

DRAFT TEXT of Chapter Phar 15

[NOTE: There are some areas which may not be contained in this draft due to my needing more input in order to address in the rule.]

15.01 Definitions. In this chapter:

- (1) Active pharmaceutical ingredient (API) means any substance or mixture of substances intended to be used in the compounding of a drug preparation and that, when used in the compounding of a drug preparation, becomes an active ingredient in the preparation intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease in humans and animals or affecting the structure and function of the body.
- (2) Added substances means ingredients that are necessary to compound a drug preparation that are not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation.
- (3) Beyond Use Date (BUD) means the date after which a non-sterile compounded preparation shall not be used, or the date or date and time after which a sterile compounded preparation shall not be ~~stored or transported~~used.
- (4) Component means any, active pharmaceutical ingredient, or added substances used in the compounding of a drug preparation.
- (5) Compounding means the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug delivery device, or a device in accordance with a prescription, medication order or initiative. Compounding includes any of the following:
 - (a) Preparation of drug dosage forms for both human and animal patients.
 - (b) Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.
 - (c) Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients. Notwithstanding this paragraph, the reconstitution or mixing that is performed pursuant to the directions contained in approved labeling provided by the manufacturer of a commercially available product is not compounding.
 - (d) Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching or chemical analysis.
 - (e) Docking and activation of proprietary bag and vial systems for future activation and administration.
- (6) Controlled room temperature means a temperature maintained thermostatically that encompasses the usual and customary working environment of 68 degrees to 77 degrees Fahrenheit.
- (7) Freezer means a place in which a the temperature is maintained between -11 degrees and 14 degrees Fahrenheit
- (8) Refrigerator means a cold place in which the temperature is maintained between 36 degrees and 46 degrees Fahrenheit
- (9) Stability means the extent to which a compounded preparation retains, within specified limits and throughout its period of storage and use, the same properties and characteristics ~~that it possessed at the time of compounding~~within specified limits throughout its BUD.
 - (a) Chemical stability means each active pharmaceutical ingredient retains its chemical integrity and labeled potency without causing harmful impurities, within specified limits.

Comment [SK1]: If chapter is intended to address hazardous compounding then USP Chapter <800> draft should be reviewed for inclusion

Comment [SK2]: Revision of 797 says that reconstitution of a drug product according to manufacturer's directions just prior to administration is NOT compounding

Comment [SK3]: Revision of 797 now defines temperature requirement as 20 degrees C or less

- (b) Physical stability means the original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
- (c) Microbiological stability means sterility or resistance to microbial growth is retained according to specified requirements and antimicrobial agents that are present retain effectiveness within specified limits.
- (d) Therapeutic stability means the therapeutic effect remains unchanged.
- (e) Toxicological stability means no significant increase in toxicity occurs.

SUBCHAPTER I – General

15.10 Facilities. A pharmacist engaged in compounding shall ensure all of the following:

- (1) An area designated for compounding.
- (2) Orderly placement of compounding equipment, materials, and components in order to minimize the potential for compounding errors.
- (3) The compounding area is well-lighted.
- (4) The compounding area is maintained in a clean and sanitary condition.
- (5) The compounding area is easily accessible to all of the following:
 - (a) Hot and cold running water, exclusive of the bathroom sink.
 - (b) Soap or detergent.
 - (c) Single-use towels.
- (6) All compounding equipment, materials and components shall be stored off the floor and in a manner to prevent contamination and permit inspection and cleaning of the compounding and storage areas

15.11 Equipment and Drug Preparation Containers.

- (1) A pharmacy shall possess equipment and drug preparation containers or packaging appropriate to the type of compounding performed at the pharmacy.
- (2) Equipment and drug preparation containers or packaging used in compounding shall be of appropriate design and capacity, and shall be suitably stored in a manner to facilitate use, cleaning, maintenance, and protect it from contamination.
- (3) Equipment and drug preparation containers/packaging used in compounding drug products shall be of suitable composition. Equipment surfaces that contact components may not be reactive, additive or adsorptive so as to alter the stability of the compounded preparation.
- (4) Equipment used in compounding shall be thoroughly cleaned and sanitized after each use, and when necessary, prior to use, according to written policies and procedures, in order to reduce bioburden and reduce the opportunity for cross-contamination.
- (5) All equipment utilized in compounding preparations shall be inspected, maintained, calibrated and validated at appropriate intervals, consistent with manufacturer's recommendations, to ensure the accuracy and reliability of equipment performance. Records shall be kept indicating the equipment was inspected, maintained, calibrated and validated.

15.12 Records. The managing pharmacist shall ensure written or electronic compounding documentation to systematically trace, evaluate, and replicate the compounding steps throughout the process of a preparation. The compounding documentation shall be maintained for a period of 5 years after the date of the last refill. The compounding documentation shall include all of the following:

(1) Master Formulation Record including all of the following:

- (a) Official or assigned name, strength, and dosage form of the preparation.
- (b) Calculations needed to determine and verify quantities of components and doses of active pharmaceutical ingredients.
- (c) Description of all ingredients and their quantities.
- (d) Compatibility and stability information, including references or laboratory testing
- (e) Equipment needed to prepare the preparation.
- (f) Mixing instructions including all of the following:
 1. Order of mixing.
 2. Mixing temperatures or other environmental controls.
 3. Duration of mixing.
 4. Other factors pertinent to the replication of the preparation as compounded.
- (g) Sample labeling information, including all of the following:
 1. Name and quantity or concentration of each active ingredient.
 2. Assigned BUD.
 3. Storage conditions.
 4. Prescription or control number.
- (h) Container used in dispensing.
- (i) Packaging and storage requirements.
- (j) Description of final preparation.
- (k) Quality control procedures, if applicable, and expected results.

(2) Compounding Record including all of the following:

- (a) Official or assigned name, strength, and dosage of the preparation.
- (b) Master Formulation Record reference for the preparation.
- (c) Names and quantities of all components.
- (d) Sources, lot numbers and expiration dates of all components.
- (e) Total quantity compounded.
- (f) Name of the person who prepared the preparation.
- (g) Name of the person who performed the quality control procedures.
- (h) Name of the person who approved the preparation.
- (i) Date of preparation.
- (j) Assigned control or prescription number.
- (k) Assigned BUD.
- (L) Copy of the label to dispense final product.
- (m) Description of the final preparation.
- (n) Results of quality control procedures.
- (o) Documentation of any quality control issues and any adverse reactions or preparation problems reported by the patient or caregiver.

Comment [ALD4]: Suggest creating two separate master formulation record / compounding records for non-sterile and sterile compounding. 797 updates specify what needs to be in compounding record. Should only be necessary for CSPs if batch preparation is undertaken in anticipation of use (not pursuant to prescription)

Comment [ALD5]: This doesn't happen with IV products. Allow compounding record to be master formulation record.

Comment [ALD6]: Add allowance to use compounding record as master formulation record.

15.13 Quality control.

(1) The pharmacist shall do a final check and review each procedure in the compounding process. A final check shall include verification of all the following:

- (a) The master formulation record, compounding record and written procedures were followed in the execution of the compounding process. Any deviation in procedures shall be documented.
- (b) There was a check and recheck of each procedure at each stage of the process.

(c) The tests or examinations conducted on the compounded preparation to ensure their uniformity and integrity followed established written procedures.

(d) The performance of compounding processes and equipment that may be responsible for causing variability in the final compounded preparations.

(2) The pharmacist shall observe the finished preparation to ensure that it appears as expected.

(3) The pharmacist shall investigate any discrepancies and take appropriate corrective action before the prescription is dispensed to the patient.

~~(4) The pharmacist completing the final check is solely responsible for the finished preparation.~~

Comment [ALD7]: Not necessary. Several RPH's may be involved with the process, including the PIC

15.14 Training. All personnel involved in the compounding, evaluation, packaging, and dispensing of compounded preparations shall be properly trained and competency is assessed for the type of compounding conducted. It is the responsibility of the managing pharmacist to ensure and document all training and competency assessments.

Comment [ALD8]: New version of 797 will be prescriptive wrt: assessments. For non-sterile, add a timeframe

SUBCHAPTER II – Non-sterile Compounding

Comment [ALD9]: Seems to be missing components

15.20 Definitions. In this subchapter:

(1) Office use means (1) Office use means a preparation that is provided directly to a prescriber for patient use during an in office procedure. There is no patient name associated with this preparation, only LOT# and Exp Date.

a. The pharmacist shall record the lot numbers and exp dates of all preparation provided to each individual prescriber.

b. The prescriber shall record the lot number and exp date of all preparations used in the treatment of their patients and provide that documentation to the compounding pharmacists on a quarterly basis.

c. There shall be a recall procedure established that would allow for all medication to be recalled in a timely manner from all prescribers.

d. It is prohibited for these preparations to be sold by prescribers or given to patients for at home use or post procedure care.

Comment [ALD10]: Label should say “not for resale” or “for in office use only” Otherwise this is not enforceable.

15.21 Component Selection.

(1) A pharmacist shall use components manufactured in a FDA registered facility. If a component is unavailable from a FDA registered facility, the pharmacist may utilize a component that has been tested by a FDA approved vendor and the component has been determined to be pure and safe documented by a Certificate of Analysis.

Comment [ALD11]: Clarify, is this a testing facility?

(2) Components with an expiration date from the manufacturer or distributor may be used before the expiration date provided all of the following:

(a) The component is stored in its original container under conditions to avoid decomposition

(b) There is minimal exposure of the remaining component each time component is withdrawn from the container.

(c) When any withdrawals from the container are performed by those trained in the proper handling of the component.

(3) Components without an expiration date assigned by the manufacturer or supplier, shall be labeled with the date of receipt and assigned a conservative expiration date, not to exceed three years after receipt, based upon the nature of the component and its degradation mechanism, the container in which it is packaged and the storage conditions.

(4) Components transferred to another container which shall provide integrity that is minimally equivalent to the original container and shall be identified with all of the following:

(a) Component name.

(b) Original supplier.

(c) Lot or control number.

(d) Transfer date.

(e) Expiration date.

(5) Manufactured drug products utilized as the source of active pharmaceutical ingredients shall be manufactured in an FDA registered facility and the manufacturer's product container shall be labeled with a lot number and expiration date.

(6) A pharmacist compounding for human use may not use components that have been withdrawn or removed from the market for safety or efficacy reasons by the FDA. A pharmacist compounding for food producing animal use may not use components prohibited for use in food producing animals.

15.221 Assigning BUD.

(1) The BUD shall not be later than the expiration date on the container of any component.

(2) In the absence of stability information that is applicable to a specific drug product and preparation, the maximum BUD for a non-sterile compounded drug preparation that is packaged in a tight, light-resistant container as follows:

(a) For nonaqueous formulations stored at controlled room temperature, the BUD shall not be later than the time remaining until the earliest expiration date of any active pharmaceutical ingredient or 6 months, whichever is earlier.

(b) For water-containing oral formulations, the BUD shall not be later than 14 days when stored at in a refrigerator

(c) For water-containing semisolid, mucosal liquid, topical or dermal formulations, stored at controlled room temperature, the BUD shall not be later than 30 days.

(3) Assignment of BUD shall include an assessment of the need for antimicrobial agents and or storage in a refrigerator to protect against bacteria, yeast, and mold contamination introduced during or after the compounding process.

SUBCHAPTER III – Sterile Compounding

15.30 Definitions. In this subchapter:

(1) Ante area means an ISO class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, **CSP handling**, labeling and other high particulate generating activities are performed. The ante area is also a transition area that

provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas and reduces the need for the heating, ventilating, and air-conditioning control system to respond to large disturbances.

(2) Buffer area means an area that must provide at least ISO Class 7 air quality where the primary engineering control(s) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding compounded sterile preparations.

(3) CACI means compounding aseptic containment isolator. A form of isolator designed to provide worker protection from exposure to undesirable levels of airborne hazardous drugs throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment may not occur unless the air is first passed through a microbial retentive filter system capable of containing airborne concentrations of the physical size and state of the drug being compounded.

(4) CAI means compounding aseptic isolator. A form of isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer process. Air exchanges into the isolator from the surrounding environment may not occur unless the air has first passed through a microbially retentive filter.

(5) Cleanroom means a room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness (ISO) class. Microorganisms in the environment are monitored so that microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class. A cleanroom includes a buffer area or room and an ante area or room.

(6) Compounded sterile preparation means the aseptic processing in a clean air environment of any pharmaceutical preparations that are required to be sterile when they are administered into patient body cavities, central nervous and vascular systems, eyes, and joints and when used as baths for live organs and tissues, including injections, aqueous bronchial and nasal inhalations, irrigations for wounds and body cavities, ophthalmic drops and ointments and tissue implants

(7) High risk level compounded sterile preparations means preparations compounded from non-sterile ingredients or from ingredients that are incorporated using non-sterile equipment before terminal sterilization, or from commercially manufactured sterile products that lack effective antimicrobial preservatives and whose preparation, transfer, sterilization, and packaging is performed in air quality worse than ISO class 5 for more than one hour. Water-containing preparations that are stored for more than six hours before terminal sterilization are also classified as high risk level compounded sterile preparations. Category 2 compounded sterile products are those that may be assigned a beyond use date of greater than 12 hours at room temperature or greater than 24 hours if refrigerated if made in accordance with all standards found in this chapter. Endotoxin testing is required if the compounded sterile product is prepared

Comment [SK12]: Revision of 797 now calls these RABS and distinguishes between CAI and CACI and isolators.

Revision of 797 also now includes definition of a BSC

Comment [SK13]: No longer defined in 797 revision. Consider adding a definition of a segregated compounding area

from nonsterile ingredient(s) and sterility testing may be required depending on the beyond use date assigned and the addition of a preservative.

(8) ~~Immediate-Urgent~~ use compounded sterile preparations means preparations intended for emergency patient care for a single patient (i.e. cardiopulmonary resuscitation) and involve only simple aseptic measuring and transfer manipulations of no more than three sterile non-hazardous commercial drug and diagnostic radiopharmaceutical drug products, including an infusion or diluent solution and preparation under appropriate conditions defined in this chapter would subject the patient to additional risk due to delays in therapy. -

(9) ISO class 5 air quality conditions means conditions in which the air particle count is no greater than a total of 3,520 particles of 0.5 micrometers and larger per cubic meter of air that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air.

(10) ISO class 7 air quality conditions means conditions in which the air particle count is no greater than a total of 352,000 particles of 0.5 micrometers and larger per cubic meter of air that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air.

(11) ISO class 8 air quality conditions means conditions in which the air particle count is no greater than a total of 3,520,000 particles of 0.5 micrometers and larger per cubic meter of air that is supplied by high-efficiency particulate air (HEPA) or HEPA-filtered air.

~~(12) Low risk level compounded sterile preparations means preparations compounded with aseptic manipulations entirely within ISO class 5 or better air quality using only sterile ingredients, products, components, and devices. The compounding process involves only assembling, transferring, measuring, and mixing, using no more than three commercially manufactured sterile products, and not more than two entries into one sterile container or package to make the compounded sterile preparations. The compounding process is limited to aseptically opening ampules, penetrating sterile 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. Category 1 compounded sterile products are those assigned a maximum beyond use date of 12 hours or less at controlled room temperature or 24 hours or less if refrigerated if made in accordance with all standards defined in this chapter.~~

~~(13) Medium risk level compounded sterile preparations means preparations compounded under low risk level conditions but which require multiple individual or small doses of sterile products to be combined or pooled to prepare compounded sterile preparations that will be administered either to multiple patients or to one patient on multiple occasions. The compounding process includes complex aseptic manipulations other than single volume transfer, and requires and unusually long duration, such as that required to complete dissolution or homogeneous mixing.~~

(14) Stability means the extent to which a preparation retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding.

15.31 General. All personnel who compound sterile preparation shall be responsible for understanding the fundamental practices and precautions, for developing and implementing appropriate procedures and for continually evaluating the procedures and the quality of the final compounded sterile preparation. These individuals must undergo annual refresher training and requalification in appropriate sterile compounding standards and practices. Training qualification and requalification must be documented.

Comment [SK14]: Revision of 797 provides a great deal of detail regarding training requirements

Written training programs must be developed that describe the required training, the frequency of training, and the process for evaluating the performance of individuals involved in sterile compounding. In addition, compounding activities of personnel should be observed by a supervisor on a daily basis and immediate corrective action taken if deficient practices are observed.

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15.32 Responsibility of compounding personnel. The managing pharmacist is responsible for ensuring that compounded sterile preparations are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed. The responsibilities include maintaining appropriate cleanliness conditions and providing labeling and supplementary instructions for the proper clinical administration of compounded sterile preparations.

15.33 Facility Design and Environmental Controls. (1) CLEANROOM. A cleanroom shall be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites. Critical sites are locations that include any component or fluid pathway surfaces, openings, exposed and at risk of direct contact with air, moisture or touch contamination. A cleanroom shall include a buffer area and an ante area. The buffer area shall contain an ISO class 5 or better primary engineering control unless the buffer area has ISO class 5 or better air quality. A cleanroom shall be all of the following:

Comment [SK15]: Cleanroom is not defined in revision of 797

- (a) Accessible only to designated personnel.
- (b) Used only for the compounding of sterile preparations or other tasks that require a cleanroom.
- (c) Structurally isolated from other areas within the pharmacy by means of restricted entry or access.
- (d) Maintained at a temperature of 59 to 77 degrees Fahrenheit 20 degrees Centigrade or cooler
- (e) Maintained at a humidity below 60%.
- (g) Maintained free of chewing gum, drinks, candy or food items.

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- (2) **CLEANROOM REQUIREMENTS.** A cleanroom shall meet all of the following:
- (a) The surfaces of ceilings, walls, floors, fixtures, shelving, counters and cabinets in the cleanroom shall be smooth, impervious, free from cracks and crevices and nonshedding, thereby minimizing spaces in which microorganisms and other contaminants may accumulate.
 - (b) Work surfaces shall be constructed of smooth, impervious materials so that the work surfaces may be readily cleaned and sanitized. All work surfaces shall be resistant to damage from cleaning and sanitizing agents.

Comment [SK16]: Revision of 797 now has these requirements for a classified area or a segregated compounding area

(c) Junctures where ceilings meet walls shall be covered, caulked, or sealed to avoid cracks and crevices in which microorganisms and other contaminants can accumulate. All areas in ceilings and walls where the surface has been penetrated shall be sealed.

(d) Ceilings that consist of inlaid panels shall be impregnated with a polymer to render them impervious and hydrophobic and shall ~~either be caulked or weighted and clipped sealed.~~

(e) Walls shall be constructed of ~~flexible durable~~ material, panels locked together and sealed or of epoxy-coated gypsum board.

(f) Floors shall have a covering that shall be seamless or have ~~the~~ heat-welded seams and coving to the sidewall. There shall be no floor drains.

(g) There shall be no dust –collection overhangs and ledges should be avoided. ~~All sprinkler heads shall be flush with the ceiling.~~

(h) Ceiling lighting fixtures shall have exterior lens surfaces which are smooth, mounted flush and ~~air tight sealed.~~

(i) Carts shall be of stainless steel wire, nonporous plastic or sheet metal construction with good quality, cleanable casters to promote mobility.

(j) Refrigerators shall be within, or reasonably accessible to, the cleanroom in order to ensure the integrity of compounded sterile preparations.

(3) ANTE AREA REQUIREMENTS. The ante area shall meet all of the following:

(a) Appropriate environmental control devices capable of maintaining ISO class 8 air quality conditions ~~for non-hazardous drug compounding activities and ISO class 7 air quality conditions for hazardous drug compounding activities.~~

(b) Contain all of the following equipment:

1. A sink with hot and cold running water with an integrated and closed plumbing system.

2. ~~Waste containers for all personal protective equipment.~~

3. ~~An eyewash station.~~

4. ~~A hazardous waste spill kit.~~

(4) BUFFER AREA REQUIREMENTS. The buffer area shall meet all of the following:

(a) The buffer area shall have appropriate environment control devices capable of maintaining ISO class 7 air quality conditions during normal activity.

(b) The buffer area shall contain only the following:

1. Items, including furniture, equipment, and supplies, that are required for the tasks to be performed in the buffer area.

2. Items that are nonpermeable, nonshedding, cleanable, and resistant to disinfectants.

3. Items that have been cleaned and disinfected immediately prior to their being placed in the buffer area.

(c) Equipment and other items used in the buffer area shall not be taken from these areas except for calibration, servicing, or other activities associated with the proper maintenance of the item.

(d) The buffer area shall be kept clean and arranged in an orderly fashion. All required equipment shall be maintained in good operating condition.

(e) The buffer area shall not be used for bulk storage, warehousing or clerical functions.

(f) The buffer area shall not contain any sinks.

Comment [SK17]: This is not a requirement in 797.

Comment [SK18]: No drug compounding activities can occur in an ante area

Comment [SK19]: Not mentioned in 797. An eyewash station does not need to be here and a hazardous waste spill kit only needs to be accessible in negative pressure areas where hazardous drug compounding takes place

(g) The buffer area shall be a minimum of 100 square feet in size and shall be compatible with the volume of compounding being conducted.

(h) The buffer area shall contain waste containers in compliance with Occupational Safety and Health Administration standards for disposal of used needles and syringes and for disposal of chemotherapy waste.

Comment [ALD20]: There doesn't need to be a specific size listed

Comment [ALD21]: Standards for pharmacy are DNR based, not OSHA.

(5) USE OF ~~CAI AND CACI LOCATED OUTSIDE OF A CLEANROOM.~~ PEC IN A SEGREGATED COMPOUNDING AREA

A pharmacy may utilize a ~~a CAI or CACI not located in a cleanroom~~ PEC in a segregated compounding area to prepare compounded sterile preparations, provided all of the following:

(a) ~~The CAI or CACI can provide isolation from the room and maintain ISO class 5 air quality during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of compounded sterile preparations. Particle counts sampled approximate 6 to 12 inches upstream of the critical exposure site must maintain ISO class 5 air quality levels during compounding operations. Only Category 1 CSPs are compounded~~

(b) ~~Compounding personnel shall obtain documentation from the manufacturer that the CAI or CACI will meet this standard when located in worse than ISO class 7 environments~~ The segregated compounding area is located away from unsealed windows, doors that connect to the outdoors, and significant traffic flow.

(c) ~~A CAI or CACI not located in a buffer area shall be located in an area that is maintained under sanitary conditions and such area shall only be traveled by persons engaging in the compounding of sterile preparations. The PEC must be located so as to avoid conditions that could adversely affect its operation.~~

15.34 Personnel cleansing and garbing requirements. (1) All personnel who engage in compounding sterile preparations shall comply with all of the following requirements before entering the buffer area:

(a) Remove personal outer garments, all cosmetics, makeup, visible jewelry and piercings, ear buds, headphones, and cell phones.

(b) The wearing of artificial nails or extenders is prohibited while working in the compounding area. Natural nails shall be kept neat and trimmed.

(c) Personnel protective equipment shall be put on in the following order:

1. ~~Dedicated shoes or s~~ Shoe covers.
2. Head and facial hair covers.
3. Face masks.
4. Eye shields, if required due to working with irritants or hazardous drugs.

(d) A hand and forearm cleansing procedure shall be performed. Personnel shall remove debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing for at least 30 seconds. Hands and forearms to the elbows shall be completely dried using either lint-free disposable towels or wipers ~~towels or an electronic hand dryer~~.

(e) Personnel shall wear non-shedding gowns with sleeves that fit snugly around the wrists and enclosed at the neck that are designed for buffer area use. If gowns are not sterile, sterile sleeves must be donned if compounding a Category 2 CSP in a laminar airflow system or biological safety cabinet.

Comment [ALD22]: Nail polish is also prohibited

- (2) Following the completion of all the steps in sub. (1) and once inside the buffer area, personnel shall perform antiseptic hand cleansing, using a waterless alcohol based ~~surgical~~ hand ~~rub~~ ~~serub~~-with persistent activity following manufacturer's ~~recommendations~~instructions on application. Once hands are dried thoroughly, personnel shall don sterile, powder-free gloves. Gloves shall be routinely inspected for holes, punctures, or tears and shall be replaced immediately if any are detected.
- (3) Gloves become contaminated when they make contact with non-sterile surfaces during compounding activities. Disinfection of contaminated gloved hands ~~may~~must be accomplished by ~~wiping or~~ rubbing sterile 70% isopropyl alcohol on all contact surface areas of the gloves and letting the gloved hands dry thoroughly. Routine application of sterile 70% isopropyl alcohol shall occur throughout the compounding process and whenever non-sterile surfaces, including vials, counter tops, chairs and carts, are touched.
- (4) When compounding personnel exit the cleanroom during a work shift, the exterior nonsterile gown may be removed and retained in the cleanroom if not visibly soiled and may be re put on during that same work shift only. Sterile gowns or sleeves must be discarded. Shoe covers, hair and facial hair covers, face masks, ~~eye shields~~ and gloves shall be replaced with new ones before re-entering the buffer area and proper hand hygiene shall be performed. Goggles must be sterilized or disinfected with 79% isopropyl alcohol before each use.

15.35 Cleaning and Disinfecting the Compounding Area. (1) Compounding personnel are responsible determining the cleaning and disinfecting products to be used and for ensuring that the frequency of cleaning and disinfecting compounding area is done in accordance with the following frequency:

- (a) ISO Class 5 primary engineering control at the beginning of each shift or before each batch, but not longer than 30 minutes following the previous surface disinfection when ongoing compounding activities are occurring: after spills; and when surface contamination is known or suspected- Additionally, surfaces in the PEC in direct contact with materials used in compounding must be cleaned before starting each batch.
- (b) Counters and easily cleanable work surfaces daily.
- (c) Floors daily.
- (d) Walls, ceilings and storage shelving monthly.

(2) All cleaning and disinfecting practices and policies for the compounding of compounding sterile preparations shall be included in written standard operating procedures and shall be followed by all compounding personnel.

(3) ~~Disinfecting sterile compounding areas shall occur on a regular basis at the intervals in sub. (1) or when any of the following occurs:~~

- ~~—— (a) Spills occur.~~
- ~~—— (b) The surface is visibly soiled.~~
- ~~—— (c) Microbial contamination is known to have been or is suspected of having been introduced into the compounding area.~~

(4) Visibly soiled areas in PEC ~~Cleaning, using a germicidal detergent, and disinfecting~~ shall occur before compounding is performed. Items shall be removed from all areas to be cleaned, and surfaces shall be cleaned by removing loose material and residue from spills, using sterile water for irrigation or injection- This shall be followed by wiping with sterile 70% isopropyl alcohol, which is allowed to dry before compounding begins.

Comment [SK23]: Need to add information on cleaning an isolator

Comment [SK24]: But not an isolator as defined in revision of 797

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(5) Work surfaces in the ISO Class 7 buffer areas and ISO Class 8 ante areas as well as segregated compounding areas shall be cleaned and disinfected at least daily. Dust and debris shall be removed when necessary from storage sites for compounding ingredients and supplies using a method that does not degrade the ISO Class 7 or 8 air quality.

Comment [SK25]: This verbiage is almost identical to what is now in the 797 revision

(6) Floors in ~~the cleanroom, buffer area and ante area in all ISO-classified and segregated compounding areas~~ are cleaned by mopping with a ~~germicidal detergent~~ cleaning and disinfecting agent once daily at a time when no aseptic operations are in progress. Mopping shall be performed by trained personnel using approved agents and procedures.

Comment [ALD26]: Not sure where this comes from, dust and debris should not be there in the first place.

(7) In ~~the cleanroom, buffer area and ante area, all ISO-classified and segregated compounding areas~~, the walls, ceilings and shelving shall be cleaned and disinfected ~~with a germicidal detergent with consideration of compatibilities, effectiveness and inappropriate or toxic residues~~ monthly.

(8) All cleaning ~~materials~~ tools shall be ~~nonshedding sterile and low lint~~ and dedicated to use in the cleanroom, buffer area and ante area and shall not be removed from these areas except for disposal. ~~If cleaning materials, including mops, are reused, procedures shall be developed based on manufacturer recommendations, that ensure that the effectiveness of the cleaning device is maintained and that repeated use does not add to the bioburden of the area being cleaned~~ All cleaning tools must be cleaned and resterilized after each use. They must be discarded after an appropriate amount of time, to be determined by the condition of the materials.

(9) Supplies and equipment removed from shipping cartons shall be wiped with a suitable disinfecting agent delivered from a spray bottle or other suitable delivery method. After the disinfectant is sprayed or wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, during which time the item shall not be used for compounding purposes.

(10) Critical sites such as vial stoppers, ampul necks, and intravenous bag septums must be disinfected by ~~w~~Wiping with ~~small~~ sterile 70% isopropyl alcohol swabs or comparable method ~~for disinfecting entry points on bags and vials~~, allowing the isopropyl alcohol to dry before piercing stoppers with sterile needles and breaking necks of ampuls. The surface of the sterile 70% isopropyl alcohol swabs used for disinfecting entry points of sterile package and devices may not contact any other object before contacting the surface of the entry point. Particle generating material may not be used to disinfect the sterile entry points of packages and devices.

(11) When sterile supplies are received in sealed pouches designed to keep them sterile until opening, the sterile supplies may be removed from the covering pouches as the supplies are introduced into the ISO Class 5 primary engineering control without the need to disinfect the individual sterile supply items.

(12) No shipping or other external cartons may be taken into the buffer or clean area or segregated compounding area.

15.36 Accuracy.

Compounding procedures and sterilization methods used for preparations require planned testing, monitoring and documentation to demonstrate adherence to environmental quality requirements, personnel practices and procedures critical to achieving and maintaining sterility. Pharmacist verification of a preparation shall include visual inspection of labeling, physical integrity and expected appearance, including final fill amount.

15.37 ~~Immediate-Urgent~~ use compounded sterile preparations.

- (1) The compounding process shall occur continuously without delays or interruptions and does not exceed one hour, ~~unless required for the preparation,~~
- (2) ~~Immediate-Urgent~~ use compounded sterile preparations shall begin administration ~~immediately upon completion of preparation within one hour of preparation. If administration has not begun within 1 hour following the start of preparing the compounded sterile preparation, the compounded sterile preparation shall be promptly, properly and safely discarded.~~
- (3) ~~Unless immediately and completely administered by the person who prepared the compounded sterile preparation or immediate and complete administration is witnessed by the preparer, the compounded sterile preparation shall have a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the compounded sterile preparation and the exact 1 hour BUD and time.~~
- (4) ~~Immediate use compounded sterile preparations shall not be compounded and stored for anticipated needs and shall not be compounded as batch preparations.~~
- (5) ~~Aseptic technique must be followed during preparation and procedures must be in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other CSPs. At no time during the compounding process, nor prior to administration, are critical sites and ingredients of the compounded sterile preparation to be directly exposed to contact contamination, including human touch, cosmetic flakes or particulates, blood, human body substances and non-sterile inanimate sources.~~

15.38 Stability and Sterility.

- (1) ~~Unless the manufacturer's package indicates a different stability time,~~ the following dates and times for storage and initiation of administration of the compounded sterile preparations shall apply:
 - (a) For ~~low risk level~~ Category 1 compounded sterile preparations, one of the following:
 1. ~~Must be used within 12 hours or less when stored at controlled room temperature (20-25 degrees C) Administration shall begin within 48 hours when the preparation is stored at controlled room temperature.~~
 2. ~~Must be used within 25 hours or less when stored at refrigerator temperature (2-8 degrees C) Administration shall begin within 14 days when the preparation is stored in a refrigerator.~~
 3. ~~Administration shall begin within 45 days when the preparation is stored in a freezer.~~
 - (b) For ~~medium risk level~~ Category 2 compounded sterile preparations prepared only with sterile ingredients and with no preservative added and no sterility testing performed, one of the following:
 1. ~~Administration shall begin~~ Must be used within 30 hours 6 days or less when the preparation is stored at controlled room temperature.
 2. ~~Administration shall begin~~ Must be used within 9 days when the preparation is stored in a refrigerator.
 3. ~~Administration shall begin~~ Must be used within 45 days when the preparation is stored in a freezer.
 - (c) For high risk level Category 2 compounded sterile preparations prepared from one or more nonsterile components and not preservative added and no sterility testing performed, one of the following:

Comment [SK27]: Also need to add BUDS for Category 2 terminally sterilized CSPs with and without sterility testing and with and without preservative

1. ~~Administration shall begin~~ Must be used within ~~24 hours~~ 4 days when the preparation is stored at controlled room temperature.
2. ~~Administration shall begin~~ Must be used within ~~3-7~~ days when the preparation is stored in a refrigerator.
3. ~~Administration shall begin within~~ Must be used within 45 days when the preparation is stored in a freezer.

(d) For Category 2 compounded sterile preparations prepared with sterile ingredients and with a preservative added and no sterility testing performed:

1. Must be used within 28 days when the preparation is stored at controlled room temperature.
2. Must be used within 42 days when the preparation is stored in the refrigerator.
3. Must be used within 45 days if the preparation is stored in a freezer

(e) For Category 2 compounded sterile preparations prepared with sterile ingredients and with no preservative added and sterility testing performed:

1. Must be used within 28 days when the preparation is stored at controlled room temperature.
2. Must be used within 42 days when the preparation is stored in the refrigerator.
3. Must be used within 45 days if the preparation is stored in a freezer

(f) For Category 2 compounded sterile preparations prepared with sterile ingredients and with a preservative added sterility testing performed:

1. Must be used within 42 days when the preparation is stored at controlled room temperature.
2. Must be used within 42 days when the preparation is stored in the refrigerator.
3. Must be used within 45 days if the preparation is stored in a freezer

~~(2) The administration dates and times established in sub. (1) shall not be exceeded or extended for compounded sterile preparations without verifiable supporting valid scientific sterility and stability information that is directly applicable to the specific preparation or compound.~~

~~(3) A pharmacist shall determine the BUD for a compounded sterile preparation consistent with sub. (1) and (2) and assign an appropriate discard after date for the compounded sterile preparation. The discard after date shall appear on the label.~~

(4) Opened or needle-punctured single dose containers of sterile products used in the compounding of sterile preparations for immediate use in an institutional pharmacy shall be used within one hour if opened in worse than ISO Class 5 air quality and any remaining contents shall be discarded.

(5) Single dose vials used in the compounding of sterile preparations exposed to ISO Class 5 or cleaner air quality may be used up to 6 hours after initial puncture.

(6) Opened single dose ampules used in the compounding of sterile preparations may not be stored for any period of time.

(7) Opened or needle punctured multiple dose vials used in the compounding of sterile preparations shall be used within 28 days after initially entering the vial, unless otherwise specified by the manufacturer.

15.39 Sterilization ~~methods.~~

(1) Sterilization methods employed shall be based on experience and appropriate information sources.

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Comment [SK28]: This entire section will need to be rewritten to address in-use times as defined in revision of 797

Comment [SK29]: This section needs to be consistent with sterility testing <71>

- (2) Presterilization requirements for high risk preparations shall meet all of the following:
- (a) During all compounding activities that precede terminal sterilization, including weighing and mixing, compounding personnel shall be garbed and gloved in the same manner as when performing compounding in an ISO Class 5 environment. All presterilization procedures shall be completed in an ISO Class 8 or superior environment.
 - (b) Immediately before use, all nonsterile measuring, mixing, and purifying devices used in the compounding process shall be thoroughly rinsed with sterile, pyrogen-free water and then thoroughly drained or dried.
- (3) High risk preparations shall be utilize one of the following sterilization methods:
- (a) Sterilization by filtration involves the passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent. This method shall meet all of the following:
 - 1. Sterile filters used to sterile filter preparations shall be pyrogen-free and have a nominal porosity of 0.22 microns. The filter dimensions and liquid material to be sterile filtered shall permit the sterilization process to be completed rapidly without the replacement of the filter during the filtering process.
 - 2. Compounding personnel shall ascertain that selected filters will achieve sterilization of the specific preparation.
 - 3. Sterilization by filtration shall be performed entirely within an ISO Class 5 or superior air quality environment.
 - (b) Terminal sterilization is the use of saturated steam under pressure or autoclaving. This method shall meet all of the following:
 - 1. All materials shall be exposed to steam at 250 degrees Fahrenheit under the recommended pressure and duration, verified by testing the sterility of the finished preparation.
 - 2. The description of steam sterilization conditions and duration for specific preparations shall be included in written documentation maintained in the compounding facility.
 - 3. Before or during entry into final containers, all high-risk preparations in solution form that are subjected to terminal steam sterilization shall pass through a filter with nominal porosity not larger than 1.2 microns for removal of particulate matter.
 - (c) Dry heat sterilization shall be completed in an oven designed for sterilization and shall be used only for those materials that cannot be sterilized by steam. The effectiveness of dry heat sterilization shall be verified using appropriate biological indicators and temperature sensing devices.
- (4) All high risk preparations, except those for inhalation and ophthalmic administration, that are prepared in groups of 25 or more identical single dose containers or in multiple dose vials for administration to multiple patients or that are exposed longer than 12 hours at 36 to 46 degrees Fahrenheit or longer than 6 hours at warmer than 46 degrees Fahrenheit before they are sterilized, shall be quarantined and tested to ensure that the preparations are sterile and that they do not contain excessive bacterial endotoxins before they are dispensed or administered.
- (5) If a preparation may be needed before the results of sterility testing have been received, the pharmacy shall daily observe the incubating test specimens and immediately recall the dispensed preparations when there is any evidence of microbial growth in the test specimens. The patient

and the physician of the patient to whom a potentially contaminated compounded sterile preparation was administered shall be notified immediately of the potential risk.

15.40 Quality Assurance. The pharmacy's quality assurance program must at a minimum address personnel qualifications and training, component selection and handling, design and maintenance of the building, facility and equipment, the compounding process and the final CSP release, shall meet all the following requirements:

- ~~(1) The pharmacist shall use adequate labeling and verbal or written instructions regarding proper storage and administration as set forth by the product manufacturer with each compounded sterile preparation dispensed.~~
- ~~(2) Encompasses all phases of sterile compounding for each unique type of compounded sterile preparation dispensed.~~
- ~~(3) After the preparation of every admixture, the contents of the container are thoroughly mixed and then visually inspected to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, or any other defects, and the accuracy and thoroughness of labeling.~~
- ~~(4) All pharmacists, pharmacy technicians, pharmacy interns, involved in compounding sterile preparations shall have their aseptic technique tested.~~
- ~~(5) All high risk level compounded sterile preparations that are prepared in groups of more than 25 identical individual single dose packages or in multiple dose vials for administration to multiple patients, or that are exposed longer than 12 hours at 35 degrees to 46 degrees Fahrenheit and longer than 6 hours at warmer than 46 degrees Fahrenheit before they are sterilized and all compounded sterile preparations whose beyond use date has been exceeded, shall be tested to ensure that they are sterile before they are dispensed or administered. The USP membrane filtration method shall be used where feasible. Another method may be used if verification results demonstrate that the alternative is at least as effective and reliable as the membrane filtration method or the USP direct inoculation of the culture medium method.~~
- ~~(6) When high risk level compounded sterile preparations are dispensed before receiving the results of the sterility tests, the written quality assurance procedures shall require daily observation of the incubating test specimens an immediate recall of the dispensed compounded sterile preparations when there is any evidence of microbial growth in the test specimens. The patient and the physician of the patient to whom a potentially contaminated compounded sterile preparation was administered shall be notified immediately of the potential risk. Positive sterility tests shall require rapid and systematic investigation of aseptic technique, environmental control and other sterility assurance controls in order to identify sources of contamination and to take corrective action.~~
- ~~(7) All high risk level compounded sterile preparations, except those for inhalation and ophthalmic administration, shall be tested to ensure that they do not contain excessive bacterial endotoxins.~~
- ~~(8) Air and surface sampling for microbial organisms in ISO class 5 primary engineering controls, including laminar airflow workbenches, CAI, CACI and biological safety cabinets, and in all other ISO classified areas is done once every 6 months and at any time when microbial contamination is suspected.~~
- ~~(9) Laminar airflow workbenches, CAI, CACI and biological safety cabinets shall be certified every 6 months and every time they are moved, by an independent certification company to ensure that these primary engineering controls meet appropriate ISO classifications.~~

~~(10) A cleanroom shall be certified by an independent certification company every 6 months and whenever the room or a primary engineering control in the room is relocated or altered, or whenever major service to the facility is performed, to ensure that the cleanroom meets appropriate ISO classifications.~~

~~(11) Whenever test results indicate that the cleanroom or any primary engineering controls do not meet the standards established in this section, the pharmacy shall immediately cease using the cleanroom or primary engineering control that is out of compliance until such time that the cleanroom or the primary engineering control meets the requisite standards. Test results indicating non-compliance with the requisite standards shall require re-evaluation of all procedures associated with the production of compounded sterile preparations in the impacted cleanroom or primary engineering control and documentation with respect to the period of time that the cleanroom or primary engineering control was out of compliance.~~

~~(12) All certification records shall be reviewed by the managing pharmacist to ensure that the controlled environments comply with the proper air cleanliness, room pressures and air change per hour.~~

15.41 Training and evaluation. (1) GENERAL. ~~All personnel~~The managing pharmacist, all pharmacists, pharmacy technicians, pharmacy interns and pharmacy externs involved in the preparation and handling of compounded sterile preparations shall have didactic and practical training in sterile preparation compounding, including proper personnel cleaning and garbing, cleaning and disinfecting the sterile compounding areas, cleanroom technology, laminar flow technology, isolator technology, if applicable, and quality assurance techniques~~hand hygiene and garbing, cleaning and disinfection, measuring and mixing, aseptic manipulation, proper cleanroom behavior, methods of sterilization and dehydrogenation, if applicable, use of equipment, documentation of the compounding process, understanding the direction of the HEPA-filtered unidirectional airflow within the ISO Class 5 area, proper use of PECs, the potential impact of personnel activities such as moving materials into and out of the compounding area.~~ This training shall be successfully completed and proficiency demonstrated through written testing and hands-on demonstration of skills. ~~documented before any compounding personnel begins to prepare compounding sterile preparations and annually thereafter for all who compound sterile preparations.~~

(2) GLOVED FINGERTIP. All compounding personnel shall successfully complete ~~a no fewer than 3~~3 gloved fingertip and thumb sampling procedures prior to compounding sterile preparations, with zero colony-forming units. Gloved fingertip and thumb sampling shall be conducted ~~annually~~quarterly for all personnel engaged in compounding with no more than a total of 3 CFUs. Each evaluation must occur after separate, full hand hygiene and garbing procedures, compounding low and medium risk level preparations and semi-annually for all personnel engaged in compounding high risk level preparations.

When gloved fingertip sample results exceed action levels after proper incubation, a review of hand hygiene and garbing procedures, glove and surface disinfection procedures and work practices shall be performed and documented.

(3) MEDIA-FILL TESTING. The pharmacy shall develop, maintain, and implement written procedures that include appropriate media-fill testing by personnel authorized to compound preparations. ~~The issues to consider in the development of a media fill test are media fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results and possible corrective actions required.~~ Tests

Comment [SK30]: Need to add garbing and hand hygiene and aseptic technique

shall be performed without interruption in an ISO Class 5 environment under conditions that closely simulate ~~the stressful the most difficult and challenging compounding procedures and processing~~ conditions encountered during a work shift. ~~compounding of the specific risk level preparations for which the test is intended.~~ The pharmacy shall maintain records of media-fill testing performed, and results of testing procedures shall be available to the board upon request. Compounding personnel whose media-fill test vials result in gross microbial colonization shall be immediately instructed and reevaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.

In addition, personnel who fail visual observation of hand hygiene, garbing, aseptic technique, gloved fingertip sampling or media fill testing must pass three successive reevaluations in the deficient area before they can resume compounding.

(4) RECORDS. Documentation of training, gloved fingertip tests and media-fill tests shall be maintained by the pharmacy for 5 years and made available to the Board upon request.

15.42 Policies and Procedures. (1) A written policy and procedure manual shall be prepared, implemented, maintained and adhered to for the compounding, dispensing, delivery, administration, storage and use of sterile preparations. The manual shall establish policies and procedures governing all of the following:

- (a) A risk management program, including documentation of incidents, adverse drug reactions and product contamination.
- (b) Security measures ensuring the premises where compounded sterile drugs are present are secured.
- (c) Procedures for use of equipment and documentation of applicable certifications.
- (d) Cleaning and disinfecting.
- (e) Reference materials.
- (f) Drug preparation, storage, handling, dispensing, labeling, delivery, destruction, recalls and returns.
- (g) Handling, dispensing and documentation of investigational new drugs, if applicable.
- (h) Quality assurance program.
- (i) Training and competency guidelines.
- (j) Sterile compounding process validation.
- (k) Garb and garbing.
- (l) Personnel responsibilities.
- (m) Patient education.
- (n) Maintaining the integrity of the interior work area of the laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators and biological safety cabinets.
- (o) Handling small and large spills of antieoplastic agents and other hazardous substances.

(2) The policy and procedures manual shall be reviewed at least once every 24 months and shall be updated, on a continuous basis, to reflect current practice. Documentation of the review shall be made available to the board upon request.

Comment [ALD31]: Is this for controlled substances? Is it needed for outsourcing facilities?