CHAPTER 13
STERILE COMPOUNDING PRACTICES

657—13.1(124,126,155A) Purpose and scope. These rules establish standards and procedures for the preparation, labeling, and distribution of sterile preparations by licensed pharmacies pursuant to a practitioner's order or prescription; for sterile product quality and characteristics; for personnel training, environmental quality, and equipment standards; and for pharmaceutical care. Sterile compounding differs from nonsterile compounding primarily by requiring the maintenance of sterility when preparations are compounded exclusively with sterile ingredients and components and by requiring the achievement of sterility when preparations are compounded with nonsterile ingredients and components. The standards and procedures outlined in this chapter apply to pharmacy practice when a preparation:

1. Is prepared according to the manufacturer's labeled instructions and requires other manipulations that expose the original contents to potential contamination;
2. Contains nonsterile ingredients or employs nonsterile components or devices that must be sterilized before administration; or
3. Is a biologic, diagnostic, drug, or nutrient that possesses characteristics of either "1" or "2" above and includes, but is not limited to, the following preparations that are required to be sterile when they are administered into patient body cavities, central nervous and vascular systems, eyes, and joints, and when used as baths for live organs and tissues, such as injections (e.g., colloidal dispersions, emulsions, solutions, and suspensions), aqueous bronchial and nasal inhalations, irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

Standards and safe practices for the compounding of radioactive preparations are identified in 657—Chapter 16.

[**ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.2(124,126,155A) Definitions. For the purposes of this chapter, the following definitions shall apply:

"Anteroom" or *"ante area"* means an ISO Class 8 or superior area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, preparation labeling, and other high-particulate generating activities.

"Aseptic processing" means a method of preparing pharmaceutical and medical products that involves the separate sterilization of the product and of the package, the transfer of the product into the container, and closure of the container under at least ISO Class 5 conditions and using procedures designed to preclude contamination of drugs, packaging, equipment, or supplies by microorganisms during processing.

"Beyond-use date" means the date or time following compounding after which the preparation shall not be stored or transported and after which administration of the preparation shall not begin. The beyond-use date is determined from the date or time compounding of the preparation is completed.

"Biological safety cabinet" or *"BSC"* means a ventilated cabinet having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection.

"Buffer area" or *"cleanroom"* means a room or area where the primary engineering control device is physically located and in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear is not exceeded for a specified cleanliness class. Activities that occur in the buffer area include the preparation and staging of components and supplies used when sterile preparations are compounded.

"Compounding" means the constitution, reconstitution, combination, dilution, or other process causing a change in the form, composition, or strength of any ingredient or of any other attribute of a product.

"Compounding aseptic isolator" or *"CAI"* means a form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. A CAI is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbially retentive filter, HEPA minimum.

"Critical site" means a location that includes any component or fluid pathway surfaces or openings, such as vial septa, injection ports, beakers, opened ampoules, and needle hubs, exposed and at risk of direct contact with air, moisture, or touch contamination.

"Hazardous drug" means a pharmaceutical that is antineoplastic, carcinogenic, mutagenic, or teratogenic.

"HEPA" means high efficiency particulate air.

"High-risk preparation" means a sterile preparation that is compounded from nonsterile ingredients; that is compounded with nonsterile components, containers, or equipment and requires terminal sterilization; or that meets the conditions of rule 657—13.13(155A).

"ISO Class 5" or *"Class 100 condition"* means an atmospheric environment that contains less than 100 particles, 0.5 microns or larger in diameter per cubic foot of air, according to ISO standards.

"ISO Class 7" or *"Class 10,000 condition"* means an atmospheric environment that contains less than 10,000 particles, 0.5 microns or larger in diameter per cubic foot of air, according to ISO standards.

"ISO Class 8" or *"Class 100,000 condition"* means an atmospheric environment that contains less than 100,000 particles, 0.5 microns or larger in diameter per cubic foot of air, according to ISO standards.

"Laminar airflow workbench" or *"LAFW"* means an apparatus designed to provide an ISO Class 5 environment for the preparation of sterile products that uses air circulation in a defined direction that passes through a HEPA filter to remove the initial particles and the particles generated within the controlled environment.

"Low-risk preparation" means a sterile preparation that is compounded with sterile equipment, sterile ingredients, and sterile contact surfaces or that meets the conditions of rule 657—13.11(155A).

"Media-fill test" or *"MFT"* means a test used to validate aseptic technique of compounding personnel or of processes and to ensure that the processes used are able to produce sterile product without microbial contamination.

"Medium-risk preparation" means a sterile preparation that is compounded with sterile equipment, sterile ingredients, and sterile contact surfaces and involves complex or numerous manipulations of a sterile product or that meets the conditions of rule 657—13.12(155A).

"Multiple-dose container" means a multiple-unit container for articles or preparations intended for parenteral administration only and usually containing antimicrobial preservatives.

"Nasal inhalation" means a drug product or preparation, including the delivery device if applicable, whose intended site of deposition is the respiratory tract or the nasal or pharyngeal region. Nasal inhalation does not include a topical nasal spray or irrigation that is deposited primarily in the nasal passages.

"Negative pressure room" means a room that is at a lower pressure compared to adjacent spaces, creating a net airflow into the room.

"Positive pressure room" means a room that is at a higher pressure compared to adjacent spaces, creating a net airflow out of the room.

"Preparation" or *"compounded sterile preparation"* means a sterile drug or nutrient that is compounded in a licensed pharmacy or other health care-related facility pursuant to the order of a licensed prescriber, which preparation may or may not contain sterile products.

"Primary engineering control device" means a device or room that provides an ISO Class 5 environment during the compounding process. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), and compounding aseptic isolators (CAIs).

"Product" means a commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the FDA.

"Segregated compounding area" means a designated space, either a demarcated area or room, which is restricted to preparing low-risk preparations with 12-hour or less beyond-use date. A segregated compounding area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for the compounding of sterile preparations and shall be void of activities and materials that are extraneous to sterile compounding.

"Single-dose container" means a single-unit container for articles or preparations intended for parenteral administration only, intended for a single use and labeled as such. Examples include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when labeled for a single use or single dose.

"Sterile compounding" means the aseptic processing in a clean air environment of any pharmaceutical preparations that are required to be sterile when they are administered into patient body cavities, central nervous and vascular systems, eyes, and joints, and when used as baths for live organs and tissues, including by not limited to injections (e.g., colloidal dispersions, emulsions, solutions, and suspensions), aqueous bronchial and nasal inhalations, irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

[**ARC 9180B**, IAB 11/3/10, effective 12/8/10; **ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.3(155A) Responsibilities.

13.3(1) *Pharmacist.* Each pharmacy shall have a pharmacist responsible for ensuring that:

a. Preparations are accurately identified, measured, diluted, and mixed; and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed.

b. Appropriate cleanliness conditions are maintained, including preservation of the sterile environment during the compounding process.

c. Beyond-use dates are established based on direct testing or extrapolation from reliable literature sources. The pharmacy shall maintain written justification of the chosen beyond-use date or, if a written standard is not available, a maximum 24-hour expiration shall be used.

d. Equipment, apparatus, and devices used to compound a preparation are consistently capable of operating properly and within acceptable tolerance limits.

13.3(2) *In-process checking procedure.* Each pharmacy shall establish a written quality assurance procedure that includes the following in-process checks:

a. Appropriate procedures are followed for measuring, mixing, diluting, purifying, sterilizing, packaging, and labeling of the specific preparation.

b. Packaging selection is appropriate to preserve the sterility and strength of the preparation.

c. All functions performed by nonpharmacists are verified by the pharmacist before the preparation is dispensed to the patient.

13.3(3) *Training documentation.* All personnel involved with compounding, repackaging, or manipulating sterile preparations shall be adequately educated and trained. Training shall include written documentation certifying that compounding personnel are able to adequately complete the following activities:

a. Perform antiseptic hand cleansing and disinfection of nonsterile compounding surfaces.

b. Select and appropriately don protective garb.

c. Maintain or achieve sterility of preparations in ISO Class 5 primary engineering control devices.

d. Identify, weigh, and measure ingredients.

e. Manipulate sterile products aseptically, sterilize high-risk preparations, and label preparations.

f. Protect personnel and compounding environments from contamination by hazardous drugs.

657—13.4 Reserved.

657—13.5(155A) References required. The pharmacy shall have sufficient current reference materials related to sterile products and preparations. References may be printed or computer-accessed. In addition to meeting the requirements set forth in rule 657—6.3(155A), 657—7.3(155A), 657—15.4(155A), or 657—16.5(155A), as applicable, all pharmacies involved in sterile compounding shall maintain

a minimum of one current reference, including access to current periodic updates, from each of the following categories:

1. A general information reference.
2. An injectable drug compatibility reference.
3. If the pharmacy is compounding hazardous drugs, a reference related to hazardous drugs.

657—13.6(126,155A) Policies and procedures. A written policy and procedure manual shall be prepared, implemented, maintained, and adhered to for the compounding, dispensing, delivery, administration, storage, and use of sterile preparations. The manual shall establish policies and procedures relating to subjects identified in this and other rules within this chapter.

13.6(1) *Quality assurance program.* The policy and procedure manual shall include a quality assurance program pursuant to rule 657—13.31(155A).

13.6(2) *Sampling.* The policy and procedure manual shall include procedures that require sampling of a preparation as provided in rule 657—13.29(126,155A) or if microbial contamination is suspected.

13.6(3) *Preparation recall.* The policy and procedure manual shall include procedures for the recall of dispensed preparations that fail to meet product quality standards.

13.6(4) *Hazardous products and infectious waste.* The policy and procedure manual shall include procedures for proper handling of hazardous drug products and infectious waste, if applicable.

13.6(5) *Periodic review.* The policy and procedure manual shall be periodically reviewed. Policies shall specify the frequency of review. The manual shall be available for inspection and copying by the board or agents of the board.

[**ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.7(126,155A) Labeling requirements.

13.7(1) *Patient-specific dispensing container.* At the time of delivery, a patient-specific dispensing container used for a preparation shall bear a label with at least the following information:

a. Name and quantity of all contents.
b. Patient's name.
c. For home care patient prescriptions, unique serial number or prescription number.
d. Preparer's and reviewing pharmacist's initials or unique identifiers.
e. Stability (beyond-use date) as set forth in the pharmacy's policy and procedure manual.
f. The prescribed flow rate in ml/hr, if applicable.
g. Auxiliary labels as needed.

13.7(2) *Batch preparation.* Each container of a batch preparation that is compounded in anticipation of later dispensing shall bear a label with at least the following information:

a. Name and quantity of all contents.
b. Internal code to identify the date and time of preparation and the preparer's and reviewing pharmacist's initials or unique identifiers.
c. Stability (beyond-use date) as set forth in the pharmacy's policy and procedure manual.
d. Auxiliary labels as needed.

657—13.8(155A) Record requirements.

13.8(1) *Production record.* A production record shall be prepared and kept for each drug product compounded for an individual patient. A production record is not required when mixing or reconstituting a drug according to the product's labeling or the manufacturer's directions. The record shall include the following information:

a. Production date;
b. List of ingredients and quantity of each ingredient used;
c. Initials or unique identification of each person involved in each of the compounding steps;
d. Initials or unique identification of each pharmacist verifying each of the compounding steps;

e. Internal control or prescription number and, if the prescription is filled using a product compounded in bulk pursuant to rule 657—20.11(126), the internal control number assigned to the batch and recorded in the batch production record.

13.8(2) *Batch master formula record.* Pursuant to the provisions of 657—subrule 20.3(3), pharmacies may compound drugs in bulk quantities for subsequent prescription labeling and dispensing. For each drug product compounded in bulk quantity, a master formula record containing the following information shall be prepared:

a. Name of the product;
b. Specimen or copy of label;
c. List of ingredients and quantities;
d. Description of container used;
e. Compounding instructions, procedures and specifications.

13.8(3) *Batch production record.* For each batch of drug product compounded, a production record containing the following information shall be prepared and maintained:

a. The information from the master formula record;
b. Records of each step in the compounding process including:
(1) Preparation date;
(2) Identification of ingredients (including lot numbers);
(3) Quantities of ingredients used;
(4) Initials or unique identification of person completing each step;
(5) Initials or unique identification of pharmacist verifying each step;
c. Expiration/beyond-use date;
d. Internal control number;
e. Total yield.

[**ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.9 Reserved.

657—13.10(126,155A) Microbial contamination risk levels. Preparations shall be assigned an appropriate risk level—low, medium or high—according to the corresponding probability of contaminating a preparation with microbial contamination such as microbial organisms, spores, and endotoxins, and chemical and physical contamination such as foreign chemicals and physical matter. The characteristics described in rules 657—13.11(155A), 657—13.12(155A), and 657—13.13(155A) are intended as guides to the diligence required in compounding at each risk level.

[**ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.11(155A) Low-risk preparations and low-risk preparations with 12-hour or less beyond-use date.

13.11(1) *Conditions defined—low-risk preparations.* Preparations compounded under all of the following conditions are at a low risk of contamination.

a. The preparations are compounded with aseptic manipulations entirely within ISO Class 5 or superior air quality using only sterile ingredients, products, components, and devices.

b. The compounding involves only transferring, measuring, and mixing not more than three commercially manufactured packages of sterile products and not more than two entries into any one container (e.g., bag, vial) of sterile product or administration container or device to make the preparation.

c. Manipulations are limited to aseptically opening ampoules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, containers of other sterile products, and containers for storage and dispensing.

d. In the absence of the preparation's passing a sterility test and provided that the preparation is properly stored before administration, storage periods shall not exceed the following:
(1) At controlled room temperature for 48 hours;
(2) At a cold temperature for 14 days; or

(3) In a solid-frozen state between minus 25 and minus 10 degrees Celsius for 45 days.

13.11(2) *Examples—low-risk preparations.* Examples of low-risk compounding include:

a. The single-volume transfer of sterile dosage forms from ampoules, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers. When ampoules are employed, solution content shall be passed through a sterile filter to remove any particles.

b. The manual measuring and mixing of no more than three manufactured products including an infusion or diluent solution to compound drug admixtures and nutritional solutions.

13.11(3) *Low-risk preparations with 12-hour or less beyond-use date.* If the primary engineering control device is a CAI and does not meet the requirements described in subrule 13.27(3) or is a BSC or LAFW that cannot be located within an ISO Class 7 buffer area, then only low-risk nonhazardous and radiopharmaceutical preparations compounded pursuant to a prescriber's order for a specific patient may be prepared, and administration of such preparations shall commence within 12 hours of the start of compounding or as recommended in the manufacturers' package insert, whichever is less. Preparations shall meet all four of the following criteria:

a. The primary engineering control device shall be certified and shall maintain ISO Class 5 for exposure of critical sites and shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of preparation contamination.

b. The segregated compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors or high traffic flow, or that is adjacent to construction sites, warehouses, food preparation areas, or other areas presenting a risk of contamination.

c. Personnel shall be appropriately garbed and shall perform appropriate cleansing activities prior to compounding. Sinks should be separated from the immediate area of the ISO Class 5 primary engineering control device.

d. Appropriate procedures for cleaning and disinfecting the sterile compounding areas, for personnel training and competency evaluation, for aseptic practices and cleaning or disinfecting processes, and for environmental air sampling and testing shall be followed.

657—13.12(155A) Medium-risk preparations.

13.12(1) *Conditions defined.* Preparations compounded aseptically under low-risk conditions with one or more of the following additional conditions are at a medium risk of contamination.

a. Multiple individual or small doses of sterile products are combined or pooled to prepare a sterile preparation for administration either to multiple patients or to one patient on multiple occasions.

b. The compounding process includes complex aseptic manipulations other than the single-volume transfer.

c. The compounding process requires an unusually long duration, such as that required to complete dissolution or homogeneous mixing.

d. In the absence of the preparation's passing a sterility test and provided that the preparation is properly stored before administration, storage periods shall not exceed the following:

(1) At controlled room temperature for 30 hours;

(2) At a cold temperature for 9 days; or

(3) In a solid-frozen state between minus 25 and minus 10 degrees Celsius for 45 days.

13.12(2) *Examples.* Examples of medium-risk compounding include:

a. Compounding total parenteral nutrition fluids, using manual or automated devices and involving multiple injections, detachments, or attachments of nutrient source products to the device or machine to deliver all nutritional components to a final sterile container.

b. Filling reservoirs of injection or infusion devices with more than three sterile drug products and evacuating air from those reservoirs before dispensing the filled device.

c. Transferring volumes from multiple ampoules or vials into one or more final sterile containers.

657—13.13(155A) High-risk preparations.

13.13(1) *Conditions defined.* Preparations that are either contaminated or likely to become contaminated with infectious microorganisms when compounded under any of the following conditions are at a high risk of contamination.

a. Nonsterile ingredients, including manufactured products not intended for sterile use, are incorporated or a nonsterile device is used in the compounding process before terminal sterilization.

b. Sterile contents of commercially manufactured products, preparations that lack effective antimicrobial preservatives, and sterile surfaces of devices and containers intended for the preparation, transfer, sterilization, and packaging of preparations are exposed to air quality inferior to ISO Class 5 for more than one hour.

c. Nonsterile procedures such as weighing and mixing in air quality inferior to ISO Class 7 are performed before sterilization, compounding personnel are not properly garbed and gloved, or nonsterile water-containing preparations are stored for more than six hours.

d. The chemical purity and content strength of bulk ingredients, whether the ingredients are in opened or unopened packages, are not verified by examination of labeling and documentation of suppliers or by direct determination.

e. For a sterilized high-risk preparation, in the absence of the preparation's passing a sterility test, the storage period beyond-use date shall not exceed the following:

(1) At controlled room temperature, 24 hours;

(2) At a cold temperature, 3 days; or

(3) In a solid-frozen state between minus 25 and minus 10 degrees Celsius, 45 days.

13.13(2) *Examples.* Examples of high-risk compounding include:

a. Dissolving nonsterile bulk drugs or nutrient powders to make solutions that will be terminally sterilized.

b. Measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.

c. Assuming, without appropriate evidence or direct determination, that packages of bulk ingredients contain at least 95 percent by weight of their active chemical moiety and have not been contaminated or adulterated between uses.

d. Exposing the sterile ingredients and components used to prepare and package the preparation to air quality inferior to ISO Class 5 for more than one hour.

[**ARC 9180B**, IAB 11/3/10, effective 12/8/10]

657—13.14(155A) Immediate-use preparations. The immediate-use provisions of this rule are intended only for those situations where there is a need for emergency or immediate administration of a sterile preparation. Such situations may include cardiopulmonary resuscitation, emergency room treatment, preparation of diagnostic agents, or critical therapy where the compounding of the preparation under low-risk level conditions would subject the patient to additional risk due to delays in therapy. Immediate-use preparations are not intended for storage for anticipated needs or for batch compounding. Medium-risk and high-risk preparations shall not be compounded as immediate-use preparations. Immediate-use preparations are exempt from the provisions of rule 657—13.11(155A) for low-risk preparations only when all of the following criteria are met:

1. The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers' original containers and not more than two entries into any one container or package of sterile infusion solution or administration container or device. Hazardous drugs shall not be compounded as immediate-use preparations.

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

3. During compounding, aseptic technique is followed and, if the preparation is not immediately administered, the 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 sterile preparations, and direct contact with outside surfaces.

4. Administration begins not later than one hour after compounding of the preparation is completed.

5. If administration has not begun within one hour after compounding of the preparation is completed, the preparation is promptly and safely discarded.

6. Unless immediately and completely administered by the person who compounded the preparation or unless immediate and complete administration is witnessed by the person who compounded the preparation, the preparation shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who compounded the preparation, and the exact one-hour beyond-use date and time.

[**ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.15(155A) Utilization of single-dose and multiple-dose containers. Pharmacies utilizing single-dose and multiple-dose containers in sterile compounding shall comply with the following:

1. Single-dose containers that are opened or needle-punctured shall be used within one hour if opened in air quality conditions inferior to ISO Class 5. Any remaining contents shall be discarded.

2. Single-dose vials that are continuously exposed to ISO Class 5 or cleaner air shall be used within six hours after initial needle puncture.

3. Opened single-dose ampoules shall not be stored for any period of time under any air quality conditions.

4. Multiple-dose containers with antimicrobial preservatives that are entered or opened shall be used within 28 days of initial entry or opening unless otherwise specified by the manufacturer.

5. Multiple-dose and single-dose sterile products shall not be combined for use as multiple-dose applications.

657—13.16(155A) Utilization of proprietary bag and vial systems. Sterility storage and beyond-use times for attached and activated container pairs of drug products for intravascular administration shall follow manufacturers' instructions for handling and storage.

657—13.17 to **13.19** Reserved.

657—13.20(124,155A) Sterile preparation of hazardous drugs. Hazardous drugs shall only be prepared for administration under conditions that protect pharmacy personnel in the preparation area.

13.20(1) *Storage and handling.* Policies and procedures shall identify appropriate storage and handling of hazardous drugs to prevent contamination and personnel exposure.

13.20(2) *Caution labeling and distribution.* Preparations containing hazardous drugs shall be labeled on the primary container and placed in an overwrap bag that is also properly labeled. Prepared doses of dispensed hazardous drugs shall be labeled and distributed in a manner to minimize the risk of accidental rupture of the primary container. Proper labeling shall include any necessary precautions.

13.20(3) *Preparation area.* All hazardous drugs shall be compounded in a vertical flow Class II or Class III biological safety cabinet or in a compounding aseptic isolator containment and control device with biohazard control capabilities. A BSC or CAI used for the compounding of hazardous drugs shall not be used for the compounding of nonhazardous sterile or nonsterile compounded products unless the BSC or CAI is decontaminated in compliance with industry standards appropriate for inactivating hazardous drugs.

a. It is preferable for the ISO Class 5 BSC or CAI to be placed in a contained environment, physically separated from other preparation areas, where air pressure is negative and where the ISO Class 5 BSC or CAI is appropriately vented to the outside of the building.

b. If the pharmacy compounds fewer than five preparations per week in a BSC or CAI and uses a closed system vial transfer device to compound the preparations, the BSC or CAI may be located in a positive pressure room.

13.20(4) *Protective apparel.* Personnel compounding hazardous drugs shall wear appropriate protective apparel in accordance with documented procedures. Protective apparel may include

disposable, nonshedding coveralls or gowns with tight cuffs, face masks, eye protection, hair covers, double gloves, and shoe covers.

13.20(5) *Techniques.* Appropriate safety and containment techniques for compounding hazardous drugs shall be used in conjunction with the aseptic techniques required for processing sterile preparations.

13.20(6) *Training required.* All personnel who compound hazardous drugs shall be fully trained in the storage, handling, and disposal of these drugs. This training shall occur before personnel prepare or handle hazardous preparations and shall be verified and documented for each person at least annually.

13.20(7) *Waste.* Disposal of hazardous waste shall comply with all applicable local, state, and federal requirements.

13.20(8) *Spills of hazardous drugs.* Written procedures for handling both major and minor spills of hazardous drugs shall be developed, maintained, implemented, and adhered to. The procedures shall be maintained with the policies and procedures required in rule 657—13.6(155A).

[**ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.21 and **13.22** Reserved.

657—13.23(124,155A) Verification of compounding accuracy and sterility. Compounding procedures and sterilization methods used for preparations require planned testing, monitoring, and documentation to demonstrate adherence to environmental quality requirements, personnel practices, and procedures critical to achieving and maintaining sterility. Pharmacist verification of a preparation shall include visual inspection of labeling, physical integrity, and expected appearance, including final fill amount.

657—13.24(124,155A) Sterilization methods. The selected sterilization method employed shall be based on experience and appropriate information sources.

13.24(1) *Presterilization requirements for high-risk preparations.*

a. During all compounding activities that precede terminal sterilization, such as weighing and mixing, compounding personnel shall be garbed and gloved in the same manner as when performing compounding in an ISO Class 5 environment. All presterilization procedures shall be completed in an ISO Class 8 or superior environment.

b. Immediately before use, all nonsterile measuring, mixing, and purifying devices used in the compounding process shall be thoroughly rinsed with sterile, pyrogen-free water, and then thoroughly drained or dried.

13.24(2) *Sterilization methods for high-risk preparations.*

a. Sterilization by filtration. This method of sterilization involves the passage of a fluid or solution through a sterilizing grade membrane to produce a sterile effluent.

(1) Sterile filters used to sterile filter preparations shall be pyrogen-free and have a nominal porosity of 0.22 microns. The filter dimensions and liquid material to be sterile filtered shall permit the sterilization process to be completed rapidly without the replacement of the filter during the filtering process.

(2) Compounding personnel shall ascertain that selected filters will achieve sterilization of the specific preparation.

(3) Sterilization by filtration shall be performed entirely within an ISO Class 5 or superior air quality environment.

b. Terminal sterilization. Use of saturated steam under pressure, or autoclaving, is the preferred method to terminally sterilize aqueous preparations.

(1) All materials shall be exposed to steam at 121 degrees Celsius under the recommended pressure and duration, verified by testing the sterility of the finished preparation.

(2) The description of steam sterilization conditions and duration for specific preparations shall be included in written documentation maintained in the compounding facility.

(3) Before or during entry into final containers, all high-risk preparations in solution form that are subjected to terminal steam sterilization shall pass through a filter with nominal porosity not larger than 1.2 microns for removal of particulate matter.

c. Dry heat sterilization. Dry heat sterilization shall be completed in an oven designed for sterilization and shall be used only for those materials that cannot be sterilized by steam. The effectiveness of dry heat sterilization shall be verified using appropriate biological indicators and temperature-sensing devices.

13.24(3) *Records.* Record requirements for high-risk preparations shall include documentation of the following:

a. Lot numbers of nonsterile components used in compounding high-risk preparations.

b. Sterilization records including methods used for each preparation.

13.24(4) *Testing and quarantine requirements.* All high-risk preparations, except those for inhalation and ophthalmic administration, that are prepared in groups of 25 or more identical single-dose containers or in multiple-dose vials for administration to multiple patients, or that are exposed longer than 12 hours at 2 to 8 degrees Celsius or longer than 6 hours at warmer than 8 degrees Celsius before they are sterilized, shall be quarantined and tested to ensure that the preparations are sterile and that they do not contain excessive bacterial endotoxins before they are dispensed or administered.

13.24(5) *Release of preparations prior to receipt of testing results.* If a preparation may be needed before the results of sterility testing have been received, the pharmacy shall have a written procedure requiring daily observation of incubating test specimens and immediate recall of the dispensed preparations when there is any evidence of microbial growth in the test specimens.

[**ARC 7633B**, IAB 3/11/09, effective 4/15/09]

657—13.25(155A) Media-fill testing by personnel. The pharmacy shall develop, maintain, and implement written procedures that include appropriate media-fill testing by personnel authorized to compound preparations. The issues to consider in the development of a media-fill test are media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required. Tests shall be performed without interruption in an ISO Class 5 environment under conditions that closely simulate the stressful conditions encountered during compounding of the specific risk level preparations for which the test is intended. The pharmacy shall maintain records of media-fill testing performed, and results of testing procedures shall be available to the board or agents of the board. Compounding personnel whose media-fill test vials result in gross microbial colonization shall be immediately reinstructed and reevaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.

13.25(1) *Low-risk MFT procedure.* Each person authorized to compound low-risk preparations shall annually perform an appropriate successful MFT procedure. The following is an example of a low-risk MFT procedure:

1. Using the same sterile 10-ml syringe and vented needle combination, aseptically transferring three sets of four 5-ml aliquots of sterile soybean-casein digest medium into separate sealed, empty, sterile 30-ml clear vials (i.e., four 5-ml aliquots into each of three 30-ml vials);
2. Affixing sterile adhesive seal closures onto the three filled vials;
3. Incubating the vials at temperatures between 25 and 35 degrees Celsius for 14 days. Failure is indicated by visible turbidity in the medium on or before the passage of 14 days.

13.25(2) *Medium-risk MFT procedure.* Each person authorized to compound medium-risk preparations shall annually perform an appropriate successful MFT procedure. The following is an example of a medium-risk MFT procedure:

1. Aseptically transferring six 100-ml aliquots of sterile soybean-casein digest medium by gravity through separate tubing sets into separate evacuated sterile containers;
2. Arranging the six containers as three pairs and using a sterile 10-ml syringe and 18-gauge needle combination to exchange two 5-ml aliquots of medium from one container to the other container in the pair (for example, adding 5-ml aliquot from the first container to the second container in the pair, agitating the second container for 10 seconds, and transferring 5-ml aliquot from the second container back to the

first container in the pair; then agitating the first container for 10 seconds and transferring the next 5-ml aliquot from the first container back to the second container in the pair; and repeating the procedure for each pair of containers);

3. Aseptically injecting a 5-ml aliquot of medium from each container into a sealed, empty, sterile 10-ml clear vial using a sterile 10-ml syringe and vented needle. Affixing sterile adhesive seals to the rubber closures on the three filled vials and incubating the vials at temperatures within a range of 20 to 35 degrees Celsius for 14 days. Failure is indicated by visible turbidity in the medium on or before the passage of 14 days.

13.25(3) *High-risk MFT procedure.* Each person authorized to compound high-risk preparations shall semiannually perform an appropriate successful MFT procedure. The following is an example of a high-risk MFT procedure:

1. Dissolving 3 gm of nonsterile commercially available soybean-casein digest medium in 100 ml of nonbacteriostatic water to make a 3 percent solution;

2. Drawing 25 ml of the medium into each of three 30-ml sterile syringes. Transferring 5 ml from each syringe into separate sterile 10-ml vials (these vials are the positive controls to generate exponential microbial growth, which is indicated by visible turbidity upon incubation);

3. Under aseptic conditions and using aseptic techniques, affixing a sterile 0.2 micron porosity filter unit and a 20-gauge needle to each syringe. Injecting the next 10 ml from each syringe into three separate 10-ml sterile vials. Repeating the process into three more vials. Labeling all vials, affixing sterile adhesive seals to the closure of the nine vials, and incubating them at temperatures between 25 and 35 degrees Celsius. Inspecting for microbial growth over 14 days. Failure is indicated by visible turbidity in the medium on or before the passage of 14 days.

657—13.26 Reserved.

657—13.27(124,126,155A) Physical environment requirements. The pharmacy shall have a designated area for compounding sterile preparations, with entry restricted to designated personnel. The area shall be used only for sterile compounding. The area shall be structurally isolated from other areas and shall be designed to avoid unnecessary traffic and airflow disturbances. The area shall be of sufficient size to accommodate at least one primary engineering control device and to provide for the storage of drugs and supplies under appropriate temperature, light, moisture, sanitation, ventilation, and security conditions.

13.27(1) *Requirement for primary engineering control device.* The primary engineering control device shall be capable of maintaining at least ISO Class 5 air quality in the area where critical objects are exposed and critical activities are performed. The device shall be capable of maintaining ISO Class 5 air quality during normal activity. A primary engineering control device includes, but is not limited to, a horizontal or vertical laminar airflow workbench or CAI.

13.27(2) *Placement of primary engineering control device.* The primary engineering control device shall be placed in a buffer area where HEPA filters are employed and the air quality is maintained at ISO Class 7. This area shall have cleanable, nonshedding, smooth surfaces; all junctures shall be coved; and all cracks and crevices shall be caulked. The ceiling shall be impervious and hydrophobic. The buffer area shall not contain any drains or sinks. Only the furniture, equipment, supplies and other material required for compounding activities to be performed shall be brought into the room. Such items brought into the room shall be cleaned and disinfected. Placement in buffer areas of objects and devices not essential to the compounding process is dictated by the measured effect of those objects and devices on the required environmental quality of air atmospheres and surfaces.

13.27(3) *Exception for placement of CAI.* The CAI shall be placed in an ISO Class 7 cleanroom unless the CAI meets each of the following conditions:

a. The CAI provides isolation from the room and maintains ISO Class 5 conditions when ingredients, components, and devices are transferred into and out of the CAI during the preparation process.

b. The manufacturer provides documentation verifying that the CAI meets the standard in paragraph *"a"* when the CAI is located in an environment inferior to ISO Class 7.

13.27(4) *Anteroom requirements.* Except for a CAI that meets the conditions specified in subrule 13.27(3) exempting the CAI from placement in an ISO Class 7 cleanroom, an anteroom or ante area shall be located adjacent to the buffer area and maintained at ISO Class 8 air quality. This area is to be used for unpacking and disinfecting supplies for storage and for hand sanitizing and gowning. If the sterile preparation area is to be used only for the compounding of low- and medium-risk preparations, the ante area shall be clearly demarcated for the compounding of low- and medium-risk preparations. If the sterile preparation area is to be used for the compounding of high-risk preparations, the ante area shall be physically separated from the buffer area.

13.27(5) *Delayed implementation.* A pharmacy whose sterile compounding area is in substantial compliance with the physical and structural requirements of this rule shall be authorized to engage in the compounding of sterile preparations pursuant to the practice standards established by this chapter and subject to the following:

a. Any pharmacy that commences, on or after July 11, 2007, new construction or remodeling of a pharmacy sterile compounding area shall comply with the physical and structural requirements of this rule.

b. Any pharmacy engaged in the compounding of sterile preparations shall, no later than December 31, 2010, complete any necessary changes or improvements to the sterile compounding area to ensure compliance with the physical and structural requirements of this rule.

[**ARC 9411B**, IAB 3/9/11, effective 4/13/11]

657—13.28(155A) Cleaning, maintenance, and supplies. The pharmacy shall have appropriate equipment and supplies and documented procedures for maintaining an environment suitable for the aseptic processing of sterile preparations.

13.28(1) *Supplies and equipment.* Required supplies and equipment shall include, but may not be limited to, the following:

a. Appropriate attire including nonshedding coveralls or gowns, head and facial covers, face masks, appropriate gloves, and shoe covers.

b. A sink with hot and cold running water, with bactericidal soap available for the purpose of hand and forearm scrubs, which shall be located convenient to the area used for compounding sterile preparations but outside the buffer area.

13.28(2) *Documented procedures.* Documented procedures shall include, but not be limited to, the following:

a. Specific cleaning procedures and frequencies for each compounding area involved.

b. Identification of the individual responsible for completing each procedure.

c. A list of approved cleaning agents for each procedure.

d. A written plan and schedule for the evaluation of airborne microorganisms in each controlled air environment (e.g., LAFW, barrier isolators, buffer area, and anteroom).

e. Equipment calibration, annual maintenance, and monitoring of proper function of equipment, apparatus, and devices used to compound sterile preparations.

f. An appropriate cleansing and garbing procedure. Coveralls and gowns may be hung outside the entry in the buffer area and reused for one shift, provided the coveralls and gowns are not visibly soiled and have not been worn during the compounding of hazardous drugs.

657—13.29(126,155A) Environmental monitoring requirements.

13.29(1) *Certification required.* All cleanrooms, laminar airflow workbenches, and barrier isolators shall be certified by an independent contractor according to ISO Standards 14644-1:1999(E) and ISO Standards 14664-3:2005(E), or National Sanitation Foundation Standard 49, for operational efficiency at least every six months and whenever the device or room is relocated or altered or whenever major service to the facility is performed. Inspection and certification records shall be maintained for two years from the date of certification.

13.29(2) *Procedures required.* The pharmacy shall establish written procedures appropriate for the risk level preparations compounded by the pharmacy. The procedures shall include environmental testing, end testing, and evaluation of validation results.

a. Air sampling. Microbial sampling of air within the primary engineering control devices, buffer areas, and anterooms is required at least semiannually as part of the recertification of facilities and equipment. If compounding occurs in multiple locations within an institution, environmental sampling is required for each individual compounding area.

b. Pressure differential monitoring. A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the anteroom and between the anteroom and the general pharmacy area. The gauge/meter shall alert the pharmacy when air conditions do not meet recommended conditions, and all compounding shall be discontinued until the alarm condition is corrected. If the gauge/meter is incapable of alerting the pharmacy to inappropriate conditions, the pharmacy shall monitor and review the gauge/meter daily and document the results in a log.

657—13.30 Reserved.

657—13.31(155A) Quality assurance (QA). The pharmacy shall establish, implement, and document an ongoing quality assurance program in order to maintain and improve facilities, equipment, personnel performance, and the provision of patient care.

13.31(1) *Physical performance QA.* The portion of the quality assurance program that monitors facilities, equipment, and personnel performance shall include, but need not be limited to, the following:

a. Methods for verification of automated compounding devices for parenteral nutrition compounding.

b. Methods for sampling finished preparations to ensure that the pharmacy is capable of consistently preparing sterile preparations that meet appropriate risk level specifications and to ensure product integrity.

c. Procedures for inspection of all prescription orders, written compounding procedures, preparation records, and materials used to compound at all contamination risk levels, to ensure accuracy of ingredients, aseptic mixing, sterilizing, packaging, labeling, and expected physical appearance of the finished preparation.

d. Procedures for visual inspection of preparations to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and the accuracy and thoroughness of labeling.

e. Procedures for review of all orders and packages of ingredients to ensure that the correct ingredients and quantity of ingredients were compounded.

f. Methods for routine disinfection and air quality testing of the direct compounding environment to minimize microbial surface contamination and maintain ISO Class 5 air quality.

g. Methods for ensuring personnel qualifications, training, and performance, including periodic performance of applicable MFT procedures.

h. Procedures for visual confirmation that compounding personnel are properly donning and wearing appropriate items and types of protective garments.

i. Methods for establishing beyond-use dates of preparations.

13.31(2) *Care outcomes QA.* The portion of the quality assurance program that monitors patient care shall include, but need not be limited to, the following:

a. Utilizing specific procedures for recording, filing, and evaluating reports of adverse events and the quality of preparation identified in the adverse event.

b. Utilizing written policies and procedures that include specific procedures or instructions for receiving, acknowledging, and dating the receipt of products.

c. Reviewing documented patient or caregiver education and training required pursuant to rule 657—13.32(155A).

d. Ensuring that a qualified pharmacist is available and accessible at all times to respond to the questions and needs of other health professionals, the patient, or the patient's caregiver.

e. Identifying activities and processes that are deemed high-risk, high-volume, or problem-prone and providing effective corrective actions to remedy these activities and processes.
[**ARC 0596C**, IAB 2/6/13, effective 3/13/13]

657—13.32(155A) Patient or caregiver education and training. If sterile preparations are provided to the patient in the home environment, the pharmacist, in conjunction with nursing or medical personnel, shall verify and document the patient's or caregiver's training and competence in managing the type of prescribed therapy.

13.32(1) *Pharmacist involvement.* A pharmacist shall be actively involved in patient training processes relating to drug compounding, labeling, administration, storage, stability, compatibility, or disposal. The pharmacist shall continually reassess the patient's or caregiver's competency in these areas.

13.32(2) *Demonstration and practice.* Training programs shall include hands-on demonstrations and practice with actual items that the patient or caregiver is expected to use in managing the specific type of therapy.

13.32(3) *Additional training tools.* Printed materials and posttraining verbal counseling shall be used periodically, as appropriate, to reinforce initial training programs and to ensure the patient's or caregiver's continuing correct and complete fulfillment of responsibilities.

657—13.33(124,155A) Storage and delivery of sterile preparations. The pharmacy is responsible for proper packaging, handling, transport, and storage of preparations compounded and dispensed by the pharmacy and for appropriate education, training, and supervision of pharmacy and nonpharmacy personnel responsible for such functions. The pharmacy shall establish, maintain, and implement written policies and procedures to ensure product quality and packaging integrity until the preparation is administered.

13.33(1) *Storage areas.* Controlled temperature storage areas within the pharmacy shall be monitored at least once daily and the results documented on a temperature log. Temperature-sensing mechanisms shall be suitably placed within the storage space to accurately reflect the area's temperature.

13.33(2) *Packaging, handling and transport.* Appropriate policies and procedures shall be established, maintained, and implemented by the pharmacy with the involvement of other departments or services whose personnel are responsible for preparation or handling functions outside the pharmacy.

a. Policies and procedures shall include instruction in proper hand washing, aseptic techniques, site care, and change of administration sets to ensure the quality and sterility of the preparation.

b. A pharmacy that compounds or prepares products or devices or uses techniques where in-line filtration, automated infusion control devices, or replenishment of drug products into reservoirs of portable infusion pumps is required shall implement policies and procedures to address the special needs related to those products and techniques.

c. Policies and procedures shall provide for the return to the pharmacy of unused preparations for appropriate disposition. Appropriate disposition may include redispensing only if the continuing quality and sterility of the preparation can be fully ensured. The pharmacy shall be the sole authority for determining whether a preparation that was not administered as originally intended can be used for an alternate patient or under alternate conditions.

d. Policies and procedures regarding the handling of hazardous preparations shall identify safeguards intended to maintain the integrity of the preparations and to minimize the exposure potential of these products to the environment and to personnel who have contact with the products.

These rules are intended to implement Iowa Code sections 124.301, 126.10, 155A.2, 155A.4, 155A.13, 155A.13A, and 155A.28.

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