugs by use of a common carrier providing a same-day courier service is not subject to subsection (b) of this section and shall comply with subsection (c) of this section.

15.2.4.1.1. The pharmacy shall ensure that all prescription drugs are delivered to the patient or patient's agent in a manner to maintain the quality and integrity of the drug(s).

15.2.4.1.2. The pharmacy shall ensure that prescription drugs are packaged in tamper evident packaging.

15.2.4.1.3. The pharmacy shall ensure that any prescription drug delivered by common carrier is packaged in a manner that maintains a temperature range appropriate for the drug. This may include, without limitation, use of temperature tags, time temperature strips, insulated packaging, gel ice packs, or a combination of these as necessary.

15.2.4.1.4. The pharmacy shall provide a method by which a patient or patient's agent can notify the pharmacy as to any irregularity in the delivery of the patient's prescription, to include but not be limited to:

15.2.4.1.4.1. Timeliness of delivery;

15.2.4.1.4.2. Condition of the prescription drug upon delivery; and

15.2.4.1.4.3. Failure to receive the proper prescription drug.

15.2.4.1.5. The pharmacy shall refuse to deliver by common carrier a prescription drug which in the professional opinion of the dispensing pharmacist may be clinically compromised by delivery by common carrier.

15.2.5. Delivery by pharmacy employee or common carrier providing a same-day courier service:

15.2.5.1. A pharmacy may deliver prescription drugs by means of its employee or a common carrier providing a same-day courier service on request of the patient or patient's agent.

15.2.5.1.1. The pharmacy is responsible for any problems in the delivery of the prescription drug.

15.2.5.1.2. The prescription drug shall be maintained within the temperature range allowed by the United States Pharmacopeia or recommended by the manufacturer until the delivery has been received by the patient or patient's agent.

15.2.6. All deliveries:

15.2.6.1. A pharmacy that delivers prescription drugs by common carrier or by pharmacy employee or by a common carrier providing a same-day courier service shall also comply with the following:

15.2.6.1.1. The pharmacy shall comply with the requirements for prescription counseling as defined in section _____.

15.2.6.1.2. The pharmacy shall notify the patient or patient's agent of the delivery of a prescription drug.

15.2.6.1.3. If a pharmacist determines a prescription drug is in any way compromised during delivery, the pharmacy shall replace the drug or arrange for the drug to be replaced, either by promptly delivering a replacement to the patient or by promptly contacting the prescriber to arrange for the drug to be dispensed to the patient by a pharmacy of the patient's or patient's agent's choice.

15.2.6.1.4. The pharmacy shall maintain records for two years on the following events:

15.2.6.1.4.1. when a prescription drug was sent and delivered to the patient or patient's agent; and

15.2.6.1.4.2. patient complaints regarding compromised deliveries, which may be documented in the patient profile.

15.2.6.1.5. A pharmacy shall comply with all state and federal laws and rules relating to the delivery of controlled substances.

16. Documentation

16.1. 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:

16.1.1. Personnel training, competency assessments

16.1.2. Equipment records (e.g., calibration, verification, and maintenance reports)

16.1.3. COAs

16.1.4. SOPs, Master Formulation Records, and Compounding Records

16.1.5. Records of cleaning the designated compounding area

16.1.6. Temperature and humidity logs for compounding areas as well as refrigerators as applicable

16.1.7. Information related to adverse events including corrective actions taken

16.1.8. Applicable Quality Control results

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

16.3. 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.

Nuclear Pharmacy Compounding Regulations/Standards

<u>Sections</u>

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Section 1. Purpose and Scope

This subsection of the South Carolina Pharmacy Practice Act applies to the practice of the sterile and non-sterile compounding of radiopharmaceuticals or radioactive materials (RAM) by South Carolina licensed nuclear pharmacies. The receipt, storage, handling, disposal, shipment, and delivery of radiopharmaceuticals and RAM falls under the jurisdiction of the US Nuclear Regulatory Commission (NRC) or the South Carolina Department of Environmental Services (DES). Compliance with the regulations set forth by the NRC and/or DHEC are required in conjunction with the standards in this subsection.

This section applies to all South Carolina licensed nuclear pharmacies who prepare, compound, dispense, or repackage radiopharmaceuticals. This section also applies to all individuals who prepare, compound, dispense, or repackage radiopharmaceuticals. Applicable individuals consist of authorized nuclear pharmacists (ANP) as well as licensed pharmacy technicians working under the supervision of an ANP.

This section does not apply to:

- Manufacturing of approved radiopharmaceuticals (e.g., NDA, ANDA, BLA) in FDA-registered manufacturing facilities.
- Manufacturing of radiopharmaceuticals as investigational agents (e,g, IND, RDRC)
- Compounding of radiopharmaceuticals in a registered FDCA 503B outsourcing facility.
- Preparation/compounding of positron emission tomography (PET) drugs that are not manufactured as approved drug products (e.g. NDA, ANDA, BLA).
- Administration of radiopharmaceuticals to patients.

Section 2. Definitions

1. "Authorized Nuclear Pharmacist" is defined as an actively licensed pharmacist in good standing with the South Carolina Board of Pharmacy, who is certified as a nuclear pharmacist that meets the following standards set forth by the NRC regulations 10 CFR 35.55.

2. "Compounding" – 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.

3. “Dispensing means 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 (eg, withdrawing a volume of finished product or preparation from a vial into a syringe). Dispensing is 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.
4. “Internal Test Assessment” means, but is not limited to, conducting those tests of quality assurance necessary to ensure the integrity of the test.
5. “Nuclear Pharmacy/Radiopharmacy” means a pharmacy providing radiopharmaceutical services or, as provided in the Model Rules for Nuclear Pharmacy/Radiopharmacy, an appropriate area of any institutional facility.
6. “Preparation” means 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.
7. “Preparation With Minor Deviations” means 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 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 (eg, dilute Tc-99m solution after, rather than before, addition to the vial, use of a venting needle or filter), using alternative devices or equipment (eg, a heating block rather than a hot water bath), and using alternative radiochemical purity testing methods.
8. “Qualified Licensed Professional” means a non-pharmacist individual (such as a physician, nurse, or technologist) who possesses a current state license, if applicable, and who has sufficient training and experience to safely handle and dispense radiopharmaceuticals as defined by the respective requirements of [cite appropriate Nuclear Regulatory Commission (NRC) or agreement state and state board of pharmacy law(s)].
9. “Cleaning” is the process of removing materials from the surfaces using a combination of mechanical processes and a cleaning agent
10. “Cleaning agents” are typically surfactants, used for the removal of substances from surfaces
11. “Disinfection agents” are chemical or physical agents used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria
12. “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.
13. “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.

14. "Radiopharmaceutical Service" means, but shall not be limited to, the procurement, storage, handling, preparation, labeling, quality assurance testing, dispensing, delivery, record keeping, and disposal of radiopharmaceuticals and other drugs.
15. "Radiopharmaceuticals" are radioactive drugs as defined South Carolina Board of Pharmacy.
16. "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.
17. "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 (eg, 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.
18. Non-Direct Infusion Generator: 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.

Section 3: Radiation Safety and Facility Considerations

Radiation Safety Considerations

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.

Facilities

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

a. All personnel performing tasks in the preparation and distribution of radioactive drugs shall be under the direct supervision of an ANP.
b. An ANP shall 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. These individuals may prepare single unit doses of radiopharmaceuticals for the immediate emergency and must document such activities. A designated qualified professional would include any of the following:
    i. A SC licensed pharmacist who does not hold an AU Certification in nuclear pharmacy.
c. Nuclear pharmacies shall 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 state board of pharmacy.
d. The nuclear pharmacy area shall be secured from unauthorized personnel.
e. Nuclear pharmacies shall maintain records of acquisition, inventory, and disposition of all radioactive drugs and other radioactive materials in accordance with DHEC and/or the NRC.
f. All pharmacies handling radiopharmaceuticals shall provide a radioactive storage and product decay area. Detailed floor plans shall be submitted to the state board of pharmacy and DHEC or NRC before approval of the license.
g. Radiopharmaceuticals are to 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 state radiation control agency (RCA) or NRC license. Copies of the RCA or NRC inspection reports shall be made available upon request for board inspection.

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.

a. Types of Secondary Engineering Controls and Design
    i. 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 an SRPA (segregated radiopharmaceutical processing area), in a manner that minimized conditions that could increase the risk of microbial contamination.
    ii. Ante-Rooms: Must be separate from the buffer area and the surrounding unclassified areas of the facility with fixed walls and doors.
b. Facility designs and controls must be in place to minimize the flow of lower-quality air into the more controlled areas.
c. Air supplied to areas of the classified area must be introduced through HEPA filters that are located in the ceiling.
d. Returns must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulates will accumulate.

e. A smoke study of the PEC must be repeated whenever a change to the placement of the PEC within the area is made.
f. The classified areas must be equipped with a pressure-differential monitoring system.
g. 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.
h. 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.
i. 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.
j. 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.

<u>Segregated Radiopharmaceutical Processing Areas (SRPA)</u>

a. Must have a PEC present for where all compounding activities are performed.
b. 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).
c. 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.
d. 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.

<u>Radiopharmaceutical Processing Environments</u>

e. 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.
    i. 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.
    ii. 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.
    iii. 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.
f. 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.
g. 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.
h. 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.

ISO Classification of Particulate Matter in Area Air

ISO Class	Particle Count[a]/m^3
3	35.2
4	352
5	3,520
6	35,200
7	352,000
7	3,520,000

a. Limits for number of particles ≥0.5μm measured under dynamic operating conditions.

Air-Exchange Requirements

a. A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7 Environments.
    i. The total HEPA-filtered air change rate must be adequate to maintain ISO Class 7 under dynamic operating conditions considering factors listed above.
    ii. At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling.
    iii. The HEPA-filtered air from the PEC, when added to the HVAC-supplied HEPA-filtered air, increases the total HEPA-filtered ACPH to at least 30 ACPH.
    iv. If the PEC is used to meet the minimum total ACPH requirements, the PEC must not be turned off except for maintenance.
    v. The ACPH from HVAC, ACPH, contributed from the PEC, and the total ACPH must be documented on certification reports.
b. A minimum of 20 ACPH of HEPA-filtered air must be supplied to ISO Class 8 areas.
    i. The total HEPA-filtered air change rate must be adequate to maintain ISO Class 8 under dynamic operating conditions considering factors listed above.
    ii. At least 15 ACPH of the total air change rate in a room must come from the HVAC through HEPA filters located in the ceiling.
    iii. Ante-rooms where activity levels are high may require more HEPA-filtered air to maintain ISO Class 8 under dynamic operating conditions.
    iv. The total ACPH must be documented on certification reports and be readily retrievable.

Summary if ACPH Requirements for Sterile Radiopharmaceutical Processing

Processing Area	ACPH Requirement
Unclassified SRPA	No requirement
ISO Class 7 area	≥ 30 ACPH
ISO Class 8 area	≥ 20 ACPH

Classified Areas

- Activities carries out within the buffer area must be limited to only those necessary. Food, drinks, and material exposed in patient care and treatment areas must not enter ante-rooms or buffer areas. 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.

Remote Aseptic Processing Involving a Hot-Cell

- 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 the 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 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.
- 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.
- 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.
- A failure of the airflow smoke pattern test requires personnel to garb in accordance with Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceutical Processing Area for all incursions into the hot-cell.
- 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.
- 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 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 4Hand Hygiene and Garbing for Buffer Areas and Segregated

Environmental Controls

- All 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 this section. 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.

- 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.
- 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. For preparation of sterile radiopharmaceuticals, consideration of both concerns could be addressed as follows:
    1. Buffer area, if present, must be positive pressure compared to the ante-room
    2. Ante-room, if present, must be positive pressure compared to unclassified portions of the restricted area
    3. Restricted area, in the presence of volatile or airborne radiopharmaceuticals, must be negative pressure compared to the unrestricted area
    4. 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).

<u>Establishing and Maintaining Environmental Controls</u>

- Any time a pressure differential is required, a pressure monitoring device is required. In a classified area, a pressure differential monitoring system must be used to continuously monitor the pressure differential between the ante-room(s) and buffer area(s) and between the ante-room and the general environment outside the classified area(s) or area(s). The results from the pressure monitoring system must be reviewed and documented at least daily on days the area is used. All pressure monitoring devices must be tested for accuracy and required performance at least every 6 months.

<u>Ambient Atmosphere for Immediate Use Preparations</u>

The following requirements should be met in ambient atmosphere environments:

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

<u>SRPA with Vertical Flow ISO Class 5 (PECs) for Radiopharmaceutical Preparations</u>

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

- Area surrounding the PEC may be ambient (unclassified) atmosphere
- Area must be clean, uncluttered, and dedicated to the processing of radiopharmaceuticals
- Appropriate for preparation, preparation with minor deviations, repackaging, and dispensing of radiopharmaceuticals

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).

Certification of PECs and Cleanrooms/SRPAs

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 the following:

- 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.
- HEPA filter integrity testing: HEPA filters must be leak tested after installation and as part of recertification.
- Total particle counts testing: Conducted under dynamic operating conditions using calibrated electronic equipment.
- 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).

Daily Monitoring of Environment

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:

- Relative humidity should be kept at 60% or lower
- Temperature and relative humidity continuous readings must be confirmed daily to have remained within the acceptable range
- Excursions must be documented and, if applicable, appropriate corrective actions taken
- Temperature monitoring devices must be verified for accuracy every 12 months or as required by the manufacturer
- Monitoring of pressure differentials must be performed

Section 4: Training/Qualifications/Validations

Training per NRC

Authorized Nuclear Pharmacist (per NRC regulations 10 CFR 35.55)

a. Is certified by a specialty board whose certification process has been recognized by the Commission or an Agreement State. The names of board certifications that have been recognized by the Commission or an Agreement State are posted on the NRC's Medical Uses Licensee Toolkit web page. To have its certification process recognized, a specialty board shall require all candidates for certification to:
    i. 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;
    ii. Hold a current, active license to practice pharmacy;

iii. 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

iv. 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;

-OR-

b. Has completed 700 hours in a structured educational program consisting of both:
   i. 200 hours of classroom and laboratory training in the following areas—
      1. Radiation physics and instrumentation;
      2. Radiation protection;
      3. Mathematics pertaining to the use and measurement of radioactivity;
      4. Chemistry of byproduct material for medical use; and
      5. Radiation biology; and
   ii. 500 hours of supervised practical experience in a nuclear pharmacy involving—
      1. Shipping, receiving, and performing related radiation surveys;
      2. 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;
      3. Calculating, assaying, and safely preparing dosages for patients or human research subjects;
      4. Using administrative controls to avoid medical events in the administration of byproduct material; and
      5. Using procedures to prevent or minimize radioactive contamination and using proper decontamination procedures; and
c. Has obtained written attestation, signed by a preceptor authorized nuclear pharmacist, that the individual has satisfactorily completed the requirements in paragraph (b)(1) of this section and is able to independently fulfill the radiation safety-related duties as an authorized nuclear pharmacist.

Aseptic Training and Validations

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 the ***Sterile compounding section*** 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:

i. Garbing and hand hygiene
j. PEC cleaning and disinfecting
k. Gloved fingertip, thumb and workstation sampling
l. Media-fill testing

Requalification after failure:

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.

Section 5: Cleaning and Disinfecting

Cleaning Process

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. 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.
5. Published data must be followed in respect to the appropriate contact time for each of the cleaning, disinfecting, and sporicidal agents used.
6. 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.
7. When diluting concentrated cleaning and disinfecting agents for use in classified areas, sterile water must be used.
8. Supplies used for cleaning and disinfection must be low lint.
9. 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.
10. 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 manufacturers instructions for use.
11. 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
12. 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.

13. 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.
14. After cleaning and disinfecting or the application of a one-step disinfectant cleaner in a PEC, apply sterile 70% IPA to remove any residue.
15. Cleaning and disinfecting of surfaces should occur at the minimum frequencies specified in the table below.
    a. If compounding activities are not performed daily, cleaning and disinfecting must be completed before initiating compounding.
16. The act of reducing or removing radioactivity (radioactive decontamination) from equipment or a surface must be balanced with the risk of spreading radioactive contamination.
17. Shielding of radioactive contamination, at times, may be necessary to lower the radiation exposure levels prior to cleaning and disinfecting.
18. The PEC should be checked for radioactive contamination
19. 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.
20. 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.
21. When sterile 70% IPA is used, it must be allowed to dry prior to proceeding to any subsequent step or activity.

Table. 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 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
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

Section 6: Microbial Air and Surface Monitoring

- Radiopharmacies must develop and implement written air and surface monitoring procedures for all sterile radiopharmaceutical classified areas.
    - The air and surface sampling procedures must include viable impact volumetric airborne particulate sampling and surface sampling.
- Results and corrective actions must be documented, and records must be readily retrievable.
- Air and surface sampling must be performed initially for classified areas in a facility to establish a baseline level of environmental quality.
- After initial sampling is performed, the classified areas must be monitored according to the minimum frequencies described hereafter to ensure that the environment remains in a suitable state for aseptic processing tasks.
- Regular review of the sampling data must be performed to detect trends such as elevated levels of microbial bioburden, elevated levels of nonviable particulates, or other adverse changes within the environment.
- Results must be reviewed in conjunction with personnel data (i.e., training records, visual observations, competency assessments) to assess the state of control and to identify potential risks of contamination. Prompt corrective actions in response to any adverse findings is required to maintain the necessary environmental quality for handling sterile radiopharmaceuticals
- Data must be reviewed following corrective actions to confirm that the actions taken have been effective in achieving the required air and surface quality levels.

- Air and surface sampling must be conducted during actual or simulated operating conditions to confirm that the required environmental quality in classified areas is maintained. Due to radiation exposure concerns for the workers involved, it is permissible for sampling to be carried out at the conclusion of sterile radiopharmaceutical processing but prior to cleaning and disinfecting the surface area. In this case, simulated tasks that are reflective of the routine aseptic activities are performed.
- In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:
    - In conjunction with the certification of new facilities or equipment
    - After any modification of facilities or equipment
    - In response to identified problems (e.g., positive growth in sterility tests of compounded radiopharmaceuticals)
    - In response to changes that could impact the controlled area environments (e.g., significant change in cleaning process or the agents involved).
- To obtain an air and surface sample that is representative of the typical aseptic operating conditions at the facility, air and surface sampling must be conducted under dynamic operating conditions in all PECs and classified areas.
- If conducted during actual sterile processing, the monitoring program must be designed and conducted in a manner that minimizes the chance that the sampling itself will contribute to contamination of the sterile radiopharmaceutical(s) or the environment.
- The air and surface monitoring must be clearly described in the established SOPs of the facility and must include a diagram of the sampling locations, SOPs for collecting samples, frequency of sampling, size of samples (e.g., surface area, volume of air), time of day of sampling in relation to activities in the classified areas, and action levels that will trigger corrective action.
- The locations of sampling should be carefully selected based on their relationship to the activities performed in the area. It is important to obtain samples from locations that pose the highest possible contamination risk to the sterile radiopharmaceuticals involved with the operation's process and that are likely to be representative of the conditions throughout the area.
- Personnel who operate the equipment should be trained in the proper operation of the air and surface sampling equipment to ensure accurate and reproductible sampling. All air sampling devices must be serviced and calibrated as recommended by the manufacturer.

Viable Air and Surface Monitoring

- A program for monitoring the viable airborne particles must be implemented to assess for microbial air quality in all classified areas.
- Volumetric active air sampling of all classified areas using an impaction device must be performed in each classified area during dynamic operating conditions at least every 6 months.
- Similarly, a program for monitoring the cleanliness of work surfaces must be developed and implemented. All sampling sites and procedures must be described in the facility's SOP.
- Surface sampling for all classified areas and pass-through chambers must be conducted at least monthly for the detection of microbial contamination.
- Each classified area must be sampled, including the following:
    - The direct processing area (DPA) of the PEC and the equipment contained in it.
    - Staging or work area(s) near the PEC
    - Pass-through enclosure(s)
    - Frequently touched surfaces

Surface Sampling Procedures

- Surface sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces.
- Certificate of Analysis (CoAs) must verify that the media meet the expected growth promotion, pH, and sterilization requirements.
- Surface sampling devices should contain general microbial growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the effects of any residual disinfecting agents.
- If used, contact plates must have a raised convex surface.
- After sampling, the sampled area must be thoroughly cleaned and disinfected.

a) Procedures for surface sampling on a flat surface:
   1) Remove the cover from the surface sampling device. Firmly press, using a rolling motion, if possible, the media surface onto the surface to be sampled. The surface sampling secede will leave a residue of growth medium on the sample site. After sampling, use sterile 70% IPA to remove the residue. Cover each sampling device.
   2) Is using plates, invert the plates.
   3) Incubate the surface sampling devices at 30°-35° Celsius for no less than 48 hours. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu/sample on an environmental sampling form based on the sample type (i.e., surface). Include sample and location date.
   4) Incubate the device at 20°-25° Celsius for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface). Include sample and location date.

b) Alternative procedure for shortened incubation period in which two samples are collected at each sample location.
   1) Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., MEA or SDA).
   2) Incubate each sample in a separate incubator. Incubate one sample at 30°-35° for no less than 48 hours, and incubate the other sample at 20°-25° for no less than 5 days.
   3) If fungal media are used as one of the samples, incubate the fungal media sample at 20°-25° for no less than 5 days.
   4) Count the total number of discrete colonies of microorganisms on each sample and record these results as cfu per sample.
   5) Record the results of the sampling.

<u>Air Sampling Procedures</u>

- Air sampling sites must be selected in all classified areas.
- When conducting sampling sites of the PEC, the process should involve not disturbing unidirectional airflow if taken during the actual sterile processing activities.
- Viable air sampling must include:
   - Follow the manufacturer's instructions for operation of the air sampling device, including placement of the media.
   - Using the sampling device, test at least 1 cubic meter or 1000 liters of air from each location sampled.
   - At the end of sampling, retrieve the media plates/devices and cover.

    - Invert the media and incubate at 30°-35° Celsius for no less than 48 hours. Examine growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m^3 of air on an environment sampling form based on sampling type (i.e., viable air). Include sample location and date.
    - Incubate the inverted media at 20°-25° Celcius for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m^3 of air on an environment sampling form based on sampling type (i.e., viable air). Include sample location and date.
- Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently. Both samples could be TSA or one sample TSA and the other fungal media (e.g., malt extract agar (MEA) or sabouraud dextrose agar (SDA).
    - Incubate each sample in a separate incubator. Incubate one sample at 30°-35° Celsius for no less than 48 hours, and incubate the other sample at 20°-25° Celsius for no less than 5 days.
    - Count the number of discrete colonies of microorganisms on each sample, and record the results as cfu per sample.
- In lieu of internal protocols for performing and incubating the air samples, the facility may use a third-party environmental testing company to perform these tests as long as all required data for documentation is included in the reports that they provide (i.e., Equipment types and models, calibrations, media used etc.).

<u>Date Evaluation and Action Levels</u>

- Evaluate cfu counts against the action levels in the table below and examine counts in relation to previous data to identify adverse results or trends.
- Surace sampling:
    - If two devices or two pieces of media were collected at a single location, all recovered growth on each must be documented and action levels are applied to each piece of media individually (i.e., results from each sampling device must be compared to the action level for the area).
- Air Sampling:
    - If two pieces of media were collected at a single location, all recovered growth on each must be documented and action levels are applied individually to each plate/device (i.e., results from each cubic meter of air sampled must be compared to the action level for that area).
- If levels measured during surface or air sampling exceed the levels in the table below for the ISO classification levels of the area sampled, an investigation must be conducted and corrective actions must be taken.
- The corrective action plan must be documented and must be dependent on the cfu count and the microorganism recovered.
- The extent of the investigation should be consistent with the deviation and should include an evaluation of trends.

Table 1. Action Levels for Surface Sampling

ISO Class	Air Sampling Action Levels [cfu/m^3(100 L) of air per plate]
5	>3
7	>5
8	>50

Table 2. Action Levels for Viable Airborne Particle Air Sampling

ISO Class	Air Sampling Action Levels [cfu/m^3(100 L) of air per plate]
5	>1
7	>10
8	>100

Section 7: Radiopharmaceutical Preparations and Compounding

Nonsterile Preparations: For these preparations, a designated area must be defined separate from any aseptic procedures. 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). The area for nonsterile preparation must be cleaned and uncluttered to ensure the overall integrity and quality of the prepared radiopharmaceutical(s). 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.

Sterile Preparations: 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. The minimum environmental standard for the preparation of sterile radiopharmaceuticals beyond immediate-use is within an ISO Classified area or device.

Preparation with Minor Deviations

- Radiopharmaceuticals prepared with minor deviations from the manufacturers instructions are sometimes necessary to accommodate circumstances not contemplated in the FDA-approved labeling. While allowed, deviations from manufacturer preparation instructions for radiopharmaceuticals must maintain the same ingredients but may differ in their proportions.
- Preparation with minor deviations must be performed in a classified area within an ISO5 PEC or within an SRPA.
- This requires 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.
- Examples of minor deviations include, but are not limited to, the following:
    - Altering the quantity of radioactivity or volume added to the vial
    - Changes in step-by-step operations (e.g., dilute Tc-99m sodium pertechnetate after rather than before addition to the vial).
    - Using alternative devices or equipment (e.g., a heating block rather than a hot water bath, using a different sized needle, different shielding materials)
    - Using QC test methods other than those described in the product labeling (e.g., radiochemical purity)
    - Filtered Tc-99m sulfur colloid
- Records for Preparation with Minor Deviations

- A record for preparation with minor deviations or compounding should include the following:
    - Name of the radiopharmaceutical
    - Physical Form (e.g., capsule or solution)
    - Name and quantity of ingredients including calibration time for radioactive ingredients (e.g., 100mCi Tc-99m sodium pertechnetate @1200)
    - Total volume
    - Reference to the MFR
    - Any deviation from the MFR, if applicable
    - Name of vendor or manufacturer, lot numbers, and expiration dates of all ingredients and components
    - Name of the person who prepared and name of the supervising personnel (ANP)
    - Date and time of preparation
    - Assigned internal identification number (e.g, lot number)
    - Unique reference [e.g., prescription number]
    - Assigned BUD and storage requirements if applicable
    - Documentation of QC results

Preparation of Radiolabeled Blood Components

- 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.
- 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.
- 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.
- Special precautions when radiolabeling of blood components for non-immediate use include:
    - 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.
    - 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.
    - 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.
    - Thorough cleaning and disinfection of the ISO Class 5 BSC and all reusable equipment within, prior to starting another blood component radiolabeling procedure.
    - 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.
    - Centrifuge should be located within the ISO Class 7 buffer area that is dedicated for blood component radiolabeling processes.

- 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.
- 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).
- Dedicated syringe shields and vial shields
- Remove and replace any garb that enters the ISO Class 5 BSC before handling anything else not related to performing this procedure.
- Removal of all disposable items from the ISO Class 5 BSC utilized in each radiolabeling procedure.
- 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.
- After the completion of blood radiolabeling procedures, follow all requirements for hand hygiene and garbing for buffer areas and segregated radiopharmaceutical processing area.

Compounding

- Each activity that involves compounding must be based on a written procedure and must include maintenance of compounding records.
- All sterile compounding must be performed in an ISO Class 5 PEC using aseptic technique.
- 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.
- 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.

a) Non-Sterile Radiopharmaceutical Compounding

- 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.
- Areas designated for nonsterile compounding must be cleaned and free from clutter and separated from areas designated for sterile radiopharmaceutical compounding.
- 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.
- 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.

b) Sterile Compounding

- 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.
- In some scenarios, systematic QC testing over time may be required to assign or validate an appropriate BUD.
- Kit splitting or fractionation of conventionally marketed FDA approved kits: may be used to meet a patient or multiple patient needs.

c) Sterile Compounding Using a Nonsterile Drug Substance or 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.
- 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.
- 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.
    - **i.** 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.
- 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.

d) Immediate use of Sterile Radiopharmaceuticals

- 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.
- 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.

Section 8: 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:

a. Source of receipt documentation
b. Quality control testing of products
c. Internal test assessments of procedures used for QC tests or related documentation to procedures being used.
d. Procedures for recall or notifications for out of specifications of products dispensed

Section 9: Assigning Beyond Use Date (BUD) of Radiopharmaceuticals

Definition of BUD: The date, or date and time (if applicable), beyond which a radiopharmaceutical preparation must not be used and must be discarded.

- 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.
- The BUD should not limit the time during which the radiopharmaceutical is administered (e.g. infused).

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

Section 10: Dispensing and Assaying

- 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.
- 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.
- The measured activity should be mathematically corrected for radioactive decay to the time of scheduled administration or calibration time.
- The activity at time of calibration must be within limits set for by the South Carolina Department of Environmental Services (DES)

Section 11: Labeling and Documentation Requirements

Labeling Requirements

- No radiopharmaceutical may be dispensed unless a label is affixed to the immediate container bearing:
    - A standard radiation safety symbol
    - The words, "Caution-Radioactive Material" and
    - The prescription number
- No radiopharmaceutical may be dispensed unless a label is affixed to the outer or delivery container bearing the:
    - Standard radiation symbol
    - Words "Caution-Radioactive Material"
    - Radionuclide and chemical form (generic name)
    - Activity and date and time of assay
    - Volume in liquid form or number of units dispensed, as applicable
    - Requested activity and the calibrated activity
    - Route of administration
    - Prescription number
    - Product expiration or BUD, as applicable, and any special storage or handling instructions for non-immediate use (e.g. refrigeration, resuspension).
    - 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
    - Name and address of the nuclear pharmacy
    - The South Carolina Radioactive Material (RAM) License number of the pharmacy dispensing the prescription
    - Name of the practitioner, and
    - Lot number of the prescription
    -

Documentation Requirements

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.
Documents should 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

Documentation related to all Preparations must be maintained and retrievable.
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.

Master Formulation Record

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.

The MFR or SOP must detail:

- Name of the radiopharmaceutical
- Detailed procedure (e.g., heating, components, incubation time)
- Range of radioactivity
- Range of volume
- PEC and SEC to be used, if applicable
- QC required
- Reference to justification of BUD

Complex radiopharmaceutical compounding must also include:

- Procedures related to depyrogenation and sterility procedures and validation, if applicable
- Name, identity, strength, purity, quality, and quantity of ingredients with validated documentation (e.g., CoA)
- Equipment to be used
- Components used in the preparation

Records related to each preparation using minor deviation or other compounding must:

- Include all documentation related to Preparations, dispensing and labeling
- Reference the MFR or preparation SOP
- Include any notations or deviation from the MFR/SOP in a note section attached to the preparation record.

Section 12: Generator Requirements

These standards establish 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.

Scope

These standards apply 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.

Supervision Requirements
Non-direct infusion generators shall only be possessed, operated, or used under the direct supervision of a South Carolina licensed authorized nuclear pharmacist. All personnel involved in generator operations must be trained and work under the direct supervision of the authorized nuclear pharmacist. Facilities are permitted to possess Tc99m generators for emergency use only under the supervision of a licensed physician.

Licensing and Permitting
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. Facilities are permitted to possess Tc99m generators for emergency use only under the supervision of a licensed physician.

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.

Generator Operation and Elution

- **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.
- **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. Breakthrough standards must follow manufacturer recommendations. Breakthrough records must be kept for a minimum of 3 years.

Transporting generators between facilities
- If transporting generators between facilities, the following standards should be followed:
    - Transport of either Mo-99 of Ga-68 generators is permitted.
    - 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.
    - The generator should be packaged and transported in a manner to maintain the integrity and sterility of the generator system.
    - Environmental monitoring should be performed during transport to ensure recommended temperature per the manufacturer is maintained.

Section 13: Repackaging

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.
If used for an individual patient, refer to the labeling requirements for individual preparations.

If not for an individual patient then the inner and outer package must display:

a. Standard radiation symbol
b. The words “Caution-Radioactive Material”
c. The radionuclide and chemical form (generic name)
d. Radioactivity with units at time of calibration and the calibration time

The outer container must also state:

a. Number of units
b. Product expiration or BUD
c. Special storage and handling instructions.

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 Incomplete draft; Needs further consolidation, consistency review, and finalization 58 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.