

Clearinghouse Rule 16-085

STATE OF WISCONSIN
PHARMACY EXAMINING BOARD

IN THE MATTER OF RULE-MAKING : PROPOSED ORDER OF THE
PROCEEDINGS BEFORE THE : PHARMACY EXAMINING BOARD
PHARMACY EXAMINING BOARD : ADOPTING RULES
: (CLEARINGHOUSE RULE)

PROPOSED ORDER

An order of the Pharmacy Examining Board to repeal and recreate ch. Phar 15 relating to compounding pharmaceuticals.

Analysis prepared by the Department of Safety and Professional Services.

ANALYSIS

Statutes interpreted: ss. 450.01 (16),

Statutory authority: ss. 15.08 (5) (b), and 450.02 (3) (d) and (e), Stats.

Explanation of agency authority:

The Board shall promulgate rules for its own guidance and for the guidance of the trade or profession to which it pertains, and define and enforce professional conduct and unethical practices not inconsistent with the law relating to the particular trade or profession. [s. 15.08 (5) (b), Stats.]

The board may promulgate rules necessary for the administration and enforcement of this chapter and ch. 961 and establish minimum standards for the practice of pharmacy. [s. 450.02 (3) (d) and (e), Stats.]

Related statute or rule: N/A

Plain language analysis:

This proposed rule repeals and recreates the Pharmacy Examining Rules related to compounding pharmaceuticals.

Phar 15.01 creates the definitions which will be used throughout the chapter.

Subchapter I are the general provisions which provide requirements for all types of compounding.

Phar 15.10 requires a facility which has a designated area for compounding and orderly placement of equipment, materials and components so that errors are minimized. The compounding area is to be maintained in a clean and sanitary manner, be easily accessible to hot and cold running water, soap and single-use towels and all compounding equipment, materials and components stored off the floor and in a way that prevents contamination.

Phar 15, 11 requires a pharmacy to possess equipment and drug preparation containers or packaging that is appropriate to the compounding performed at the pharmacy, minimize contamination and not alter stability of the compounded preparation. The equipment needs to be maintained consistent with the manufacturer's recommendations.

Phar 15.12 requires compounding documentation necessary to trace, evaluate and replicate the compounding steps throughout the process of a preparation to be maintained for a period of 5 years after the date of the last refill of the preparation.

Phar 15.13 requires a final check of the compounding, investigate any discrepancies and take corrective action before the prescription is dispensed.

Phar 15.14 requires all personnel involved in the compounding, evaluation, packaging and dispensing of compounded preparations be properly trained and competency tested for the type of compounding conducted. It is the managing pharmacist's responsibility to ensure personnel training and competency assessments are completed and documented. The pharmacy shall establish written policies and procedures governing compounding and reflect current compounding practice.

Phar 15.15 requires in addition to the regular labeling requirements, to include storage conditions, beyond use date and special handling instructions.

Phar 15.16 Active pharmaceutical ingredients or added substances shall be manufactured by an FDA registered facility or accompanied by a certificate of analysis and USP or NF monograph specifications when available. Components for human use may not be used if they have been withdrawn or removed from the market based by the FDA. Compounding for food producing animal use may not use any components prohibited for use in food producing animals.

Phar 15.17 Compounded preparations dispensed or distributed directly to a practitioner to be administered to an individual patient without a patient specific prescription shall meet the following: the prescription shall include the name, address, drug, quantity and purpose of the compounded preparation; the label shall include the practitioner's name and state "For Practitioner Use Only – Not for Dispensing or Distribution" and marked for "Single Dose Only" if the sterility or integrity is not maintained after the opening of the container; the pharmacist shall record the name and address of the location the compounded preparation was dispensed or distributed, the lot number and beyond use date; and there shall be a procedure for immediate notification to all practitioners of a preparation which is recalled.

Subchapter II provisions relate to non-sterile compounding.

Phar 15.20 allows components with an expiration date from the manufacturer or distributor may be used before the expiration date provided the component is stored in its original container and there is minimal exposure of the remaining component each time component is withdrawn from the container. Components without an expiration date assigned by the manufacturer or supplier shall be assigned an expiration date based upon the nature of the component and its degradation mechanism, the container in which it is packaged and the storage conditions.

Phar 15.21 requires the beyond use date not be later than the expiration date on the container of any component. In the absence of stability information the beyond use date if based upon the type of formulations. Assignment of the beyond use date includes an assessment of the need for antimicrobial agents or refrigeration to protect against contamination introduced during or after the compounding.

Subchapter III provisions relate to sterile compounding.

Phar 15.30 contains definitions of words used throughout the subchapter.

Phar 15.31 indicates the requirements necessary for the segregated compounding area and the classified area to ensure there is not contamination. The primary engineering control shall be certified prior to initial use and then every six months in addition to a redesign of facility, or the replacement or relocation of the primary engineering control.

Phar 15.32 indicates the personnel hygiene, garbing and protective gear required to ensure there is not contamination.

Phar 15.33 requires the compounding area to be cleaned and disinfected with designated minimum frequency. The pharmacy shall have written standard operating procedures which are followed by all compounding and environmental services personnel for cleaning and disinfecting the compounding area. Storage sites for the compounding ingredients and supplies shall remain free from dust and debris. Supplies and equipments removed from shipping cartons shall be disinfected. Entry points on bags and vials shall be disinfected before piercing.

Phar 15.34 requires urgent use compounded sterile preparations to be prepared within one hour and administration shall begin within one hour of the completion of the preparation. Aseptic technique shall be followed and procedures to minimize contamination. Unless immediately and completely administered or witnessed by the person who prepared the preparation, the preparation shall have a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who did the preparation and the 1 hour beyond use date and time.

Phar 15.35 indicates the sterilization methods for maintaining physical and chemical stability and the packaging integrity of the compounding sterile preparations. The sterilization methods are by filtration, steam heat or dry heat based upon the components utilized in the preparation. Dry heat depyrogenation shall be used to render glassware and other thermostable containers pyrogen free.

Phar 15.36 requires after the completion of compounding, the preparation shall be physical inspected and upon any observed defects be discarded or segregated in a manner which prevents it from being dispensed and pass a sterility test. Any preparation containing a preservative shall also pass an antimicrobial effectiveness testing before being dispensed.

Phar 15.37 indicates the requirements for establishing a beyond use date. Sterility and stability considerations shall be considered when establishing a beyond use date. Administration date and times based upon the requirements listed in the rule can't be exceeded or extended without verifiable supporting valid scientific sterility and stability information that applies to the specific preparation or compound. If the beyond use date is based upon storage in a freezer, the integrity of the container closure system with the specific preparation in it shall have been demonstrated for 45 days at frozen storage.

Phar 15.38 provides that the managing pharmacist, all pharmacists, technicians, interns and externs involved in compounding sterile preparations shall successfully complete didactic and practical training initially and then annually. All personnel shall be evaluated initially and annually on all of the following: visual observation of hand hygiene and garbing; visual observation of aseptic technique; gloved fingertip and thumb sampling; and media-fill tests. Records of the training and evaluations shall be maintained by the pharmacy for 5 years.

Summary of, and comparison with, existing or proposed federal regulation:

None. There is federal compounding regulation relating to outsourcing facilities.

Comparison with rules in adjacent states:

Illinois: Illinois requires a specific area for compounding; records to be kept of each compounded prescription and the components; reference books; and a pharmacy operations manual with policies and procedures pertinent to the complexity and size of the compounding operations. The pharmacy may compound drug products to be used by practitioners in their office for administration to patients. Sterile compounding requires: a designated area of sufficient size to accommodate a laminar airflow hood, barrier isolation chamber and proper storage of drugs and supplies; the laminar airflow hood shall be certified annually; sink with hot and cold water; refrigerator and/or freezer with a thermometer or temperature recording device; current resource materials and texts; patient profile or medication system; specific labeling requirements including beyond use date and time; and compounding records are to be maintained for 5 years.

Iowa: Iowa requires compliance with United States Pharmacopeia, Chapters 795 and 797. In addition, an FDA registered outsourcing facility must be licensed as a pharmacy in Iowa.

Michigan: Michigan requires a pharmacy that provides compounding services to be licensed as a pharmacy and authorized to provide compounding services. The pharmacy must be accredited by the Pharmacy Compounding Accreditation Board and be in compliance with United States

Pharmacopeia standards. In addition, any outsourcing facility must be licensed as a pharmacy in Michigan.

Minnesota: Minnesota requires pharmacies compounding nonsterile drug preparations to follow United States Pharmacopeia, chapter 795 standards and pharmacies compounding sterile drug preparations to follow United States Pharmacopeia, chapter 797 standards.

Summary of factual data and analytical methodologies:

The Pharmacy Examining Board primarily utilized United States Pharmacopeia chapters 795 and 797 which are the recognized pharmacopeial standards. In addition, the Pharmacy Examining Board reviewed the code other states which have been revised since the New England Compounding Center meningitis outbreak in 2012.

Analysis and supporting documents used to determine effect on small business or in preparation of economic impact analysis:

The Board does not know how many or which pharmacies are compounding sterile pharmaceuticals and UPS 795 and 797 are the recognized pharmacopeial standards. Therefore the Board was unable to determine whether there will be an effect on small businesses. This rule was posted for 30 days for economic comments and none were received.

Fiscal Estimate and Economic Impact Analysis:

The Fiscal Estimate and Economic Impact Analysis is attached.

Effect on small business:

These proposed rules may have an economic impact on small businesses, as defined in s. 227.114 (1), Stats. and are submitted to the Small Business Regulatory Review Board for a determination on whether the rules will have a significant economic impact on a substantial number of small businesses. The Department's Regulatory Review Coordinator may be contacted by email at Jeffrey.Weigand@wisconsin.gov, or by calling (608) 267-2435

Agency contact person:

Sharon Henes, Administrative Rules Coordinator, Department of Safety and Professional Services, Division of Policy Development, 1400 East Washington Avenue, Room 151, P.O. Box 8366, Madison, Wisconsin 53708; telephone 608-261-2377; email at DSPSAdminRules@wisconsin.gov.

Place where comments are to be submitted and deadline for submission:

Comments may be submitted to Sharon Henes, Administrative Rules Coordinator, Department of Safety and Professional Services, Division of Policy Development, 1400 East Washington Avenue, Room 151, P.O. Box 8366, Madison, WI 53708-8366, or by email to

DSPSAdminRules@wisconsin.gov. Comments must be received on or before January 17, 2016 to be included in the record of rule-making proceedings.

TEXT OF RULE

SECTION 1. Repeals and recreates ch Phar 15 to read:

CHAPTER Phar 15
COMPOUNDING PHARMACEUTICALS

15.01 Definitions. In this chapter:

- (1) “Active pharmaceutical ingredient” or “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” or “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 sterile compounded sterile preparation shall not be used.
- (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) “Component” means any, active pharmaceutical ingredient, or added substances used in the compounding of a drug preparation.
- (8) “Compounding” means the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug delivery device, or a device in accordance with a prescription, or medication order. Compounding does not include repackaging. 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 in accordance with the directions contained in approved labeling provided by the manufacturer is not compounding.
 - (d) Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching or chemical analysis.

- (9) “Container-closure system” means the sum of packaging components that together contain and protect a dosage form including primary packaging components and secondary packaging components.
- (10) “Controlled room temperature” means a temperature maintained thermostatically that encompasses the usual and customary working environment of 68 degrees to 77 degrees Fahrenheit.
- (11) “Freezer” means a place in which the temperature is maintained between -13 degrees and 14 degrees Fahrenheit
- (12) “NF” means the National Formulary.
- (13) “Refrigerator” means a cold place in which the temperature is maintained between 36 degrees and 46 degrees Fahrenheit
- (14) “Stability” means the extent to which a compounded preparation retains, within specified limits and throughout its beyond use date, 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.
- (15) “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 maintained in a clean and sanitary condition.
- (4) 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.
- (5) 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 or packaging used in compounding drug products shall be of suitable composition. Equipment surfaces that contact components may not be reactive, additive, adsorptive or absorptive 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 of all APIs and added substances and their quantities.
- (3) Vendor or manufacturer, lot number and expiration date of each APIs and added substances.
- (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.
- (7) Container or container-closure system used in dispensing.
- (8) Packaging and storage requirements.
- (9) Quality control procedures.
- (10) Sterilization method when using non sterile ingredients to make a sterile preparation.
- (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.
- (19) Documentation of any adverse reactions or preparation problems reported by the patient or caregiver.

15.13 Quality control.

(1) A pharmacist shall complete a final check which shall include verification of all the following:

- (a) Written procedures were followed in the compounding process.

- (b) Preparation instructions were followed.
- (c) Finished preparation appears as expected.
- (d) Label includes all required elements.
- (e) Quality control procedures were completed.
- (f) Compounding records are complete

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

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 and managing pharmacist shall establish written policies and procedures governing all of the following:

- (a) Personnel qualifications and training, responsibilities, and competencies.
- (b) Personal hygiene, garb, garbing, and personal protective gear.
- (c) Use and maintenance of compounding facilities and equipment, including applicable certifications.
- (d) Environmental monitoring including storage, handling, packaging and transport.
- (e) Cleaning and disinfection of compounding area.
- (f) Component selection.
- (g) Sterilization and depyrogenation, if pharmacy does sterilization and depyrogenation.
- (h) Documentation requirements.
- (i) Establishing BUD.
- (j) Reporting of adverse drug events.
- (k) A risk management program, including documentation of incidents, adverse drug reactions and product contamination.
- (L) Quality assurance program.
- (m) Maintaining the integrity of the classified work area of the laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators and biological safety cabinets.
- (n) Handling small and large spills of antineoplastic agents and other hazardous substances.

(3) REVIEW OF POLICIES AND PROCEDURES The policy and procedures shall be reviewed at least once every 36 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) Labeling requirements in s. Phar 7.02 and 8.08.
- (2) Storage conditions if other than controlled room temperature.
- (3) BUD.
- (4) Special handling instructions.

15.16 Component Selection. (1) Active pharmaceutical ingredients or added substances used in compounding shall be manufactured by an FDA registered facility or accompanied by a certificate of analysis.

(2) APIs and added substances shall meet USP or NF monograph specifications when monographs are available.

(3) 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.

(4) 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 United States food and drug administration. A pharmacist compounding for food producing animal use may not use components prohibited for use in food producing animals.

15.17 Non-patient specific compounding. Compounded preparations dispensed or distributed directly to a practitioner to be administered to an individual patient 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) The label shall include the practitioner's name in place of the patient's name and state "For Practitioner Use Only – Not for Dispensing or Distribution". If the sterility or integrity of the compounded preparation is not maintained after the initial opening of the container, the label shall state "Single-Dose Only".

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

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

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.

(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 is 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 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 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, 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 primary engineering control 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.

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

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

(7) “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.

(8) “HEPA” means high-efficiency particulate air.

(9) “ISO Class 5” 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.

(10) “ISO Class 7” 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.

- (11) "ISO Class 8" 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.
- (12) "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.
- (13) "Primary engineering control" means a device or zone that provides an ISO Class 5 environment for sterile compounding.
- (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 isolators and compounding aseptic containment isolators.
- (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, area, or room that contains a primary engineering control.
- (17) "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.
 - (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.
- (4) PRIMARYENGINEERING CONTROL.** The primary engineering control shall be certified by an independent, qualified individual prior to initial use and then every six months. It shall also be certified when any of the following occurs:
- (a) Redesign of the facility.
 - (b) Replacement of the primary engineering control.
 - (c) Relocation of the primary engineering control.

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) Abstain from eating, chewing gum or drinking in the compounding area or bringing food, gum or drink into the compounding area.

(c) Artificial nails, nail extenders or nail polish may not be worn while working in the compounding area. Nails shall be neat and trim.

(d) 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.

(e) A hand hygiene procedure shall be performed after performing the protective equipment in par (d). The hand hygiene procedure includes all of the following:

1. Wash hands and forearms up to the elbows with unscented soap and water for at least 30 seconds.

2. Hands and forearms to the elbows shall be completely dried using either lint-free disposable towels or wipes.

3. 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.

(f) Personnel shall wear one of the following:

1. Non-cotton, low-lint sterile gown and sterile gloves.

2. Non-cotton, low-lint gown, sterile sleeves and sterile gloves.

(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 and decontaminated once it is closed after each time it is opened. If cleaning occurs without opening, decontaminate 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, detergents 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 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 filtration. 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, sterility testing and antimicrobial effectiveness.

(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.

(3) ANTIMICROBIAL EFFECTIVENESS. Compounded sterile preparations containing a preservative shall pass an antimicrobial effectiveness testing with the results obtained on the specific formulation before any of the compounded sterile preparation is dispensed. The test may be conducted only once on each formulation in the particular container-closure system in which it will be stored or dispensed. The antimicrobial effectiveness test shall occur at one of the following times:

(a) At the completion of the sterility test.

(b) At the time of preparation for compounded sterile preparations which have not undergone a sterility testing.

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. May not exceed 12 hours when the preparation is stored at controlled room temperature.
2. May not exceed 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.
4. Prepared with sterile ingredients, preservative added and no sterility testing, 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.
5. Prepared with sterile ingredients, preservative added and sterility testing, 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.

(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 14 days when the preparation is stored at controlled room temperature.
 - b. Within 28 days when the preparation is stored in a refrigerator.
 - c. Within 45 days when the preparation is stored in a freezer.
2. Prepared with 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.
3. Prepared with 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.
4. 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.

(3) For compounded sterile preparations which have been assigned a BUD based upon storage in a freezer, the integrity of the container closure system with the specific compounded sterile preparation in it shall have been demonstrated for 45 days at frozen storage. The container closure integrity test may be conducted only once on each formulation in the specific container closure system in which it will be stored or dispensed.

15.38 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.
- (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.

SECTION 2. EFFECTIVE DATE. The rules adopted in this order shall take effect on the first day of the month following publication in the Wisconsin Administrative Register, pursuant to s. 227.22 (2) (intro.), Stats.

(END OF TEXT OF RULE)
