

## **21.00.00 COMPOUNDING.**

The purpose of this regulation is to codify the compounding of preparations to assure that they are of acceptable strength, quality and purity.

If the pharmacist compounds a preparation according to the manufacturer's labeling instructions, then further documentation is not required. All other compounded preparations require further documentation as set forth in this rule.

Compounding of investigational products may be exempt from sections of Regulation 21.00.00 when compounding is restricted to utilizing ingredients that are regulated by the Federal Food and Drug Administration through an Investigational Review Board (IRB) and when the IRB-approved protocol requires deviation from this regulation.

### **21.00.10 Limitations.**

- a. No preparation shall be compounded in advance in such quantity as may exceed a 90-day supply or is necessary to accurately compound the preparation. A 90-day supply shall be determined by the average number of dosage units dispensed or distributed of said preparation during the previous 6 month period.
- b. No expired components may be used in compounding. No component may be used which will expire prior to the beyond-use date of the final compounded product.

### **21.00.20 Casual Sales/Distribution of Compounded Products.**

- a. A prescription drug outlet may only distribute a compounded product to a practitioner authorized by law to prescribe the drug for the purposes of administration. A compounding prescription drug outlet registered pursuant to CRS 12-22-120(9) may distribute compounded product pursuant to CRS 12-22-121(18)(a) and (b)(I) and (II).
- b. The prescription drug outlet must retain the following information on a current basis for each practitioner or, when allowable, each prescription drug outlet, to whom it distributes compounded products:
  - (1) Verification of practitioner's license or prescription drug outlet's registration from the jurisdiction in which licensed;
  - (2) Verification of practitioner's or prescription drug outlet's current DEA registration, if controlled substances are distributed to the practitioner;
  - (3) If the products are distributed to practitioners located outside of Colorado, the pharmacy shall verify that the practitioner is legally authorized to prescribe the drug in the jurisdiction in which the practitioner is licensed;
  - (4) If the products are distributed outside of the United States, the pharmacy shall maintain written documentation of the above in English; and

- (5) **Controlled substances may not be distributed outside of the United States unless the pharmacy has obtained registration with the Drug Enforcement Administration (DEA) as an exporter.**
  - c. **Labeling of compounded products which are distributed shall comply with Regulation 21.11.10(c) or (d) or 21.21.70(c) or (d), whichever is applicable.**
  - d. **Records of distribution shall comply with Regulation 11.07.10 or 11.07.20, whichever is applicable.**
- 21.00.30 Definitions. When used in this Regulation 21.00.00, the following words and terms shall have the following meanings, unless the context clearly indicates otherwise.**
- a. **Active Ingredient: Chemicals, substances or other components of preparations intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in human or other animals or for use as dietary supplements.**
  - b. **Batch (Lot): Multiple units of the same compounded preparation in a single discrete process, by the same individuals, carried out during one limited time period.**
  - c. **Beyond-Use Date (BUD): A date after which a compounded preparation should not be stored, used or transferred and is determined from the date the preparation is compounded.**
  - d. **Component (ingredient): Any substance which is contained in a compounded preparation.**
  - e. **Compounding:**
    - (1) **The preparation, mixing, or assembling, of one or more active ingredients with one or more other substances, or the assembling of a finished device:**
      - (a) **Formulated for use on or for the patient as the result of a practitioner's prescription drug order, chart order, or initiative, based on the relationship between the practitioner, patient, and pharmacist in the course of professional practice; or**
      - (b) **For the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing; or**
      - (c) **In anticipation of prescription orders based on routine, regularly-observed prescribing patterns.**
    - (2) **Compounding does not include the preparation of copies of commercially available drug products. Compounded preparations that produce, for the patient, a significant difference between the compounded drug and the comparable commercially available drug product as determined, by the prescriber, as necessary for the medical best interest of the patient are not copies of commercially available products. "Significant differences" may include, but are not limited to, the removal of a dye for medical reasons (such as allergic reaction), changes in strength, and changes in dosage form or delivery mechanism. Price differences are not a "significant" difference to justify compounding.**

- f. **Preparation or Product:** A compounded drug dosage form, a compounded dietary supplement, or a finished device.
- g. **Quality Assurance (QA):** Set of activities used to ensure that the processes used in the preparation of non-sterile or sterile drug products lead to products that meet predetermined standards of quality.
- h. **Quality Control (QC):** Set of testing activities used to determine that the ingredients, components and final non-sterile or sterile drug products prepared meet pre-determined requirements with respect to strength, identity, quality, and purity.
- i. **Repackaging:** The subdivision or transfer of a product from one container or device to a different container or device. Repackaging does not constitute compounding, whether or not the product being repackaged was previously compounded.
- j. **SOPS:** Standard operating procedures.
- k. **Stability:** Extent to which a preparation retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding.
- l. **USP/NF:** The current edition of the United States Pharmacopeia/National Formulary.
- m. **Validation:** Documented evidence providing a high degree of assurance that specific processes will consistently produce a product meeting predetermined specifications and quality attributes.

**21.10.00 Compounding of Non-Sterile Products.**

**21.10.10 Policy and Procedure Manual.**

- a. **A manual, outlining policies and procedures encompassing all aspects of non-sterile compounding shall be available for inspection at the pharmacy. The manual shall be complied with and shall be reviewed on an annual basis. Such review shall be signed and dated by the pharmacist manager. In the event the pharmacist manager changes, the new manager shall review, sign, and date the manual within 30 days of becoming pharmacist manager. The pharmacist manager shall ensure compliance with the manual.**
- b. **The policy and procedure manual shall address at least the following:**
  - (1) **Responsibility of compounding personnel;**
  - (2) **Verification of compounding accuracy;**
  - (3) **Personnel training and evaluation in compounding skills;**
  - (4) **Environmental quality and control;**
  - (5) **Labeling and recordkeeping;**
  - (6) **Finished preparation release check;**

- (7) Quality control procedures, as appropriate;
- (8) Storage and beyond-use dating;
- (9) Adverse event reporting and recalls; and
- (10) Quality assurance program.

**21.10.20 Personnel Education, Training and Evaluation.**

- a. All pharmacy personnel preparing non-sterile compounded products must receive suitable training.
- b. Documentation of training of personnel shall be retained at the pharmacy and be available for inspection.

**21.10.30 Environmental Quality and Controls.**

- a. The area used for compounding shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups between ingredients, containers, labels, in-process materials, and finished preparations.
- b. The compounding area shall be designed, arranged, used, and maintained to prevent adventitious cross-contamination.
- c. Non-sterile compounding areas shall be separate and distinct from any sterile compounding area.
- d. The entire compounding area is to be well-lighted. Heating, ventilation, and air conditioning systems are to be controlled to avoid decomposition of chemicals.
- e. Storage areas shall provide an environment suitably controlled to ensure quality and stability of bulk chemicals and finished preparations.
- f. Compounding areas shall be maintained in a clean and sanitary condition. Adequate washing facilities are to be provided, including hot and cold running water, soap or detergent, and air driers or single-service towels.
- g. Sewage, trash, and other refuse in the compounding area are to be disposed of in a safe, sanitary, and timely manner.
- h. Special precautions shall be taken to clean equipment and compounding areas meticulously after compounding preparations that contain allergenic ingredients.

**21.10.40 Equipment.**

- a. Equipment shall be of appropriate design and capacity, and be operated within designed operational limits.
- b. Equipment shall be of suitable composition so that surfaces that contact components, in-process material, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the desired result.

- c. **Appropriate cleaning processes shall be in place to insure cleanliness of equipment.**
- d. **Written procedures outlining required equipment, calibration, appropriate maintenance, monitoring for proper function, controlled procedures for use of the equipment and specified time frames for these activities shall be established and followed. Results of equipment calibration and appropriate maintenance reports shall be kept on file at the outlet for at least two years from the report date. These results shall be available for inspection.**

**21.10.60 Components.**

- a. **Compounding personnel shall ascertain that ingredients for compounded products are in compliance with Regulation 21.00.10(b) and are of the correct identity and appropriate quality using the following information: vendors' labels, labeling, certificates of analysis, direct chemical analysis, and knowledge of compounding facility storage conditions. No expired components may be used in compounding. No component may be used which will expire prior to the beyond-use date of the preparation.**
- b. **Ingredients used in a compounded preparation shall either originate from FDA-approved sources, if available, or be USP/NF grade substances.**
- c. **If neither USP/NF grade substances nor FDA-approved substances are available, or when food, cosmetics, or other substances are, or must be used, the substance shall be of a chemical grade in one of the following categories:**
  - (1) **Chemically Pure (CP);**
  - (2) **Analytical Reagent (AR); or**
  - (3) **American Chemical Society (ACS); or**
  - (4) **Food Chemical Codex.**
- d. **For all ingredients, unless FDA-approved, the pharmacist shall establish purity and stability by obtaining a certificate of analysis from the supplier. The certificate of analysis, when applicable, shall be maintained at the prescription drug outlet for at least two years from the date of preparation.**
- e. **A manufactured drug product may be a source of active ingredient. Only manufactured drugs from containers labeled with a lot number and an expiration date are acceptable as a potential source of active ingredients. When compounding with manufactured drug products, the compounder must consider all ingredients present in the drug product relative to the intended use of a compounded preparation.**
- f. **Drug preparations that appear on the FDA list of drug products withdrawn or removed from the market for safety reasons shall not be compounded. Such preparations may be compounded exclusively for veterinary use provided no documentation exists which indicates that the preparation is unsafe for such use.**

- g. Any ingredient regulated by the FDA through an Investigational Review Board (IRB) is exempt from Regulation 21.10.60 provided the research requirements for the receipt of the ingredient is followed and meets the requirements of CRS 12-22-128(2).**

**21.10.70 Finished Preparation Release Checks.**

- a. Physical Inspection**

- (1) Written procedures for physical inspection of compounded preparations shall be followed. Immediately after compounding, and prior to dispensing or distribution, each product shall be inspected for evidence of particulates or other foreign matter, container-closure integrity, and any other apparent visual defect. Defective product shall be segregated from other product and shall not be dispensed or distributed.**

- b. Compounding Accuracy Checks**

- (1) Written procedures for double-checking compounding accuracy shall be followed for every compounded product during preparation and immediately prior to release. Outlets which compound shall have at least the following written procedures for verifying the correct identity and quality of compounded products prior to dispensing or distribution:**

- (a) Verification of label for accuracy; and**

- (b) Correct identities, purities, and amounts of ingredients have been used by comparing the original written order to the written compounding record for the compounded product.**

**21.10.80 Storage and Beyond-Use Dating.**

- a. Completed compounded preparations that are not immediately dispensed or distributed shall be stored according to the guidelines in the formulation record.**

- b. In the absence of stability information that is applicable to a specific drug and preparation, the following maximum beyond-use dates are to be used for non-sterile compounded preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated.**

- (1) For non-aqueous liquids and solid formulations**

- (a) Where the manufactured drug product is the source of the active ingredient, the beyond-use date shall not exceed 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier;**

- (b) Where a USP/NF substance is the source of active ingredient, the beyond-use date shall not be greater than 6 months;**

- (2) For water-containing formulations prepared from ingredients in solid form, the beyond-use date shall not be greater than 14 days when stored at cold temperatures;**

- (3) For all other formulations, the beyond-use date shall not be greater than the intended duration of therapy or 30 days, whichever is earlier;
- (4) The beyond-use date limits may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation. This information shall be retained on-site at the outlet and be available for inspection.

**21.10.90 Formulation Record.**

- a. For each compounded preparation, a uniform, readily retrievable formulation record shall be maintained and available for inspection for two years from the date last utilized, documenting:
  - (1) The name, strength, dosage form, and route of administration of the compounded preparation;
  - (2) All ingredients and their quantities;
  - (3) The equipment used to compound the preparation, when appropriate, and mixing instructions;
  - (4) The beyond-use date;
  - (5) The containers used in dispensing;
  - (6) Storage requirements; and
  - (7) Procedures for quality control, if applicable.

**21.11.00 Compounding Record.**

- a. For each compounded product prepared, a record shall be maintained and available for inspection for two years on the original order, or on a separate, uniform, and readily retrievable record documenting the following:
  - (1) Name and strength of the compounded preparation;
  - (2) Formulation record reference for the preparation;
  - (3) Sources and lot numbers of each ingredient;
  - (4) Manufacturer's expiration date of each ingredient, when applicable;
  - (5) Total number of dosage units compounded;
  - (6) Name of the person who compounded the preparation;
  - (7) Name of the pharmacist who approved the preparation;
  - (8) Batch (lot) number assigned, if multiple units compounded;
  - (9) Date prepared;
  - (10) Beyond use date;

- (11) Prescription number(s), if appropriate; and
- (12) Results of quality control procedures, if applicable.

**21.11.10 Labeling of Non-Sterile Compounded Preparations.**

- a. Labeling of non-sterile compounded products dispensed pursuant to a prescription order or LTCF chart order shall include at least the following:
  - (1) All requirements of CRS 12-22-123;
  - (2) Batch (lot) number, if appropriate;
  - (3) Beyond-use date;
  - (4) Storage directions when appropriate; and
  - (5) “This product was compounded by the pharmacy”.
- b. Labeling of non-sterile compounded products dispensed pursuant to a hospital chart order shall include at least the following:
  - (1) All requirements of CRS 12-22-123;
  - (2) Batch (lot) number, if appropriate;
  - (3) Beyond-use date; and
  - (4) Storage directions, when appropriate.
- c. Labeling of non-sterile compounded products distributed to practitioners or other prescription drug outlets allowed by law or made in anticipation of orders shall include at least the following:
  - (1) Name and address of the outlet;
  - (2) Name and strength of the drug(s) / active ingredient(s) in the final product;
  - (3) Total quantity in package;
  - (4) Beyond-use date;
  - (5) Batch (lot) number;
  - (6) Specific route of administration;
  - (7) Storage directions, when appropriate;
  - (8) “Rx only”; and
  - (9) “This product was compounded by the pharmacy”.

- d. **Labeling of non-sterile compounded products distributed within hospitals as floor stock shall include at least the following:**
- (1) **Name of the outlet;**
  - (2) **Name and strength of the drug(s);**
  - (3) **Total quantity in package;**
  - (4) **Quantity of active ingredient in each dosage unit;**
  - (5) **Beyond-use date;**
  - (6) **Batch (lot) number;**
  - (7) **Specific route of administration; and**
  - (8) **Storage directions, if appropriate.**

**21.11.20 Patient Monitoring, Adverse Events Reporting, and Product Recall.**

- a. **Outlets which compound shall provide patients and other recipients of compounded preparations with a way to address their questions and report any concerns that they may have with these preparations.**
- b. **The outlet shall have written policies describing specific instructions for receiving, acknowledging; and for recording, or filing, and evaluating reports of adverse events and of the quality of preparation claimed to be associated with compounded preparations.**
- c. **The pharmacist manager shall report to the board in writing significant errors related to compounded preparations such as those that result in serious personal injury or death of a patient.**
- d. **If a compounded preparation is believed to be defective in any way, the outlet shall immediately recall any product dispensed or distributed. Any product remaining in the outlet shall be immediately quarantined and shall not be dispensed or distributed. Recall records shall include at least the following:**
  - (1) **Product name, strength, dosage form;**
  - (2) **Reason for recall;**
  - (3) **Amount of product made;**
  - (4) **Date made; and**
  - (5) **Amount of product dispensed or distributed.**
- e. **The outlet shall conduct tests, as appropriate, on the recalled product to identify reason product was defective. Results of these tests shall be retained at the outlet.**
- f. **Adverse event reports and product recall records shall be retained and available for inspection at the outlet for at least two years.**

**21.20.00 Compounding of Sterile Products (CSPs).**

**21.20.10 Definitions.** In addition to the definitions set forth above in Regulation 21.00.30, when used in these Regulations 21.20.00 et seq., 21.21.00 et seq. and 21.22.00 et seq., the following words and terms shall have the following meanings, unless the context clearly indicates otherwise.

- a. **Anteroom:** An ISO Class 8 (Class 100,000) or better area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, labeling, and other activities which generate particulates. It is a transition area that provides assurance that air flows from clean to dirty areas.
- b. **Aseptic Processing:** A mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the packaging and the transfer of the product into the container and its closure under at least ISO Class 5 conditions.
- c. **Biological Safety Cabinet (BSC):** A ventilated containment unit for personnel, product, and environmental protections having an open front with inward airflow for personnel protection, downward HEPA filtered laminar airflow for product protections, and HEPA filtered exhausted air for environmental protections.
- d. **Buffer Area:** An ISO Class 7 (Class 10,000) area where the primary engineering control is physically located. Activities conducted in this area include the preparation and staging of components and supplies when compounding sterile products. This area may also be referred to as a buffer or core room, buffer or clean room areas, buffer room area, buffer or clean area.
- e. **Class 100 Environment (ISO Class 5):** An atmospheric environment which contains less than one hundred (100) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.
- f. **Class 10,000 Environment (ISO Class 7):** An atmospheric environment which contains less than ten thousand (10,000) particles 0.5 microns in diameter per cubic foot of air, according to federal standards.
- g. **Class 100,000 Environment (ISO Class 8):** An atmospheric environment which contains less than one hundred thousand (100,000) particles 0.5 microns in diameter per cubic foot of air according to federal standards.
- h. **Clean Room:** A room 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 is not exceeded for a specified cleanliness class.
- i. **Compounding Aseptic Containment Isolator (CACI):** A compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer process and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where volatile drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation.

- j. **Compounding Aseptic Isolator (CAI):** A closed system made up of solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with covering between wall junctures. The air-handling system provides HEPA filtration of inlet air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half suits. A barrier isolator is designed for compounding sterile products. 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 has first passed through a HEPA filter.
- k. **Compounded Sterile Products (CSPs):** A sterile drug or nutrient compounded in a registered prescription drug outlet or other outlet. Such products may include, but are not limited to, implants, injectables, parenteral nutrition solutions, irrigation solutions, inhalation solutions, intravenous solutions and ophthalmic preparations.
- l. **Critical Area:** An ISO Class 5 environment.
- m. **Critical Sites:** Include sterile ingredients of CSPs and locations on devices and components used to prepare, package, and transfer CSPs that provide opportunity for contamination.
- n. **Cytotoxic Drugs:** A pharmaceutical product that has the capability of direct toxic action on living tissue that can result in severe leucopenia and thrombocytopenia, depression of the immune system and the alteration of a host's inflammatory response system.
- o. **Disinfectant:** An agent that frees from infections. It is usually a chemical agent but sometimes a physical one. It destroys disease-causing pathogens or other harmful microorganisms but may or may not kill bacterial spores. It refers to substances applied to inanimate objects.
- p. **High-Efficiency Particulate Air (HEPA) filter:** A filter composed of pleats of filter medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air forced through the filter in a uniform parallel flow. HEPA filters remove 99.97% of all particles three-tenths (0.3) microns or larger. When HEPA filters are used as a component of a horizontal or vertical-laminar-airflow workbench, an environment can be created consistent with standards for a class 100 clean room.
- q. **Media-Fill Test:** A test which is used to qualify aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce sterile product without microbial contamination. A microbiological growth medium such as soybean-casein digest medium (SCDM) is substituted for the actual drug product to simulate admixture compounding.
- r. **Multiple-Dose Container:** A multiple-unit container for articles or preparations intended for parenteral administration only. These containers usually contain antimicrobial preservatives. The beyond-use date (BUD) for an opened or entered multi-dose container with antimicrobial preservatives is 28 days, unless otherwise specified by the manufacturer.

- s. **Parenteral:** A sterile preparation of drugs for injection through one or more layers of skin.
- t. **Pharmacy Bulk Package:** A container of a sterile preparation for parenteral use that contains multiple single doses. The contents of the package are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. The pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood or an equivalent clean air compounding area. Such container shall be labeled with the following:
  - (1) The name, strength and quantity of drug or base solution;
  - (2) The statement “Pharmacy Bulk Package—Not For Direct Infusion;”
  - (3) Information on the proper technique to assure safe use of the product; and
  - (4) A statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions.
- u. **Primary Engineering Control (PEC):** A device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but are not limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs) and compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs).
- v. **Process Validation or Simulation:** Microbiological simulation of an aseptic process with growth medium processed in a manner similar to the processing of the product and with the same container or closure system.
- w. **Segregated Compounding Area:** A part of the designated compounding / dispensing area that is a specifically designated space, either a demarcated area or room, and that is restricted to preparing low-risk level CSPs with a 12-hour or less BUD. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of CSPs and shall be void of activities and materials that are extraneous to sterile compounding.
- x. **Single-Dose Container:** A single-unit container for articles or preparations intended for parenteral administration only. It is intended for single use and is labeled as such. Examples include, but are not limited to, prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.
- y. **Sterile Pharmaceutical:** A dosage form free from living microorganisms.
- z. **Sterilization:** A validated process used to render a product free of viable organisms.

- aa. **Sterilizing Grade Filter Membranes:** Filter membranes that are documented to retain 100% of a culture of  $10^7$  microorganisms of a strain of *Brevundimonas (Pseudomonas) diminuta* per square centimeter of membrane surface under a pressure of not less than 30 psi (2.0 bar). Such filter membranes are nominally at 0.22 or 0.2 micrometer porosity, depending on the manufacturer's practice.
- bb. **Sterilization by Filtration:** Passage of a fluid or solution through a sterilizing grade filter to produce a sterile effluent.
- cc. **Terminal Sterilization:** The application of a lethal process (e.g. steam under pressure or autoclaving) to sealed containers for the purpose of achieving a predetermined sterile assurance level of usually less than  $10^{-6}$ , or a probability of less than one in one million of a non-sterile unit.
- dd. **Temperatures:**
  - 1. **Frozen** means temperatures between twenty five degrees below zero and ten degrees below zero Celsius (-25 and -10 degrees C.) or thirteen degrees below zero and fourteen degrees Fahrenheit (-13 and 14 degrees F.).
  - 2. **Refrigerated** means temperatures between two and eight degrees Celsius (2 and 8 degrees C.) or thirty-six and forty-six degrees Fahrenheit (36 and 46 degrees F.).
  - 3. **Room temperatures** mean room temperatures between fifteen and thirty degrees Celsius (15 and 30 degrees C.) or fifty-nine and eighty-six degrees Fahrenheit (59 and 86 degrees F.).
- ee. **Unidirectional Flow:** An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

#### 21.20.20 Definitions of Sterile Compounded Products by Risk Level.

- a. **Low Risk CSPs;**
  - (1) **Low risk CSPs with greater than 12-hour BUD:** Applies to compounding sterile products that exhibit characteristics (a) and (b) stated below. All low risk CSPs shall be compounded with aseptic manipulations entirely within ISO Class 5 or better air quality. The products shall be prepared with sterile equipment, sterile ingredients and solutions and sterile contact surfaces for the final product. Low risk includes the following:
    - (a) The compounding involves only transfer, measuring, and mixing manipulations using no more than three commercially manufactured sterile products and entries into one container package of sterile product to make the CSP; and
    - (b) Manipulations are limited to aseptically opening ampules, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.

- (2) **Low risk CSPs with 12-hour or less BUD:** Applies to CSPs if the PEC is a CAI, CACI, LAFW, or BSC that cannot be located within an ISO Class 7 buffer area and that exhibit characteristics (a) through (e) as stated below:
- (a) This subsection (a) shall only apply to low risk level non-hazardous and radiopharmaceuticals which are compounded pursuant to a patient-specific order. Administration must occur only within the same location where prepared, except in the case of radiopharmaceuticals, and shall begin within 12 hours of preparation or as recommended in the manufacturer's package insert, whichever is less. This subsection (a) shall not apply to anti-neoplastic preparations;
  - (b) PECs (LAFWs, BSCs, CAIs, CACIs) shall be certified as required and shall maintain ISO Class 5 air quality;
  - (c) PECs shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of CSP contamination;
  - (d) 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, or food preparation or any area that could cause contamination. The segregated area shall not be located next to a sink; and
  - (e) Personnel shall follow garbing and cleaning requirements.
- b. **Medium Risk CSPs:** Sterile products exhibit characteristics 1., 2., or 3., stated below. When CSPs are compounded aseptically under low risk conditions, and one or more of the following conditions exists, such CSPs are at a medium risk level of contamination:
- (1) 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; or
  - (2) The compounding process includes complex aseptic manipulations other than the single volume transfer; or
  - (3) The compounding process requires unusually long duration, such as that required to complete dissolution or homogeneous mixing.
- c. **High Risk CSPs:** CSPs compounded under any of the following conditions are either contaminated or at high risk to become contaminated with infectious microorganisms:
- (1) Products compounded from non-sterile ingredients or compounded with non-sterile components, containers or equipment before terminal sterilization; or

- (2) Sterile contents of commercially manufactured products, CSPs that lack effective antimicrobial preservatives, and 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 1 hour; or
- (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; or
- (4) It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients.

**21.20.23 Single-Dose and Multiple-Dose Containers.**

- a. Opened or needle-punctured single-dose containers shall be used within 1 hour if opened in worse than ISO Class 5 air quality. Single-dose containers exposed to ISO Class 5 air quality or cleaner air may be used up to 6 hours after initial puncture.
- b. If multiple-dose containers include antimicrobial preservatives, the BUD shall not exceed 28 days from the initial date of entering or opening, unless otherwise specified by the manufacturer.

**21.20.25 Radiopharmaceuticals as CSPs.**

- a. Production of radiopharmaceuticals for positron emission tomography (PET) shall comply with the most current Chapter 823 of the USP/NF <Radiopharmaceuticals for Positron Emission>.
- b. All other radiopharmaceuticals shall be compounded in conformity to Regulations 21.20.25(b)(1) through (5) below, Regulation 12.00.00, and all other applicable sections of Regulation 21.00.00.
  - (1) Radiopharmaceuticals compounded from sterile components in closed sterile containers and with a volume of 100 ml or less for a 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 CSPs.
  - (2) Radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO Class 5 PEC located in an ISO Class 8 or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements.
  - (3) Radiopharmaceutical vials designated for multiple use, compounded with technetium-99m, exposed to an ISO Class 5 environment, and punctured by needles with no direct contact contamination may be used up to the time indicated by the manufacturer's recommendations.

- (4) Technetium-99m/molybdenum-99 generator systems shall be stored and operated under conditions recommended by the manufacturer and applicable state and federal regulations. Such generator systems shall be operated in an ISO Class 8 or cleaner air environment to permit special handling, shielding, and air flow requirements. To limit acute and chronic radiation exposure of inspecting personnel to a level that is as low as reasonably achievable (ALARA), direct visual inspection of radiopharmaceutical CSPs containing high concentrations of doses of radioactivity shall be conducted in accordance with ALARA.
- (5) Radiopharmaceuticals prepared as low risk CSPs with 12-hour or less BUD shall be prepared in a segregated compounding area. A line of demarcation defining the segregated compounding area shall be established. Materials and garbing exposed in a patient care and treatment area shall not cross a line of demarcation into the segregated compounding area.

**21.20.30 Policy and Procedure Manual.**

- a. A manual, outlining policies and procedures encompassing all aspects of compounding low, medium or high risk products, shall be available for inspection at the pharmacy. This manual shall be complied with and shall be reviewed on an annual basis. Such review shall be signed and dated by the pharmacist manager. In the event the pharmacist manager changes, the new manager shall review, sign, and date the manual within 30 days of becoming pharmacist manager. The pharmacist manager shall ensure compliance with the manual.
- b. The policy and procedure manual shall address at least the following:
  - (1) Responsibility of compounding personnel;
  - (2) Verification of compounding accuracy and sterilization;
  - (3) Personnel training and evaluation in aseptic manipulation skills;
  - (4) Environmental quality and control;
  - (5) Aseptic processing;
  - (6) Labeling and recordkeeping;
  - (7) Finished preparation release check;
  - (8) Storage and beyond-use dating;
  - (9) Maintaining product quality and control during transportation and delivery after the CSP leaves the pharmacy;
  - (10) Patient or caregiver training;
  - (11) Adverse event reporting and recalls;
  - (12) Quality assurance program; and
  - (13) Quality control procedures, as appropriate.

**21.20.40 Personnel Education and Training.**

- a. **Low risk:** All pharmacy personnel preparing sterile products must receive suitable didactic and experiential training.
- b. **Medium risk:** In addition to low risk requirements, personnel training includes assessment of competency in all medium risk procedures.
- c. **High risk:** In addition to low and medium risk requirements, operators have specific education, training and experience to prepare high risk products. The pharmacist knows principles of good compounding practice for risk level products, including:
  - (1) Aseptic processing;
  - (2) Quality assurance of environmental, component, and end-product testing;
  - (3) Sterilization; and
  - (4) Selection and use of containers, equipment, and closures.

**21.20.50 Personnel Evaluation in Aseptic Manipulation Skills.**

- a. Personnel who prepare CSPs shall be provided appropriate training before they begin preparing CSPs.
- b. Compounding personnel shall perform didactic review and pass written and media-fill testing of aseptic manipulative skills initially; at least annually thereafter for low and medium risk products; and every six months, thereafter, for high risk products.
- c. Personnel who fail written tests, or whose media-fill test vials result in gross microbial colonization, must be immediately reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.
- d. Results of these tests shall be retained and be available for inspection at the outlet for at least two years.

**21.20.60 Environmental Quality and Controls.**

- a. All CSPs shall be compounded in air quality of a Class 100 (ISO Class 5) environment or better.
- b. For the compounding of non-radiopharmaceuticals, all primary engineering controls shall be placed in a buffer area that is of air quality Class 10,000 (ISO Class 7) or better. For the compounding of radiopharmaceuticals, all primary engineering controls shall be placed in a buffer area that is of air quality Class 100,000 (ISO Class 8) or better.
- c. The surfaces of the ceiling, walls, floor, fixtures, shelving, counters, and cabinets in the buffer area or clean room shall be smooth, impervious, free from cracks and crevices and non-shedding. Junctures of ceilings to walls shall be coved or caulked. There shall be no sink or floor drains in the buffer area or clean room.

- d. An anteroom shall be physically isolated from the buffer area or clean room. In this area, supplies are uncartoned and disinfected. Hand sanitizing and gowning occurs in this area. A demarcation line or barrier identifies the separation of the buffer area from the anteroom area. The air quality of the anteroom shall be Class 100,000 (ISO Class 8) or better.

**21.20.70 Environmental Monitoring.**

- a. Class 100 or better clean rooms and/or primary engineering controls shall be certified by qualified operators at least every six months and whenever the device or room is relocated or major service to the facility is performed. Certification records shall be maintained and be available for inspection at the outlet for at least two years from the certification date.
- b. Certification that each ISO classified area is within established guidelines shall be performed no less than every six months and whenever the primary engineering control is relocated or the physical structure of the buffer area or anteroom has been altered. The testing shall be performed by qualified operators using state-of-the-art electronic equipment with the following results:
  - (1) Not more than 3,520 particles 0.5 micrometer size and larger per cubic meter of air for any primary engineering control (ISO Class 5).
  - (2) Not more than 352,000 particles of 0.5 micrometer size and larger per cubic meter of air (ISO Class 7) for any buffer room; and
  - (3) Not more than 3,520,000 particles of 0.5 micrometer size and larger per cubic meter of air (ISO Class 8) for any anteroom/area.
- c. Certification records shall be maintained and be available for inspection at the outlet for at least two years from the certification date.
- d. Tests shall be done for airborne microorganisms. Electronic air samplers are the preferred method. The instructions in the manufacturer's user manual for verification and use of the electronic air sample that actively collects volumes of air for evaluation must be followed. The sampling is performed at locations judged by compounding personnel to be the most prone to contamination. These tests shall be done at least every six months. The outlet shall have written policies to reevaluate cleaning procedures, operational procedures, and air filtration efficiency if the number of colony forming units increases over the normal baseline level. Records of these tests shall be maintained and be available for inspection at the outlet for at least two years from the testing date.
- e. Glove fingertip sampling shall be conducted at least annually for all compounding personnel if compounding low and medium risk CSPs and semi-annually if compounding high risk CSPs. When a finger plate result for personnel monitoring after proper incubation exceeds the action limit, a review of hand hygiene and garbing procedures as well as glove and surface disinfection procedures and work practices shall occur.
- f. A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the clean room and anteroom and the anteroom and the general pharmacy area. The results shall be reviewed and documented on a daily basis. The pressure between the ISO Class 7 and general pharmacy area shall not be less than 5 pa (0.02-inch water column, w.c.).

**21.20.80 Cleaning and Disinfecting the Workspaces.**

- a. The cleaning and sanitizing of the workspaces shall be done pursuant to written procedures and shall be the responsibility of trained operators, using appropriate disinfecting agents.
- b. The direct and contiguous compounding area (DCCA), including ISO Class 5 areas, shall be cleaned and disinfected prior to the beginning of each shift. All items shall be removed from the DCCA and all surfaces shall be cleaned of loose material and residue from spills prior to cleaning.
- c. Work surfaces in the ISO Class 7 buffer areas and ISO Class 8 anteroom/areas are cleaned and disinfected at least daily.
- d. Dust and debris shall be removed as necessary from the storage areas for compounding ingredients and supplies.
- e. Storage shelving shall be disinfected at least monthly. All items shall be removed from the shelving prior to cleaning.
- f. The walls and ceilings in the buffer and anteroom areas shall be cleaned and disinfected at least monthly.
- g. Floors in the buffer and anteroom areas shall be mopped daily when no aseptic operations are in progress.
- h. All cleaning tools, such as wipers, sponges, and mops shall be non-shedding and dedicated to use in the buffer or clean area. Floor mops may be used in both the buffer or clean area and anteroom area, but only in that order. Most wipers shall be discarded after one use. If cleaning tools are reused, their cleanliness shall be maintained by thorough rinsing and disinfection after use and by storing in a clean environment between uses. Trash shall be collected in suitable plastic bags and removed with minimal agitation.

**21.20.90 Personnel Cleansing and Garbing.**

- a. Prior to entering the controlled (buffer) area, operators shall remove personal outer garments (such as lab jackets), makeup, and jewelry.
- b. After donning dedicated shoes or shoe covers, head and facial hair coverings, and face masks, hands and arms shall be thoroughly scrubbed up to the elbow. After drying hands and arms, operators shall properly don non-shedding gowns that fit snugly around the wrists and enclosed at the neck.
- c. Once inside the clean area, hands shall be cleansed with an antiseptic hand cleanser. Sterile powder-free gloves shall then be donned.
- d. During protracted compounding activities, personnel shall intermittently resanitize their gloves.
- e. For low and medium risk compounding: If personnel leave the buffer area, they shall don new hair covers, masks, shoe covers, and gloves prior to reentry. Gowns may be reused during the same compounding session if hung in the anteroom.

- f. For high risk: If personnel leave the buffer area, they must don new hair covers, masks, shoe covers, gowns and gloves prior to reentry.

**21.21.10 Components.**

- a. Compounding personnel shall ascertain that ingredients for CSPs are in compliance with Regulation 21.00.10(b) and are of the correct identity and appropriate quality using the following information: vendors' labels, labeling, certificates of analysis, direct chemical analysis, and knowledge of compounding facility storage conditions. No expired components may be used in compounding. No component may be used which will expire prior to the beyond-use date of the finished CSP.
- b. Ingredients used in a compounded preparation shall either originate from FDA-approved sources, if available, or be USP/NF grade substances.
- c. If neither USP/NF grade substances nor FDA-approved substances are available, or when food, cosmetics, or other substances are, or must be used, the substance shall be of a chemical grade in one of the following categories:
  - (1) Chemically Pure (CP);
  - (2) Analytical Reagent (AR); or
  - (3) American Chemical Society (ACS); or
  - (4) Food Chemical Codex.
- d. For all ingredients, unless FDA-approved, the pharmacist shall establish purity and stability by obtaining a certificate of analysis from the supplier. The certificate of analysis, when applicable, shall be maintained at the prescription drug outlet for at least two years from the date of preparation.
- e. A manufactured drug product may be a source of active ingredient. Only manufactured drugs from containers labeled with a lot number and an expiration date are acceptable as a potential source of active ingredients. When compounding with manufactured drug products, the compounder must consider all ingredients present in the drug product relative to the intended use of a compounded preparation.
- f. Drug preparations that appear on the FDA list of drug products withdrawn or removed from the market for safety reasons shall not be compounded. Such preparations may be compounded exclusively for veterinary use provided no documentation exists which indicates that the preparation is unsafe for such use.
- g. Sterile ingredients and components:
  - (1) A written procedure for physical inspection of ingredients and components prior to compounding shall be followed.
- h. Non-sterile ingredients and components:
  - (1) If any non-sterile components or ingredients, including containers, devices, and ingredients, are utilized to make the CSP, the product shall be compounded at high risk.

- (2) If non-USP or non-NF active ingredients, added substances, or excipients are utilized, a certificate of analysis from the supplier of the ingredient shall be maintained at the prescription drug outlet for at least two from the date of preparation.
  - (3) When non-sterile ingredients and components are received at the outlet, their container shall be marked, in indelible pencil or ink, with the date of receipt. In the absence of a supplier's expiration date on the product, the expiration date of the ingredient shall be one-year from the date of receipt, unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in CSPs.
  - (4) Prior to compounding with non-sterile ingredients and components, the ingredients shall be visually inspected for evidence of deterioration, other types of unacceptable quality and wrong identification.
- i. Any ingredient regulated by the FDA through an Investigational Review Board (IRB) is exempt from regulation 21.21.10 provided the research requirements for the receipt of the ingredient is followed and meets the requirements of CRS 12-22-128(2).

**21.21.20 Equipment.**

- a. Written procedures outlining required equipment, calibration, appropriate maintenance, monitoring for proper function, controlled procedures for use of the equipment and specified time frames for these activities shall be established and followed. Results of equipment calibration and appropriate maintenance reports shall be kept on file at the outlet for at least two years from the report date and shall be available for inspection.
- b. Accuracy assessments of automated compounding devices (ACD) shall be conducted daily for each day used. At routine intervals, the pharmacist manager, or his or her designee, shall review these assessments to avoid potentially clinically significant cumulative errors over time. These assessments shall be documented and be maintained and available for inspection at the outlet for at least two years.

**21.21.30 Finished Preparation Release Checks and Tests.**

**a. Physical Inspection**

- (1) Finished CSPs shall be individually inspected after compounding pursuant to written procedures. Immediately after compounding, and prior to dispensing or distribution, each product shall be inspected for evidence of particulates or other foreign matter, container-closure integrity, precipitation, cloudiness, and any other apparent visual defect. Defective product shall be segregated from other product and shall not be dispensed or distributed.

**b. Compounding Accuracy Checks.**

- (1) Written procedures for double-checking compounding accuracy shall be followed for every CSP during preparation and immediately prior to release. Outlets which compound CSPs shall have at least the following written procedures for verifying the correct identity and quality of CSPs prior to dispensing or distribution:**
  - (a) Verification of label for accuracy;**
  - (b) Correct identities, purities, and amounts of ingredients have been used; and**
  - (c) Correct fill volumes in CSPs and correct quantities of filled units of the CSPs were obtained.**

**c. Sterility Testing.**

- (1) Sterility testing shall be done on the following high risk CSPs:**
  - (a) Batches larger than 25 identical individual single-dose packages (ampules, bags, syringes, vials, etc);**
  - (b) Multiple dose vials for administration to multiple patients;**
  - (c) Product is exposed longer than 12 hours at refrigerator temperatures prior to sterilization; or**
  - (d) Product is exposed longer than 6 hours to temperatures warmer than refrigerator temperature prior to sterilization.**
- (2) The sterility test shall be compliant with the most current USP/NF Chapter 71 <Sterility Tests>. A method not described in the USP/NF may be used if verification results demonstrate that the alternative is at least as effective and reliable as the USP/NF methods.**
- (3) When a high risk CSP is dispensed or distributed before receiving the results of the sterility test, there shall be a written procedure requiring daily observation of the incubating test specimens and requiring an immediate recall if there is any evidence of microbial growth. In addition, the patient and the practitioner of the patient to whom a potentially contaminated CSP was administered shall be notified of the potential risk. Positive sterility results shall prompt a rapid and systematic investigation of aseptic technique, environmental and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes.**

**d. Bacterial Endotoxin (Pyrogen) Testing.**

- (1) Endotoxin testing shall be done on the following high risk CSPs that are to be administered parenterally:**
  - (a) Batches larger than 25 identical individual single-dose packages (ampules, bags, syringes, vials, etc.);**

- (b) Multiple dose vials for administration to multiple patients;
  - (c) Product is exposed longer than 12 hours at refrigerator temperatures prior to sterilization; or
  - (d) Product is exposed longer than 6 hours to temperatures warmer than refrigerator temperature prior to sterilization.
- (2) The endotoxin test shall be compliant with the most current USP/NF Chapter 85 <Bacterial Endotoxins Test>. In the absence of a bacterial endotoxins limit in the official monograph or other CSP formula source, the CSP must not exceed the amount of USP/NF Endotoxin Units (EU per hour per kg of body weight) specified for the route of administration.

**21.21.40 Storage and Beyond-Use Dating.**

- a. The temperature of drug storage areas of CSPs shall be monitored and recorded daily, either manually or electronically. Temperature records shall be maintained and be available for inspection for at least two years.
- b. Finished CSPs that are not immediately dispensed or administered shall be refrigerated or frozen unless their chemical and physical stability are known to be adversely affected by cold or freezing temperatures.
- c. In the absence of sterility testing compliant with the most current USP/NF Chapter 71 <Sterility Tests>, the beyond-use date (before administration) shall not exceed the following:
  - (1) Low risk CSPs with greater than 12-hour BUD:
 

Room temperature:	No more than 48 hours
Refrigerated temperature:	No more than 14 days
Frozen:	No more than 45 days
  - (2) Low risk CSPs with 12-hour or less BUD:
 

Room temperature:	No more than 12 hours
Refrigerated temperature:	No more than 12 hours
Frozen:	Not applicable
  - (3) Medium risk CSPs:
 

Room temperature:	No more than 30 hours
Refrigerated temperature:	No more than 9 days
Frozen:	No more than 45 days

- (4) **High risk CSPs:**
- |                           |                       |
|---------------------------|-----------------------|
| Room temperature:         | No more than 24 hours |
| Refrigerated temperature: | No more than 3 days   |
| Frozen:                   | No more than 45 days  |

- d. For high risk products, there must be a reliable method for establishing all expiration dates, including sterility. There must be a reliable method for establishing all beyond-use dating. Products maintaining beyond-use dating of greater than thirty (30) days shall have lab testing of product stability and potency.
- e. Each outlet shall adhere to manufacturers' instructions for handling and storing of Add-Vantage®, Mini Bag Plus®, Add A Vial®, Add-Ease® products, and any similar products.

**21.21.50 Formulation Record.**

- a. For each CSP, a uniform, readily retrievable formulation record shall be maintained and available for inspection for two years from the date last utilized, documenting:
- (1) The name, strength, dosage form, and route of administration of the compounded preparation;
  - (2) All ingredients and their quantities;
  - (3) The equipment used to compound the preparation, when appropriate, and mixing instructions;
  - (4) The beyond use date;
  - (5) The containers used in dispensing;
  - (6) Storage requirements; and
  - (7) Procedures for quality control, if applicable.

**21.21.60 Compounding Record.**

- a. For each CSP prepared, a record shall be maintained and available for inspection for two years on the original order, or on a separate, uniform, readily retrievable record documenting the following:
- (1) Name and strength of the compounded preparation;
  - (2) Formulation record reference for the preparation;
  - (3) Sources and lot number of each ingredient;
  - (4) Manufacturer's expiration date of each ingredient, when applicable;
  - (5) Total number of dosage units compounded;
  - (6) Name of the person who compounded the preparation;

- (7) Name of the pharmacist who approved the preparation;
- (8) Batch (lot) number assigned, if multiple units compounded;
- (9) Date of preparation;
- (10) Beyond use date;
- (11) Prescription number(s), if appropriate;
- (12) Results of quality control procedures; and
- (13) If a high risk product, the record shall also include comparisons of actual with anticipated yields, sterilization methods, and quarantine specifications.

**21.21.70 Labeling of CSPs.**

- a. Labeling of CSPs dispensed pursuant to a prescription order or LTCF chart order shall include at least the following:
  - (1) All requirements of CRS 12-22-123;
  - (2) Batch (lot) number, if appropriate;
  - (3) Beyond-use date;
  - (4) If for parenteral administration, the following shall be included:
    - (a) Name of base solution; and
    - (b) name and amounts of drugs added.
  - (5) Storage directions; and
  - (6) "This product was compounded by the pharmacy."
- b. Labeling of CSPs dispensed pursuant to a hospital chart order shall include at least the following:
  - (1) All requirements of CRS 12-22-123;
  - (2) Batch (lot) number, if appropriate;
  - (3) Beyond-use date;
  - (4) If for parenteral administration, the following shall be included;
    - (a) Name of base solution; and
    - (b) Name and amounts of drugs added; and
  - (5) Storage directions.

- c. **Labeling of CSPs distributed to practitioners or other prescription drug outlets allowed by law shall include at least the following:**
  - (1) **Name of the outlet;**
  - (2) **Name and strength of the drug(s);**
  - (3) **Total quantity in package;**
  - (4) **Quantity of active ingredient in each dosage unit;**
  - (5) **Beyond-use date;**
  - (6) **Batch (lot) number;**
  - (7) **Specific route of administration;**
  - (8) **Storage directions;**
  - (9) **“Rx only”; and**
  - (10) **“This product was compounded by the pharmacy.”**
  
- d. **Labeling of CSPs distributed within hospitals as floor stock shall include at least the following:**
  - (1) **Name of the outlet;**
  - (2) **Name and strength of the drug(s);**
  - (3) **Total quantity in package;**
  - (4) **Quantity of active ingredient in each dosage unit;**
  - (5) **Beyond-use date;**
  - (6) **Batch (lot) number;**
  - (7) **Specific route of administration; and**
  - (8) **Storage directions.**

**21.21.80 Maintaining Product Quality and Control After the CSP Leaves the Outlet or Hospital Location.**

- a. **The outlet shall have written policies and procedures that are adhered to which shall ensure the CSP is packaged properly for transit, stored properly during transit, and stored properly at site of administration. Such policies and procedures shall also discuss patient or caregiver training.**

**21.21.90 Patient Monitoring, Adverse Events Reporting, and Product Recall.**

- a. **Outlets which compound CSPs shall provide patients and other recipients of CSPs with a way to address their questions and report any concerns that they may have with CSPs and their administration devices.**

- b. The outlet shall have written policies describing specific instructions for receiving, acknowledging, and dating receipts; and for recording, or filing, and evaluating reports of adverse events and of the quality of preparation claimed to be associated with CSPs.
- c. The pharmacist manager shall report to the board in writing significant errors related to compounded CSPs such as those that result in serious personal injury or death of a patient.
- d. If a CSP is believed to be defective in any way, the outlet shall immediately recall any product dispensed or distributed. Any product remaining in the outlet shall be immediately quarantined and shall not be dispensed or distributed. Recall records shall include at least the following:
  - (1) Product name, strength, dosage form;
  - (2) Reason for recall;
  - (3) Amount of product made;
  - (4) Date made; and
  - (5) Amount of product dispensed or distributed.
- e. The outlet shall conduct tests, as appropriate, on the recalled product to identify the reason the product was defective. Results of these tests shall be maintained at the outlet for at least two years.
- f. Adverse event reports and product recall records shall be retained and be available for inspection at the outlet for at least two years.

**21.22.00 Quality Assurance Program.**

- a. Outlets that make CSPs shall have a formal written quality assurance (QA) program which shall provide a mechanism for monitoring, evaluating, correcting, and improving the activities and processes regarding the compounding of sterile products.
- b. At a minimum, the written QA program shall include the following:
  - (1) Consideration of all aspects of the preparation, dispensing, and distribution of products, including environmental testing, validation results, etc;
  - (2) Describe specific monitoring and evaluation activities;
  - (3) Specification of how results are to be reported and evaluated;
  - (4) Identification of appropriate follow-up mechanisms when action limits or thresholds are exceeded; and
  - (5) Delineation of the individuals responsible for each aspect of the QA program.

**21.22.10 Cytotoxic Drug Preparation.**

- a. **Cytotoxic drugs shall be compounded in a vertical flow, Class II biological safety cabinet (BSC) or CACI. Such BSC or CACI shall be placed in an ISO Class 7 area that is physically separated from other preparation areas and is negative pressure to adjacent positive pressure anteroom. If used for other products, the cabinet must be thoroughly cleaned;**
- b. **Appropriate personnel protective equipment (PPE) shall be worn when compounding in a BSC or CACI and when using closed-system vial transfer devices (CSTDs). PPE should include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, double gloving with sterile chemo-type gloves, and compliance with manufacturers' recommendations when using a CACI;**
- c. **Appropriate safety and containment techniques for compounding cytotoxic drugs shall be used in conjunction with the aseptic techniques required for preparing sterile products;**
- d. **Appropriate disposal containers for used needles, syringes, and if applicable, cytotoxic waste from the preparation of chemotherapy agents and infectious waste from patients' homes. Disposal of cytotoxic waste shall comply with all applicable local, state and federal requirements;**
- e. **Written procedures for handling major and minor spills and generated waste of cytotoxic agents must be developed and must be included in the policy and procedure manual; and**
- f. **Prepared doses of cytotoxic drugs must be labeled with proper precautions inside and outside, and shipped in a manner to minimize the risk of accidental rupture of the primary container.**

**21.22.20 Exemption for Sterile Compounding of Products in Closed or Sealed System.**

- a. **Pharmacists and pharmacies or other outlets where sterile compounding is provided may be exempt from this rule when compounding is restricted to utilizing compounds or products that are contained only in a closed or sealed system and can be transferred or compounded within this self-contained system or topical products that require further transfer or combination in order to achieve a finished product without further modification of the product.**