64B16-27.797 Standards of Practice for Compounding Sterile Preparations (CSPs).

The purpose of this section is to assure positive patient outcomes through the provision of standards for 1) pharmaceutical care; 2) the preparation, labeling, and distribution of sterile pharmaceuticals by pharmacies, pursuant to or in anticipation of a prescription drug order, and 3) product quality and characteristics. These standards are intended to apply to all sterile pharmaceuticals, notwithstanding the location of the patient (e.g., home, hospital, nursing home, hospice, doctor's office).

(1) Definitions:

(a) "Anteroom" means an area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate generating activities. It is also a transition area that provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas. The Anteroom area is to be maintained within ISO Class 8 level of particulate contamination.

(b) "Antineoplastic" means a pharmaceutical agent that has the intent of causing cell death targeted to cancer cells, metastatic cells, or other cells involved in a severe inflammatory or autoimmune response.

(c) "Beyond-use-date" means the date after which a compounded preparation should not be used and is determined from the date the preparation was compounded.

(d) "Biological safety cabinet" means a containment unit suitable for the preparation of low, moderate, and high risk agents where there is a need for protection of the product, personnel, and environment.

(e) "Bulk Compounding" means the compounding of CSPs in increments of twenty-five (25) or more doses from a single source.

(f) "Buffer area" (Clean room) is an area where the activities of CSP take place; it shall not contain sinks or drains. In High-Risk compounding this must be a separate room. The Buffer area is to be maintained within ISO Class 7 level of particulate contamination.

(g) "Class 100 environment" means an atmospheric environment which contains no more than one hundred particles of 0.5 microns in diameter or larger per cubic foot of air. A class 100 environment is equivalent to ISO Class 5 level of particulate contamination.

(h) "Compounding Aseptic Isolator" (CAI) – is a form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer process. Air exchange into the isolator from the surrounding environment should not occur unless it is first passed through a microbially retentive filter (HEPA minimum 0.2 microns).

(i) "High-Risk Level CSPs" – are products compounded under any of the following conditions are either non-sterile or at high risk to become non-sterile with infectious microorganisms.

1. Non-sterile ingredients, including manufactured products for routes of administration other than sterile parenteral administration are incorporated or a non-sterile device is employed before terminal sterilization.

2. Sterile contents of commercially manufactured products, CSP that lack effective antimicrobial preservatives, sterile surfaces of devices and containers for the preparation, transfer, sterilization, and packaging of CSPs are exposed to air quality worse than ISO Class 5 for more than one (1) hour.

3. Before sterilization, non-sterile procedures such as weighing and mixing are conducted in air quality worse than ISO Class 7, compounding personnel are improperly garbed and gloved, or water-containing preparations are stored for more than 6 hours.

4. For properly stored sterilized high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and exposed for not more than 24 hours at controlled room temperature, and for not more than 3 days at a cold temperature (2-8 degrees Celsius) and for not more than 45 days in solid frozen state at -20 degrees celsius or colder.

5. Examples of high-risk compounding include: (1) dissolving non-sterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized; (2) exposing the sterile ingredients and components used to prepare and package CSPs to room air quality worse than ISO Class 5 for more than one (1) hour; (3) measuring and mixing sterile ingredients in non-sterile devices before sterilization is performed; (4) assuming, without appropriate evidence or direct determination, that packages of bulk ingredients contain at least 95% by weight of their active chemical moiety and have not been contaminated or adulterated between uses.

6. All high risk category products must be rendered sterile by heat sterilization, gas sterilization, or filtration sterilization in order to become a CSP.

7. Quality assurance practices for high-risk level CSPs include all those for low-risk level CSPs. In addition, each person authorized to compound high-risk level CSPs demonstrates competency by completing a media-filled test that represents high-level compounding semiannually.

(j) Immediate Use CSPs:

1. Requires only simple aseptic measuring and transfer manipulations are performed with not more than three (3) sterile non-hazardous drug or diagnostic radiopharmaceutical drug preparations, including an infusion or dilution solution.

2. The preparation procedure occurs continuously without delays or interruptions and does not exceed 1 hour.

3. At no point during preparation and prior to administration are critical surfaces and ingredients of the CSP directly exposed to contact contamination such as human touch, cosmetic flakes or particulates, blood, human body substances (excretions and secretions, e.g., nasal or oral) and non-sterile inanimate sources.

4. Administration begins not later than one (1) hour following the start of preparing the CSP.

5. When the CSP is not administered by the person who prepared it, or its administration is not witnessed by the person who prepared it, the CSP container shall bear a label listing patient identification information (name, identification numbers), and the names and amounts of all active ingredients, and the name or identifiable initials of the person who prepared the CSP, and one (1) hour beyond-use time and date.

6. If administration has not begun within one (1) hour following the start of preparing the CSP, the CSP is promptly and safely discarded. Immediate use CSPs shall not be stored for later use.

(k) ISO Class 5 guidelines are met when particulate contamination is measured at “not more than 3,520 particles 0.5 micron size or larger per cubic meter of air for any lamiar airflow workbench (LAWF), BSC, or CAI. (Also referred to as a “Class 100 environment.”)

(l) ISO Class 7 guidelines are met when particulate contamination is measured at “not more than 352,000 particles 0.5 micron size or larger per cubic meter of air for any buffer area (room).”

(m) ISO Class 8 guidelines are met when particulate contamination is measured at “not more than 3,520,000 particles 0.5 micron size or larger per cubic meter of air for any anteroom (area).”

(n) Low-Risk Level CSPs compounded under all of the following are at a low risk of contamination:

1. The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 (class 100) or better air quality using only sterile ingredients, products, components, and devices.

2. The compounding involves only transfer, measuring, and mixing manipulations using no more than three commercially manufactured sterile products and entries into one container (e.g., bag, vial) of sterile product to make the CSP.

3. 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, package containers for storage and dispensing. The contents of ampoules shall be passed through a sterile filter to remove any particles.

4. For low-risk preparation, in the absence of passing a sterility test or a documented validated process, the storage periods cannot exceed the following time periods; before administration, the CSPs are properly stored and exposed for not more than 48 hours at controlled room temperature, and for not more than 14 days at a cold temperature (2-8 degrees celsius) and for 45 days in solid frozen state at -20 degrees celsius or colder.

5. Quality Assurance practices include, but are not limited to, the following: (1) routine disinfection and air quality testing of the direct compounding environment to minimize microbial surface contamination and maintain ISO Class 5 air quality; (2) Visual confirmation that compounding personnel are properly donning and wearing appropriate items and types of protective garments; (3) Review of all orders and packages of ingredients to ensure that the correct identity and amounts of ingredients were compounded; (4) Visual inspection of CSPs to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and accuracy and thoroughness of labeling.

6. All compounding personnel are required to demonstrate competency by completing a media-filled test that represents low-level compounding annually. A media-filled test is a commercially available sterile fluid culture media that shall be able to promote exponential colonization of bacteria that are both likely to be transmitted to CSP from the compounding personnel and environment. Media filled vials are incubated at 25-35 degrees celsius for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

(o) Medium-Risk Level CSPs – When CSPs are compounded aseptically under Low-Risk Conditions, and one or more of the following conditions exist, such CSPs are at a medium risk of contamination:

1. CSPs containing more than three (3) commercial sterile drug products and those requiring complex manipulations and/or preparation methods.

2. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions.

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

4. For Medium-risk preparation, in the absence of passing a sterility test or a documented validated process, the storage periods cannot exceed the following time periods; before administration, the CSPs are properly stored and exposed for not more than 30 hours at controlled room temperature, and for not more than 9 days at a cold temperature and for 45 days in solid frozen state at -20 degrees celsius or colder.

5. These include compounding of total parenteral nutrition (TPN) using either manual or automated devices during which there are multiple injections, detachments, and attachments of nutrient source products to the device or machine to deliver all nutritional components to a final sterile container.

6. Filling of reservoirs of injection and infusion devices with more than three (3) sterile drug products and evacuation of air from those reservoirs before the filled devices are dispensed.

7. Transfer of volumes from multiple ampules or vials into one or more final sterile containers.

8. Quality assurance practices for medium-risk level CSPs include all those for low-risk level CSPs.

9. Demonstrates competency by completing a media-filled test that represents medium-level compounding annually.

(p) Parenteral means a sterile preparation of drugs for injection through one or more layers of the skin.

(q) Risk level of the sterile preparation means the level assigned to a sterile product by a pharmacist that represents the probability that the sterile product will be contaminated with microbial organisms, spores, endotoxins, foreign chemicals or other physical matter.

(r) Sterile preparation means any dosage form devoid of viable microorganisms, including but not limited to, parenterals, injectables, ophthalmics, and aqueous inhalant solutions for respiratory treatments.

(2) Compounded sterile preparations include, but are not limited, to the following:

(a) Total Parenteral Nutrition (TPN) solutions;

(b) Parenteral analgesic drugs;

(c) Parenteral antibiotics;

(d) Parenteral antineoplastic agents;

(e) Parenteral electrolytes;

(f) Parenteral vitamins;

(g) Irrigating fluids;

(h) Ophthalmic preparations; and

(i) Aqueous inhalant solutions for respiratory treatments.

(3) Sterile preparations shall not include commercially manufactured products that do not require compounding prior to dispensing.

(4) Policy & Procedure Manual. A policy and procedure manual shall be prepared and maintained for the compounding, dispensing, and delivery of sterile preparation prescriptions. The policy and procedure manual shall be available for inspection by the Department and include at a minimum:

(a) Use of single dose and multiple dose containers not to exceed United States Pharmacopeia 797 guidelines.

(b) Verification of compounding accuracy and sterility.

(c) Personnel training and evaluation in aseptic manipulation skills.

(d) Environmental quality and control:

1. Air particle monitoring for hoods (or Barrier Isolator), clean room and buffer area (or anteroom) when applicable;

2. Unidirectional airflow (pressure differential monitoring);

3. Cleaning and disinfecting the sterile compounding areas;

4. Personnel cleansing and garbing;

5. Environmental monitoring (air and surfaces).

(e) Personnel monitoring and validation.

(f) Finished product checks and tests.

(g) Method to identify and verify ingredients used in compounding.

(h) Labeling requirements for bulk compounded products:

1. Contents;

2. Beyond-Use-Date; and

3. Storage requirements.

(i) Packing, storage, and transportation conditions.

(5) Physical Requirements.

(a) The pharmacy shall have a designated area with entry restricted to designated personnel for preparing parenteral products. This area shall have a specified ante area and buffer area; in high risk compounding, this shall be separate rooms. This area shall be structurally isolated from other areas with restricted entry or access, and must be designed to avoid unnecessary traffic and interference with unidirectional airflow. It shall be used only for the preparation of these sterile preparations. It shall be of sufficient size to accommodate a laminar airflow hood and to provide for the proper storage of drugs and supplies under appropriate conditions of temperature, light, moisture, sanitation, ventilation, and security.

(b) The pharmacy compounding parenteral and sterile preparation shall have the following:

1. Appropriate environmental control devices capable of maintaining at least class 100 conditions in the work place where critical objects are exposed and critical activities are performed; furthermore, these devices must be capable of maintaining class 100 conditions during normal activity. Examples of appropriate devices include laminar airflow hoods and zonal laminar flow of high efficiency particulate air (HEPA) filtered air;

2. Appropriate disposal containers for used needles, syringes, and if applicable, for antineoplastic waste from the preparation of chemotherapy agents;

3. Appropriate environmental control including approved biohazard cabinetry when antineoplastic drug products are prepared;

4. Appropriate temperature and transport containers;

5. Infusion devices and equipment, if appropriate.

(c) The pharmacy shall maintain and use supplies adequate to preserve an environment suitable for the aseptic preparation of sterile preparations, such as:

1. Gloves, masks, shoe covers, head and facial hair covers, and non-shedding gowns;

2. Needles and syringes of various standard sizes;

3. Disinfectant cleaning agents;

4. Clean towels;

5. Hand washing materials with bactericidal properties;

6. Vacuum containers and various transfer sets;

7. “Spill kits” for antineoplastic agent spills.

(d) The pharmacy should have current reference material in hard copy or readily available on line:

1. USP Pharmacist Pharmacopeia (optional) or Handbook of Injectable Drugs by American Society of Hospital Pharmacists; or other nationally recognized standard reference; and

2. “Practice Guidelines for Personnel Dealing with Cytotoxic Drugs,” or other nationally recognized standard cytotoxic reference if applicable.

(e) Barrier isolator is exempt from all physical requirements subject to manufacturer guidelines for proper placement.

(6) Antineoplastic Drugs. The following requirements are necessary for those pharmacies that prepare antineoplastic drugs to ensure the protection of the personnel involved:

(a) All antineoplastic drugs shall be compounded in a vertical flow, Class II, biological safety cabinet placed in negative pressure room unless using barrier isolators. Other preparations shall not be compounded in this cabinet.

(b) Protective apparel shall be worn by personnel compounding antineoplastic drugs. This shall include at least gloves and gowns with tight cuffs.

(c) Appropriate safety and containment techniques for compounding antineoplastic drugs shall be used in conjunction with the aseptic techniques required for preparing sterile products.

(d) Disposal of antineoplastic waste shall comply with all applicable local, state, and federal requirements.

(e) Written procedures for handling both major and minor spills of antineoplastic agents shall be developed and shall be included in the policy and procedure manual.

(f) Prepared doses of antineoplastic drugs shall be dispensed, labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.

(7) Quality Assurance:

(a) There shall be a documented, ongoing quality assurance control program that monitors personnel performance, equipment, and preparations. Appropriate samples of finished preparations shall be examined to assure that the pharmacy is capable of consistently preparing sterile preparations meeting specifications:

1. All clean rooms and laminar flow hoods shall be certified by an independent contractor or National Sanitation Foundation Standard 49, for operational efficiency at least semiannually for high risk CSPs and annually for low and medium risk CSPs or any time the hood is relocated or the structure is altered and records shall be maintained for two years.

2. There shall be written procedures developed requiring sampling if microbial contamination is suspected for batches greater than 25 units.

3. High risk greater than 25 units have antimicrobial testing prior to dispensing.

4. There shall be referenced written justification of the chosen beyond-use-dates for compounded products.

5. There shall be documentation of quality assurance audits at regular planned intervals, including infection control and sterile technique audits.

(b) Compounding personnel shall be adequately skilled, educated, instructed, and trained to correctly perform and document the following activities in their sterile compounding duties:

1. Demonstrate by observation or test a functional understanding of USP Chapter 797 and definitions, to include Risk Category assessment;

2. Understand the characteristics of touch contamination and airborne microbial contaminants;

3. Perform antiseptic hand cleaning and disinfections of non-sterile compounding surfaces;

4. Select and appropriately don protective garb;

5. Demonstrate aseptic techniques and requirements while handling medications;

6. Maintain and achieve sterility of CSPs in ISO Class 5 (Class 100) primary engineering devices and protect personnel and compounding environments from contamination by antineoplastic and chemotoxic or other hazardous drugs or substances;

7. Manipulate sterile products aseptically, sterilize high-risk level CSPs (where applicable) and quality inspect CSPs;

8. Identify, weigh and measure ingredients;

9. Prepare product labeling requirements and “beyond use” requirements of product expiration;

10. Prepare equipment and barrier requirement work requirements to maintain sterility;

11. Prepare end point testing and demonstrated competencies for relevant risk levels;

12. Prepare media fills to test aseptic technique.

(8) Radiopharmaceuticals as Compounded Sterile Products

(a) Upon release of a Positron Emission Tomography (PET) radiopharmaceutical as a finished drug product from a PET production facility, the further manipulation, handling, or use of the product will be considered compounding and will be subject to the rules of this section.

(b) Radiopharmaceuticals compounded from sterile components in closed, sterile containers and with a volume of 100 ml or less for single dose injection or not more than 30 ml taken from a multiple dose container, shall be designated as, and conform to, the standards for low risk compounding.

(c) Radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning ISO Class 5 PEC (Primary Engineering Control), located in an ISO Class 8 or better buffer area environment in compliance with special handling, shielding, air flow requirements, and radiation safety programs to maintain radiation exposure as low as reasonably achievable.

(d) Radiopharmaceuticals designed for multi use, compounded with Tc-99m, exposed to an ISO Class 5 environment by components with no direct contact contamination, may be used up until the time indicated by manufacturers recommendations.

(e) Technetium 99/Molybdnenum 99 generator systems shall be stored and eluted in an ISO Class 8 or cleaner environment to permit special handling, shielding, and airflow requirements.

(f) Manipulation of blood or blood derived products (e.g. radiolabeling white blood cells) shall be conducted in an area that is clearly separated from routine material handling areas and equipment, and shall be controlled by specific standard operating procedures to avoid cross contamination of products. The buffer area for manipulation of blood or blood derived products shall be maintained as an ISO 7 environment and direct manipulations shall occur in an ISO 5 PEC suitable for these products (e.g. biological safety cabinet).

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