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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**  
**April 7, 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 (2-13)**
  - 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**

[NOTE: *March 2016 Draft. This Draft incorporates most of Phillip's recommendations. I have questions on some items which relate to rule drafting protocols and need to discuss in order to appropriately place in the rule. I also note some items which Phillip has suggested removing and the Committee had previously wanted to include and I did not want to delete without Committee discussion.*]

### **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, 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) Buffer area means an ISO Class 7 or ISO Class 8 if using an isolator or cleaner area where the PEC that generates and maintains an ISO Class 5 environment is physically located.

(3) Category 1 means a compounded sterile preparation compounded with a primary engineering control in a segregated compounding area.

(4) Category 2 means a compounded sterile preparation compounded with a primary engineering control in a classified area.

[*Note: Maintain in sterile or in general definitions?* (5) Certificate of analysis means a report from the supplier of a component, container or closure that accompanies the component, container or closure and contains the specifications and results of all analyses and a description.]

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

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

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

(9) Critical site means a location that includes any component or fluid pathway surfaces or openings that are exposed and at risk of direct contact with air, moisture or touch contamination.

(10) HEPA means high-efficiency particulate air.

(11) 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.

(12) 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.

(13) 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.

(14) 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.

- (15) Primary engineering control means a device or zone that provides an ISO Class 5 environment for sterile compounding.
- (16) 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 isolators and compounding aseptic containment isolators.
- (17) Sterility assurance level of  $10^{-6}$  means an equivalent to a probability that 1 unit in a million is nonsterile.
- (18) Segregated compounding area means a designated, unclassified space, area, or room that contains a primary engineering control.
- (19) Urgent use compounded sterile preparation means a preparation needed urgently for a single patient and preparation of the compounded sterile preparation under Category 1 or Category 2 requirements would subject the patient to additional risk due to delays.

**15.31 Facility design and environmental controls. (1) GENERAL.** Facilities shall meet all of the following requirements:

- (a) Be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites.
  - (b) Be accessible only to designated personnel.
  - (c) Have a heating, ventilation, and air conditioning system controlling the temperature and humidity.
- (2) SEGREGATED COMPOUNDING AREA. A segregated compounding area shall meet all of the following requirements:
- (a) Be located in an area away from unsealed windows and doors that connect to the outdoors, or significant traffic flow.
  - (b) Be located in an area which is not adjacent to construction sites, warehouses and food preparation areas.
  - (c) Have a defined perimeter.
  - (d) Locate the primary engineering control at least 1 meter from any sink.
- (3) CLASSIFIED AREA. A classified area shall meet all of the following:
- (a) The surfaces of ceilings, walls, floors, fixtures, shelving, counters and cabinets shall be smooth, impervious, free from cracks and crevices and nonshedding.
  - (b) Work surfaces shall be constructed of smooth, impervious materials. 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 a durable material, panels locked together and sealed or of epoxy-coated gypsum board.
  - (f) Floors shall have a covering that shall be seamless or have heat-welded seams and coving to the sidewall. There shall be no floor drains.
  - (g) All sprinkler heads shall be flush with the ceiling.

- (h) Ceiling lighting fixtures shall have exterior lens surfaces which are smooth, mounted flush and sealed [NOTE: *sealed instead of air tight*].
- (i) Carts shall be constructed of stainless steel wire, nonporous plastic or sheet metal with cleanable casters.
- (j) Tacky mats may not be used in a classified area.
- (k) HEPA filters and unidirectional airflow shall be used to maintain the appropriate airborne particulate classification.
- (L) The classified area shall measure not less than 30 air changes per hour of which at least half shall be HEPA-filtered fresh air.
- (m) A minimum differential positive pressure of 0.02-inch water column is required to separate each classified area. A pressure gauge or velocity meter shall be used to monitor the pressure differential or airflow between classified areas with results documented at least daily.
- (n) Devices and objects essential to compounding shall be located at an appropriate distance from the primary engineering control.
- (o) The ante area and buffer area shall be separate rooms, with walls and doors between them and controls to prevent the flow of lower quality air into the higher ISO class areas. If a pass through is used, only one door shall be opened at a time.
- (p) The ante area shall meet all of the following requirements:
  - 1. Be capable of maintaining an ISO class 8 air or higher.
  - 2. Have a sink with running hot and cold running water.
- (q) The buffer area shall meet all of the following requirements:
  - 1. Be capable of maintaining an ISO class 7 air or better.
  - 2. Only contain any of the following:
    - a. Items, including furniture, equipment, and supplies, that are required for the tasks to be performed in the buffer area.
    - b. Items that are smooth, impervious, free from cracks and crevices, nonshedding, and easily cleaned and disinfected.
    - c. Items that have been cleaned and disinfected immediately prior to their being placed in the buffer area.
  - 3. Does not contain any sinks.
  - 4. Does not contain any course cardboard, external shipping containers and nonessential paper.

**15.32 Personnel hygiene, garbing and protective gear. (1)** Personnel suffering from rashes, sunburn, oozing tattoos or sores, conjunctivitis, active respiratory infection, or other active communicable disease shall be excluded from working in compounding areas until the condition is resolved.

**(2)** All personnel who engage in compounding sterile preparations shall comply with all of the following requirements before entering the compounding area:

- (a) Remove personal outer garments, all cosmetics, exposed jewelry and piercings, headphones, ear buds, and cell phones.
- (b) Artificial nails, nail extenders or nail polish may not be worn while working in the compounding area.
- (c) Personnel protective equipment shall be put on in the following order:
  - 1. Low-lint, disposable 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 and biological safety cabinet.
  4. Eye shields, if required due to working with irritants or hazardous drugs.
- (d) A hand hygiene procedure shall be performed after performing the protective equipment in par (c). The hand hygiene procedure includes all of the following:
1. Personnel shall remove debris from underneath fingernails using a nail cleaner under running warm water.
  2. Wash hands and forearms up to the elbows with unscented soap and water for at least 30 seconds.
  3. Hands and forearms to the elbows shall be completely dried using either lint-free disposable towels or wipes.
  4. Prior to donning sterile gloves hand antisepsis shall be performed using an alcohol-based hand rub with sustained antimicrobial activity following the manufacturers labeled instructions and application times.
- (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. The sterile gown or coverall shall be put on after the sterile gloves are donned.
- (3) Gloves on hands and gauntlet sleeves on RABS shall be routinely inspected for holes, punctures, or tears and shall be replaced immediately if any are detected.
- (4) 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.
- (5) When compounding personnel exit the buffer or segregated compounding area during a work shift, a nonsterile gown may be removed and retained in the ante area or segregated compounding area if not visibly soiled, to be worn again during the same work shift. Coveralls, sterile gowns, shoe covers, hair and facial hair covers, face masks, eye shields, gloves and sleeves shall be replaced with new ones before re-entering the compounding area.
- (6) Garbing items, including gowns, shall be segregated and stored before use in an enclosure to prevent contamination.
- (7) Coveralls and sterile gowns shall not be reused. Visibly soiled gowns shall be changed immediately.
- (8) Gloves shall be sterile and powder free and tested by the manufacturer for compatibility with alcohol disinfection.

**15.33 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, end of each shift and 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 outside the primary engineering control in the buffer area, ante room and segregated compounding areas daily.
  - (c) Floors daily.
  - (d) Walls, ceilings and storage shelving monthly.
- (2) An isolator shall be cleaned each time it is opened. An isolator shall be decontaminated once it is closed after each time it is opened, or if cleaning occurs without opening, after each cleaning cycle.
- (3) Cleaning and disinfecting sterile compounding areas shall occur on a regular basis at the intervals in sub. (1) or when any of the following occurs:
- (a) Spills occur.
  - (b) The surface is visibly soiled.
  - (c) Microbial contamination is known to have been or is suspected of having been introduced into the compounding area.
- (4) All cleaning and disinfecting practices and policies for the compounding area shall be included in written standard operating procedures and shall be followed by all compounding and environmental services personnel.
- (5) 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. Disinfectants shall have antifungal, antibacterial and antiviral activity. Sporicidal agents shall be used at least weekly to clean compounding areas.
- (6) Storage sites for compounding ingredients and supplies shall remain free from dust and debris.
- (7) Floors, walls, ceiling and shelving in the classified and segregated compounding areas are cleaned when no aseptic operations are in progress. Cleaning shall be performed in the direction from cleanest to dirtiest areas.
- (8) All cleaning tools and materials shall be sterile, low-lint and dedicated for use in the buffer room, ante room and segregated compounding areas. If cleaning tools and materials 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.
- (9) Supplies and equipment removed from shipping cartons shall be wiped with a suitable disinfecting agent delivered from a spray bottle or other suitable delivery method. After the disinfectant is sprayed or wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, during which time the item shall not be used for compounding purposes.
- (10) Entry points on bags and vials shall be wiped with small sterile 70% isopropyl alcohol swabs or comparable method for disinfecting, allowing the isopropyl alcohol to dry before piercing stoppers with sterile needles and breaking necks of ampuls. The surface of the sterile 70% isopropyl alcohol swabs used for disinfecting entry points of sterile package and devices may not contact any other object before contacting the surface of the entry point. Particle generating material may not be used to disinfect the sterile entry points of packages and devices.
- (11) When sterile supplies are received in sealed pouches designed to keep them sterile until opening, the sterile supplies may be removed from the covering pouches as the supplies are introduced into the ISO Class 5 primary engineering control without the need to disinfect the individual sterile supply items.

### **15.34 Urgent use compounded sterile preparations.**

- (1) The compounding process shall be a continuous process that does not exceed one hour, unless required for the preparation.
- (2) Administration shall begin within one hour of preparation of the completion of the preparation.
- (3) Aseptic technique shall be followed during preparation, and procedures shall be used to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other compounded sterile products.
- (4) 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 1 hour BUD and time.

### **15.35 Sterilization methods.**

- (1) Sterilization methods employed shall sterilize 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) Pre-sterilization 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 pre-sterilization procedures shall be completed in an ISO Class 8 or better 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) Sterilization shall be performed utilizing one of the following 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 better air quality environment.
  5. Filter units used to sterilize compounded sterile preparations shall 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 microns 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 [*or other means*]. 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 at least a 3-log reduction in endotoxins.

### **15.36 Inspection and Sterility Testing.**

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

1. Visually inspect the container closure for leakage, cracks in the container or improper seals.
2. Visually check the compounded sterile preparation for phase separation.
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 prescriber 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 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.
- (e) Notwithstanding par. (d), 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, and that burden is found acceptable.
  - 2. The pharmacy has predetermined the endotoxins burden of the nonsterile ingredient and that burden is found acceptable.

**15.37 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. 12 hours when the preparation is stored at controlled room temperature.
  - 2. 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 with one or more nonsterile ingredients, no preservative added and no sterility testing performed, one of the following:
    - a. Within 4 days when the preparation is stored at controlled room temperature.
    - b. Within 7 days when the preparation is stored in a refrigerator.
    - c. Within 45 days when the preparation is stored in a freezer.

2. Prepared only with sterile ingredients, no preservative added and no sterility testing performed, one of the following:
    - a. Within 6 days when the preparation is stored at controlled room temperature.
    - b. Within 9 days when the preparation is stored in a refrigerator.
    - c. 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. Within 28 days when the preparation is stored at controlled room temperature.
    - b. Within 42 days when the preparation is stored in a refrigerator.
    - c. 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 with no preservative added and no sterility testing performed, one of the following:
    - a. Within 28 days when the preparation is stored at controlled room temperature.
    - b. Within 42 days when the preparation is stored in a refrigerator.
    - c. Within 45 days when the preparation is stored in a freezer.
  2. Prepared with preservative added and sterility testing performed, one of the following:
    - a. Within 42 days when the preparation is stored at controlled room temperature.
    - b. Within 42 days when the preparation is stored in a refrigerator.
    - c. Within 45 days when the preparation is stored in a freezer.
- (2) The administration dates and times established in sub. (1) may 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.

[ NOTE: Remove? **15.38 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 and 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. ]

**15.39 Training and evaluation.** (1) GENERAL. The managing pharmacist, all pharmacists, pharmacy technicians, pharmacy interns and pharmacy externs involved in compounding sterile preparations shall successfully complete didactic and practical training. The didactic and practical training shall be done before any compounding personnel initially prepares compounded sterile preparations and annually thereafter and shall include all of the following:

- (a) Hand hygiene and garbing.
- (b) Cleaning and disinfection.
- (c) Measuring and mixing.
- (d) Aseptic manipulation.
- (e) Cleanroom behavior.
- (f) Sterilization and depyrogenation.
- (g) Use of equipment.
- (h) Documentation.
- (i) Use of primary engineering controls.

**(2) EVALUATION.** Compounding personnel shall successfully complete an initial and annual evaluation which includes all of the following:

- (a) Visual observation of hand hygiene and garbing.
- (b) Visual observation of aseptic technique.
- (c) Gloved fingertip and thumb sampling.
- (d) Media-fill tests.

**(3) GLOVED FINGERTIP.** Successfully gloved and thumb sampling is measured by samplings resulting in zero colony-forming units no fewer than three times. Sampling shall be performed on sterile gloves inside of an ISO Class 5 primary engineering control. Gloved fingertip and thumb sampling in a RABS or an isolator shall be taken from the sterile gloves placed over the gauntlet gloves. When gloved fingertip sample results exceed action levels defined by the pharmacy, a review of hand hygiene and garbing procedures, glove and surface disinfection procedures and work practices shall be performed and documented.

[NOTE: *Remove?* **(4) 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.]

**(5) RECORDS.** The pharmacy shall maintain written policies and procedures for the initial and ongoing training and evaluation of persons involved in compounding sterile preparations. Documentation of all training, assessments, gloved fingertip tests and media-fill simulations shall be maintained by the pharmacy for 5 years and made available to the Board upon request.