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**PHARMACY RULES COMMITTEE  
of the  
PHARMACY EXAMINING BOARD**

**Room 121A, 1400 East Washington Avenue, Madison, WI 53703**  
**Contact: Dan Williams (608) 266-2112**  
**February 24, 2016**

*Notice: The following agenda describes the issues that the Committee plans to consider at the meeting. At the time of the meeting, items may be removed from the agenda. A **quorum of the Board may be present during any committee meetings.***

**AGENDA**

**8:30 A.M.**

**OPEN SESSION – CALL TO ORDER**

- A. Approval of Agenda (1)**
- B. Legislation and Rule Matters – Discussion and Consideration (2-39)**
  - 1) Phar 15 Relating to Compounding
  - 2) Phar 7 Relating to Practice of Pharmacy
  - 3) Update on Legislation and Pending or Possible Rulemaking Projects
- C. Public Comments**

**ADJOURNMENT**

**State of Wisconsin  
Department of Safety & Professional Services**

**AGENDA REQUEST FORM**

|  |  |   |      |
|--|--|---|------|
| 1) Name and Title of Person Submitting the Request:<br><br><b>Sharon Henes<br/>Administrative Rules Coordinator</b>  |  | 2) Date When Request Submitted:<br><br>Items will be considered late if submitted after 12:00 p.m. on the deadline date:<br>▪ 8 business days before the meeting    |      |
| 3) Name of Board, Committee, Council, Sections:<br><br><b>Pharmacy Rules Committee</b>   |  |   |      |
| 4) Meeting Date:   | 5) Attachments:<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No   | 6) How should the item be titled on the agenda page?<br><b>Legislation and Rule Matters – Discussion and Consideration</b><br><b>1. Phar 15</b><br><b>2. Phar 7</b> |      |
| 7) Place Item in:<br><input checked="" type="checkbox"/> Open Session<br><input type="checkbox"/> Closed Session<br><input type="checkbox"/> Both  | 8) Is an appearance before the Board being scheduled?<br><br><input type="checkbox"/> Yes ( <a href="#">Fill out Board Appearance Request</a> )<br><input type="checkbox"/> No | 9) Name of Case Advisor(s), if required:  |      |
| 10) Describe the issue and action that should be addressed:<br><br><b>The first document is the same draft the Committee was working on at the January meeting. The Committee reviewed up to 15.35.</b><br><br><b>The second document is provided by PSW. This is the same version of the document, however, it does contain their comments.</b>   |  |   |      |
| 11) Authorization  |  |   |      |
| <p style="font-size: 1.5em; font-family: cursive;"><i>Sharon Henes</i></p>   |  |   |      |
| Signature of person making this request  |  |   | Date |
| Supervisor (if required)   |  |   | Date |
| Executive Director signature (indicates approval to add post agenda deadline item to agenda)   |  |   | Date |
| Directions for including supporting documents:<br>1. This form should be attached to any documents submitted to the agenda.<br>2. Post Agenda Deadline items must be authorized by a Supervisor and the Policy Development Executive Director.<br>3. If necessary, Provide original documents needing Board Chairperson signature to the Bureau Assistant prior to the start of a meeting. |  |   |      |

## DRAFT TEXT of Chapter Phar 15

[NOTE: This draft incorporates the feedback provided by the Committee members as best as I was able. There are some areas which I have questions.]

**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) Adverse Drug Event means an injury resulting from the use of a drug.
- (4) Beyond Use Date (BUD) means one of the following:
  - (a) The date after which a non-sterile compounded preparation shall not be used.
  - (b) The date and time after which a non-infused compounded sterile preparation shall not be used.
  - (c) The date and time after which an infused compounded sterile preparation shall not be initiated.
- (5) Component means any, active pharmaceutical ingredient, or added substances used in the compounding of a drug preparation.
- (6) 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.
- (7) Container-closure system is the sum of packaging components that together contain and protect a dosage form including primary packaging components and secondary packaging components.
- (8) Controlled room temperature means a temperature maintained thermostatically that encompasses the usual and customary working environment of 68 degrees to 77 degrees Fahrenheit.
- (9) Freezer means a place in which the temperature is maintained between -11 degrees and 14 degrees Fahrenheit
- (10) NF means the National Formulary.
- (11) Refrigerator means a cold place in which the temperature is maintained between 36 degrees and 46 degrees Fahrenheit

(12) 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.

(a) Chemical stability means each active pharmaceutical ingredient retains its chemical integrity and labeled potency, within specified limits.

(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.

(13) USP means the United States Pharmacopeia.

## **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) Official or assigned name, strength, and dosage form of the preparation.
- (2) List [*Description*] of all ingredients and their quantities.
- (3) Vendor or manufacturer, lot number and expiration date of each ingredient and container closure-system.
- (4) Equipment and supplies needed to prepare the preparation.
- (5) Mixing instructions including all of the following:
  - (a) Order of mixing.
  - (b) Mixing temperatures or other environmental controls.
  - (c) Duration of mixing.
  - (d) Other factors pertinent to the replication of the preparation as compounded.
- (6) Compatibility and stability information, including references or laboratory testing, if applicable.
- (7) Container or container-closure system used in dispensing.
- (8) Packaging and storage requirements.
- (9) Quality control procedures, if applicable, and expected results.
- (10) Sterilization method, if applicable.
- (11) Total quantity compounded.
- (12) Name of the person who prepared the preparation.
- (13) Name of the person who performed the quality control procedures.
- (14) Name of the person who approved the preparation.
- (15) Date of preparation.
- (16) Assigned control or prescription number.
- (17) Assigned BUD.
- (18) Copy of the label to dispense final product.

[Discuss whether these previously included items should be removed:

- (1) Calculations needed to determine and verify quantities of components and doses of active pharmaceutical ingredients.
- (2) Sample labeling information, including all of the following:
  - (a) Name and quantity or concentration of each active ingredient.
  - (b) Assigned BUD.
  - (c) Storage conditions.
  - (d) Prescription or control number.
- (3) Description of final preparation.
- (4) Official or assigned name, strength, and dosage of the preparation.
- (5) Description of the final preparation.
- (6) Results of quality control procedures.
- (7) Documentation of any quality control issues and any adverse reactions or preparation problems reported by the patient or caregiver.]

### **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) Written procedures were followed in the execution of the compounding process.
- (b) Compounding records are complete.
- (c) Preparation instructions were followed.
- (d) Finished preparation appears as expected.
- (e) Label includes all required elements.
- (f) Quality control procedures were completed, if applicable.

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

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

**15.14 Training, Policies and Procedures.** (1) 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 personnel training and competency assessments are completed and documented.

(2) POLICIES AND PROCEDURES. The pharmacy shall establish written policies and procedures governing all of the following:

- (a) Personnel qualifications and training.
- (b) Personal hygiene and personal protective gear.
- (c) Maintenance of compounding facilities and equipment.
- (d) Environmental monitoring.
- (e) Cleaning and disinfection of compounding area.
- (f) Component selection.
- (g) Sterilization and depyrogenation, if applicable.
- (h) Storage, handling, packaging and transport.
- (i) Documentation requirements.
- (j) Establishing BUD.
- (k) Reporting of adverse drug events related to compounded preparations.
- (L) A risk management program, including documentation of incidents, adverse drug reactions and product contamination.
- (m) Use of equipment and documentation of applicable certifications.
- (n) Reference materials.
- (o) Handling, dispensing and documentation of investigational new drugs.
- (p) Quality assurance program.
- (q) Training and competency guidelines.
- (r) Garb and garbing.
- (s) Personnel responsibilities.
- (t) Patient education.
- (u) Maintaining the integrity of the interior work area of the laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators and biological safety cabinets.
- (v) Handling small and large spills of antieoplastic agents and other hazardous substances.

(3) REVIEW OF POLICIES AND PROCEDURES 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.

**15.15 Labeling.** The label of a compounded preparation shall include all of the following:

- (1) The preparation is compounded.
- (2) Storage conditions.
- (3) BUD date for non-sterile preparations or BUD date and time for sterile preparations.
- (4) Special handling instructions, if applicable.

**15.16 Component Selection.** (1) Active pharmaceutical ingredients used in compounding shall be manufactured by an FDA registered facility.

(2) Bulk ingredients shall be manufactured by an FDA registered facility or accompanied by a certificate of analysis.

(3) Ingredients shall meet USP or NF monograph specifications when monographs are available.

(4) All components shall be stored and handled consistent with the manufacturer's labeling or USP-NF monographs and in a manner that prevents contamination and deterioration.

(5) 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.

**15.17 Office or Hospital Use.** Compounded preparations distributed or dispensed that are dispensed directly to a practitioner for office use or a hospital to be administered to an individual patient in the hospital without a patient-specific prescription shall meet all of the following:

(1) The prescription order shall include the name, address, drug, quantity and the purpose of the compounded preparation.

(2) Labeling shall include the practitioner's name in place of the patient's name and state "For Office Use Only – Not for Resale". If the sterility or integrity of the compounded preparation cannot be maintained after the initial opening of the container, the label shall state "Single-Dose Only."

(3) Compounded preparations distributed for office or hospital use may not be distributed to other practitioners or to patients for administration outside of the office or hospital.

(4) The pharmacist shall record the name and address of the location the compounded preparation was dispensed and the lot number and BUD of all preparations dispensed to the practitioner.

(5) There shall be a procedure for immediate notification to all practitioners of a preparation which is recalled.

(6) Human use compounded preparations shall comply with federal law.

{Does the Board want to be notified of recalls}

## **SUBCHAPTER II – Non-sterile Compounding**

**15.20 Component Selection.** (1) 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.
- (2) 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.
- (3) 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.

**15.21 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, compound sterile preparation, labeling and other high particulate generating activities are performed. The ante-area is the transition area between the unclassified area of the facility and the buffer area.
- (2) Batch means more than one unit of compounded sterile preparation prepared in a single process and intended to have uniform characteristics and quality, within specified limits.
- (3) Buffer area means an area where the primary engineering control is physically located and generates and maintains an ISO Class 5 environment. Activities that occur in this area include the

preparation and staging of components and supplies used when compounding compounded sterile preparations.

(4) Classified space means a space that maintains an air cleanliness classification based on the International Organization for Standardization (ISO).

(5) Cleanroom means a room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness (ISO) class. A cleanroom includes a buffer area or room and an ante area or room.

(6) Compounded sterile preparation means a compounded final preparation intended to be sterile through the BUD.

(7) Compounded stock solution means a compounded solution into be used in the preparation of multiple units of a finished compounded sterile preparation.

(8) HEPA means high-efficiency particulate air.

(9) *Immediate use compounded sterile preparations* means preparations intended for emergency patient care 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.

(10) 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 HEPA or HEPA-filtered air.

(11) 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 HEPA or HEPA-filtered air.

(12) 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 HEPA or HEPA-filtered air.

(13) Isolator means an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated a continuously higher pressure than its surrounding environment and is decontaminated using an automated system. An isolator uses only decontaminated interfaces or rapid transfer ports for materials transfer.

(14) Restricted access barrier system (RABS) means an enclosure that provides HEPA filtered ISO Class 5 unidirectional air that allows for the ingress or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. RABS include compounding aseptic isolator and compounding aseptic isolator.

(15) Sterility assurance level of  $10^{-6}$  means an equivalent to a probability that 1 unit in a million is nonsterile.

(16) Segregated compounding area means a designated, unclassified space with a defined perimeter that does not have an ante-area or buffer area and is located away from unsealed windows and doors that connect to the outdoors, significant traffic flow, sinks and environments that may compromise the effectiveness of a primary engineering control to maintain air cleanliness.

**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.

**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) CLASSIFIED OR SEGREGATED COMPOUNDING AREA.** A classified or segregated compounding area 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 classified or segregated compounding area 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 classified or segregated compounding area shall be all of the following:

- (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.
- (g) Maintained free of chewing gum, drinks, candy or food items.

**(2) CLASSIFIED OR SEGREGATED COMPOUNDING AREA REQUIREMENTS.** A classified or segregated compounding area 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.
- (c) Junctures where ceilings meet walls shall be covered, caulked, or sealed to avoid cracks and crevices in which microorganisms and other contaminate 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.
- (e) Walls shall be constructed of flexible material, panels locked together and sealed or of epoxy-coated gypsum board.
- (f) Floors shall have a covering that shall be seamless or have teat-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.
- (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.
  - (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.

**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, exposed jewelry, piercings, headphones, and cell phones.
- (b) Natural nails shall be kept neat and trimmed. The wearing of artificial nails, extenders or nail polish is prohibited while working in the compounding area.
- (c) Personnel protective equipment shall be put on in the following order:
  - 1. Dedicated shoes or shoe covers.
  - 2. Low-lint, disposable covers for head and facial hair that cover the ears and forehead.

3. Face masks if compounding Category 2 compounded sterile preparations using laminar airflow system or biological safety cabinet.

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 with unscented soap and water for at least 30 seconds. Hands and forearms to the elbows shall be completely dried using either lint-free disposable towels or wipes.

(e) Personnel shall wear non-cotton, low-lint, disposable gown or coveralls with sleeves that fit snugly around the wrists and enclosed at the neck that are designed for buffer area use.

(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 scrub with persistent activity following manufacturer's recommendations. Once hands are dried thoroughly, personnel shall put on sterile 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 shall 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. Gloves shall be replaced immediately if holes, punctures or tears are detected.

(4) When compounding personnel exit the buffer or segregated compounding area during a work shift, the gown, coveralls, shoe covers, hair and facial hair covers, face masks, eye shields, gloves and sleeves shall be replaced with new ones before re-entering the buffer area. Before resuming sterile compounding, proper hand hygiene shall be performed.

**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 minimum frequency:

(a) Primary engineering control work surfaces, excluding isolators, 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.

(b) Counters and work surfaces in the buffer, ante and segregated compounding areas daily.

(c) Floors daily.

(d) Walls, ceilings and storage shelving monthly.

(2) 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.

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

(4) Cleaning and disinfection agents shall be selected and used with consideration of compatibilities, effectiveness and inappropriate or toxic residues. The selection and use of disinfectants shall be guided by microbicidal activities, inactivation by organic matter, residue, and shelf life

(5) Cleaning 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. This shall be followed by wiping with sterile 70% isopropyl alcohol, which is allowed to dry before compounding begins.

(6) Storage sites for compounding ingredients and supplies shall remain free from dust and debris.

(7) Floors in the classified and segregated compounding areas are cleaned by mopping with a germicidal detergent when no aseptic operations are in progress. Mopping shall be performed in the direction from clean to dirty areas.

(8) The walls, ceilings and shelving shall be cleaned and disinfected with a germicidal detergent with consideration of compatibilities, effectiveness and inappropriate or toxic residues.

(9) All cleaning tools and materials shall be sterile, low-lint and dedicated to use in the buffer, ante and segregated compounding areas 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.

(10) 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.

(11) 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.

(12) 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.

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

(14) Equipment and items used in a buffer area or segregated compounding area shall not be removed except for activities associated with proper maintenance including calibration and servicing.

#### **15.36 Immediate 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 use compounded sterile preparations shall begin administration 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) 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.

### **15.37 Sterilization methods.**

(1) Sterilization methods employed shall sterilize the compounded sterile preparation while maintaining its physical and chemical stability and the packaging integrity of the compounding sterile preparations. The efficacy of sterilization and depyrogenation of container closure systems performed in the pharmacy shall be established, documented, and reproducible.

(2) Presterilization requirements 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.* Sterilization by filtration involves the passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent. Filtration may not be used when compounding a suspension when the suspended particles are removed by the filter being used. This method shall meet all of the following:

1. Sterile filters used to sterile filter preparations shall meet all of the following requirements:

a. Be pyrogen-free and have a nominal pore size of 0.22 microns.

b. Be certified by the manufacturer to retain at least  $10^7$  microorganisms of a strain of *Brevundimonas diminuta* per square centimeter of upstream filter surface area under conditions similar to those in which the compounded sterile preparations will be filtered.

c. Be chemically and physically stable at the compounding pressure and temperature conditions.

d. Have sufficient capacity to filter the required volumes.

e. Yield a sterile filtrate while maintaining pre-filtration pharmaceutical quality, including strength of ingredients of the specific compounded sterile preparations

2. 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.

3. When compounded sterile preparations are known to contain excessive particulate matter, one of the following shall occur:
  - a. A pre-filtration step using a filter of larger nominal pore size.
  - b. A separate filter of larger nominal pore size placed upstream of the sterilizing filter to remove gross particulate contaminants before the compounding sterile compound is passed through the sterilizing grade filter.
4. Sterilization by filtration shall be performed entirely within an ISO Class 5 or superior air quality environment.
5. Filter units used to sterilize compounded sterile preparations must be subjected to the manufacturers' recommended post-use integrity test.

(b) *Sterilization by steam heat.* The process of thermal sterilization using saturated steam under pressure shall be the method for terminal sterilization of aqueous preparations in their final, sealed container closure system. The effectiveness of steam sterilization shall be established and verified with each sterilization run or load by using biological indicators, physicochemical indicators and integrators. This method shall meet all of the following:

1. 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. The duration of the exposure period shall include sufficient time for the compounded sterile preparation to reach the sterilizing temperature.
2. The compounded sterile preparation and other items shall remain at the sterilizing temperature for the duration of the sterilization period. The sterilization cycle shall be designed to achieve a SAL of  $10^{-6}$ .
3. Compounded sterile preparations shall be placed in trays which allow steam to reach the compounded sterile preparations without entrapment of air. Paper, glass and metal devices or items shall be wrapped in low lint protective fabric, paper or sealed in envelopes that will permit steam penetration and prevent post sterilization microbial contamination.
4. Immediately before filling ampules and vials, solutions shall be passed through a filter having a nominal pore size of not larger than 1.2  $\mu\text{m}$  for removal of particulate matter.
5. Sealed containers shall be able to generate steam internally. Stoppered and crimped empty vials shall contain a small amount of moisture to generate steam. Deep containers, including beakers and graduated cylinders, shall be placed on their sides to prevent air entrapment or have a small amount of water placed in them.
6. Porous materials and items with occluded pathways shall only be sterilized by steam if the autoclave chamber has cycles for dry goods.
7. The steam supplied shall be free of contaminants and generated using clean water.
8. The seals on the doors of autoclave chambers shall be examined visually every day they are used for cracks or damage and the seal surfaces shall be kept clean.
9. A data recorder or chart shall be used to monitor each cycle and the data shall be reviewed to identify cycle irregularities in temperature or exposure time.
10. Materials in direct contact with the compounded sterile preparation shall undergo a depyrogenation process before being sterilized using steam heat unless the materials used are certified to be pyrogen-free.

(c) *Sterilization by dry heat.* Dry heat sterilization 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. This method shall meet all of the following:

1. The duration of the exposure period shall include sufficient time for the compounding sterile preparation or items to reach the sterilizing temperature. The compounded sterile preparation and items shall remain at the sterilizing temperature for the duration of the sterilization period.
2. Heated air shall be evenly distributed throughout the chamber.
3. Sufficient space shall be left between materials to allow for good circulation of the hot air.
4. The oven shall be equipped with temperature controls and a timer.
5. A data recorder or chart shall be used to monitor each cycle and the data shall be reviewed to identify cycle irregularities in temperature or exposure time.
6. Materials shall first undergo a depyrogenation process before being sterilized using dry heat, unless the materials used are certified to be pyrogen-free.

(4) Dry heat depyrogenation shall be used to render glassware and other thermostable containers pyrogen free. The duration of the exposure period shall include sufficient time for the items to reach the depyrogenation temperature. The items shall remain at the depyrogenation temperature for the duration of the depyrogenation period. The effectiveness of the dry heat depyrogenation cycle shall be established and verified annually using endotoxin challenge vials to demonstrate that the cycle is capable of achieving a  $\geq 3$ -log reduction in endotoxins.

### **15.38 Inspection and Sterility Testing.**

(1) **PHYSICAL INSPECTION.** (a) At the completion of compounding, the compounded sterile preparation shall be inspected by doing all of the following:

1. Visually inspect the container closure integrity for leakage, cracks in the container or improper seals.
2. Visually check the compounded sterile preparation for phase separation, when applicable.
3. Each individual injectable unit shall be inspected against a lighted white background and a black background for evidence of visible particulates or other foreign matter or discoloration.

(b) For compounded sterile preparations which will not be dispensed promptly after preparation, an inspection shall be conducted immediately before it is dispensed for any defects, including precipitation, cloudiness or leakage, which may develop during storage.

(c) Compounded sterile preparations with any observed defects shall be immediately discarded or marked and segregated from acceptable units in a manner that prevents them from being dispensed.

(2) **STERILITY TESTING.** (a) The membrane filtration method shall be used for sterility testing unless it is not possible due to the compounded sterile preparation formulation. The direct inoculation of the culture method shall be used when the membrane filtration method is not possible.

(b) 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.

(c) Positive sterility test results shall prompt a rapid and systematic investigation into the causes of the sterility failure, including identification of the contaminating organism and any aspects of the facility, process or personnel that may have contributed to the sterility failure. The investigation and resulting corrective actions shall be documented.

(d) All Category 2 compounded sterile 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.

(e) All Category 2 compounded sterile preparations made from one or more nonsterile ingredients, except those for inhalation and ophthalmic administration, shall be tested to ensure that they do not contain excessive bacterial endotoxins.

(f) Notwithstanding par. (f), a compounded sterile preparation does not need to be tested for bacterial endotoxins if the material is stored under cool and dry conditions and one of the following:

1. The certificate of analysis for the nonsterile ingredient lists the endotoxins burden.
2. The pharmacy has predetermined the endotoxins burden of the nonsterile ingredient and found it acceptable.

### **15.39 Beyond Use Dating.**

(1) Sterility and stability considerations shall be taken into account when establishing a BUD. The following dates and times for storage and initiation of administration of the compounded sterile preparations shall apply:

(a) For compounded sterile preparations including components from conventionally manufactured products, the BUD shall not exceed the shortest expiration of any of the starting components. If the compounded sterile preparation includes non conventionally manufactured products, the BUD may not exceed the shortest BUD of any of the starting components.

(b) For Category I compounded sterile preparations, one of the following:

1. Administration shall begin within 12 hours when the preparation is stored at controlled room temperature.
2. Administration shall begin within 24 hours when the preparation is stored in a refrigerator.

(c) For aseptically prepared Category 2 compounded sterile preparations, one of the following:

1. Prepared only with sterile ingredients, with no preservative added and no sterility testing performed, one of the following:
  - a. Administration shall begin within 6 days when the preparation is stored at controlled room temperature.

- b. Administration shall begin within 9 days when the preparation is stored in a refrigerator.
      - c. Administration shall begin within 45 days when the preparation is stored in a freezer.
    2. Prepared with one or more nonsterile ingredients, no preservative added and no sterility testing performed, one of the following:
      - a. Administration shall begin within 4 days when the preparation is stored at controlled room temperature.
      - b. Administration shall begin within 7 days when the preparation is stored in a refrigerator.
      - c. Administration shall begin within 45 days when the preparation is stored in a freezer.
    3. Prepared with sterile ingredients, no preservative added and sterility testing performed, one of the following:
      - a. Administration shall begin within 28 days when the preparation is stored at controlled room temperature.
      - b. Administration shall begin within 42 days when the preparation is stored in a refrigerator.
      - c. Administration shall begin within 45 days when the preparation is stored in a freezer.
  - (d) For terminally sterilized Category 2 compounded sterile preparations, one of the following:
    1. Prepared only with sterile ingredients, with no preservative added and no sterility testing performed, one of the following:
      - a. Administration shall begin within 14 days when the preparation is stored at controlled room temperature.
      - b. Administration shall begin within 28 days when the preparation is stored in a refrigerator.
      - c. Administration shall begin within 45 days when the preparation is stored in a freezer.
    2. Prepared with sterile ingredients, no preservative added and sterility testing performed, one of the following:
      - a. Administration shall begin within 28 days when the preparation is stored at controlled room temperature.
      - b. Administration shall begin within 42 days when the preparation is stored in a refrigerator.
      - c. Administration shall begin within 45 days when 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.

**15.40 Quality Assurance.** The pharmacy's quality assurance program 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.** The managing pharmacist, all pharmacists, pharmacy technicians, pharmacy interns and pharmacy externs involved in compounding 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. This training shall be successfully completed and 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 gloved fingertip and thumb sampling procedure prior to compounding sterile preparations. Gloved fingertip and thumb sampling shall be conducted annually for all personnel engaged in 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 shall be performed without interruption in an ISO Class 5 environment under conditions that closely simulate the stressful conditions encountered during 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.

**(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.

## DRAFT TEXT of Chapter Phar 15

[NOTE: This draft incorporates the feedback provided by the Committee members as best as I was able. There are some areas which I have questions.]

### 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) Adverse Drug Event means an injury resulting from the use of a drug.
- (4) Beyond Use Date (BUD) means one of the following:
  - (a) The date and time after which a non-sterile compounded preparation shall not be used.
  - (b) The date and time after which a non-infused compounded sterile preparation shall not be used.
  - ~~(c) The date and time after which an infused compounded sterile preparation shall not be initiated.~~
- (5) Component means any, active pharmaceutical ingredient, or added substances used in the compounding of a drug preparation.
- (6) 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.
- (7) Container-closure system is the sum of packaging components that together contain and protect a dosage form including primary packaging components and secondary packaging components.
- (8) Controlled room temperature means a temperature maintained thermostatically that encompasses the usual and customary working environment of 68 degrees to 77 degrees Fahrenheit.
- (9) Freezer means a place in which the temperature is maintained between -11 degrees and 14 degrees Fahrenheit
- (10) NF means the National Formulary.
- (11) Refrigerator means a cold place in which the temperature is maintained between 36 degrees and 46 degrees Fahrenheit
- (12) 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.

**Comment [1]:** Statutory limitations for inspections. Sharon asked Rocky to provide language to change legal interpretation for ability to do within rules. Ask PSW members about other states or pursue statutory change to allow inspections.

**Comment [2]:** I am not sure the need of this definition here. But, if it is in regards to errors, (according to NCCMERP) the focus is to clarify this further because it is associated with significant confusion. Recommend defining as Preventable ADEs and Non-Preventable ADEs

**Comment [3]:** Discussion here – allow for an infusion to continue rather than stopping and changing. Clarification of which point it should not be used.

**Comment [4]:** Is "time" really going to a part of the documented BUD for non-sterile preparations? If so this definition does not appear to be consistent with 15.15 where it states that labeling should require: BUD date for non-sterile and BUD date and time for sterile preparations.

**Comment [5]:** I agree that time should be removed. More prescriptive than 795 and seems unnecessary given how this date is assigned for these products

**Comment [6]:** remove time for non-sterile compds

**Comment [7]:** Would suggest rewording - I found "non-infusing" confusing and it took awhile to understand what this meant. Per current 797 def: Date or time after which a CSP shall not be stored or transported. Per proposed 797 def: Date or time after which a CSP cannot be used and must be discarded. Would recommend more consistent language with 797. Additionally, since the proposed version will result in significant practice changes, not sure how they want to reconcile if this published prior to the new version.

**Comment [8]:** Suggest changing to -13 degrees F (remain consistent with USP - 25degrees celsius)

- (a) Chemical stability means each active pharmaceutical ingredient retains its chemical integrity and labeled potency, within specified limits.
- (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.

(13) USP means the United States Pharmacopeia.

### 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

**Comment [9]:** Consider statement in lines with "Heating, ventilation, and air conditioning systems shall be controlled to avoid decomposition and contamination of chemicals." Additionally, a statement like "Appropriate temperature and humidity monitoring should be maintained as required for certain components and compounded dosage forms." Both verbiage from 795 but applicable to 797.

**Comment [10]:** Both 795 and 797 state that the area should be well-lit and a comfortable working environment. Also, well-lit areas have been encouraged in ISMP pharmacy self assessment work due to studies showing increased errors in poorly lit environments -for what its worth:)

**Comment [11]:** Discussion about striking. This is not easily defined or enforceable. Decided to strike.

**Comment [12]:** It seems to like this should be kept. I'm thinking that if upon inspection the lighting situation seems dangerous or upon an investigation poor/inadequate lighting played a role then recourse may be difficult.

**Comment [13]:** Is there going to be any discussion about hazardous drug storage and handling?

**Comment [14]:** Consider change to "sorptive" thus both adsorp and absorp fall into this category

**Comment [15]:** Per proposed 797, Compounding personnel must conduct an accuracy assessment of the automated compounding device (ACD) each day it is used to compound CSPs. Compounding personnel must keep a daily record and review weekly for trends.

years after the date of the last refill. The compounding documentation shall include all of the following:

- (1) Official or assigned name, strength, and dosage form of the preparation.
- (2) List ~~[Description]~~ of all ingredients and their quantities.
- (3) Vendor or manufacturer, lot number and expiration date of each ingredient and container closure-system.
- (4) Equipment and supplies needed to prepare the preparation.
- (5) Mixing instructions including all of the following:
  - (a) Order of mixing.
  - (b) Mixing temperatures or other environmental controls.
  - (c) Duration of mixing.
  - (d) Other factors pertinent to the replication of the preparation as compounded.
- (6) Compatibility and stability information, including references or laboratory testing, if applicable.
- (8) Packaging and storage requirements.
- (9) Quality control procedures, if applicable, and expected results.
- (10) Sterilization method, if applicable.
- (11) Total quantity compounded.
- (12) Name of the person who prepared the preparation.
- (13) Name of the person who performed the quality control procedures.
- (14) Name of the person who approved the preparation.
- (15) Date of preparation.
- (16) Assigned control or prescription number.
- (17) Assigned BUD.
- (18) Copy of the label to dispense final product.

[Discuss whether these previously included items should be removed:

- (1) Calculations needed to determine and verify quantities of components and doses of active pharmaceutical ingredients.
- (2) Sample labeling information, including all of the following:
  - (a) Name and quantity or concentration of each active ingredient.
  - (b) Assigned BUD.
  - (c) Storage conditions.
  - (d) Prescription or control number.
- (3) Description of final preparation.
- (4) Official or assigned name, strength, and dosage of the preparation.
- (5) ~~Description of the final preparation.~~
- (6) Results of quality control procedures.
- (7) Documentation of any quality control issues and any adverse reactions or preparation problems reported by the patient or caregiver.]

### 15.13 Quality control.

- (1) ~~The A~~ pharmacist shall do a final check and review each procedure in the compounding process by verifying the following: ~~A final check shall include verification of all the following:~~
  - (a) Written procedures were followed in the execution of the compounding process.
  - (b) Compounding records are complete.
  - (c) Preparation instructions were followed.
  - (d) Finished preparation appears as expected.

**Comment [16]:** I would take this to mean in sterile compounding to include syringes, needles, alcohol pads, etc. This statement may be okay when you are talking about a master formulation record but doesn't seem necessary for a compounding record? For 795, non-sterile compounds require both a master formulation and compounding record. For 797, MFR is required only for CSPs prepared in a batch or from nonsterile ingredients. In my opinion, including everything together is very confusing. Consider including two required records (when applicable): MFR and compounding record

**Comment [17]:** This is part of a MFR. Not required for all CSP compounding in 797

**Comment [18]:** True in 795, in 797 - Date and time

**Comment [19]:** Per 795: this is true Per 797: only needed if product prepared in a batch. If true for all, this would be a lot of duplicate labels for CSPs (unless consider prep labels ok)

**Comment [20]:** It seems awfully redundant to keep this since 15.12 (18) includes a copy of the label.

**Comment [21]:** Removed in last meeting?

**Comment [22]:** Not consistent with practice. Not going to be included on the label.

**Comment [23]:** I believe (3) through (7) were removed in last meeting?

**Comment [24]:** Agreed.

- (e) Label includes all required elements.
- (f) Quality control procedures were completed, if applicable.
- [(g) The tests or examinations conducted on the compounded preparation to ensure their uniformity and integrity followed established written procedures.]

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

**15.14 Training, Policies and Procedures.** (1) 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 personnel training and competency assessments are completed and documented.

- (a) Personnel qualifications and training.
- (b) Personal hygiene and personal protective gear.
- (c) Maintenance of compounding facilities and equipment.
- (d) Environmental monitoring.
- (e) Cleaning and disinfection of compounding area.
- (f) Component selection.
- (g) Sterilization and depyrogenation, if applicable.
- (h) Storage, handling, packaging and transport.
- (i) Documentation requirements.
- (j) Establishing BUD.
- (k) Reporting of adverse drug events related to compounded preparations.
- (L) A risk management program, including documentation of incidents, adverse drug reactions and product contamination.
- (m) Use of equipment and documentation of applicable certifications.
- ~~(n) Reference materials.~~
- (o) Handling, dispensing and documentation of investigational new drugs.
- (p) Quality assurance program.
- ~~(q) Training and competency guidelines.~~
- (r) Garb and garbing.
- ~~(s) Personnel responsibilities.~~
- ~~(t) Patient education.~~
- (u) Maintaining the integrity of the interior work area of the laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators and biological safety cabinets.
- (v) Handling small and large spills of antineoplastic agents and other hazardous substances.

(3) REVIEW OF POLICIES AND PROCEDURES The policy and procedures manual shall be reviewed at least once every ~~36~~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.

**15.15 Labeling.** The label of a compounded preparation shall include all of the following:

- ~~(1) The preparation is compounded.~~
- (2) Storage conditions.
- (3) BUD date for non-sterile preparations or BUD date and time for sterile preparations.
- (4) Special handling instructions, if applicable.

**Comment [25]:** Consider include verbiage: describe training, frequency of training and process for evaluating the performance of individuals

**Comment [26]:** Combine with (h)

**Comment [27]:** Consider reword: Aseptic manipulation, sterilization....

**Comment [28]:** Combine with (c)

**Comment [29]:** This surprises me - I wouldn't think that compounding with investigational new drugs is a very common occurrence...

**Comment [30]:** Maybe consider combining r with b.

**Comment [31]:** Consider rewording: Maintaining the integrity of ISO classified work areas.

**Comment [32]:** typo - antineoplastic

**Comment [33]:** It is interesting to me that this was struck - it has been common practice among compounding specialists to disclose on the label that the preparation was compounded. The exact verbiage recommended by IACP and PCAB is "This prescription was compounded at the direction of your physician." This helps ensure full disclosure to the end user.

**Comment [34]:** Agree. Per the proposed 797, this is a requirement.

**Comment [35]:** add "if other than room temperature."

**Comment [36]:** I think "if applicable" should be kept because not all preparations are going to have special handling instructions.

**15.16 Component Selection.** (1) Active pharmaceutical ingredients used in compounding shall be manufactured by an FDA registered facility.

(2) Bulk ingredients shall be manufactured by an FDA registered facility or accompanied by a certificate of analysis.

(3) Ingredients shall meet USP or NF monograph specifications when monographs are available.

(4) All components shall be stored and handled consistent with the manufacturer's labeling or USP-NF monographs and in a manner that prevents contamination and deterioration.

(5) 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.

**15.17 Office or Hospital Use.** Compounded preparations distributed or dispensed that are dispensed directly to a practitioner for office use or a hospital to be administered to an individual patient in the hospital health care setting without a patient-specific prescription shall meet all of the following:

(1) The prescription order shall include the name, address, drug, quantity and the purpose of the compounded preparation.

(2) Labeling shall include the practitioner's name in place of the patient's name and state "For Office Use Only – Not for Resale". If the sterility or integrity of the compounded preparation cannot be maintained after the initial opening of the container, the label shall state "Single-Dose Only."

(3) Compounded preparations distributed for office or hospital use may not be distributed to other practitioners or to patients for administration outside of the office or hospital.

(4) The pharmacist shall record the name and address of the location the compounded preparation was dispensed and the lot number and BUD of all preparations dispensed to the practitioner.

(5) There shall be a procedure for immediate notification to all practitioners of a preparation which is recalled.

(6) Human use compounded preparations shall comply with federal law.

{Does the Board want to be notified of recalls}

## SUBCHAPTER II – Non-sterile Compounding

**15.20 Component Selection.** (1) 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.

(2) 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.

**Comment [37]:** I would propose: "Components must be obtained from a chemical supply company registered with the FDA, as well as be licensed as a wholesaler in the state of Wisconsin."

Please note: Supply companies do not necessarily "manufacture" their own ingredients

**Comment [38]:** Modification "Active pharmaceutical ingredients used in compounding shall be obtained from an FDA registered facility." Manufacturers might not be wholesalers and vice versa - cannot require a manufacturer to get a wholesaler license if they're not a wholesaler.

**Comment [39]:** clarify this - what are bulk ingredients? Inactive and excipients included or just APIs?

**Comment [40]:** \_Marked as resolved\_

**Comment [41]:** \_Re-opened\_ DQSA says Bulk Drug Substances

**Comment [42]:** Compounded prescriptions without an individual patient

**Comment [43]:** Consider defining office use

**Comment [44]:** Office use is not dispensed it is distributed. Congress has recently clarified this in the Appropriations Bill signed late in 12/15.

**Comment [45]:** Discussion about whether or not to use "office use" to avoid stigma

**Comment [46]:** PEB wouldn't have a mechanism to handle this right now. Removed.

**Comment [47]:** distributor or wholesaler? Wholesaler mentioned previously.

(3) 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.

**15.21 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 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, compound sterile preparation, labeling and other high particulate generating activities are performed. The ante-area is the transition area between the unclassified area of the facility and the buffer area.
- (2) Batch means more than one unit of compounded sterile preparation prepared in a single process and intended to have uniform characteristics and quality, within specified limits.
- (3) Buffer area means an area where the primary engineering control is physically located and generates and maintains an ISO Class 5 environment. Activities that occur in this area include the preparation and staging of components and supplies used when compounding compounded sterile preparations.
- (4) Classified space means a space that maintains an air cleanliness classification based on the International Organization for Standardization (ISO).
- (5) Cleanroom means a room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness (ISO) class. A cleanroom includes a buffer area or room and an ante area or room.
- (6) Compounded sterile preparation means a compounded final preparation intended to be sterile through the BUD.
- (7) Compounded stock solution means a compounded solution into be used in the preparation of multiple units of a finished compounded sterile preparation.
- (8) HEPA means high-efficiency particulate air.

**Comment [48]:** Definition needed for category I and II

**Comment [49]:** Category 1 and 2 CSP is in the new proposed version. This may stick in the actual revision but certainly has been a source of national consternation - particularly the BUD associated with them.

**Comment [50]:** Recommend reword to proposed def: An ISO Class 8 or cleaner area where personnel hand hygiene and garbing procedures and other activities that generate high particulate levels are performed. The ante-area is the transition area between the unclassified area of the facility and the buffer area. --Many folks are labeling in the cleanroom, staging of components is now being done in non-iso prep rooms. I would recommend not be so prescriptive.

**Comment [51]:** reword to: an ISO Class 7 (or ISO Class 8 if using an isolator) or cleaner area where the PEC is physically located.

**Comment [52]:** consider removing this sentence. If you want to talk about activities, rec: Activities in this area must be carefully controlled to avoid affecting the air quality in the area where CSP preparation occurs.

**Comment [53]:** add (CSP) and use throughout document?; additionally, how this is written is confusing to me. I would recommend using the proposed 797 language :A preparation intended to be sterile that is created by combining, diluting, pooling, or otherwise altering a drug product or bulk product substance. The following sentence may be duplicative of 6c but I'll include for your reference: A product produced by reconstituting a conventionally manufactured product for an individual patient strictly in accordance with the directions contained in the approved labeling provided by the product manufacturer is not considered a CSP.

(9) Immediate use compounded sterile preparations means preparations intended for emergency patient care 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.

**Comment [54]:** In proposed 797: changes to Urgent-Use CSPs. No limit on manipulations or ingredients used

(10) 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 HEPA or HEPA-filtered air.

**Comment [55]:** Do you need to define ISO Class: An air quality classification from the International Organization for Standardization.

(11) 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 HEPA or HEPA-filtered air.

(12) 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 HEPA or HEPA-filtered air.

(13) Isolator means an enclosure that provides HEPA-filtered ISO Class 5 unidirectional air operated at a continuously higher pressure than its surrounding environment and is decontaminated using an automated system. An isolator uses only decontaminated interfaces or rapid transfer ports for materials transfer.

**Comment [56]:** Do you need a definition for a media fill challenge test?

(14) Restricted access barrier system (RABS) means an enclosure that provides HEPA filtered ISO Class 5 unidirectional air that allows for the ingress or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination, and that generally are not to be opened during operations. RABS include compounding aseptic isolator and compounding aseptic isolator.

**Comment [57]:** Recommend including def for PEC: primary engineering control: a device or zone that provides an ISO Class 5 environment for sterile compoundign.

(15) Sterility assurance level of  $10^{-6}$  means an equivalent to a probability that 1 unit in a million is nonsterile.

(16) Segregated compounding area means a designated, unclassified space with a defined perimeter that does not have an ante-area or buffer area and is located away from unsealed windows and doors that connect to the outdoors, significant traffic flow, sinks and environments that may compromise the effectiveness of a primary engineering control to maintain air cleanliness.

**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.

**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.

**Comment [58]:** Does 15.32 need to be specifically stated for reprimand? Likely, in many egregious errors, multiple pharmacists would have some involvement in that error occurring

**15.33 Facility Design and Environmental Controls.** (1) CLASSIFIED OR SEGREGATED COMPOUNDING AREA. A classified or segregated compounding area 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 classified or segregated compounding area shall include a buffer area and an ante area. The buffer area shall contain an ISO

**Comment [59]:** Combine 1 & 2

**Comment [60]:** Recommend moving this up to the definitions

class 5 or better primary engineering control unless the buffer area has ISO class 5 or better air quality. A classified or segregated compounding area shall be all of the following:

- (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.

(2) CLASSIFIED OR SEGREGATED COMPOUNDING AREA REQUIREMENTS. A classified or segregated compounding area 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.
- (c) Junctures where ceilings meet walls shall be covered, caulked, or sealed to avoid cracks and crevices in which microorganisms and other contaminate 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.
- (e) Walls shall be constructed of flexible material, panels locked together and sealed or of epoxy-coated gypsum board.
- (f) Floors shall have a covering that shall be seamless or have 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.
- (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:

**Comment [61]:** Restate?: A compounding facility generally consists of separate, designated operational clean areas, including an ante-area, buffer area and a PEC, or a segregated compounding area containing a PEC where CSPs are prepared.

**Comment [62]:** ?

**Comment [63]:** Change cleanroom to classified area or segregated compounding area

**Comment [64]:** change sanitize to disinfect.

**Comment [65]:** typo: heat

- (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.
- (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 [66]:** Do you want to talk about air pressure, ACPH, placement of PEC?

**Comment [67]:** Reference state and federal requirements so to avoid needing specifics from OSHA, DNR, etc.

**Comment [68]:** Recommend including a section on certification and recertification requirement of facilities - what's included, frequency, by whom; Additionally, follow that up with an Environmental Monitoring section

**Comment [69]:** Recommend remove this section. They could compound in the segregated compounding area and still should do this.

**Comment [70]:** Include: low-lint, disposable

**Comment [71]:** Change to washing of the hands and forearms

**Comment [72]:** in Proposed 797: True for category 2 Rabs compounding. For C2 LAFS or BSC or any C1s, if don non-sterile gown, this should be put on before hand hygiene and need to wear sterile gloves and sterile sleeves. If don sterile gown, this is after hand hygiene and sterile gloving. Since this is tricky, wonder if USP will edit in final version.

**Comment [73]:** remove statement

**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, exposed jewelry, piercings, headphones, and cell phones.
- (b) Natural nails shall be kept neat and trimmed. The wearing of artificial nails, extenders or nail polish is prohibited while working in the compounding area.
- (c) Personnel protective equipment shall be put on in the following order:
  1. Dedicated shoes or shoe covers.
  2. Low-lint, disposable covers for head and facial hair that cover the ears and forehead.
  3. Face masks if compounding Category 2 compounded sterile preparations using laminar airflow system or biological safety cabinet.
  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 with unscented soap and water for at least 30 seconds. Hands and forearms to the elbows shall be completely dried using either lint-free disposable towels or wipes.
- (e) Personnel shall wear non-cotton, low-lint, disposable gown or coveralls with sleeves that fit snugly around the wrists and enclosed at the neck that are designed for buffer area use.

(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 scrub with persistent activity following manufacturer's recommendations. Once hands are dried thoroughly,

personnel shall put on sterile 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 shall 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. Gloves shall be replaced immediately if holes, punctures or tears are detected.

(4) When compounding personnel exit the buffer or segregated compounding area during a work shift, the gown, coveralls, shoe covers, hair and facial hair covers, face masks, eye shields, gloves and sleeves shall be replaced with new ones before re-entering the buffer area. Before resuming sterile compounding, proper hand hygiene shall be performed.

**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 minimum frequency:

- (a) Primary engineering control work surfaces, excluding isolators, 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.
- (b) Counters and work surfaces in the buffer, ante and segregated compounding areas daily.
- (c) Floors daily.
- (d) Walls, ceilings and storage shelving monthly.

(2) 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.

(3) 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.

(4) Cleaning and disinfection agents shall be selected and used with consideration of compatibilities, effectiveness and inappropriate or toxic residues. The selection and use of disinfectants shall be guided by microbicidal activities, inactivation by organic matter, residue, and shelf life

(5) Cleaning 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. This shall be followed by wiping with sterile 70% isopropyl alcohol, which is allowed to dry before compounding begins.

(6) Storage sites for compounding ingredients and supplies shall remain free from dust and debris.

(7) Floors in the classified and segregated compounding areas are cleaned by mopping with a germicidal detergent when no aseptic operations are in progress. Mopping shall be performed in the direction from clean to dirty areas.

- (8) The walls, ceilings and shelving shall be cleaned and disinfected with a germicidal detergent with consideration of compatibilities, effectiveness and inappropriate or toxic residues.
- (9) All cleaning tools and materials shall be sterile, low-lint and dedicated to use in the buffer, ante and segregated compounding areas 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.
- (10) 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.
- (11) 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.
- (12) 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.
- (13) No shipping or other external cartons may be taken into the buffer or clean area or segregated compounding area.
- (14) Equipment and items used in a buffer area or segregated compounding area shall not be removed except for activities associated with proper maintenance including calibration and servicing.

#### **15.36 Immediate 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 use compounded sterile preparations shall begin administration 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) 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.

#### **15.37 Sterilization methods.**

**Comment [74]:** Start here next time.

- (1) Sterilization methods employed shall sterilize the compounded sterile preparation while maintaining its physical and chemical stability and the packaging integrity of the compounding sterile preparations. The efficacy of sterilization and depyrogenation of container closure systems performed in the pharmacy shall be established, documented, and reproducible.
- (2) Presterilization requirements 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 utilize one of the following sterilization methods:
- (a) *Sterilization by filtration.* Sterilization by filtration involves the passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent. Filtration may not be used when compounding a suspension when the suspended particles are removed by the filter being used. This method shall meet all of the following:
    - 1. Sterile filters used to sterile filter preparations shall meet all of the following requirements:
      - a. Be pyrogen-free and have a nominal pore size of 0.22 microns.
      - b. Be certified by the manufacturer to retain at least  $10^7$  microorganisms of a strain of *Brevundimonas diminuta* per square centimeter of upstream filter surface area under conditions similar to those in which the compounded sterile preparations will be filtered.
      - c. Be chemically and physically stable at the compounding pressure and temperature conditions.
      - d. Have sufficient capacity to filter the required volumes.
      - e. Yield a sterile filtrate while maintaining pre-filtration pharmaceutical quality, including strength of ingredients of the specific compounded sterile preparations
    - 2. 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.
    - 3. When compounded sterile preparations are known to contain excessive particulate matter, one of the following shall occur:
      - a. A pre-filtration step using a filter of larger nominal pore size.
      - b. A separate filter of larger nominal pore size placed upstream of the sterilizing filter to remove gross particulate contaminants before the compounding sterile compound is passed through the sterilizing grade filter.
    - 4. Sterilization by filtration shall be performed entirely within an ISO Class 5 or superior air quality environment.
    - 5. Filter units used to sterilize compounded sterile preparations must be subjected to the manufacturers' recommended post-use integrity test.
  - (b) *Sterilization by steam heat.* The process of thermal sterilization using saturated steam under pressure shall be the method for terminal sterilization of aqueous preparations in their final, sealed container closure system. The effectiveness of steam sterilization shall be

established and verified with each sterilization run or load by using biological indicators, physicochemical indicators and integrators. This method shall meet all of the following:

1. 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. The duration of the exposure period shall include sufficient time for the compounded sterile preparation to reach the sterilizing temperature.
2. The compounded sterile preparation and other items shall remain at the sterilizing temperature for the duration of the sterilization period. The sterilization cycle shall be designed to achieve a SAL of  $10^{-6}$ .
3. Compounded sterile preparations shall be placed in trays which allow steam to reach the compounded sterile preparations without entrapment of air. Paper, glass and metal devices or items shall be wrapped in low lint protective fabric, paper or sealed in envelopes that will permit steam penetration and prevent post sterilization microbial contamination.
4. Immediately before filling ampules and vials, solutions shall be passed through a filter having a nominal pore size of not larger than 1.2  $\mu\text{m}$  for removal of particulate matter.
5. Sealed containers shall be able to generate steam internally. Stoppered and crimped empty vials shall contain a small amount of moisture to generate steam. Deep containers, including beakers and graduated cylinders, shall be placed on their sides to prevent air entrapment or have a small amount of water placed in them.
6. Porous materials and items with occluded pathways shall only be sterilized by steam if the autoclave chamber has cycles for dry goods.
7. The steam supplied shall be free of contaminants and generated using clean water.
8. The seals on the doors of autoclave chambers shall be examined visually every day they are used for cracks or damage and the seal surfaces shall be kept clean.
9. A data recorder or chart shall be used to monitor each cycle and the data shall be reviewed to identify cycle irregularities in temperature or exposure time.
10. Materials in direct contact with the compounded sterile preparation shall undergo a depyrogenation process before being sterilized using steam heat unless the materials used are certified to be pyrogen-free.

(c) *Sterilization by dry heat.* Dry heat sterilization 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. This method shall meet all of the following:

1. The duration of the exposure period shall include sufficient time for the compounding sterile preparation or items to reach the sterilizing temperature. The compounded sterile preparation and items shall remain at the sterilizing temperature for the duration of the sterilization period.
2. Heated air shall be evenly distributed throughout the chamber.
3. Sufficient space shall be left between materials to allow for good circulation of the hot air.
4. The oven shall be equipped with temperature controls and a timer.
5. A data recorder or chart shall be used to monitor each cycle and the data shall be reviewed to identify cycle irregularities in temperature or exposure time.

6. Materials shall first undergo a depyrogenation process before being sterilized using dry heat, unless the materials used are certified to be pyrogen-free.

(4) Dry heat depyrogenation shall be used to render glassware and other thermostable containers pyrogen free. The duration of the exposure period shall include sufficient time for the items to reach the depyrogenation temperature. The items shall remain at the depyrogenation temperature for the duration of the depyrogenation period. The effectiveness of the dry heat depyrogenation cycle shall be established and verified annually using endotoxin challenge vials to demonstrate that the cycle is capable of achieving a  $\geq 3$ -log reduction in endotoxins.

### **15.38 Inspection and Sterility Testing.**

(1) PHYSICAL INSPECTION. (a) At the completion of compounding, the compounded sterile preparation shall be inspected by doing all of the following:

1. Visually inspect the container closure integrity for leakage, cracks in the container or improper seals.
2. Visually check the compounded sterile preparation for phase separation, when applicable.
3. Each individual injectable unit shall be inspected against a lighted white background and a black background for evidence of visible particulates or other foreign matter or discoloration.

(b) For compounded sterile preparations which will not be dispensed promptly after preparation, an inspection shall be conducted immediately before it is dispensed for any defects, including precipitation, cloudiness or leakage, which may develop during storage.

(c) Compounded sterile preparations with any observed defects shall be immediately discarded or marked and segregated from acceptable units in a manner that prevents them from being dispensed.

(2) STERILITY TESTING. (a) The membrane filtration method shall be used for sterility testing unless it is not possible due to the compounded sterile preparation formulation. The direct inoculation of the culture method shall be used when the membrane filtration method is not possible.

(b) 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.

(c) Positive sterility test results shall prompt a rapid and systematic investigation into the causes of the sterility failure, including identification of the contaminating organism and any aspects of the facility, process or personnel that may have contributed to the sterility failure. The investigation and resulting corrective actions shall be documented.

(d) All Category 2 compounded sterile 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.

(e) All Category 2 compounded sterile preparations made from one or more nonsterile ingredients, except those for inhalation and ophthalmic administration, shall be tested to ensure that they do not contain excessive bacterial endotoxins.

(f) Notwithstanding par. (f), a compounded sterile preparation does not need to be tested for bacterial endotoxins if the material is stored under cool and dry conditions and one of the following:

1. The certificate of analysis for the nonsterile ingredient lists the endotoxins burden.
2. The pharmacy has predetermined the endotoxins burden of the nonsterile ingredient and found it acceptable.

### **15.39 Beyond Use Dating.**

(1) Sterility and stability considerations shall be taken into account when establishing a BUD. The following dates and times for storage and initiation of administration of the compounded sterile preparations shall apply:

(a) For compounded sterile preparations including components from conventionally manufactured products, the BUD shall not exceed the shortest expiration of any of the starting components. If the compounded sterile preparation includes non conventionally manufactured products, the BUD may not exceed the shortest BUD of any of the starting components.

(b) For Category I compounded sterile preparations, one of the following:

1. Administration shall begin within 12 hours when the preparation is stored at controlled room temperature.
2. Administration shall begin within 24 hours when the preparation is stored in a refrigerator.

(c) For aseptically prepared Category 2 compounded sterile preparations, one of the following:

1. Prepared only with sterile ingredients, with no preservative added and no sterility testing performed, one of the following:
  - a. Administration shall begin within 6 days when the preparation is stored at controlled room temperature.
  - b. Administration shall begin within 9 days when the preparation is stored in a refrigerator.
  - c. Administration shall begin within 45 days when the preparation is stored in a freezer.
2. Prepared with one or more nonsterile ingredients, no preservative added and no sterility testing performed, one of the following:
  - a. Administration shall begin within 4 days when the preparation is stored at controlled room temperature.
  - b. Administration shall begin within 7 days when the preparation is stored in a refrigerator.
  - c. Administration shall begin within 45 days when the preparation is stored in a freezer.
3. Prepared with sterile ingredients, no preservative added and sterility testing performed, one of the following:

- a. Administration shall begin within 28 days when the preparation is stored at controlled room temperature.
- b. Administration shall begin within 42 days when the preparation is stored in a refrigerator.
- c. Administration shall begin within 45 days when the preparation is stored in a freezer.

(d) For terminally sterilized Category 2 compounded sterile preparations, one of the following:

1. Prepared only with sterile ingredients, with no preservative added and no sterility testing performed, one of the following:
  - a. Administration shall begin within 14 days when the preparation is stored at controlled room temperature.
  - b. Administration shall begin within 28 days when the preparation is stored in a refrigerator.
  - c. Administration shall begin within 45 days when the preparation is stored in a freezer.
2. Prepared with sterile ingredients, no preservative added and sterility testing performed, one of the following:
  - a. Administration shall begin within 28 days when the preparation is stored at controlled room temperature.
  - b. Administration shall begin within 42 days when the preparation is stored in a refrigerator.
  - c. Administration shall begin within 45 days when 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.

**15.40 Quality Assurance.** The pharmacy's quality assurance program 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.** The managing pharmacist, all pharmacists, pharmacy technicians, pharmacy interns and pharmacy externs involved in compounding 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. This training shall be successfully completed and 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 gloved fingertip and thumb sampling procedure prior to compounding sterile preparations. Gloved fingertip and thumb sampling shall be conducted annually for all personnel engaged in 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 shall be performed without interruption in an ISO Class 5 environment under conditions that closely simulate the stressful conditions encountered during 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.

(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.