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SUBCHAPTER 10. GOOD COMPOUNDING PRACTICES

PART 1. GOOD COMPOUNDING PRACTICES FOR NON-STERILE PRODUCTS

535:15-10-2. Definitions

The following words or terms, when used in this Subchapter, shall have the following meaning, unless the context clearly indicates otherwise:

'Beyond-Use Date (BUD)' means the date and time, as appropriate, after which a compounded preparation is not to be used and is determined from the date the preparation is compounded.

'Biological Safety Cabinet (BSC)' means a ventilated cabinet for hazardous drugs, personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward high-efficiency particulate air (HEPA)-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection meeting USP standards.

'Compounder' means a compounder is a pharmacist or anyone compounding under the direct supervision of a pharmacist pursuant to a prescription order by a licensed prescriber.

'Compounding' means the preparation, mixing, assembling, packaging, and labeling of a drug or device ~~as the result of~~ in accordance with a licensed practitioner's prescription drug order ~~or~~ under an initiative based on the Practitioner/Patient/Pharmacist/Compounder relationship in the course of professional practice.

(A) Compounding may be for the purpose of, or as an incident to, research, teaching, or chemical analysis.

(B) Compounding includes the preparation of Drugs or Devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.

(C) Reconstitution of commercial products is not considered compounding for the purposes of this subchapter.

(D) Manipulation of commercial available products according to or beyond the manufacturer's instructions or copying commercially products for the reason of non-availability or component specifications would be considered compounding as pertaining to a practitioner / patient / compounder relationship.

'Component' means any ingredient used in the compounding of a drug product, including those that may not appear on the labeling of such a product.

'Hazardous drug' means any drug listed as such by NIOSH and/or any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or animals, genotoxicity, or new drugs that mimic existing hazardous drugs in structure or toxicity.

'Inordinate Amount' means an amount of compounded drug that exceeds the amount a pharmacy anticipates may be used or dispensed before the BUD of the compounded drug and/or is unreasonable considering the intended use of the compounded drug.

'Isolator' means a device that is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated.

'Labeling' means all labels and other written, printed, or graphic matter on an immediate container of an article or preparation or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term 'label' designates that part of the

labeling on the immediate container.

'Manufacturing' means the production, ~~preparation,~~ propagation, conversion, or processing of a drug or device, either directly or indirectly by extraction from substances of natural origin or independently by means of chemical or biological synthesis and includes any packaging or repackaging of the substance(s) or labeling or re-labeling of its container, ~~and~~ for the promotion and marketing of such drugs or devices. Manufacturing also includes any preparation of a drug or device that is given or sold for resale by pharmacies, practitioners, or other persons. The distribution of inordinate amounts of compounded products without a prescriber/patient/pharmacist relationship is considered manufacturing.

'Personal Protective Equipment (PPE)' means items such as gloves, gowns, respirators, goggles, face shields, and others that protect individual workers from hazardous physical or chemical exposures.

'Pharmacy Generated Products' or **'(PGP)'** means a medical product that is prepared, packaged and labeled in a pharmacy that can be sold by the pharmacy without a prescription.

'Preparation' means an article compounded in a licensed pharmacy pursuant to the order of a licensed prescriber.

'Product' means a commercially manufactured drug or nutrient that has been evaluated for safety and efficacy by the FDA. Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or product package insert.

'USP' means 'United States Pharmacopeia'

535:15-10-3. Pharmacist responsibilities

(a) All Pharmacists who engage in drug compounding, shall be proficient in compounding and should continually expand their compounding knowledge by participating in seminars and/or studying appropriate literature.

(b) Every pharmacist engaging in drug compounding shall be familiar with all details of ~~Good~~ USP Compounding ~~Practices~~ Standards and should be familiar with ~~FDAMA related~~ patent regulations.

(c) The pharmacist has the responsibility to:

(1) ensure the validity of all prescriptions

~~(1)~~ (2) certify all prescriptions.

~~(2)~~ (3) approve or reject all components, drug product containers, closures, in-process materials, and labeling.

(4) ensure preparations are of acceptable strength, quality, and purity.

(5) verify all critical processes to ensure that procedures will consistently result in the expected qualities in the finished preparation.

~~(3)~~ (6) prepare and review all compounding records to ~~assure~~ ensure that no errors have occurred in the compounding process.

(7) ensure appropriate stability evaluation is performed or determined from the literature for establishing reliable beyond-use dating.

~~(4)~~ (8) ~~assure~~ ensure the proper maintenance, cleanliness, and use of all equipment used in a prescription compounding practice; and,

~~(5)~~ (9) ~~assure~~ ensure only authorized personnel shall be in the immediate vicinity of the drug compounding operation.

(10) perform final check of preparations prior to their release from the pharmacy.

(A) A check for compounding accuracy must ensure accuracy of the label and volumes or quantities of all drugs and solutions

(B) A visual examination procedure must ensure:

(i) Comparison with original order for initial dispensing

(ii) Accuracy of calculations

(iii) Use of proper solutions, additives and equipment

(iv) Labels are complete

(v) Proper assignment of beyond use date and time

(vi) Integrity of the container, including visual defects

(vii) Proper storage

(viii) Absence of particulate matter, precipitates, turbidity, discoloration, evidence of contamination or other signs that the preparation should not be used

(C) The pharmacist shall reject and destroy all preparations that do not pass the final examination.

(D) Pharmacists shall document final preparation examinations prior to releasing the Compounded Sterile Preparations from the pharmacy.

(d) The pharmacist-in-charge has the responsibility to ensure that all compounders who compound pharmaceuticals meet all requirements for training, testing and education set forth in these regulations and contained in the regulations set forth in USP standards.

(1) Competency shall be demonstrated prior to preparing any products for patient use, and

(2) Whenever the quality assurance program yields unacceptable results, and

(3) Whenever unacceptable or questionable techniques are observed, and

(4) Evaluated at least annually.

(e) Pharmacist requirements. Any pharmacist in charge who performs or supervises the preparation of compounded medications shall:

(1) Have available written policies and procedures for all steps in the compounding of preparations. In addition, said policies and procedures shall address personnel education and training and evaluation, storage and handling, clothing, personal hygiene, hand washing, quality assurance, expiration dating, and other procedures as needed.

(2) Certify that all participating pharmacists and pharmacy technicians have completed training and testing program in product preparation. Documentation of training and testing shall be available for review.

(3) Develop policies and procedures to annually test and review the techniques of participating pharmacists and pharmacy technicians.

(f) Staff will be trained and evaluated according as follows:

(1) Training is required for any individual who prepares compounded products. This training must be completed before the employee is allowed to prepare compounded products.

(2) Training may consist of any combination of didactic and experiential methods which must convey proper technique, infection control procedures, etc. required by USP standards.

(3) A written test shall be administered and passed based on the material referenced above upon initial hire or prior to assignment to prepare compounded products.

(4) Testing will be conducted annually for every employee involved in product preparation. Compounding personnel who fail written tests shall be immediately reinstructed and reevaluated by expert compounding personnel to ensure correction of all practice deficiencies.
(5) An 'Individual Training Record' shall be maintained for every employee involved in sterile product preparation.
(6) Nothing in these regulations shall prohibit a licensed student pharmacy intern engaged in experiential classes from assisting a properly qualified pharmacist in preparing sterile products under that pharmacist's direct supervision.
(7) Complete documentation by a pharmacist of training and testing shall be available for inspection.

(g) Pharmacy technician requirements. Pharmacy technicians participating in the preparation of compounded products shall have completed a pharmacist supervised training and testing program in product preparation. Completed documentation by a pharmacist of training and testing shall be available for inspection.

535:15-10-4. Drug compounding facilities

(a) Pharmacies engaging in compounding shall have a specifically designated and adequate space for the orderly compounding of prescriptions, including the placement and storage of equipment and materials.
(b) The aseptic processing for sterile products shall be in an area separate and distinct from the area used for the compounding of non-sterile drug products.
(c) The area(s) used for the compounding of drugs shall be maintained in a good state of repair. These area(s) shall also be maintained in a clean and sanitary condition. Adequate washing facilities are to be provided and sewage, trash and other refuse in the compounding area is to be disposed of in a safe, sanitary, and timely manner.
(d) Hazardous drugs shall be prepared within a certified Class II, Type A (exhaust may be discharged to the outdoors) or Class II, Type B (exhaust may be discharged to the outdoors) laminar flow biological safety cabinet. All new construction, and those undergoing renovation requiring the moving of existing hoods used in the preparation of cytotoxic drugs, shall exhaust the hood to the outdoors, unless the Board of Pharmacy grants an exception. Hazardous drug compounding shall have negative pressure to adjacent positive pressure areas, thus providing inward airflow to contain any airborne drug. All vented cabinets shall be vented through HEPA filtration, preferably to outside air or through use of suitable technology or equipment. Ventilation exhaust shall be placed as not to reenter the facility at any point.
(~~d~~) (e) Bulk drugs and other chemicals or materials used in the compounding of drugs must be stored as directed by the manufacturer, or according to USP monograph requirements, in a clean, dry area, under appropriate temperature conditions (controlled room temperature, refrigerator, or freezer in adequately labeled containers). Bulk drugs shall also be stored such that they are protected from contamination.
(~~e~~) (f) Adequate lighting and ventilation shall be provided in all compounding areas.
(~~f~~) (g) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any compounded drug product.
~~(g) These area(s) used for compounding shall be maintained in a clean and sanitary condition.~~
(h) Purified water must be used for compounding non-sterile drug preparations when

formulations indicate the inclusion of water.
~~(h) If parenteral products are being compounded, the rules in Subchapter 9 must be met.~~

535:15-10-5. Compounding equipment
(a) Equipment used in the compounding of drug products shall be of appropriate design and capacity as well as suitably located to facilitate operations for its intended use, cleaning and maintenance.
(b) Compounding equipment shall be of suitable composition so the surfaces that contact components shall ~~not~~ neither be reactive, additive nor absorptive ~~so as to alter~~, therefore not affecting or altering the purity of the ~~product~~ compounded preparation.
(c) Equipment and utensils used for compounding shall be thoroughly cleaned ~~and sanitized immediately prior to~~ promptly after every use to prevent contamination and ~~(d) Equipment and utensils~~ must be stored in a manner to protect them from contamination.
(d) Defective equipment shall be clearly labeled as such.
(e) Automated, mechanical, electronic, limited commercial scale manufacturing or testing equipment, and other types of equipment may be used in the compounding of drug products. If such equipment is used, it shall be routinely inspected, calibrated ~~(if~~ as necessary~~),~~ or checked to ensure proper performance.
~~(f) Immediately prior to the initiation of compounding operations, the equipment and utensils must be inspected by the pharmacist and determined to be suitable for use.~~
~~(g)~~ (f) When drug products with special precautions (antibiotics~~,~~ and hazardous materials ~~and radiopharmaceuticals~~) are involved~~,~~ appropriate measures must be utilized in order to prevent cross-contamination and proper disposal procedures must be followed. These measures include either the dedication of equipment for such operations or the meticulous cleaning of equipment prior to its use for the preparation of other drugs. Equipment dedicated for specific use (i.e. penicillin) shall be clearly designated as such.

535:15-10-6. Component selection requirements
(a) The ~~Pharmacist~~ pharmacist shall first attempt to use USP-NF drug substances and inactive components ~~for compounding~~ that have been made in an FDA ~~inspected~~ registered facility.
(b) If components are not obtainable from an FDA ~~inspected~~ registered facility or if the FDA and/or the company cannot document FDA ~~inspection~~ registration, pharmacists compounding prescriptions shall use their professional judgment in first receiving, storing or using drug components that meet official compendia requirements or another high quality source.
(c) If components of compendial quality are not obtainable, components of high quality such as those that are chemically pure, analytical reagent grade, American Chemical Society-certified, or Food Chemicals Codex grade may be used.
(d) Components shall be stored off the floor, handled and stored to prevent contamination, and rotated so that the oldest stock is used first.

535:15-10-7. Control of drug product containers
(a) Drug product containers and closures shall be handled and stored in a manner to prevent contamination and to permit inspection and cleaning of the work area.
(b) Containers and closures shall be of suitable material as to not alter the compounded drug as to quality, strength or purity of the compounded preparation.

535:15-10-8. Drug compounding controls

(a) There shall be written procedures for the compounding of drug products to assure that the finished products have the identity, strength, quality and purity they purport ~~or are represented~~ to have ~~possess~~. These procedures should be available in either written form or electronically stored with printable documentation.

(b) The objective of the documentation is to allow another compounder to reproduce an equivalent prescription at a future date.

~~(b)~~ (c) Procedures shall include a listing of the components, their amounts (in weight or volume), the order of component mixing, and a description of the compounding process. ~~(c)~~ In addition, ~~All~~ all equipment and utensils and the container/closure system, relevant to the sterility and stability of the intended use of the drug shall be listed.

(d) These written procedures shall be followed in the execution of the compounding procedure and are designed to enable a compounder, whenever, necessary, to systematically trace, evaluate, and replicate the steps included throughout the preparation process of a compounded preparation.

(e) Components shall be accurately weighed, measured, ~~or~~ and subdivided as appropriate. These operations should be checked and rechecked by the compounding pharmacist at each stage of the process to ensure that each weight and measure is correct as stated in the written compounding procedures.

(f) Written procedures shall be established and followed that describe the tests or examinations to be conducted on the product compounded (e.g., degree of weight variation among capsules) to assure reasonable uniformity and integrity of compounded drug ~~products~~ preparations. Unless otherwise indicated or appropriate, compounded preparations are to be prepared to ensure that each preparation shall contain not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of active ingredient per unit weight or volume and not less than 90% and not more than 110% of the theoretically calculated weight or volume per unit of the preparation.

(1) Such control procedures shall be established to monitor the output and to validate the performance of those compounding processes that may be responsible for causing variability in the final drug product. ~~(2) Such control~~ These procedures shall include, but are not limited to, the following (where appropriate):

(A) Capsule weight variation to ensure that each unit shall be not less than 90% and not more than 110% of the theoretically calculated weight for each unit;

(B) Adequacy of mixing to assure uniformity and homogeneity;

(C) Clarity, completeness or pH of solutions.

(2) The compounder shall label any excess compounded products so as to reference them to the formula used, the assigned batch number, and beyond use date based on the compounder's appropriate testing, published data, or USP-NF standard.

~~(g) Appropriate written procedures designed to prevent microbiological contamination of compounded drug products purporting to be sterile shall be established and followed. Such procedures shall include validation of any sterilization process.~~

~~(h) Beyond use dates and storage requirements (e.g., refrigeration) should be established. The U.S.P. NF Guidelines should be used.~~

(g) Material safety data sheet (MSDS) files should be easily accessible.

(h) General requirements:

(1) Compounding a drug product that is commercially available in the marketplace or that is essentially a copy of an available FDA-approved drug product is generally prohibited unless patient therapy is compromised.

(2) However, in special circumstances a pharmacist may compound an appropriate quantity of a drug that is different from an FDA-approved drug that is commercially available based on documentation provided by the prescribing physician of a patient specific medical need (e.g. the physician requests an alternate product due to hypersensitivity to excipients or preservative in the FDA-approved product, or the physician requests an effective alternate dosage form) or if the drug product is not commercially available.

(A) The unavailability of such drug product must be documented prior to compounding.

(B) This or similar documentation must be available when requested by the Board.

(3) Except for those products where stability prohibits advanced compounding, all products dispensed by the pharmacy shall be in a form ready for administration, except in health care facilities where medications may be provided as demanded by policies and procedures.

535:15-10-8.1. Transfer of compounded prescriptions

(a) If a patient requests a transfer of their prescription, a copy of the original prescription shall be transmitted upon the request of the receiving pharmacist.

(b) The information included in the transfer of the prescription shall include:

(1) Active ingredient(s),

(2) Concentration,

(3) Dosage Form e.g. capsule, cream, suspension, injectable, etc.

(4) Route of delivery e.g. oral, injectable, topical, vaginal, etc.

(5) Delivery mechanism e.g. topical, transdermal, immediate release, sublingual, etc.

(6) Dosing Duration e.g. Q12H, Q24H, Q72H, etc.

(7) Details about the compounding procedure must be reasonably available from the transferring pharmacy.

535:15-10-8.2. Beyond-use dating

(a) Pharmacies engaging in compounding shall assign every compounded preparation an appropriate beyond-use date.

(b) Beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

(c) BUD dates are to be assigned conservatively**,** and should be based on the following USP-NF standards:

(1) For Non-aqueous liquids and solid formulations

(A) Where the manufactured drug product is the source of active Ingredient – The beyond-use date is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier.

(B) Where a USP of NF substance is the source of active ingredient – the beyond-use date is not later than 6 months for

(i) Water-containing formulations (prepared from ingredients in solid form) – the beyond-use date is not later than 14 days for liquid preparations when

stored at cold temperatures between 2º and 8ºC (36º and 46º F).
(ii) All other formulations – The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier.
(2) The USP-NF standards listed above may be exceeded when there is supporting scientific stability information that is directly applicable to the specific preparation (i.e., the same drug concentration range, pH, excipients, vehicle, water content, etc.)
(3) Information to be considered when assigning a beyond-use date includes chemical, physical and microbiological stability; nature of the drug, its chemical degradation mechanism, the container in which it is packaged, expected storage conditions, and the intended duration of therapy.

535:15-10-9. Labeling

(a) If a component is transferred from the original container to another (e.g., a powder is taken from the original container, weighed, placed in ~~a container~~, and stored in another container) the new container shall be identified with the:
(1) Component name,
(2) Lot and ~~expiration date~~ BUD if available,
(3) Strength and/or concentration, and;
(4) Weight or measure

(b) Products prepared in anticipation of a prescription prior to receiving a valid prescription should not be an inordinate amount.
(1) A regularly used amount should be prepared based on a history of prescriptions filled by the pharmacy.
(2) These products shall be labeled or documentation referenced with the:
(A) Complete list of ingredients or preparation name and reference,
(B) Preparation date,
(C) Assigned beyond-use date:
(i) Based on published data, or;
(ii) Appropriate testing, or;
(iii) USP-NF standards.
(D) Specific storage ~~under~~ conditions dictated by ~~its~~ composition and stability ~~e.g., in a clean, dry place or in the refrigerator~~ shall be specified (refrigerator, freezer etc), except where clean dry area is dictated, and;
(E) Batch or lot number.

(c) Upon the completion of the drug preparation operation, the pharmacist shall examine the product for correct labeling.
(d) The containers and closures shall be of suitable material so as not to alter the quality, strength, or purity of the compounded drug.
(e) The outpatient prescription label shall contain the following:
(1) Patient name,
(2) Prescriber's name,
(3) Name & address of pharmacy,
(4) Directions for use,
(5) Date filled,
(6) Beyond use date & storage (may be auxiliary labels), and;

(7) An appropriate designation that this is a compounded prescription, such as 'Compounded Rx'.

535:15-10-10. Records and reports

(a) Any procedures or other records required to comply with USP Compounding Standards ~~Good Compounding Practices~~ shall be retained for the same period of time as required for retention of prescription records; and copies of such records, shall be readily available for authorized inspection.

~~(b) All records required to be retained under Good Compounding Practices, or copies of such records, shall be readily available for authorized inspection.~~

~~(c)~~ (b) Computer information and the hard copy of the prescription should indicate that the prescription is to be compounded.

~~(d)~~ (c) Adequate records must be kept of controlled dangerous substances (Scheduled drugs) used in compounding.

535:15-10-11. Pharmacy generated product requirements

(a) A Pharmacy Generated Product (PGP) ~~may be~~ if prepared from RX Only drugs, ~~not to~~ may not exceed recommended OTC strengths and doses.

(b) PGP will be labeled properly and will be sold with the public's health and welfare in mind.

(c) Compounded PGP's are to be sold directly to the consumer after professional interaction or consultation with the health care provider and the consumer.

(d) A PGP cannot be bulk compounded to sell to a second entity for resale. This would require a manufacturer's license.

535:15-10-12. Compounding for a prescriber's office use

(a) Pharmacies engaging in compounding may prepare compounded drug ~~products~~ preparations for a licensed prescriber's office use.

(b) An order by the licensed prescriber indicating the formula and quantity ordered will be filed in the pharmacy.

(c) The ~~product~~ preparation is to be administered in the office and not dispensed to the patient. The preparation label should state 'for office use only-not for resale'.

(d) An invoice shall be kept on file by the pharmacy. This invoice shall include, but not be limited to, the name and address of purchaser, quantity sold, drug description, price, and date of transaction. These invoices must be readily available for inspection. A drug supplier permit is required per OAC 535:15-7.

~~(d)~~ (e) A record of the compounded drug ~~product~~ may be kept as a prescription record in the pharmacy computer and ~~(e) A~~ a label may be generated and a number assigned by the pharmacy computer for the compounded drug ~~product.~~

(f) Under Oklahoma Bureau of Narcotics rules [475:30-1-3 (b) et seq.], a prescription for controlled dangerous substances cannot be filled 'for office or medical bag use'.

(g) Compounded preparations may not be given or sold for resale by practitioners or other persons.

535:15-10-13. Compounding veterinarian products

(a) Prescriptions for animals may be compounded based on an order or prescription from a

licensed prescriber. Compounding for office use for administration by veterinarians is allowed.
(b) These prescriptions are to be handled and filled the same as the human prescriptions.
(c) The preparation is to be administered by a veterinarian and not dispensed to the patient. The preparation label should state 'for office use only-not for resale'.
~~(c)~~ (d) Caution should be taken as to not violate federal patent laws by duplicating an available product in inordinate quantities.
(e) An invoice shall be kept on file by the pharmacy. This invoice shall include, but not be limited to, the name and address of purchaser, quantity sold, drug description, price, and date of transaction. These invoices must be readily available for inspection. A drug supplier permit is required per OAC 535:15-7.
~~(d)~~ (f) Under Oklahoma Bureau of Narcotics rules [475:30-1-3 (b) et seq.], a prescription for controlled dangerous substances cannot be filled 'for office or medical bag use'.
(g) Compounding with bulk chemicals for food-producing animals is not permitted.

535:15-10-14. Compounding of non-sterile hazardous drugs

Pharmacies engaging in compounding of hazardous drugs shall be responsible for meeting the following criteria:

(1) Non-sterile hazardous drugs shall include the NIOSH list of hazardous drugs as well as any individual products named per each individual pharmacy by referencing MSDS sheets or any other reference relating to above definition.

(2) Exposure control shall begin when hazardous drugs enter the facility. The PIC shall be responsible to confirm that medical products have labeling on the outer container that can be understood by all workers who will be separating hazardous from nonhazardous drugs.

(3) All employees must wear PPE when opening containers to unpack hazardous drugs. Employees must also wear chemotherapy gloves to prevent contamination when transporting the drug to the work area.

(4) Hazardous drugs must be stored separately from other drugs, as recommended by current ASHP guidelines on handling hazardous drugs. Hazardous drugs must be stored and transported in closed containers that minimize the risk of breakage.

(5) Pharmacies and pharmacist shall make sure the storage area has sufficient general exhaust ventilation to dilute and remove any airborne contaminants. Use a ventilated cabinet designed to reduce worker exposures while preparing hazardous drugs. When asepsis is not required, a Class I BSC, powder containment hood or an isolator intended for containment applications may be sufficient. Do not use a ventilated cabinet that re-circulates air inside the cabinet or exhausts air back into the room environment unless the hazardous drug(s) in use will not volatize while they are being handled or after they are captured by the HEPA filter.

(6) Staff should be fully trained and procedures established for their particular equipment and unique workplace setting.

(7) All staff shall wear PPE while working with hazardous drugs.

(8) Mix, prepare, and otherwise manipulate, count, crush, compound powders, or pour liquid hazardous drugs inside a ventilated cabinet designed to prevent hazardous drugs from being released into the work environment.

(9) Do not use supplemental engineering or process controls (such as needleless

systems, glove bags and closed-system drug transfer devices) as a substitution for ventilated cabinets, even though such controls may reduce the potential for exposure when preparing and administering hazardous drugs.
(10) Use a high-efficiency particulate air filter (HEPA filter) for the exhaust from these controls.
(11) When drug preparation is complete, seal the final product in a plastic bag or other sealable container for transport before taking it out of the ventilated cabinet.
(12) Wash hands with soap and water immediately before donning and after removing gloves.
(13) Develop a written safety plan for all routine maintenance activities performed on equipment that could be contaminated with hazardous drugs.
(14) Manage hazardous drug spills according to policies and procedures for each workplace according to size of spill, possible spreading etc. Locate spill kits and other cleanup materials in the immediate area where exposures may occur.
(15) Consider a medical surveillance program or allow workers to have routine medical care.

535:15-10-15. Compounding of non-sterile radiopharmaceuticals

(a) The unique circumstances and requirements for radiopharmaceutical preparations necessitate specific stipulations that must not only satisfy pharmaceutical drug quality, but also consider crucial radiation safety concerns to operators. Facility design and variation in certain chapter standards may be required and shall be documented with supporting evidence upon request.
(b) Radiopharmaceuticals prepared for oral administration shall be designated as, and conform to, the standards for non-sterile preparations. Any variation in certain chapter standards may be required to meet radiation safety concerns to operators and shall be documented with supporting evidence upon request.

PART 3. GOOD COMPOUNDING PRACTICES FOR STERILE PRODUCTS

535:15-10-50. Purpose

(a) The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (non-sterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles or 10% for nonofficial articles, (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in compounded sterile preparations (CSPs). Contaminated CSPs are potentially most hazardous to patients when administered into body cavities, central nervous and vascular systems, eyes, and joints, and when used as baths for live organs and tissues. When CSPs contain excessive bacterial endotoxins they are potentially most hazardous to patients when administered into the central nervous system.
(b) To achieve the above five conditions and practices, this chapter provides minimum practice and quality standards for CSPs of drugs and nutrients based on current scientific information and best sterile compounding practices. The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have

been proven to be equivalent or superior with statistical significance to those described herein. The standards in this chapter do not pertain to the clinical administration of CSPs to patients via application, implantation, infusion, inhalation, injection, insertion, instillation, and irrigation, which are the routes of administration. Four specific categories of CSPs are described in this chapter: low-risk level, medium-risk level, and high-risk level, and immediate use. For the purposes of this chapter, CSPs include, but are not limited to the following:

(1) Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

(2) Manufactured sterile products prepared according to the instructions in manufacturers' approved labeling. Product package inserts usually refer to aseptic technique, but do not usually describe environmental quality controls, storage, or BUD and times for radiopharmaceuticals.

(c) All personnel who prepare CSPs shall be responsible for understanding these fundamental practices and precautions, for developing and implementing appropriate procedures, and for continually evaluating these procedures and the quality of final CSPs to prevent harm.

535:15-10-51. Definitions

The following words or terms, when used in this Subchapter, shall have the following meaning, unless the context clearly indicates otherwise:

'ACPH' means 'air changes per hour'.

'ALARA' means 'as low as reasonably achievable'.

'Ante-Area' means an ISO Class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate generating activities are performed. It is also a transition area that (1) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas and (2) reduces the need for the heating, ventilating, and air-conditioning (HVAC) control system to respond to large disturbances.

'Beyond-use date (BUD)' means the date and time, as appropriate, after which a compounded preparation is not to be used and is determined from the date the preparation is compounded.

'Biological Safety Cabinet (BSC)' means a ventilated cabinet for CSPs, personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward high-efficiency particulate air (HEPA)-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection.

'Buffer Area' means an ISO Class 7 or better area where the primary engineering control (PEC) is physically located. Activities that occur in this area include the staging of components and supplies used when compounding CSPs.

'Clean Room' means an ISO Class 5 or better 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 gear are not exceeded for a specified cleanliness class.

Effective 7/01/2009

'Component' means any ingredient used in the compounding of a drug product, including those that may not appear on the labeling of ~~in~~ such a product.

'Compounder' is a pharmacist or anyone compounding under the direct supervision of a pharmacist pursuant to a prescription order by a licensed prescriber.

'Compounding' means the preparation, mixing, assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner's prescription drug order ~~or~~ under an initiative based on the Practitioner/Patient/Pharmacist relationship in the course of professional practice.

(A) Compounding may be for the purpose of, or as an incident to, research, teaching, or chemical analysis.

(B) Compounding includes the preparation of Drugs or Devices in anticipation of Prescription Drug Orders based on routine, regularly observed prescribing patterns.

(C) Reconstitution of commercial products is not considered compounding for the purposes of this subchapter.

(D) Manipulation of commercial available products according to or beyond the manufacturer's instructions or copying commercial products for the reason of non-availability or component specifications would be considered compounding as pertaining to a practitioner / patient / compounder relationship.

'Compounding Aseptic Containment Isolator (CACI)' means a compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes 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 hazardous drugs are prepared, the exhaust air from the isolator should be appropriately removed by properly designed building ventilation.

'Compounding Aseptic Isolator (CAI)' means a form of 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 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).[2]

'Critical Site' means a location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampuls, needle hubs) exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

'CSP' means 'Compounded Sterile Preparation'

'CSTD' means 'Closed-System Vial-Transfer Device'

'FDA' means the federal 'Food and Drug Administration'

'Hazardous drug' means any drug listed as such by NIOSH and/or any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or animals, genotoxicity, or new drugs that mimic existing hazardous drugs in structure or toxicity.

'HEPA' means 'High Efficiency Particulate Air'

Effective 7/01/2009

'Immediate Use' means 'administration begins not later than 1 hour following the start of the compounding procedure'.

'Inordinate Amount' means an amount of compounded drug that exceeds the amount a pharmacy anticipates may be used or dispensed before the BUD of the compounded drug and is unreasonable considering the intended use of the compounded drug.

'ISO' means 'International Organization for Standardization'

'ISO 5' means air containing no more than 100 P/ft^3 of air of a size at least 0.5 micron or larger in diameter (3520 P/m^3), formerly FS209e Class 100.

'ISO 7' means air containing no more than 10,000 P/ft^3 of air of a size at least 0.5 micron or larger in diameter (352,000 P/m^3), formerly FS209e Class 10,000.

'ISO 8' means air containing no more than 100,000 P/ft^3 of air of a size at least 0.5 micron or larger in diameter (3,520,000 P/m^3), formerly FS209e Class 100,000.

'Isolator' means a device that is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated.

'Labeling' means a term that designates all labels and other written, printed, or graphic matter on an immediate container of an article or preparation or on, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term 'label' designates that part of the labeling on the immediate container.

'LAFW' means 'Laminar Airflow Workbench'

'Manufacturing' means the production, propagation, conversion, or processing of a drug or device, either directly or indirectly by extraction from substances of natural origin or independently by means of chemical or biological synthesis and includes any packaging or repackaging of the substance(s) or labeling or re-labeling of its container, for the promotion and marketing of such drugs or devices. Manufacturing also includes any preparation of a drug or device that is given or sold for resale by pharmacies, practitioners, or other persons. The distribution of inordinate amounts of compounded products without a prescriber/patient/pharmacist relationship is considered manufacturing.

'MDV' means 'Multiple Dose Vial'

'Media-Fill Test' means a test 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. During this test, a microbiological growth medium such as Soybean–Casein Digest Medium is substituted for the actual drug product to simulate admixture compounding.[3] 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.

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

'Negative Pressure Room' means a room that is at a lower pressure than the adjacent spaces and therefore, the net flow of air is into the room.

'NIOSH' means 'National Institute for Occupational Safety and Health'

'PEC' means 'Primary Engineering Control'

'PET' means 'Positron Emission Tomography'

'Personal Protective Equipment (PPE)' items such as gloves, gowns, respirators, goggles, face shields, and others that protect individual workers from hazardous physical or chemical exposures.

'Primary Engineering Control (PEC)' means a device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs).

'Preparation' means an article compounded in a licensed pharmacy pursuant to the order of a licensed prescriber; the article may or may not contain sterile products.

'Product' means a commercially manufactured drug or nutrient that has been evaluated for safety and efficacy by the FDA. Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or product package insert.

'Positive Pressure Room' means a room that is at a higher pressure than the adjacent spaces and, therefore, the net airflow is out *of* the room.

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

'Segregated Compounding Area' means a designated space, either a demarcated area or room, that is restricted to preparing low-risk level CSPs with 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.

'Terminal Sterilization' means the application of a lethal process (e.g., steam under pressure or autoclaving) to sealed containers for the purpose of achieving a predetermined sterility assurance level of usually less than 10^{-6}, or a probability of less than one in one million of a non-sterile unit.

'Unidirectional Flow' means 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.

'USP' means 'United States Pharmacopeia'

535:15-10-52. Pharmacist responsibilities

(a) All Pharmacists who engage in drug compounding, shall be proficient in compounding and should continually expand their compounding knowledge by participating in seminars and/or studying appropriate
literature.

(b) Every pharmacist engaging in drug compounding must be familiar with all details of USP Compounding Standards.

(c) The pharmacist has the responsibility to:

(1) ensure the validity of all prescriptions

(2) certify all prescriptions.

(3) approve or reject all components, drug product containers, closures, in-process materials, and labeling.

(4) ensure preparations are of acceptable strength, quality, and purity.

(5) verify all critical processes to ensure that procedures will consistently result in the

expected qualities in the finished preparation.
(6) prepare and review all compounding records to ensure that no errors have occurred in the compounding process.
(7) ensure appropriate stability evaluation is performed or determined from the literature for establishing reliable beyond-use dating.
(8) ensure the proper maintenance, cleanliness, and use of all equipment used in a prescription compounding practice; and,
(9) ensure only authorized personnel shall be in the immediate vicinity of the drug compounding operation.
(10) perform final check of preparations prior to their release from the pharmacy.
(A) A check for compounding accuracy must ensure accuracy of the label and volumes or quantities of all drugs and solutions
(B) A visual examination procedure must ensure:
(i) Comparison with original order for initial dispensing
(ii) Accuracy of calculations
(iii) Use of proper solutions, additives and equipment
(iv) Labels are complete
(v) Proper assignment of beyond use date and time
(vi) Integrity of the container, including visual defects
(vii) Proper storage
(viii) Absence of particulate matter, precipitates, turbidity, discoloration, evidence of contamination or other signs that the preparation should not be used.
(C) The pharmacist shall reject and destroy all preparations that do not pass the final examination.
(D) Pharmacists shall document final preparation examinations prior to releasing the Compounded Sterile Preparations from the pharmacy.

(d) The pharmacist-in-charge has the responsibility to ensure that all compounders who compound sterile pharmaceuticals meet all requirements for training, testing and education set forth in these regulations and contained in the regulations set forth in USP standards.
(1) Competency shall be demonstrated prior to preparing any sterile products for patient use, and
(2) Whenever the quality assurance program yields unacceptable results, and
(3) Whenever unacceptable or questionable techniques are observed, and
(4) Evaluated at least annually.

(e) **Pharmacist requirements**. Any pharmacist in charge who performs or supervises the preparation or sterilization of sterile medications shall:
(1) Have available written policies and procedures for all steps in the compounding of ~~sterile~~ preparations. In addition, said policies and procedures shall address personnel education and training and evaluation, storage and handling, clothing, personal hygiene, hand washing, aseptic technique, quality assurance, expiration dating, and other procedures as needed.
(2) Certify that all participating pharmacists and pharmacy technicians have completed training and testing program in sterile product preparation. Documentation of training and testing shall be available for review.
(3) Develop policies and procedures to annually test and review the techniques of

participating pharmacists and pharmacy technicians to assure adherence to aseptic procedures.

(f) Staff will be trained and evaluated according as follows:

(1) Training is required for any individual who prepares sterile products. This training must be completed before the employee is allowed to prepare sterile products.

(2) Training may consist of any combination of didactic and experiential methods which must convey proper technique, infection control procedures, etc. required by USP standards,

(3) A written test shall be administered and passed based on the material referenced above upon initial hire or prior to assignment to prepare sterile products.

(4) Media-fill challenge tests will be used to evaluate sterile technique.

(5) Results of the media challenge tests shall be documented and logged.

(6) End product testing that results in a failure will result in a review of the aseptic technique of the individual involved.

(7) Testing involving media challenge tests will be conducted annually for every employee involved in sterile product preparation. Semiannual testing will be conducted for personnel involved in high-risk level compounding. Compounding personnel who fail written tests or 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.

(8) Glove fingertip sampling using processes compliant with the most current USP-required procedures shall be used to evaluate competency of personnel in performing hand hygiene and garbing procedures initially and at least annually.

(9) An 'Individual Training Record' shall be maintained for every employee involved in sterile product preparation.

(10) Nothing in these regulations shall prohibit a licensed student pharmacy intern engaged in experiential classes from assisting a properly qualified pharmacist in preparing sterile products under that pharmacist's direct supervision.

(11) Complete documentation by a pharmacist of training and testing shall be available for inspection.

(g) **Pharmacy technician requirements**. Pharmacy technicians participating in the preparation of sterile products shall have completed a pharmacist supervised training and testing program in sterile product preparation. Completed documentation by a pharmacist of training and testing shall be available for inspection.

535:15-10-53. General requirements

(a) Compounding a drug product that is commercially available in the marketplace or that is essentially a copy of an available FDA-approved drug product is generally prohibited unless patient therapy is compromised.

(b) However, in special circumstances a pharmacist may compound an appropriate quantity of a drug that is different from an FDA-approved drug that is commercially available based on documentation provided by the prescribing physician of a patient specific medical need (e.g. the physician requests an alternate product due to hypersensitivity to excipients or preservative in the FDA-approved product, or the physician requests an effective alternate dosage form) or if the drug product is not commercially available.

(1) The unavailability of such drug product must be documented prior to compounding.
(2) This or similar documentation must be available when requested by the Board.

(c) Except for those products where stability prohibits advanced compounding, all products dispensed by the pharmacy shall be in a form ready for administration, except in health care facilities where medications may be provided as demanded by policies and procedures.

535:15-10-54. CSP microbial contamination risk levels

(a) **Sterile products**. Pharmacies and pharmacists dispensing sterile products shall comply with all applicable federal, state, and local law and regulation concerning pharmacy.

If the PEC (primary engineering control) is a compounding aseptic isolator that does not meet the environmental requirements described in USP <797> or is a laminar air-flow workbench (LAFW) or a biological safety cabinet (BSC) that cannot be located within an ISO Class 7 buffer area, then only low-risk level nonhazardous CSPs pursuant to a physician's order for a specific patient may be prepared, and administration of such CSPs shall commence within 12 hours of preparation or as recommended in the manufacturers' package insert, whichever is less. Low-risk level CSPs with a 12-hour or less BUD shall meet all of the following criteria:

(1) PECs (LAFWs, BSCs, CAIs, CACIs,) shall be certified and maintain ISO Class 5 as described in USP <797> for exposure of critical sites and shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of CSP contamination.

(2) 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. Sinks should not be located adjacent to the ISO Class 5 PEC. Sinks should be separated from the immediate area of the ISO Class 5 PEC device.

(3) Personnel shall follow proper procedures for personnel cleansing and garbing prior to compounding and maintain proper competency of aseptic work practices.

(4) Personnel will follow proper procedures in ensure cleaning and disinfection of sterile compounding areas. Additionally, viable and non-viable environmental air sampling must be performed according to facility written procedures.

(b) **Risk level**. Requirements for preparation of sterile products will be based on the distinction of sterile products as either low-risk, medium-risk or high-risk products. These risk levels apply to the quality of CSPs immediately after the final aseptic mixing or filling or immediately after the final sterilization, unless precluded by the specific characteristics of the preparation.

(1) **Low-Risk Level CSPs**. Sterile products compounded under all of the following conditions are at a low risk of contamination:

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

(B) The compounding involves only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package (e.g., bag, vial) of sterile product or administration container/device to prepare the CSP.

(C) Manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring

sterile liquids in sterile syringes to sterile administration devices and package containers of other sterile products, and containers for storage and dispensing.

(2) **Medium-Risk Level CSPs**. When CSPs compounded aseptically under low-risk conditions, and one or more of the following conditions exists, such CSPs are at a medium risk of contamination.

(A) Multiple individual or small doses of sterile products are combined or pooled to prepare a sterile product that will be administered 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 unusually long duration, such as that required to complete the dissolution or homogeneous mixing.

(3) **High-risk sterile products**. CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated.

(A) Non-sterile ingredients are incorporated, or a non-sterile device is employed before terminal sterilization

(B) Any of the following are exposed to air quality worse than ISO Class 5 for more than 1 hour

(i) Sterile contents of commercially manufactured products,

(ii) CSPs that lack effective antimicrobial preservatives, and

(iii) Sterile surfaces of devices and containers for the preparation, transfer, sterilization, and packaging of CSPs.

(C) Compounding personnel are improperly garbed and gloved as outlined by USP.

(D) Sterile water-containing preparations are stored for more than 6 hours before being sterilized.

(E) 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.

(c) **Immediate use**. The immediate-use provision is intended only for those situations where there is a need for emergency or immediate patient administration of a CSP. Such situations may include cardiopulmonary resuscitation, emergency room treatment, preparation of diagnostic agents, or critical therapy where the preparation of the CSP under conditions described for Low-Risk Level subjects the patient to additional risk due to delays in therapy. Immediate-use CSPs are not intended for storage for anticipated needs or batch compounding. Preparations that are medium-risk level and high-risk level CSPs shall not be prepared as immediate-use CSPs.

Immediate-use CSPs are exempt from the requirements described for *Low-Risk Level CSPs* 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 from the manufacturers' original containers and not more than two entries into any one container or package (e.g., bag, vial) of sterile infusion solution or administration container/device. For example, anti-neoplastics shall not be prepared as immediate-use CSPs because

they are hazardous drugs.

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

(3) During preparation, aseptic technique is followed and, if not immediately administered, the finished CSP is under continuous supervision to minimize the potential for contact with non-sterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other CSPs, and direct contact of outside surfaces.

(A) Administration begins not later than 1 hour following the start of the preparation of the CSP. (B) Unless immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the CSP shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour beyond use date and time.

(C) If administration has not begun within 1 hour following the start of preparing the CSP; the CSP shall be promptly, properly, and safely discarded.

(d) Opened or needle-punctured single dose containers, such as bags, bottles, syringes, and vials of sterile products and CSPs shall be used within 1 hour if opened in worse than ISO Class 5 air quality and any remaining contents must be discarded.

(e) Single-dose vials exposed to ISO Class 5 or cleaner air may be used for multiple needle entries up to 6 hours after initial needle puncture. Opened single-dose ampuls shall not be stored for any time period. Multiple-dose containers (e.g., vials) are formulated for removal of portions on multiple occasions because they usually contain antimicrobial preservatives.

(f) The BUD after initially entering or opening (e.g., needle-punctured) multiple-dose containers is 28 days unless an alternate time period is otherwise specified by the manufacturer. This does not mean the expiration date of the unopened container.

(g) **Quality Assurance**. 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, such as eye protection and face masks.

(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 the accuracy and thoroughness of labeling.

(A) Semiannual certification of the primary engineering controls.

(B) Semiannual certification of nonviable environmental monitoring of all ISO 5, ISO 7, ISO 8 and segregated compounding areas.

(C) Semiannual certification of viable environmental monitoring of all ISO 5, ISO 7, ISO 8 and segregated compounding areas.

(D) Removable prefilters shall be inspected monthly, cleaned or changed at least quarterly or as directed by a qualified certifier, and the date documented.

(E) HEPA filters shall be repaired or replaced when recommended by a qualified certifier.

Initial and annual competence documentation of personnel, including

(i) Written test

(ii) Hand Hygiene and garbing
(iii) Gloved fingertip sampling
(iv) Aseptic manipulation
(v) Aseptic media-fill test
(vi) Cleaning and disinfecting
(vii) Surface sampling
(viii) Equipment
(ix) Routine visual inspection of all compounded sterile preparations
(x) Provision of guidelines to nursing education for competence documentation for non-pharmacy personnel who mix sterile preparations for immediate use

(h) Quality control practices will include:

(1) Daily documentation of temperature in areas where sterile products or sterile preparations are stored or compounded

(2) Daily documentation of the accuracy and precision of devices such as automated compounders and repeater pumps

(i) The PIC or designee will prepare a periodic report of infection control procedures to track quality control and quality assurance activities, as appropriate.

(j) Records of laminar air flow workbench maintenance and certification and ante-area, clean-room and buffer area certifications shall be kept in the pharmacy. A certification stamp shall be affixed to the hood.

(k) **Storage.** All pharmacies preparing and dispensing compounded sterile products must provide:

(1) Adequate controlled room temperature storage space for all raw materials.

(2) Adequate storage space for all equipment. All drugs and supplies shall be stocked on shelving above the floor.

(3) Adequate refrigerator storage space for compounded solutions, with routinely documented temperatures. Temperature ranges required are 36-46° F or 2-8° C.

(4) Adequate freezer storage space if finished products are to be frozen (e.g. reconstituted antibiotics.) There shall be a procedure to routinely document temperatures.

(l) **Labeling.** In addition to regular labeling requirements, the label shall include:

(1) Parenteral products shall have the rate of infusion when applicable.

(2) Expiration date (Policies and procedures shall address label change procedures as required by physician orders.)

(3) Storage requirements or special conditions.

(4) Name of ingredients and amounts contained in each dispensing unit.

(5) All products dispensed to outpatients, and removed from the site of preparation for administration different than the site of preparation, shall have label information as required by state law.

(m) **Shipping**. Sterile product shipping:

(1) Policies and procedures shall assure preparation storage requirements during delivery.

(2) Pharmacy must assure ability to deliver products within an appropriate time frame.

(n) **Home patient care services**. The pharmacist in charge of the pharmacy dispensing sterile parenteral solutions shall provide the following or assure that they are provided prior to providing medications.

(1) The pharmacist must assure that the patient is properly trained if self-administering.

(2) In situations where a pharmacy or pharmacist employs a nurse to administer medications, the pharmacist in charge must:

(A) Employ a registered nurse.

(B) Assure that proper records are maintained in compliance with laws and regulations.

(C) Make these records available to inspectors from appropriate agencies.

(3) 24-hour service shall be assured by the pharmacy.

(4) Pharmacists shall recommend and monitor clinical laboratory data as requested.

(5) Side effects and potential drug interactions should be documented and reported to the physician.

(6) Patient histories and therapy plans should be maintained.

(o) **Pharmacist-in-charge responsibilities for high-risk sterile products**. When preparing high-risk sterile products, the pharmacist in charge is responsible for making sure the above procedures, in addition to the following, shall be met:

(1) Compound all medications in one of the following environments:

(A) A separate controlled limited access area with a positive air flow room inspected and certified as meeting ISO Class 7 requirements.

(B) An enclosed room providing an ISO Class 5 environment for compounding.

(C) A barrier isolator that provides an ISO Class 5 environment for compounding. It is recommended that all pharmacies have an anteroom designed to be separate from the buffer room. The anteroom should be available for the decontamination of supplies and equipment, and donning of protective apparel. A sink should be available in the anteroom area so that personnel can scrub prior to entering the buffer room.

(2) Use total aseptic techniques, including gowning, mask, and hair net.

(3) Provide a system for tracking each compounded product including:

(A) Personnel involved in each stage of compounding;

(B) Raw materials used including quantities, manufacturer, lot number, and expiration date;

(C) Labeling;

(D) Compounding records shall be kept for ~~2~~ 5 years.

(4) Establishment of procedures for sterilization of all products prepared with any non-sterile ingredients by filtration with 0.22 micron or other means appropriate for the product components.

(5) All high-risk level compounded sterile products for administration by injection into the vascular and central nervous systems that are prepared:

(A) in groups of more than twenty-five (25) identical individual single-dose packages (such as ampules, bags, syringes, and/or vials), or;

(B) in multiple dose vials for administration to multiple patients, or;

(C) are exposed longer than twelve (12) hours at a two (2) to eight (8) degrees centigrade and longer than six (6) hours at warmer than eight (8) degrees centigrade before they are sterilized; and shall be tested to ensure they are sterile, do not contain excessive bacterial endotoxins, and are of labeled potency before they are dispensed or administered as provided below.

(i) Sterility testing (bacterial and fungal) – The USP Membrane Filtration

Method is the method of choice where feasible (e.g. components are compatible with the membrane). The USP Direct Transfer Method is preferred when the membrane filtration is not feasible. An alternative method may be used if verification results demonstrate that the alternative is at least as effective and reliable as the USP Membrane Filtration Method or the USP Direct Transfer Method. The pharmacist in charge shall establish written procedures requiring daily observation of the media and requiring an immediate recall if there is any evidence of microbial growth and said procedures must be available to Board inspectors.

(ii) Bacterial endotoxin (pyrogen) testing – The USP Bacterial Endotoxin Test, or verified equivalent, shall be used to ensure compounded sterile products do not contain excessive endotoxins.

(6) Establishment of procedures for yearly testing the techniques of pharmacists using simulated aseptic procedures and documentation thereof.

(7) Any facility improvements as required by this regulation (i.e. separate controlled limited access area and certification of ISO Class 5 must be complied with one year after approval of these rules.

535:15-10-55. Drug compounding facilities

(a) Pharmacies engaging in compounding shall have a specifically designated and adequate space for the orderly compounding of prescriptions, including the placement and storage of equipment and materials.

(b) The aseptic processing for sterile products shall be in an area separate and distinct from the area used for the compounding of non-sterile drug products. If parenteral products are being compounded, the rules in OAC 535:15-10-3.1 should be met. A primary engineering control (PEC), (laminar airflow workbench (LAFW), biological safety cabinet (BSC), compounding aseptic isolator (CAI) or compounding aseptic containment isolator (CACI)) will be used to prepare all sterile preparations, except those compounded for Immediate Use.

(c) The area(s) used for the compounding of drugs shall be maintained in a good state of repair. These area(s) shall also be maintained in a clean and sanitary condition. Adequate washing facilities are to be provided and sewage, trash and other refuse in the compounding area is to be disposed of in a safe, sanitary, and timely manner.

(d) Bulk drugs and other chemicals or materials used in the compounding of drugs must be stored as directed by the manufacturer, or according to USP monograph requirements, in a clean, dry area under appropriate temperature conditions (controlled room temperature, refrigerator, or freezer in adequately labeled containers.) Bulk drugs shall also be stored such that they are protected from contamination.

(e) Adequate lighting and ventilation shall be provided in all compounding areas.

(f) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any compounded drug product.

(g) Work area and equipment. Any pharmacy dispensing compounded sterile preparations shall meet or exceed the following requirements:

(1) A separate controlled limited access area (also called a buffer area or buffer room) for compounding sterile solutions, which shall be of adequate space for compounding, labeling, dispensing, and sterile preparation of the medication. This area shall have

controlled temperature. Cleanliness of the area is of critical importance. Drugs and other materials, taken into the limited access area, shall be removed from cardboard and other particle generating materials before being taken into the area.
(2) The controlled limited access area shall have a certified and inspected ISO Class 5 environment. Such an environment exists inside a certified laminar airflow hood (clean room, biological safety cabinet or other barrier isolator meeting ISO Class 5 requirements) used for the preparation of all compounded sterile products. The ISO Class 5 environment device or area is to be inspected and certified semiannually. Barrier isolator workstations are closed systems and are not as sensitive to their external environment as laminar airflow equipment. It is recommended to place them in a limited access area with cleaning and sanitizing in the surrounding area on a routine basis.
(3) A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the clean room and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device. The pressure between the ISO Class 7 and the general pharmacy area shall not be less than 5 Pa (0.02 inch water column). In facilities where low- and medium-risk level CSPs are prepared, differential airflow shall maintain a minimum velocity of 0.2 meters per second (40 feet per minute) between buffer area and ante-area.
(4) Hazardous drugs shall be prepared within a certified Class II, Type A (exhaust may be discharged to the outdoors) or Class II, Type B (exhaust may be discharged to the outdoors) laminar flow biological safety cabinet. Hazardous drug compounding shall have negative pressure to adjacent positive pressure ISO Class 7 or better ante-areas, thus providing inward airflow to contain any airborne drug. All vented cabinets shall be vented through HEPA filtration, preferably to outside air or through use of suitable technology or equipment. Ventilation exhaust shall be placed as not to reenter the facility at any point.
(5)The area shall be designed to avoid excessive traffic and airflow disturbances.
(6) The area shall be ventilated in a manner not interfering with laminar flow hood conditions.
(7) Daily procedures must be established for cleaning the compounding area.
(8) PECs should be left on continuously. If a PEC has been turned off, allow the blowers to run continuously for at least 30 minutes before using.

535:15-10-56. Compounding equipment

(a) Equipment used in the compounding of drug products shall be of appropriate design and capacity as well as suitably located to facilitate operations for its intended use, cleaning and maintenance.
(b) Compounding equipment shall be of suitable composition so the surfaces that contact components shall neither be reactive, additive or absorptive, therefore not affecting or altering the purity of the ~~product~~ compounded preparation.
(c) Equipment and utensils used for compounding shall be thoroughly cleaned promptly after every use to prevent contamination and must be stored in a manner to protect from contamination.
(d) Defective equipment shall be clearly labeled as such.
(e) Automated, mechanical, electronic, limited commercial scale manufacturing or testing

equipment, and other types of equipment may be used in the compounding of drug products. If such equipment is used, it shall be routinely inspected, calibrated as necessary or checked to ensure proper performance.
(f) When drug products with special precautions (antibiotics and hazardous materials) are involved, appropriate measures must be utilized in order to prevent cross-contamination and proper disposal procedures must be followed. These measures include either the dedication of equipment for such operations or the meticulous cleaning of equipment prior to its use for the preparation of other drugs. Equipment dedicated for specific use (i.e. penicillin) shall be clearly designated as such.

535:15-10-57. Component selection requirements
(a) The pharmacists shall first attempt to use U.S.P.-NF drug substances and inactive component that have been made in an FDA registered facility.
(b) If components are not obtainable from a FDA registered facility or if the FDA and/or the company cannot document FDA registration, pharmacists compounding prescriptions shall use their professional judgment in first receiving, storing or using drug components that meet official compendia requirements or another high quality source.
(c) If components of compendial quality are non obtainable, components of high quality such as those that are chemically pure, analytical reagent grade, American Chemical Society-certified, or Food Chemicals Codex grade may be used.
(d) Components shall be stored off the floor, handled and stored to prevent contamination, and rotated so that the oldest stock is used first.

535:15-10-58. Control of drug product containers
(a) Drug product containers and closures shall be handled and stored in a manner to prevent contamination and to permit inspection and cleaning of the work area.
(b) Containers and closures shall be of suitable material as to not alter the compounded drug as to quality, strength or purity of the compounded preparation.

535:15-10-59. Drug compounding controls
(a) There shall be written procedures for the compounding of drug products to assure that the finished products have the identity, strength, quality and purity they purport to have. These procedures should be available in either written form or electronically stored with printable documentation.
(b) The objective of the documentation is to allow another compounder to reproduce the identical prescription at a future date.
(c) Procedures shall include a listing of the components, their amounts (in weight or volume), the order of component mixing, and a description of the compounding process. In addition, all equipment and utensils and the container/closure system, relevant to the sterility and stability of the intended use of the drug shall be listed.
(d) These written procedures shall be followed in the execution of the compounding procedure and are designed to enable a compounder, whenever necessary, to systematically trace, evaluate, and replicate the steps included throughout the preparation process of a compounded preparation.
(e) Components shall be accurately weighed, measured, and subdivided as appropriate. These

operations should be checked and rechecked by the compounding pharmacist at each stage of the process to ensure that each weight and measure is correct as stated in the written compounding procedures.
(f) Written procedures shall be established and followed that describe the tests or examinations to be conducted on the product compounded (e.g., degree of variation) to ensure reasonable uniformity and integrity of compounded drug preparations. Unless otherwise indicated or appropriate, compounded preparations are to be prepared to ensure that each preparation shall contain not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of active ingredient per unit weight or volume and not less than 90% and not more than 110% of the theoretically calculated weight or volume per unit of the preparation.

(1) Such control procedures shall be established to monitor the output and to verify the performance of those compounding processes that may be responsible for causing variability in the final drug product. These procedures shall include, but are not limited to, the following (where appropriate):

(A) Adequacy of mixing to assure uniformity and homogeneity;

(B) Clarity, completeness or pH of solutions.

(2) The compounder shall label any excess compounded products so as to reference them to the formula used, the assigned batch number, and beyond use date based on the compounder's appropriate testing, published data, or USP-NF standard.

(g) MSDS (material data safety sheet) files should be easily accessible.

535:15-10-60. Transfer of sterile compounded prescriptions

(a) If a patient requests a transfer of their prescription, a copy of the original prescription shall be transmitted upon the request of the receiving pharmacist.
(b) The information included in the transfer of the prescription shall include:

(1) Active ingredient(s)
(2) Concentration
(3) Dosage Form
(4) Route of delivery
(5) Delivery mechanism
(6) Dosing Duration i.e. Q12H, Q24H, Q72H
(7) Details about the compounding procedure must be reasonably available from the transferring pharmacy.

535:15-10.61. Beyond use dating

(a) Beyond-use dates (BUDs) shall be assigned to all compounded sterile preparations. The shorter of the chemical stability (established by the manufacturer, or listed in a current authoritative reference, or established by direct testing following USP standards or equivalent) and microbial limits of sterility (USP <797> requirements) shall be used to determine the date.

(1) If a pharmacy does not have a program of sterility and endotoxin testing in place and additional documentation for longer dates, then the following BUDs are to be used for compounded sterile preparations, (as illustrated in the Appendix A Chart):

(A) If USP <797> Risk Level is 'Immediate Use' Beyond Use Dates (BUD), and if kept

(i) at room temperature; use within 1 hour,

(ii) refrigerated; use within 1 hour, or
(iii) in freezer, N/A.
(B) If USP <797> Risk Level is 'Low Risk' BUD, and if kept
(i) at room temperature, use within 48 hours,
(ii) refrigerated, use within 14 days, or
(iii) in freezer, use within 45 days.
(C) If USP <797> Risk Level is 'Low Risk with 12 hour or less' BUD, and if kept
(i) at room temperature use within 12 hours or less
(ii) refrigerated, use within 12 hours or less, or
(iii) in freezer, N/A
(D) If USP <797> Risk Level is 'Medium Risk' BUD, and if kept
(i) at room temperature, use within 30 hours,
(ii) refrigerated, use within 9 days, or,
(iii) in freezer, use within 45 days
(E) If USP <797> Risk Level is 'High Risk' BUD, and if kept
(i) at room temperature, use within 24 hours
(ii) refrigerated, use within 3 days, or
(iii) in freezer, use within 45 days
(2) If a pharmacy does have a program of sterility and endotoxin testing in place, then the BUDs for the non-sterile preparations are to be used, as previously presented in OAC 535:15-10-8.2.
(b) Reusable compounded preparations that are returned to a hospital pharmacy shall be placed in the refrigerator (unless contraindicated) with the original BUD on the label.

535:15-10-62. Labeling
(a) If a component is transferred from the original container to another (e.g., a powder is taken from the original container, weighed, placed in, and stored in another container) the new container shall be identified with the:
(1) Component name,
(2) Lot and BUD if available,
(3) Strength and/or concentration, and;
(4) Weight or measure
(b) Products prepared in anticipation of a prescription prior to receiving a valid prescription should not be an inordinate amount.
(1) A regularly used amount should be prepared based on a history of prescriptions filled by the pharmacy.
(2) These products shall be labeled or documentation referenced with the:
(A) Complete list of ingredients or preparation name and reference,
(B) Preparation date,
(C) Assigned beyond-use date:
(i) Based on published data, or;
(ii) Appropriate testing, or;
(iii) U.S.P.-NF standards.
(D) Specific storage conditions dictated by composition and stability shall be specified (refrigerator, freezer, etc.), except where clean dry area is dictated, and;
(E) Batch or lot number.

(c) Upon the completion of the drug preparation operation, the pharmacist shall examine the product for correct labeling.
(d) The outpatient prescription label shall contain the following:
(1) Patient name,
(2) Prescriber's name,
(3) Name & address of pharmacy,
(4) Directions for use,
(5) Date filled,
(6) Beyond use date & storage (may be auxiliary labels), and;
(7) An appropriate designation that this is a compounded prescription, such as 'Compounded Rx'.

535:15-10-63. Records and reports
(a) Any procedures or other records required to comply with Good Compounding Practices shall be retained for the same period of time as required for retention of prescription records and copies of such records shall be readily available for authorized inspection.
(c) Computer information and the hard copy of the prescription should indicate that the prescription is to be compounded.
(d) Adequate records must be kept of controlled dangerous substances (Scheduled drugs) used in compounding.

535:15-10-64. Compounding for institution and/or practitioner administration
(a) The purpose of this section is to provide standards for the compounding of preparations pursuant to a prescription for a patient from a practitioner in a different health care facility or institutional pharmacy. Since compounding is already based on the practitioner/patient/pharmacist triad, this should be satisfied when a practitioner writes an order to administer the drug in the medical record.
(b) A compounded product shall NOT be sold to a third party for resale.
(c) A retail pharmacy that provides compounded preparations to an institutional pharmacy shall obtain a Compounding Drug Supplier Permit from the Board prior to such activity.
(d) A retail pharmacy that provides compounded preparations to practitioners for office use or to an institutional pharmacy shall enter into a written agreement with the practitioner or pharmacy. The written agreement shall:
(1) Address acceptable standards of practice for each party entering into agreement and include a statement that the compounded preparation may only be administered to the patient and may not be dispensed to the patient or sold to any other person or entity
(2) Include liability language, references to performance improvement and quality controls
(3) require the practitioner or receiving pharmacy to include on patient's ~~chart~~ record, medication order, or medication administration record the ~~lot~~ batch number and BUD of the compounded preparation administered to a patient
(4) Describe the scope of services to be performed by the filling pharmacy and practitioner or receiving pharmacy, including a statement of the process for:
(A) A patient to report an adverse reaction or submit a complaint; and
(B) The pharmacy to recall compounded preparations.

(e) Records of orders and distributions of compounded preparations to a practitioner for office use or receiving pharmacy shall be kept by pharmacy for at least 5 years and be available for inspection. These records shall be maintained separately from the records of products dispensed pursuant to a prescription.
(f) Orders shall include the following information:
(1) Date of order
(2) Name, address and phone number of the practitioner who ordered the preparation and, if applicable, the name, address, and phone number of pharmacy to receive compounded preparation
(3) Name, strength, and quantity of preparation ordered.
(4) Patient name, when available.
(g) Distribution records shall include the following information:
(1) Date the preparation was compounded
(2) Date the preparation was distributed
(3) Name, strength, and quantity in each container of the preparation
(4) Lot number of the preparation
(5) Quantity of containers delivered
(6) Name, address, and phone number of the facility to whom the preparation is being distributed
(7) patient name, when available.

535:15-10-65. Compounding of sterile hazardous drugs
(a) Although the potential therapeutic benefits of compounded sterile and non-sterile hazardous drug preparations outweigh the risks of their adverse effects in ill patients, exposed healthcare workers risk similar adverse effects with no therapeutic benefit. Occupational exposure to hazardous drugs can result in:
(1) Acute effects, such as skin rashes;
(2) Chronic effects, including adverse reproductive events; and
(3) Possibly cancer.
Each facility must have a communication program that identifies hazardous drugs and communicates this list to all workers that participate in product acquisition, storage, transportation, housekeeping and waste disposal.
(b) Hazardous drugs shall be any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or animals, or genotoxicity. A new or investigational drug that has no information on toxicity should be treated as a hazardous drug. At a minimum, the hazardous drug communication list shall be drugs received in the facility that are recognized as such by the National Institute for Occupational Safety and Health (NIOSH).
(c) Hazardous drugs shall be prepared for administration only under conditions that protect the healthcare workers and other personnel in the preparation and storage areas. Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure. Many hazardous drugs have sufficient vapor pressures that allow volatilization at room temperature; thus storage is preferably within a containment area such as a negative pressure room. The storage area should have sufficient general exhaust ventilation, at least 12 air changes per hour (ACPH) to dilute and remove any airborne contaminants.

(d) Hazardous drugs shall be handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking, inventorying, preparation for administration, and disposal.
(e) Hazardous sterile drugs shall be prepared in an ISO Class 5 environment with protective engineering controls in place as specified in 535.15-10.5-5. Hazardous drug compounding shall have negative pressure to adjacent positive pressure ISO Class 7 or better ante-areas, thus providing inward airflow to contain any airborne drug. All vented cabinets shall be vented through HEPA filtration, preferably to outside air or through use of suitable technology or equipment. Ventilation exhaust shall be placed as not to reenter the facility at any point.
(f) If a CACI that meets the requirements of this chapter is used outside of an ISO class 7 buffer area, the compounding area shall maintain negative pressure and have a minimum of 12 ACPHs. Manufacturer's guidelines or NISF guidelines shall be followed for isolators, containment hoods and BSC. Quality control certification for proper function shall be performed every six months by NISF certified personnel.
(g) When closed-system vial-transfer devices (CSTDs) (i.e., vial-transfer systems that allow no venting or exposure of hazardous substance to the environment, Add-Vantage and PhaSeal) are used, they shall be used within the vented cabinet.
(h) In facilities that prepare a low volume, an average of no more than two per day, of hazardous drugs, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable.
(i) Appropriate personnel protective equipment (PPE) shall be worn when compounding hazardous drugs. PPE should include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, gloving with chemotherapy gloves; and compliance with manufacturers' recommendations when using a CACI.
(j) All personnel who compound hazardous drugs shall be fully trained in the storage, handling, and disposal of these drugs. This training shall occur prior to preparing or handling hazardous drugs, and its effectiveness shall be verified by testing specific hazardous drugs preparation techniques. Such verification shall be documented for each person at least annually. This training shall include didactic overview of hazardous drugs, including mutagenic, teratogenic, and carcinogenic properties, and it shall include ongoing training for each new hazardous drug that enters the marketplace. Compounding personnel of reproductive capability shall confirm in writing that they understand the risks of handling hazardous drugs. The training shall include at least the following: (1) safe aseptic manipulation practices; (2) negative pressure techniques when utilizing a BSC, powder containment hood or CACI; (3) correct use of CSTD devices; (4) containment, cleanup, and disposal procedures for breakages and spills; and (5) treatment of personnel contact and inhalation exposure.
(k) Consider a medical surveillance program or allow workers to have routine medical care.
(l) Disposal of all hazardous drug wastes shall comply with all applicable federal and state regulations. All personnel who perform routine custodial waste removal and cleaning activities in storage and preparation areas for hazardous drugs shall be trained in appropriate procedures to protect themselves and prevent contamination.

535:15-10-66. Compounding of sterile radiopharmaceuticals
(a)In the case of production of radiopharmaceuticals for positron emission tomography (PET), the USP general test chapter *Radiopharmaceuticals for Positron Emission Tomography—*

Compounding <823> supersedes this chapter or applicable federal manufacturing regulations. Upon release of a PET radiopharmaceutical as a finished drug product from a production facility, the further handling, manipulation, or use of the product will be considered compounding, and the content of this section and chapter is applicable.
(b) For the purposes of this chapter, 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 Level CSPs***'**
(c) The unique circumstances and requirements for radiopharmaceutical preparations necessitate specific stipulations that must not only satisfy pharmaceutical drug quality, but also consider crucial radiation safety concerns to operators. An integrated approach which addresses both aseptic and radiation safety techniques is necessary. Facility design and variation in certain chapter standards may be required and shall be documented with supporting evidence upon request.
(d) These 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 applicable state and federal regulations.
(e) Storage and transport of properly shielded vials of radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO class designation.
(f) Technetium-99m/molybdenum-99 generator systems shall be stored and eluted (operated) under conditions recommended by manufacturers and applicable state and federal regulations. Such generator systems shall be eluted in an ISO Class 8 or cleaner air environment.
(g) Direct visual inspection of radiopharmaceutical CSPs shall be conducted in accordance with ALARA.
(h) The handling of radiopharmaceuticals is controlled through the licensing of **'**Authorized Users**'** by the Oklahoma Department of Environmental Quality. As such, limited numbers of distribution channels exist to obtain radiopharmaceuticals It is recognized that there is a special population that is outside the daily distribution range of a commercial nuclear pharmacy and that radiopharmaceuticals are not reasonably available. For these facilities, if the PEC is a CAI, CACI, a laminar airflow workbench (LAFW) or a biological safety cabinet (BSC) that cannot be located within an ISO Class 8 or better buffer area, then only low-risk CSPs pursuant to a physician's order may be prepared, and administration of such CSPs shall commence within 12 hours of preparation or as recommended in the manufacturers' package insert, whichever is less. These Low-risk level radiopharmaceutical CSPs with a 12-hour or less BUD shall be prepared in PECs (LAFWs, BSCs, CAIs, CACIs), which shall be certified and maintain ISO Class 5 and shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of CSP contamination. A line of demarcation defining the segregated compounding area shall be established. Materials and garb exposed in a patient care and treatment areas must be cleaned before being brought into controlled compounding area. Other requirements as dictated by Low-Risk Radiopharmaceuticals shall be followed as described in this chapter.
(i) Preparation of radiopharmaceuticals for Immediate-Use category is reserved for radiopharmaceuticals needed for emergency or immediate patient care. Radiopharmaceuticals under this exemption shall apply only to diagnostic radiopharmaceuticals and administration must begin not later than one hour following the start of preparing the CSP. Certain

preparations may necessitate more than two punctures into the same septum, i.e. Technetium 99mTc-Red Blood Cell labeling.
(j) Preparation of radio-labeled leukocytes or blood products requires the procedure be performed in an ISO Class 5 PEC that is located in an ISO Class 8 or cleaner air environment. Blood manipulations shall be clearly separated from routine procedures and have specific standard operating procedures to avoid cross contamination.
(k) Labeling requirements for this chapter do not supersede the labeling requirements of 535:15-17-5.

535:15-10-67. Compounding of sterile allergen extracts

(a) Allergen extracts as CSPs are single-dose and multiple-dose *intradermal or subcutaneous injections* that are prepared by specially trained physicians and pharmacy personnel under their direct supervision. Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all *CSP Microbial Contamination Risk Levels* in this chapter only when all of the following criteria are met:

(1) The compounding process involves simple transfer via sterile needles and syringes of commercial sterile allergen products and appropriate sterile added substances (e.g., glycerin, phenol in sodium chloride injection).

(2) All allergen extracts as CSPs shall contain appropriate substances in effective concentrations to prevent the growth of microorganisms. Non-preserved allergen extracts shall comply with the appropriate CSP risk level requirements in the chapter.

(3) Before beginning compounding activities, personnel perform a thorough hand-cleansing procedure by removing debris from under fingernails using a nail cleaner under running warm water followed by vigorous hand and arm washing to the elbows for at least 30 seconds with either non-antimicrobial or antimicrobial soap and water.

(4) Compounding personnel don hair covers facial hair covers, gowns, and face masks.

(5) Compounding personnel perform antiseptic hand cleansing with an alcohol-based surgical hand scrub with persistent activity.

(6) Compounding personnel don powder-free sterile gloves that are compatible with sterile 70% isopropyl alcohol (IPA) before beginning compounding manipulations.

(7) Compounding personnel disinfect their gloves intermittently with sterile 70% IPA when preparing multiple allergen extracts as CSPs.

(8) Ampul necks and vial stoppers on packages of manufactured sterile ingredients are disinfected by careful wiping with sterile 70% IPA swabs to ensure that the critical sites are wet for at least 10 seconds and allowed to dry before they are used to compound allergen extracts as CSPs.

(9) The aseptic compounding manipulations minimize direct contact contamination (e.g., from glove fingertips, blood, nasal and oral secretions, shed skin and cosmetics, other non-sterile materials) of critical sites (e.g., needles, opened ampuls, vial stoppers).

(10) The label of each multiple-dose vial (MDV) of allergen extracts as CSPs lists the name of one specific patient and a BUD and storage temperature range that is assigned based on manufacturers' recommendations or peer-reviewed publications.

(11) Single-dose allergen extracts as CSPs shall not be stored for subsequent additional use.

(b) Personnel who compound allergen extracts as CSPs must be aware of greater potential risk

of microbial and foreign material contamination when allergen extracts as CSPs are compounded in compliance with the foregoing criteria instead of the more rigorous standards in this chapter for *CSP Microbial Contamination Risk Levels.* Although contaminated allergen extracts as CSPs can pose health risks to patients when they are injected *intradermally or subcutaneously,* these risks are substantially greater if the extract is inadvertently injected *intravenously*.

Appendix A USP <797> Beyond-Use Date Limits Chart

USP <797> Risk Level	Room Temperature	Refrigerated	Freezer
Immediate Use	1 hour	1 hour	N/A
Low Risk	48 hours	14 days	45 days
Low Risk with 12 hour or less BUD	12 hours or less	12 hours or less	N/A
Medium Risk	30 hours	9 days	45 days
High Risk	24 hours	3 days	45 days