Pharmacy, Board of

Pharmacy, Board of

Chapter 17: Sterile Compounding

Effective Date: 05/13/2021 to Current

Rule Type: Current Rules & Regulations

Reference Number: 059.0001.17.05132021

Chapter 17

Sterile Compounding

Section 1. Authority.

These regulations are promulgated pursuant to the Wyoming Pharmacy Act W.S. § 33-24-101 through -301.

Section 2. Definitions.

(a) "Ante-room" means an ISO Class 8 or cleaner room with fixed walls and doors where activities that generate high particulate levels are performed. It is the transition room between the unclassified area of the facility and the buffer room, in which pressure relationships are constantly maintained and large disturbances requiring response from the heating, ventilating, and air-conditioning control system are reduced.

(b) "Aseptic Technique" means processing of pharmaceutical products that involves the separate sterilization of the product and of the package, if not already sterilized, and the transfer of the product into the container and its closure under at least ISO Class 5 conditions.

(c) "Beyond-Use Date" (BUD) means the date, or the time and date, beyond which a preparation shall not be used and shall be discarded. It is determined from the date or time that preparation of the CSP is initiated and is dependent on individual compounding factors.

(d) "Buffer Room" means an ISO Class 7 or cleaner room with fixed walls and doors where the Primary Engineering Control is physically located. The buffer room may only be accessed through the ante-room.

(e) "Cleaning agent" means an agent for the removal of residues from surfaces.

(f) "Cleanroom Suite" means the classified area consisting of both the ante-room and buffer room.

(g) "Closed System Transfer Device" (CSTD) means a drug transfer device that mechanically prohibits entrance of contaminants into the system and escape of hazardous drug or vapor from the system.

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

(i) “Disinfectant” means a chemical or physical agent used on an inanimate surface and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial and fungal spores.

(j) “Dynamic operating conditions” means conditions in which operating pharmacy staff are present and simulating or performing compounding. The conditions shall reflect the largest number of pharmacy staff and highest complexity of compounding expected during routine operations as determined by the designated person(s).

(k) “Hazardous Drugs” (HDs) means drugs in which studies in animals or humans indicate that exposures to them have a potential for causing cancer, development or reproductive toxicity, or harm to organs.

(l) “ISO Class” means an air-quality classification from the International Organization for Standardization that limits the number of particles of 0.5 micrometers and larger per cubic meter.

Class Name	Particle Count:
ISO Class 3	35.2/m3
ISO Class 4	352/m3
ISO Class 5	3,520/m3
ISO Class 6	35,200/m3
ISO Class 7	352,000/m3
ISO Class 8	3,520,000/m3

(m) “Media-Fill Test” means a simulation used to qualify processes and pharmacy staff engaged in sterile compounding to ensure that the processes and personnel are able to prepare CSPs without contamination.

(n) “One-step disinfectant cleaner” means a product with an EPA-registered or equivalent claim that it can clean and disinfect a non-porous surface in the presence of light to moderate organic soiling without a separate cleaning step.

(o) “Primary Engineering Control” (PEC) means a device that provides an ISO Class 5 or better air quality environment and utilizes unidirectional HEPA filtration for sterile compounding.

(p) “Quality Assurance” (QA) means the system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.

(q) “Quality Control” (QC) means the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CSP.

(r) “Secondary Engineering Control” (SEC) means the area where the PEC is placed.

(s) “Segregated Compounding Area” (SCA) means a designated, unclassified space, area, or room with a defined perimeter that contains a PEC and is suitable for preparation of Low-Risk CSPs only.

(t) “Sporicidal agent” means a chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Section 3. Pharmacy Staff Training and Evaluation.

(a) Each sterile compounding pharmacy shall develop a written training program that describes the required training, the frequency of training, and the process for evaluating the performance of pharmacy staff involved in preparing CSPs.

(b) Compounding pharmacy staff shall be initially trained and qualified by demonstrating knowledge of principles and proficiency in core competencies for performing sterile manipulations and achieving and maintaining appropriate environmental conditions. A designated person shall oversee the training of pharmacy staff.

(c) Training and evaluation of pharmacy staff shall be documented.

(d) Compounding pharmacy staff shall be able to demonstrate knowledge and competency in the following:

(i) Using proper aseptic technique

(A) All compounding pharmacy staff shall perform a media-fill test to assess aseptic technique. The media-fill test shall simulate the most difficult and challenging compounding procedures and processing conditions encountered by the person replacing all the components used in the CSPs with soybean-casein digest media.

(B) Gloved fingertip and thumb sampling shall be performed inside the PEC following the media-fill test to evaluate aseptic technique.

(C) If using commercial sterile microbial growth media, a certificate of analysis (COA) shall be obtained from the supplier stating that the lot of the growth media will support the growth of microorganisms.

D) If preparing sterile microbial growth media in-house for sterile to sterile media fill testing, the growth promotion capability of the media shall be demonstrated for each batch and documented as described in USP <71>.

(E) Failure of the media fill test is indicated by visible turbidity or other visual manifestation of growth in the media in one or more container-closure unit(s) on or before the end of the incubation period.

(F) Results of the evaluation and corrective actions, in the event of failure, shall be documented and include, at a minimum the name of the person evaluated, evaluation date/time, media and components used, including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

(ii) Appropriately and accurately preparing, identifying, purifying, sterilizing, packaging, labeling, storing, dispensing, distributing, documenting and recordkeeping for CSPs.

(iii) Appropriately cleaning and maintaining the compounding area.

(iv) How to recognize potential problems, deviations, failures, or errors related to equipment, facilities, materials, or compounding processes that could potentially result in contamination or other adverse impact on CSP quality.

(v) Hand hygiene and garbing procedures

(A) All compounding pharmacy staff shall be visually observed while performing hand hygiene and garbing procedures.

(B) Before being allowed to independently compound, all compounding pharmacy staff shall successfully complete an initial gloved fingertip and thumb sampling on both hands, no fewer than 3 separate times. Each evaluation shall occur after performing a separate and complete hand hygiene and full garbing procedure.

(C) The initial evaluation shall be performed on donned sterile gloves in a classified area or SCA. Subsequent sampling shall be performed on donned sterile gloves inside of the PEC. If conducting sampling in a compounding aseptic isolator (CAI), compounding

aseptic containment isolator (CACI), or a pharmaceutical isolator, samples shall be taken from the sterile gloves placed over the gloves attached to the restricted-access barrier system (RABS).

(D) Successful completion of initial gloved fingertip and thumb sampling is defined as zero colony-forming units (cfu). Successful completion of subsequent gloved fingertip and thumb sampling after media-fill testing is defined as ≤ 3 cfu (total from both hands).

(E) Failure is indicated by visual observation of improper hand hygiene and garbing procedures and/or gloved fingertip and thumb sampling results that exceed action levels.

(F) Results of the evaluation and corrective actions, in the event of failure, must be documented. Documentation must include, at a minimum, the name of the person evaluated, evaluation date/time, media and components used, including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, the results, and the identification of the observer and the person who reads and documents the results.

(e) Competencies shall be reevaluated every twelve (12) months for low and medium risk level compounding, and every six (6) months for high-risk level compounding.

Section 4. Personal Hygiene and Garbing.

(a) Pharmacy staff shall not handle CSPs if they have open sores, infected wounds, or an upper respiratory infection.

(b) When entering a cleanroom suite or SCA, compounding pharmacy staff shall remove any items that are not easily cleanable or that are not necessary for compounding. At a minimum pharmacy staff shall:

(i) Remove all cosmetics and personal outer garments including, but not limited to bandanas, coats, hats, jackets, sweaters, and vests. If worn, eyeglasses shall be wiped;

(ii) Remove all hand, wrist, and other exposed jewelry including but not limited to piercings that could interfere with the effectiveness of garbing or otherwise increase the risk of contamination of the CSP. Compounding pharmacy staff shall cover any jewelry that cannot be removed;

(iii) Not wear earbuds or headphones;

(iv) Not bring electronic devices that are not necessary for required tasks into the cleanroom suite or SCA; and

(v) Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures. Nail products, including, but not limited to polish, artificial nails, or extenders shall not be worn.

(c) Handwashing and garbing order shall be outlined in the facility's policies and procedures. Compounding pharmacy staff shall follow established hand hygiene and garbing procedures when entering the cleanroom suite or SCA and prior to handling CSPs.

(i) Compounding pharmacy staff shall wash hands and forearms up to the elbows and remove visible debris from underneath the fingernails with soap and water for at least thirty (30) seconds. Low-lint disposable towels or wipes shall be used to dry hands and forearm. Brushes and hand dryers shall not be used for hand hygiene;

(ii) After handwashing, and alcohol-based hand rub shall be applied to dry hands prior to donning sterile gloves;

(iii) Garb shall consist of the following minimum requirements:

(A) Low-lint garment with sleeves that fit snugly around the wrists and that is enclosed at the neck;

(B) Low-lint, disposable shoe covers;

(C) Low-lint, disposable cover for head that covers the hair and ears, and if applicable, a disposable cover for facial hair;

(D) Face mask;

(E) Sterile, powder-free gloves; and

(F) If using a RABS, disposable gloves should be worn inside the gloves attached to the RABS sleeves. Sterile gloves shall be worn over the gloves attached to the RABS sleeves.

(iv) Garb shall be donned or doffed in an order that reduces the risk of contamination. Skin shall not be exposed inside the PEC. Garb shall be replaced immediately if it becomes visibly soiled or if its integrity is compromised;

(v) Compounding pharmacy staff may re-use gowns within the same shift if the gown is maintained in the classified area or within the perimeter of the SCA and used for non-hazardous drug compounding. All other gab shall be discarded after use;

(vi) All gloves shall be inspected for holes, punctures, or tears and shall be replaced immediately if such defects are detected. The RABS sleeves and gloves should be changed per the manufacturer's recommendations and as defined in the facility's policies and procedures; and

(vii) Compounding pharmacy staff shall apply sterile 70% isopropyl alcohol (IPA) to gloves regularly throughout the compounding process and whenever nonsterile surfaces are touched.

Section 5. Facilities and Engineering Controls.

(a) The cleanroom suite shall be designed as follows:

(i) The ante-room and buffer rooms shall be separated from areas not directly related to compounding by fixed walls and doors;

(ii) The ante-room shall have a line of demarcation separating the dirty side and the clean side. Alternatively, the facility can have two (2) separate ante-rooms, one dirty and one clean;

(iii) Buffer rooms shall maintain a minimum differential positive presser of 0.02-inch water column between the buffer and ante-rooms;

(iv) Ante-rooms shall maintain a minimum differential positive pressure of 0.02-inch water column between the ante-room and unclassified areas;

(v) A pressure differential monitoring device shall be used to continuously monitor pressure differentials. Results from the pressure monitoring device shall be reviewed and documented at least daily on the days when compounding is occurring;

(vi) Ante-rooms shall maintain ISO Class 8 or better quality of air and maintain a minimum of 20 to HEPA-filtered air changes per hour (ACPH);

(vii) Buffer rooms shall maintain ISO Class 7 or better air quality and maintain a minimum of 30 total HEPA-filtered ACPH. At least 15 ACPH shall be supplied through the buffer room's heating, ventilation, and air-conditioning (HVAC) system;

(viii) Air supplied to the cleanroom suite shall be introduced through HEPA filters located in the ceiling. Air returns shall be located low in the wall, unless a visual smoke study demonstrates the absence of stagnant flow where particles can accumulate;

(ix) Temperature and humidity shall be controlled through a HVAC system. Free-standing humidifiers/dehumidifiers and air conditioners shall not be used within the classified area;

(A) The cleanroom suite should be maintained at a temperature of 20° C (68° F) or cooler and a relative humidity below 60% to minimize the risk for microbial proliferation and provide comfortable conditions for compounding pharmacy staff;

(B) The designated person shall monitor temperature and humidity and each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device;

(C) The designated person shall verify the accuracy of temperature and humidity monitoring devices at least every twelve (12) months or as required by the manufacturer.

(x) The cleanroom suite shall provide a well-lighted working environment;

(xi) The cleanroom suite shall be designed to allow for easily cleanable conditions:

(A) The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, and non-shedding. These surfaces should be resistant to damage by cleaning agents, disinfectants, sporicidal agents and tools used to clean them;

(B) Overhangs and ledges should be limited, but easily cleanable, if present;

(C) Floors shall include coving to the sidewall, or the juncture between the floor and wall shall be sealed. The junctures between the ceiling and the walls shall be sealed. All penetrations through the ceiling or walls shall be sealed;

(D) If ceilings consist of inlaid panels, the panels shall be caulked around each panel to seal them to the support frame;

(E) The exterior lens surface of all ceiling light fixtures shall be smooth, mounted flush, and sealed;

(F) The walls shall be either constructed of or covered with durable material including but not limited to epoxy painted walls or heavy-gauge polymer. The integrity if the surfaces shall be maintained. Panels shall be joined together and sealed to each other and the support structure;

(G) All furniture, equipment, and other materials necessary for compounding activities should be low-shedding and easily cleaned and disinfected; and

(H) Carts used to transport components or equipment into classified areas shall be constructed from nonporous material with cleanable casters and wheels to allow for cleaning and disinfection. Carts shall not be moved from the dirty side to the clean side of the ante-room unless the entire cart, including casters, is cleaned and disinfected.

(xii) Water supplied to the cleanroom suite shall meet the following requirements:

(A) The sink used for hand hygiene may be placed either inside or outside the ante-room. If placed outside the ante-room, it shall be located in a clean space. If the sink is located inside the ante-room, it may be placed on either the clean side or dirty side of the ante-room;

(B) The sink should allow for hand-free use;

(C) The ante-room shall not contain floor drains;

(D) The buffer room shall not contain plumbed water sources; and

(E) Sprinkler systems shall be recessed, covered, and easily cleanable.

(b) The SCA shall meet the following requirements:

(i) The SCA shall be separated from general pharmacy areas not directly related to compounding by fixed doors and walls;

(ii) The SCA shall be located away from unsealed windows, doors that connect to the outdoors, traffic flow, and other environmental control challenges that could affect the air quality of the PEC within the SCA;

(iii) A visible perimeter shall be established to mark the boundaries of the SCA;

(iv) The SCA shall provide a well-lighted working environment.

(v) Free-standing humidifiers/dehumidifiers and air conditioners shall not be used within the perimeter of the SCA;

(vi) All surfaces shall be clean, uncluttered, and dedicated to compounding;

(vii) All surfaces shall be smooth, impervious, free from cracks and crevices, and non-shedding;

(viii) All surfaces should be resistant to damage by cleaning agents; disinfectants, sporicidal agents, and tools used to clean them;

(ix) Dust-collecting overhangs and ledges should be limited, but shall be easily cleanable if present; and

(x) The sink shall be at least one (1) meter away from the PEC and shall not be placed inside the perimeter of the SCA. The sink should allow for hands free use.

Section 6. Requirements for Certification and Recertification.

(a) Before a classified area or SCA can be used to compound CSPs, it shall be certified using procedures in the current controlled Environmental Testing Association (CETA) certification guideline for sterile compounding facilities or an equivalent guideline. Certifications hall be performed by properly trained individuals.

(b) Certification shall be performed initially, and recertification shall be performed at least every six (6) months. Recertification shall be performed if there are changes to the area including, but not limited to redesign, construction, replacement or relocation if a PEC, or alteration in the configuration of the room that could affect airflow or air quality.

(c) Certification shall include the following:

(i) Airflow testing to determine acceptable pressure differentials in doorways between adjacent rooms and ACPH from the HVAC, ACPH from the PEC and total ACPH;

(ii) HEPA filter integrity testing to include leak testing. HEPA filters shall be tested after installation and as part of recertification;

(iii) Total particle count testing in all classified areas under dynamic conditions;

(iv) Dynamic airflow smoke patter tests for each PED during dynamic operating conditions to demonstrate unidirectional airflow and sweeping action over and away from the CSP;

(v) Viable air and surface sampling in each classified area during dynamic operating conditions.

(A) Viable air sampled shall be take using an impaction device that tests at least 1,000 liters of air from each location sampled;

(B) A general microbial growth media that supports the growth of bacteria and fungi shall be used for surface samples;

(C) Action levels for viable air sampling are > 1CFU for ISO Class 5, > 10 CFU for ISO Class 7, and > 100 CFU for ISO Class 8; and

(D) Action levels for surface sampling are > 3 CFU for ISO Class 5, > 5 CFU for ISO Class 7, and > 50 CFU for ISO Class 8.

(d) The certification report shall document the results of all required resting. The certification report shall be readily retrievable.

(e) A certification report shall document the results of the above required rests.

(i) The report shall indicate the locations of viable air and surface sampled, size of the sampled taken, incubation times and temperatures, and growth results; and

(ii) The number of pharmacy staff present in each PEC and SEC during testing shall be documented.

(f) All certification and recertification records shall be reviewed by the designated person(s) to ensure that the classified environments meet the above requirements of this chapter.

(g) In the event of failure, the designated person(s) shall identify the cause and implement a corrective action plan. Data collected in response to corrective actions shall be documented and reviewed by the designated person(s) to confirm the actions taken have been effective.

Section 7. Cleaning, Disinfecting, and Applying Sporicidal Agents in Compounding Areas.

(a) All activities in this section shall be performed by trained and appropriately garbed facility staff.

(b) Facility staff shall clean surfaces prior to being disinfected. Facility staff may use an EPA-registered on-step disinfectant cleaner to accomplish cleaning and disinfection in one step.

(c) Facility staff shall perform cleaning in the direction of cleanest to dirtiest areas.

(d) Facility staff shall follow the manufacturer's directions or published data for the minimum contact time of the cleaning, disinfecting, and sporicidal agents.

(e) Facility staff shall apply sterile 70$ isopropyl alcohol (IPA) after cleaning, disinfecting, or applications of a sporicidal agent in the PEC to remove any residue and allow it to dry.

(f) All cleaning supplies with the exception of toll handles and holders shall be low-lint.

(g) Wipers, pads, and mop heads should be disposable. Facility staff shall discard disposable cleaning supplies after each cleaning activity.

(h) Reusable cleaning tolls shall be made of cleanable materials, cleaned and disinfected before and after each use, dedicated for use in the classified are or SCA, and not removed except for disposal.

(i) Cleaning, disinfecting, and application of sporicidal agents in classifies areas and within the perimeter of the SCA shall occur at the following minimum frequencies and include the following surfaces, at a minimum:

(i) Facility staff shall clean and disinfect surfaces of sink(s) at least daily and a sporicidal agent shall be used at least monthly;

(ii) Facility staff shall clean and disinfect all interior surfaces and equipment inside the PEC, pass-through(s), work surfaces outside the PEC, and floors daily. A sporicidal agent shall be used on these surfaces at least monthly;

(iii) Facility staff shall perform cleaning and disinfecting before initiating compounding if compounding is not performed daily; and

(iv) Facility staff shall clean and disinfect walls, doors, door frames, ceilings, storage shelving and bins, and equipment outside the PEC monthly. A sporicidal agent shall be used on these surfaces.

(j) Facility staff shall document all cleaning, disinfecting, and application of sporicidal agents. Records shall be readily retrievable.

Section 8. Introducing Items into the SEC and PEC.

(a) Only furniture, equipment, and other materials necessary for compounding activities shall be permitted in a classified area or SCA. Items shall be placed in a manner that facilitates sterile compounding operations.

(b) Pharmacy staff shall not introduce shipping carton(s) or other corrugated or uncoated cardboard into a classified area or SCA.

(c) Pharmacy staff shall wipe down and item with a sporicidal agent, EPA-registered one-step disinfectant cleaner, or sterile 70% IPA using low-lint wipes prior to introducing the item into the clean side of the ante-room, pass-through, or inside the perimeter of the SCA. Pharmacy staff shall wear gloves when wiping down items.

(i) If a sporicidal agent or EPA-registered one-step disinfectant cleaner is used to wipe an item down, the item shall be allowed to dwell for the minimum contact time specified by the manufacturer before introducing the item into the classified area;

(ii) Pharmacy staff shall allow the item to dry if sterile 70% IPA is used to wipe it down; and

(iii) The wiping procedure shall not render the product label unreadable.

(d) Compounding pharmacy staff shall wipe down any item with sterile 70% IPA using low-lint wipes and allowed to dry prior to introducing the item into the PEC.

(i) Compounding pharmacy staff may remove items from sterile coverings as they are introduced into the PWC without the need to wipe them with sterile 70% IPA;

(ii) The wiping procedure shall not render the product label unreadable; and

(iii) Compounding pharmacy staff shall wipe all critical sires with sterile 70% IPA in the PEC and allowed to dry prior to entering or puncturing vial stoppers, IV bag septums, or ampule necks.

(e) Only equipment necessary for performing compounding activities shall be permitted in the PEC.

(i) Proper placement of equipment in the PEC shall be initially verified by a dynamic airflow smoke patter test during certification or recertification that demonstrates minimal disruption in airflow. The smoke pattern rest shall be repeated if equipment is moved to a different location in the PEC; and

(ii) Pharmacy staff shall not remove equipment used in the cleanroom suite or within the perimeter of the SCA except for calibration, servicing, cleaning, or other activities associated with maintenance.

Section 9. Equipment, Supplies, and Components.

(a) When using an automated compounding device (ACD), balance, or other automated or electronic equipment to compound a CAP, pharmacy staff shall:

(i) Calibrate all equipment to ensure proper operation;

(ii) Ensure all equipment shall not be reactive or sorptive with compounding components;

(iii) Conduct an accuracy assessment of the ACD before first use and again each day it is used to compound; and

(iv) Maintain records of all equipment calibration, verification, and maintenance.

(b) Pharmacy staff shall ensure that all supplies used in compounding, including, but not limited to beakers, utensils, needles, syringes, filters and tubing sets meet the following requirements:

(i) Supplies shall not be reactive or sorptive with compounding components; and

(ii) Supplies in direct contact with CSPs shall be sterile and depyrogenated.

(c) Pharmacy staff shall ensure all components used in compounding meet the following requirements:

(i) Pharmacy staff shall use conventionally manufactured sterile products when available and appropriate;

(ii) Active pharmaceutical ingredients (APIs) shall comply with criteria in the USP-NF monograph, if one exists, or have a COA that includes the specifications and test results.

(iii) The sterile compounding pharmacy shall obtain APIs from and FDA-registered facility;

(iv) The sterile compounding pharmacy may obtain components other than APIs from an acceptable and reliable source if not available from an FDA-registered facility; and

(v) The sterile compounding pharmacy shall establish the identity, strength, purity, and quality of all components obtained.

Section 10. Master Formulation Records, Compounding Records and Labeling.

(a) Sterile compounding pharmacies shall maintain a master formulation record:

(i) A master formulation record shall be maintained for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredients;

(ii) Any changes or alterations to the master formulation record shall be approved by the designated person(s) and documents; and

(iii) The master formulations record shall include, but is not limited to, the following information:

(A) Name, strength or activity, and dosage form of the CSP;

(B) Identities and amounts of all ingredients;

(C) Type and size of container-closure system(s);

(D) Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions;

(E) Physical description of the final CSP;

(F) BUD and storage requirements;

(G) Reference source to support the stability of the CSP;

(H) Quality control (QC) procedures; and

(I) Other information as needed to describe the compounding process and ensure repeatability.

(b) Pharmacy staff shall create a compounding record for all CSPs:

(i) The prescription, medication order, or label may serve as the compounding record;

(ii) The compounding record may be stored electronically if an ACD workflow management system, or other equipment is used to compound the CSP;

(iii) The compounding record shall be readily retrievable;

(iv) The master formulation record may serve as the basis for preparing the compounding record; and

(v) The compounding record shall include, but is not limited to, the following information:

(A) Name, strength or activity, and dosage form of the CSP;

(B) Date and time of preparation of the CSP;

(C) Assigned internal identification number;

(D) A method to identify the individuals involved in the compounding process and verifying the final CSP;

(E) Name of each component;

(F) Vendor, lot number, and expiration date for each component for CSPs prepared for more that one patient and for CSPs prepared from nonsterile ingredients(s);

(G) Weight or volume of each component;

(H) Strength or activity of each component;

(I) Total quantity compounded;

(J) Assigned BUD and storage requirements;

(K) Results of QC procedures;

(L) Master formulation record reference for the CSP, if applicable; and

(M) Calculations made to determine and verify quantities and/or concentrations of components, if applicable.

(c) The label on the immediate container of the CSP shall, at a minimum, display the following information:

(i) Assigned internal identification number;

(ii) Active ingredient(s) and their amounts, activities, or concentrations;

(iii) Storage conditions if other than controlled room temperature;

(iv) BUD;

(v) Route of administration;

(vi) Total amount or volume if it is not obvious from the container;

(vii) If it is a single dose container, a statement stating such when space permits; and

(viii) If it is a multiple dose container, a statement stating such.

Section 11. Quality Assurance and Quality Control Programs.

(a) The designated person(s) shall establish a quality assurance (QA) and quality control (QC) program.

(b) The program shall be reviewed at least every twelve (12) months. The results of the review shall be documented and appropriate actions shall be taken if needed.

(c) The QA and QC program shall include systems to establish the following:

(i) Adherence to procedures;

(ii) Prevention and detection of errors and quality problems;

(iii) Evaluation of complaints and adverse events; and

(iv) Appropriate investigations and corrective actions.

(d) If a CSP is dispensed or administered before the results of release testing are known, the pharmacy shall have a procedure in place to notify the prescriber of a failure of specifications and determine whether a recall is necessary.

(e) Recall out of specification dispensed CSPs shall include the following:

(i) Determination of the severity of the problem and the urgency for implementation and completions of the recall;

(ii) Determination of the distribution of any affected CSP; including the date and quantity of distribution;

(iii) Identification of patients who received the CSP; and

(iv) Disposition and reconciliation of the recalled CSP.

(f) Complaint handling shall include the following:

(i) A designated person(s) shall review all complaints to determine whether there is a potential quality problem with the CSP;

(ii) A thorough investigation shall be initiated and completed for all complaints that involve a quality problem with a CSP;

(iii) The sterile compounding pharmacy shall maintain a record of each complaint. The record shall contain the following information, at a minimum:

(A) The name of the complainant or unique identifier;

(B) The date the complaint was received;

(C) The nature of the complaint;

(D) The response to the complaint;

(E) The name and strength of the CSP and its' internal identification number; and

(F) Findings of the investigation and any follow up.

(iv) A CSP that is returned in connection with a complaint shall be quarantined until destroyed after completion of the investigation.

(g) The designated person(s) shall report adverse events potentially associated with a CSP to the Board.

Section 12. Establishing Beyond Use Dates.

(a) Low-risk level CSPs are prepared under the following conditions:

(i) The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 or better air quality using only sterile ingredients, products, components, and devices;

(ii) Compounding only involved transferring, measuring and mixing manipulations using not more than three (3) commercially manufactured packages of sterile products, and no more than two (2) entries into any sterile container, product, or administration container/device;

(iii) Manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing; and

(iv) In the absence of passing a sterility test, the storage periods shall not exceed forty-eight (48) hours at controlled room temperature (20-25°C/68-77°F), fourteen (14) days at a cold temperature (2-8°C/36-46°F), and forty-five (45) days in a solid frozen state (-25 to -10°C/-13 to 14°F).

(b) Medium-risk level CSPs are prepared aseptically under low-risk level conditions and one or more of the following conditions exists:

(i) Multiple individual or small doses od sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions;

(ii) The compounding process includes complex aseptic manipulations other than a single-volume transfer;

(iii) The compounding process requires unusually long duration; and

(iv) In the absence of passing a sterility test, the storage periods shall not exceed thirty (30) hours at controlled room temperature, nine (9) days at cold temperature and forty-five (45) days in a solid, frozen state.

(c) High-risk level CSPs are prepared under the following conditions:

(i) Nonsterile ingredients, including manufactured products not intended for sterile routes of administration, are incorporated, or a nonsterile device is employed before terminal sterilization;

(ii) Any of the following are exposed to air quality worse than ISO Class 5 for more than one (1) hour:

(A) Sterile contents of commercially manufactured products;

(B) CSPs that lack effective antimicrobial preservatives; and

(C) Sterile surfaces of devices and containers for the preparation, transfer, sterilization, and packaging of CSPs.

(iii) Pharmacy compounding staff are improperly garbed and gloved;

(iv) Nonsterile water-containing preparations are stored for more than six (6) hours before being sterilized; and

(v) In the absence of passing a sterility test, storage periods shall not exceed twenty-four (24) hours at controlled room temperature, three (3) days at a cold temperature, and forty-five (45) days in solid, frozen state.

(d) Pharmacy staff shall meet the following requirements for high-risk level compounding:

(i) Batches of twenty-five (25) or more CSPs shall undergo sterility testing;

(ii) All nonsterile measuring, mixing, and purifying devices shall be sensed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use;

(iii) All high-risk level CSPs subjected to terminal sterilization shall be pre-filtered by passing through a filter with nominal port size no larger than 1.2 microns preceding or during filling into their final containers, to remove particulate matter; and

(iv) Sterilization by filtration shall be performed with a sterile 0.2 or 0.22 micron nominal pore size filter, entirely within an ISO Class 5 or superior air quality environment.

(e) A sterile compounding pharmacy with a cleanroom suite may compound low, medium, or high-risk level CSPs.

(f) A sterile compounding pharmacy with a SCA may compound low-risk level CSPs and shall not assign a BUD greater than twelve (12) hours at controlled room temperature, or twenty-four (24) hours at refrigerated temperature.

(g) CSPs that have undergone extended sterility and stability testing may be assigned a BUD greater than outlined in this Chapter. CSPs that are assembled according to the manufacturer's instructions may be assigned a BUD in accordance with the manufacturer's recommendations.

Section 13. Immediate Use CSPs.

(a) Compounding of CSPs by pharmacy staff outside of a classified area or SCA for direct and immediate administration to patients is not subject to the requirements of this Chapter, when all of the following conditions are met:

(i) Aseptic processes are followed and written procedures are in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs;

(ii) Compounding is performed in accordance with the evidence-based information for physical and chemical compatibility of the drugs;

(iii) The preparation involves not more than three (3) different sterile products;

(iv) Any unused starting component from a single-dose container shall be discarded after preparation for the individual patient is complete. Single-dose containers shall not be used for more than one (1) patient;

(v) Administration of the CSP begins within four (4) hours following the start of preparation. If administration has not begun within four (4) hours following the start of preparations, it shall be promptly, appropriately, and safely discarded; and

(vi) Unless the CSP is administered by the person who prepared the CSP or administration is witnessed by the preparer, the CSP shall be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the CSP, and the exact four (4) hour time period within the administration shall begin.

(b) Immediate use CSPs shall not be prepared:

(i) For medium-risk level or high-risk level CSPs;

(ii) In advance for anticipated needs; or

(iii) For batch compounding.

(c) Situations for which the immediate use CSPs can be administered include, but are not limited to:

(i) Cardiopulmonary resuscitation;

(ii) Emergency room treatment;

(iii) Preparation of diagnostic agents, or

(iv) Critical therapy where preparation under conditions for low-risk level CSPs causes delays that subject the patient to additional risk.

Section 14. Sterilization and Depyrogenation.

(a) Pharmacy staff shall sterilize all CSPs that contain nonsterile components or that come into contact with nonsterile devices during any phase of compounding, within six (6) hours after completing the CSP.

(b) Pharmacy staff shall sterilize the CSP in a method without degrading its physical and chemical stability or the packaging integrity.

(c) Pharmacy staff shall document a description of the sterilization process, including temperature, pressure (if applicable), duration, permissible load conditions for each cycle, the use of biological indicators and endotoxin challenge vials, and be readily retrievable.

(d) Pharmacy staff shall document results of terminal sterilization. Documentation shall include, but is not limited to, the temperature, pressure, duration, permissible load conditions for each cycle, and the used of biological indicators and endotoxin challenge vials.

(e) Equipment used to terminally sterilize CSPs shall be appropriately maintained, calibrated, and cleaned. Maintenance, calibration and cleaning shall be documented by pharmacy staff.

(f) Depyrogenation processes shall meet the following requirements:

(i) Depyrogenation shall be used to render glassware, metal, and other thermostable containers and components pyrogen-free;

(ii) The duration of the exposure period shall include sufficient time for the items to reach the depyrogenation temperature;

(iii) The items shall remain at the depyrogenation temperature for the durations of the depyrogenation period;

(iv) The effectiveness of the depyrogenation cycle shall be verified and documented initially and annually thereafter using endotoxin challenge vials to demonstrate the cycle is capable of achieving a 3-log reduction or more in endotoxins;

(v) The effectiveness of the depyrogenation cycle shall be re-established for any changes to the depyrogenation cycle; and

(vi) Items that are not thermostable shall be depyrogenated by rinsing with sterile, non-pyrogenic water, and thoroughly drained or dried immediately before use in compounding.

(g) Sterilization by filtration shall meet the following requirements:

(i) Sterilizing filters shall be sterile, depyrogenated, have a nominal pore size for 0.22 microns or small, and include labeling for pharmaceutical use;

(ii) Sterilizing filters labeled "for laboratory use only" shall not be used for compounding CSPs;

(iii) Sterilizing filters shall be certified by the manufacturer to retain at least 10^7 microorganisms of a stain of *Bredundimonas diminuta* per square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be filtered;

(iv) The designated person(s) shall use available published information, supplier documentation, or direct challenge to ensure sterilizing filters:

(A) Are chemically and physical compatible with all ingredients in the CSP;

(B) Are chemically stable at the pressure and temperature conditions that will be used; and

(C) Have enough capacity to filter the required volumes.

(v) Pharmacy staff shall integrity test filters used to sterilize a CSP according to the manufacturer's recommendations. If multiple filters are required for the compounding process, each filter shall pass a filter-integrity test;

(vi) CSPs prepared using a filter that fails an integrity tests shall be discarded, or, after investigating the cause of the failure and selection of an appropriate filter, re-filtered for sterilization no more than one additional time; and

(vii) Pharmacy staff shall pre-filter a CSP when it is known to contain excessive particulate matter, performed using a filter of larger nominal pore size to remove gross particulate contaminants before the CSP is passed through the sterilizing-grade filter.

(h) Sterilization be steam heat shall meet the following requirements:

(i) All materials shall be directly exposed to steam under adequate pressure for the length of time necessary, as determined by use of appropriate biological indicators, to render the items sterile;

(ii) The duration of the exposure period shall include sufficient time for the entire contents of the CSP and other items to reach sterilizing temperature;

(iii) Items shall remain at the sterilizing temperature for the duration of the sterilization period;

(iv) CSPs shall be placed in the autoclave to allow steam to reach the CSPs without entrapment of air;

(v) Prior to filling ampules and vials that will be steam sterilized, solutions shall be passed through a filter with a nominal pore size no larger than 1.2 microns for removal of particulate matter;

(vi) Sealed containers shall be able to generate steam internals. Stoppered and crimped vials shall contain a small amount of sterile water to generate steam;

(vii) Deep containers shall be inverted or placed on their sides at a downward-sloping angle to minimize air entrapment, and to facilitate condensate drainage, or shall shave a small amount of sterile water placed in them before steam sterilization;

(viii) Porous materials and items with occluded pathways shall only be sterilized by steam if the autoclave chamber has suitable cycles for dry goods;

(ix) The effectiveness of steam sterilization shall be verified with each sterilization run or load by using appropriate biological and physiochemical indicators and integrators. Verification shall be documented;

(x) The steam supplied shall be free of contaminants and generated using water per the manufacturer’s recommendation.

(xi) A calibrated data recorder or chart shall be used to monitor each cycle and identify cycle irregularities; and

(xii) The date, run, and load numbers of the steam sterilizer used to sterilize a CSP shall be documented.

(i) Sterilization by dry hear shall meet the following requirements:

(i) The duration of the exposure period shall include sufficient time for the entire contents of the CSPs and other items to reach the sterilizing temperature;

(ii) The CSP and other items shall remain at the sterilizing temperature for the duration of the sterilization period;

(iii) The effectiveness of the dry hear method shall be verified and documented with each sterilization run or load, using appropriate biological indicators and confirmation methods;

(iv) The dry heat oven shall be calibrated. Calibration shall be documented;

(v) A calibrated data recorder or chart shall be used to monitor each cycle and identify cycle irregularities; and

(vi) The date, run, and load numbers of the dry heat oven used to sterilize a CSP shall be documented.

Section 15. Release Inspections and Testing.

(a) Pharmacy staff shall visually inspect all CSPs at the completion of compounding, before release and dispensing to:

(i) Determine whether the physical appearance of the CSP is as expected;

(ii) Confirm the CSP and its labeling match the prescription or medication order; and

(iii) Ensure the integrity of the container-closure system.

(b) Pharmacy staff shall visually inspect a CSP immediately before it is released or dispensed; if not released or dispensed on the day of preparation.

(c) CSPs with observed defects shall be discarded or marked and segregated from acceptable CSPs in a manner that prevents them from being released or dispensed.

Section 16. Hazardous Drugs as CSPs.

(a) Hazardous drugs shall be prepared for administration only under conditions that protect personnel in the preparation and storage areas.

(b) Pharmacy staff shall store hazardous drugs separately from other inventory, in a manner to prevent contamination and personnel exposure.

(c) Pharmacy staff shall handle hazardous drugs with caution at all times using appropriate chemotherapy gloves during receiving, distributions, stocking, inventorying, preparation for administration, and disposal.

(d) Hazardous drugs shall be prepared in a BSC or CACI with ISO Class 5 or better air quality.

(e) CSTDs shall be used when the compounding process allows.

(f) A hazardous drug buffer room shall maintain a minimum differential negative pressure of 0.01-inch water column between the buffer room and the ante-room.

(g) The pharmacy shall limit access to areas where hazardous drugs are stored and prepared to protect persons not involved in drug preparation.

(h) Compounding pharmacy staff shall wear PPE when compounding in a BSC or CACI and when using CSTDs.

(i) PPE shall include gowns, face masks, eye protections, hair covers, shoe covers or dedicated shows, and double gloving with sterile chemo-type gloves.

(i) All pharmacy staff who handle or compound hazardous drugs shall be fully trained in the storage, handling, and disposal of hazardous drugs.

(i) Training shall occur prior to preparing or handling hazardous CSPs;

(ii) Training shall be documented for each person, at least annually; and

(iii) Training shall include, but is not limited to the following:

(A) Didactic overview of hazardous drugs in the pharmacy, including mutagenic, teratogenic, and carcinogenic properties;

(B) Ongoing training for each new hazardous drug in the pharmacy;

(C) Pharmacy staff of reproductive capability shall confirm, in writing, that they understand the risks of handling hazardous drugs;

(D) Safe aseptic manipulation practices;

(E) Negative pressure techniques when utilizing a BSC or CACI;

(F) Correct use of CSTDs;

(G) Containment, cleanup, and disposal procedures for breakages and spills; and

(H) Treatment of pharmacy staff in the event of contact and inhalation exposure.

(j) Pharmacy staff shall comply with applicable state and federal regulations when disposing of hazardous drugs.

(k) While preparing hazardous drugs for emergency use, pharmacy staff may compound the hazardous drug outside of a PEC, so long as a CSTD and PPE for hazardous drug compounding are used.

Section 17. Radiopharmaceuticals as CSPs.

(a) Radiopharmaceuticals compounded from sterile components in closed, sterile containers, and with a volume of 100 mL or less for a single-dose injection, or no more than 30 mL taken from a multiple-dose container, are considered low-risk level CSPs and shall comply with the requirements in this Chapter.

(b) Radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes, in a properly functioning and certified PEC, located in an ISO Class 8 or cleaner SEC.

(c) Radiopharmaceuticals vials designed for multi-use, compounded with technetium-99m, exposed to ISO Class 5 environments and punctured by needles with no direct

contact contamination, may be used up to the time indicated by the manufacturer's recommendations.

(d) Technetium-99m/molybdenum-99 generator systems shall be stored and operated under conditions recommended by manufacturers, and applicable state and federal regulations.

(i) Generator systems shall be eluted in an ISO Class 8 or cleaner air environment, to permit special handling, shielding, and air flow requirements.

(e) Direct visual inspection of radiopharmaceutical CSPs containing high concentrations of doses of radioactivity, shall be conducted to limit acute and chronic radiation exposure to a level that is as low as reasonably achievable (ALARA).

(f) A sterile compounding pharmacy with a SCA may compound radiopharmaceutical CSPs as low-risk level CSPs and shall not assign a BUD greater than twelve (12) hours at controlled room temperature, or twenty-four (24) hours at refrigerated temperature.