Chapter Phar 15

COMPOUNDING PHARMACEUTICALS

Note: Chapter Phar 15 is shown as repealed and recreated by CR 16-085, effective November 1, 2018, Register April 2018 No. 748.

Phar 15.01 Intent. The intent of this chapter is to create a state regulatory standard that aligns with compounding standards found in the United States Pharmaceopeia cUSPd general chapters lower than the number 1000.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.015 Definitions. In this chapter:

c1d XActive pharmaceutical ingredientY or XAPIY 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.

c2d XAdded substancesY 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.

c3d XAdverse drug eventY means an injury resulting from the use of a drug.

c4d XBeyond use dateY or XBUDY means one of the following:

cad The date after which a non-sterile compounded preparation shall not be used.

cbd The date and time after which a sterile compounded preparation shall not be used.

c5d XCertificate of analysisY 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.

c6d XChemical stabilityY means each active pharmaceutical ingredient retains its chemical integrity and labeled potency, within specified limits.

c7d XClassified areaY means a space that maintains an air cleanliness classification based on the International Organization for Standardization cISOd.

c8d XComponentY means any active pharmaceutical ingredient, or added substances used in the compounding of a drug preparation.

c9d XCompoundingY 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:

cad Preparation of drug dosage forms for both human and animal patients.

cbd Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.

ccd Reconstitution or manipulation of commercial products that may require the addition of one or more ingredients. Notwithstanding this paragraph, the reconstituting, mixing, or storage and beyond use dating that is performed for non-sterile preparations in accordance with the directions contained in approved labeling provided by the manufacturer is not compounding.

cdd Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching, or chemical analysis.

c10d XContainer-closure systemY means the sum of packaging components that together contain and protect a dosage form, including primary packaging components and secondary packaging components.

c11d XControlled room temperatureY means a temperature maintained thermostatically that encompasses the usual and customary working environment of 68 degrees to 77 degrees Fahrenheit or 20 degrees to 25 degrees Celsius.

c12d XFDAY means the United States food and drug administration.

c13d XFreezerY means a place in which the temperature is maintained between -13 degrees and 14 degrees Fahrenheit or -25 degrees and -10 degrees Celsius.

c14d XMicrobiological stabilityY means sterility or resistance to microbial growth is retained according to specified requirements and antimicrobial agents that are present retain effectiveness within specified limits.

c15d XNFY means the National Formulary.

c16d XPhysical stabilityY means the original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.

c17d XRefrigeratorY means a cold place in which the temperature is maintained between 36 degrees and 46 degrees Fahrenheit or 2 degrees and 8 degrees Celsius.

c18d XStabilityY means the extent to which a compounded preparation retains, within specified limits and through its beyond use date, the same properties and characteristics that it possessed at the time of compounding.

c19d XTherapeutic stabilityY means the therapeutic effect remains unchanged.

c20d XToxicological stabilityY means no significant increase in toxicity occurs.

c21d XUSPY means the United States Pharmacopeia.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18; CR 22-007: am. c11d, c13d, c17d Register July 2022 No. 799, eff. 8-1-22.

Subchapter I — General

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

c1d An area designated for compounding.

c2d Orderly placement of compounding equipment, materials, and components in order to minimize the potential for compounding errors.

c3d The compounding area is maintained in a clean and sanitary condition.

c4d The compounding area is easily accessible to all of the following:

cad Hot and cold running water, exclusive of the bathroom sink.

cbd Soap or detergent.

ccd Single-use towels.

c5d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.11 Equipment and Drug Preparation Containers. c1d A pharmacy shall possess equipment and drug preparation containers or packaging appropriate to the type of compounding performed at the pharmacy.

c2d 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.

c3d Equipment and drug preparation containers or packaging used in compounding drug products shall be of suitable composition and may not be reactive, additive, adsorptive, or absorptive so as to alter the stability of the compounded preparation.

c4d 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.

c5d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.12 Records of compounding. 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:

c1d Official or assigned name, strength, and dosage form of the preparation.

c2d List of all APIs and added substances and their quantities.

c3d Vendor or manufacturer, lot number and expiration date of each APIs and added substances.

c4d Equipment and supplies needed to prepare the preparation.

c5d Mixing instructions pertinent to the replication of the preparation as compounded.

c6d Compatibility and stability information, including references or laboratory testing.

c7d Container or container-closure system used in dispensing.

c8d Packaging and storage requirements.

c9d Quality control procedures.

c10d Sterilization method when using non-sterile ingredients to make a sterile preparation.

c11d Total quantity compounded.

c12d Name of the person who prepared the preparation.

c13d Name of the person who performed the quality control procedures.

c14d Name of the person who approved the preparation.

c15d Date of preparation.

c16d Assigned control or prescription number.

c17d Assigned BUD.

c18d Copy of the label to dispense final product.

c19d Documentation of any adverse reactions or preparation problems reported by the patient or caregiver.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.13 Quality control. c1d One or more pharmacists shall complete a verification of all the following before dispensing:

cad Written procedures were followed in the compounding process.

cbd Preparation instructions were followed.

ccd Finished preparation appears as expected.

cdd Label includes all required elements.

ced Quality control procedures were completed.

cfd Compounding records are complete.

c2d A pharmacist shall investigate any discrepancies found during any of verifications and take appropriate corrective action before dispensing.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.14 Training, Policies, and Procedures. c1d 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.

c2d POLICIES AND PROCEDURES. The pharmacy and managing pharmacist shall establish written policies and procedures governing all of the following:

cad Personnel qualifications and training, responsibilities, and competencies.

cbd Personal hygiene, garb, garbing, and personal protective gear.

ccd Use and maintenance of compounding facilities and equipment, including applicable certifications.

cdd Environmental monitoring.

ced Cleaning and disinfection of compounding area.

cfd Component selection.

cgd Sterilization and depyrogenation, if pharmacy does sterilization and depyrogenation.

chd Documentation requirements.

cid Establishing BUD.

cjd Reporting of adverse drug events.

ckd A risk management program, including documentation of incidents, adverse drug reactions and product contamination.

cLd A quality assurance program.

cmd Maintaining the integrity of any classified work areas.

cnd Handling small and large spills of antineoplastic agents and other hazardous substances.

cod Notification to patients or practitioners of a preparation which is recalled when there is potential for patient harm.

c3d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18; correction in c2d cod made under s. 35.17, Stats., Register April 2018 No. 748.

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

c1d Labeling requirements in s. Phar 7.02 and 8.08.

c2d Storage conditions if other than controlled room temperature.

c3d BUD.

c4d Special handling instructions, when applicable.

c5d Indication that the preparation is compounded unless administered by health care personnel.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.16 Component Selection. c1d Active pharmaceutical ingredients or added substances used in compounding shall be manufactured by an FDA registered facility or accompanied by a certificate of analysis.

c2d APIs and added substances shall meet USP or NF monograph specifications when monographs are available. A pharmacist shall use professional judgement in selection of APIs if USP or NF grade is not available.

c3d All components shall be stored and handled consistent with the manufacturer[s labeling or USP or NF monographs and in a manner that prevents contamination and deterioration.

c4d A pharmacist compounding for human use may not use components that have been withdrawn or removed from the market for safety or efficacy reasons by the FDA. A pharmacist compounding for food producing animal use may not use components prohibited for use in food producing animals.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.17 Non-patient specific compounding. Compounded preparations dispensed or distributed to a practitioner pursuant to a non-patient specific order to be administered by a practitioner or practitioner[s agent shall meet all of the following:

c1d The order shall include the name and address of the practitioner, drug, strength, quantity, and the purpose of the compounded preparation.

c2d The label shall include the practitioner[s name in place of the patient[s name and state XFor Practitioner Administration Only — Not for Dispensing or Distribution.Y If the sterility or integrity of the compounded preparation is not maintained after the initial opening of the container, the label shall state XSingle-Dose Only.Y

c3d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Subchapter II — Non-sterile Compounding

Phar 15.20 Component Selection. c1d Components with an expiration date from the manufacturer or distributor may be used before the expiration date provided all of the following:

cad The component is stored in its original container under conditions to avoid decomposition.

cbd There is minimal exposure of the remaining component each time component is withdrawn from the container.

c2d 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.

c3d 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:

cad Component name.

cbd Original supplier.

ccd Lot or control number.

cdd Transfer date.

ced Expiration date.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.21 Assigning BUD. c1d The BUD shall not be later than the expiration date on the container of any component.

c2d Only 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:

cad 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.

cbd For water-containing oral formulations, the BUD shall not be later than 14 days when stored in a refrigerator.

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

c3d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Subchapter III — Sterile Compounding

Phar 15.30 Definitions. In this subchapter:

c1d XAnte areaY 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.

c2d XBuffer areaY 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.

c3d XCategory 1Y means a compounded sterile preparation compounded with a primary engineering control in a segregated compounding area.

c4d XCategory 2Y means a compounded sterile preparation compounded with a primary engineering control in a classified area.

c5d XCleanY means to physically remove debris, dirt, dust, and other impurities from surfaces or objects using a cleaning agent with a detergent.

c6d XCompounded sterile preparationY means a compounded final preparation intended to be sterile through the BUD.

c7d XCompounded stock solutionY means a compounded solution to be used in the preparation of multiple units of a finished compounded sterile preparation.

c8d XCritical siteY 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.

c9d XDisinfectY means the killing of microorganisms when used according to the disinfectant[s label.

c10d XHEPAY means high-efficiency particulate air.

c10md XHigh-risk level compounded sterile preparationsY means preparations compounded from non-sterile ingredients or from ingredients that are incorporated using non-sterile equipment before terminal sterilization, or from commercially manufactured sterile products that lack effective antimicrobial preservatives and whose preparation, transfer, sterilization, and packaging is performed in air quality worse than ISO class 5 for more than one hour. High-risk level compounded sterile preparations include water containing preparations that are stored for more than six hours before terminal sterilization.

c11d XISO Class 5Y 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.

c12d XISO Class 7Y 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.

c13d XISO Class 8Y 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.

c14d XIsolatorY 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.

c14gd XLow-risk level compounded sterile preparationsY means preparations compounded with aseptic manipulations entirely within ISO class 5 or better air quality using only sterile ingredients, products, components, and devices. The low-risk level sterile compounding process involves only transfer, measuring, and mixing, using no more than three commercially manufactured sterile products, and not more than two entries into one sterile container or package to make the compounded sterile preparations.

c14rd XMedium-risk level compounded sterile preparationsY means preparations compounded under low-risk level conditions but which require multiple individual or small doses of sterile products to be combined or pooled to prepare compounded sterile preparations that will be administered either to multiple patients or to one patient on multiple occasions. The medium-risk level sterile compounding process includes complex aseptic manipulations other than single volume transfer, and requires an unusually long duration, such as that required to complete dissolution or homogeneous mixing.

c15d XPrimary engineering controlY means a device or zone that provides an ISO Class 5 environment for sterile compounding.

c16d XRestricted access barrier system cRABSdY 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.

c17d XSterility assurance level of 10^{-6}Y means an equivalent to a probability that one unit in a million is nonsterile.

c18d XSegregated compounding areaY means a designated, unclassified space, area, or room that contains a primary engineering control.

c19d XUrgent use compounded sterile preparationY 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18; CR 22-007: cr. c10md, c14gd, c14rd Register July 2022 No. 799, eff. 8-1-22.

Phar 15.31 Facility design and environmental controls. c1d GENERAL. Facilities shall meet all of the following requirements:

cad Be physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites.

cbd Be accessible only to designated personnel.

ccd Have a heating, ventilation, and air conditioning system controlling the temperature and humidity.

c2d SEGREGATED COMPOUNDING AREA. A segregated compounding area shall meet all of the following requirements:

cad Be located in an area away from unsealed windows and doors that connect to the outdoors, or significant traffic flow.

cbd Be located in an area which is not adjacent to construction sites, warehouses, and food preparation areas.

ccd Have a defined perimeter.

cdd Locate the primary engineering control at least one meter from any sink.

c3d CLASSIFIED AREA. A classified area shall meet all of the following:

cad The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, and nonshedding.

cbd Work surfaces shall be constructed of smooth, impervious materials. All work surfaces shall be resistant to damage from cleaning and sanitizing agents.

ccd 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.

cdd 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.

ced Walls shall be constructed of a durable material, panels locked together and sealed or of epoxy-coated gypsum board.

cfd 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.

chd Ceiling lighting fixtures shall have exterior lens surfaces which are smooth, mounted flush, and sealed.

cid Carts shall be constructed of stainless steel wire, nonporous plastic or sheet metal with cleanable casters.

cjd Tacky mats may not be used in a classified area.

ckd HEPA filters and unidirectional airflow shall be used to maintain the appropriate airborne particulate classification.

cLd The classified area shall measure not less than 30 air changes per hour of which at least half shall be HEPA-filtered fresh air.

cmd For classified areas physically separated through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02-inch water column is required to separate each classified area. If a pass-through is used, only one door shall be opened at a time. 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.

cmmd For classified areas not physically separated, no sterile compounded preparation may be compounded using any ingredient that was at any time non-sterile in a classified area not physically separated and all of the following shall be met:

1. The buffer and ante areas shall be designated with a line of demarcation.

2. The principle of displacement airflow shall be used with an air velocity of 40 feet per minute or more from the buffer area across the entire plane of the line of demarcation.

cnd Devices and objects essential to compounding shall be located at an appropriate distance from the primary engineering control.

cpd 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.

cqd 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.

c4d PRIMARY ENGINEERING CONTROL. The primary engineering control shall be certified by an independent, qualified individual certified by the Controlled Environment Testing Association[s National Board of Testing or another Board approved entity prior to initial use and then every six months. It shall also be certified when any of the following occurs:

cad Redesign of the facility.

cbd Replacement of the primary engineering control.

ccd Relocation of the primary engineering control.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.32 Personnel hygiene, garbing and protective gear. c1d 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.

c2d All personnel who engage in compounding sterile preparations shall comply with all of the following requirements before entering the compounding area:

cad Remove personal outer garments, all cosmetics, exposed jewelry and piercings, headphones, ear buds, and cell phones.

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

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

cdd Don personnel protective equipment and perform hand hygiene 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 and face masks.

3. Eye shields, if required due to working with irritants or hazardous drugs.

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

5. Don low lint disposable gown or overalls.

6. 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.

c3d 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. Sterile gloves shall be donned over the RABS gloves.

c4d 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.

c5d When compounding personnel exit the buffer or segregated compounding area, a 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, shoe covers, hair and facial hair covers, face masks, eye shields, and gloves shall be replaced with new ones before re-entering the compounding area.

c6d Garbing items, including gowns, shall be segregated and stored before use in an enclosure to prevent contamination.

c7d Visibly soiled gowns shall be changed immediately.

c8d Gloves shall be sterile and powder free and tested by the manufacturer for compatibility with alcohol disinfection.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.33 Cleaning and Disinfecting the Compounding Area and Supplies. **c1d** 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.

c2d Compounding personnel shall clean in accordance with the following:

cad Primary engineering control work surfaces, counters, floors and work surfaces in the buffer zone area, ante room and segregated compounding areas daily.

cbd Walls, ceilings and storage shelving monthly.

ccd When a spill occurs or the surface is visibly soiled.

cdd Sporicidal agents shall be used at least weekly to clean compounding areas.

c3d Compounding personnel shall disinfect in accordance with the following:

cad Primary engineering control work surfaces at the beginning and end of each compounding business day and before each batch, but not longer than 4 hours following the previous disinfection when ongoing compounding activities are occurring.

cbd When microbial contamination is known to have been or is suspected of having been introduced into the compounding area.

c4d 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.

c5d 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.

c6d Storage sites for compounding ingredients and supplies shall remain free from dust and debris.

c7d 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.

c8d All cleaning tools and materials shall be 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.

c9d 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 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.

c10d 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 ampules. 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.

c11d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18; CR 22-007: am. c10d Register July 2022 No. 799, eff. 8-1-22.

Phar 15.34 Immediate-use compounded sterile preparations. Immediate-use compounded sterile preparations are exempt from the requirements described for low-risk level, Category 1, and Category 2 compounding sterile preparations only when all the following criteria are met:

c1d The compounding process involves simple transfer of not more than three commercially manufactured sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers[original containers and not more than two entries into any one container or product of sterile infusion solution or administration container or device.

c2d Unless required for the preparation, the compounding procedure is a continuous process not to exceed 1 hour.

c3d During preparation, aseptic technique is followed and, if not immediately administered, the finished compound sterile preparation is under continuous supervision to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other compound sterile preparations, and direct contact of outside surfaces.

c4d Administration begins not later than 4 hours following the start of the preparation.

c5d Unless immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the compounded sterile preparation shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared it, and the exact 4-hour BUD and time.

c6d If administration of the compounded sterile preparation has not begun within 4 hours following the start of preparation, it shall be promptly, properly, and safely discarded.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18; CR 22-007: r. and recr. Register July 2022 No. 799, eff. 8-1-22.

Phar 15.35 Sterilization methods. **c1d** 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.

c2d Pre-sterilization requirements shall meet all of the following:

cad 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.

cbd 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.

c3d Sterilization shall be performed utilizing one of the following methods:

cad *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.

cbd *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 sterility assurance level 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.

ccd *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.

c4d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.36 Inspection, sterility testing and antimicrobial effectiveness. c1d PHYSICAL INSPECTION. cad 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.

cbd 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.

ccd 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.

c2d STERILITY TESTING. cad 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.

cbd 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.

ccd 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.

cdd 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.

ced Notwithstanding par. cdd, 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.

c3d ANTIMICROBIAL EFFECTIVENESS. Compounded sterile preparations containing a preservative added by the compounder 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:

cad At the completion of the sterility test.

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

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.

Phar 15.37 Beyond use dating. c1d Sterility and stability considerations shall be taken into account when establishing a BUD. Either Category 1 and 2, or low, medium, and high-risk compounding preparation standards may be used, but not a combination of the two within the same pharmacy. The following dates and times for storage and initiation of administration of the compounded sterile preparations shall apply:

cad 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.

cbd For Category 1 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.

ccd For aseptically processed Category 2 processed sterile preparations, one of the following:

1. No sterility testing performed or sterility testing not passed, and prepared with one or more nonsterile starting components, one of the following:

a. Within 1 day when the preparation is stored at controlled room temperature.

b. Within 4 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

2. No sterility testing performed or sterility testing not passed, and prepared with only sterile starting components, one of the following:

a. Within 4 days when the preparation is stored at controlled room temperature.

b. Within 10 days when the preparation is stored in a refrigerator.

c. Within 45 days when the preparation is stored in a freezer.

3. Sterility testing performed and passed, one of the following:

a. Within 30 days when the preparation is stored at controlled room temperature.

b. Within 45 days when the preparation is stored in a refrigerator.

c. Within 60 days when the preparation is stored in a freezer.

cdd For Category 2 compounded sterile preparations, terminally sterilized by a validated procedure, one of the following:

1. No sterility testing performed or sterility testing not passed, 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. Sterility testing performed and passed, one of the following:

a. Within 45 days when the preparation is stored at controlled room temperature.

b. Within 60 days when the preparation is stored in a refrigerator.

c. Within 90 days when the preparation is stored in a freezer.

c2d The BUD established in sub. c1d 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.

c3d 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.

c4d When a preservative is added, the compounded sterile formulation shall pass antimicrobial effectiveness testing that shall include inoculation of standardized microorganisms, incubation serial sampling, and calculation of the changes in colony forming unit concentrations in terms of log reduction. The results of antimicrobial effectiveness testing shall be obtained before any of the compounded sterile preparation is dispensed. Preservatives shall not be used as a substitute for good compounding practices.

c5d For low-risk level compounded sterile preparations, in the absence of passing a sterility test:

cad Within 48 hours when the preparation is stored at controlled room temperature.

cbd Within 14 days when the preparation is stored in a refrigerator.

ccd Within 45 days when the preparation is stored in a freezer.

cdd For products prepared in an airflow workbench not located in a buffer area, administration shall begin within 12 hours or less of preparation.

c6d For medium-risk level compounded sterile preparations, in the absence of passing a sterility test:

cad Within 30 hours when the preparation is stored at controlled room temperature.

cbd Within 9 days when the preparation is stored in a refrigerator.

ccd Within 45 days when the preparation is stored in a freezer.

c7d For high-risk level compounded sterile preparations, in the absence of passing a sterility test:

cad Within 24 hours when the preparation is stored at controlled room temperature.

cbd Within 3 days when the preparation is stored in a refrigerator.

ccd Within 45 days when the preparation is stored in a freezer.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18; CR 22-007: am. c1d cintro.d, ccd cintro.d, 1. cintro.d, a., b., 2. cintro.d, a., b., 3., r. c1d ccd 4., 5., am. c1d cdd 1. cintro.d, 2., r. c1d cdd 3., 4., cr. c5d to c7d Register July 2022 No. 799, eff. 8-1-22; correction in c6d cbd, c7d cbd made under s. 35.17, Stats. July 2022 No. 799.

Phar 15.38 Training and evaluation. c1d GENERAL. The managing pharmacist, pharmacists, pharmacy technicians, pharmacy interns and pharmacy externs compounding sterile preparations shall successfully complete didactic or practical training. The didactic or practical training shall be done before any compounding personnel initially prepares compounded sterile preparations and annually thereafter and shall include all of the following:

cad Hand hygiene and garbing.

cbd Cleaning and disinfection.

ccd Measuring and mixing.

cdd Aseptic manipulation.

ced Cleanroom behavior.

cfd Sterilization and depyrogenation.

cgd Use of equipment.

chd Documentation.

cid Use of primary engineering controls.

c2d EVALUATION. Compounding personnel shall successfully complete an initial and annual evaluation which includes all of the following:

cad Visual observation of hand hygiene and garbing.

cbd Visual observation of aseptic technique.

ccd Gloved fingertip and thumb sampling.

cdd Media-fill tests.

c3d 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.

c5d 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.

History: CR 16-085: cr. Register April 2018 No. 748 eff. 11-1-18.