USP (797) Pharmaceutical Compounding – Sterile Preparations

Effective date: November 1, 2023

The following information is excerpted from the final USP (797) guidelines that will go into effect on November 1, 2023. These are the minimum standards for allergy practice; individual states may enact more stringent requirements. All allergy practices should review their current extract mixing facilities and processes and be prepared to meet these guidelines by November 1. Visit the AAAAI Compounding Corner for practical resources and additional information.

1.1.2 SPECIFIC PRACTICES – ALLERGENIC EXTRACTS

Licensed allergenic extracts are mixed and diluted to prepare prescription sets for administration to patients. A prescription set is a vial or set of vials of premixed licensed allergenic extracts for subcutaneous immunotherapy that have been diluted with an appropriate diluent for an individual patient. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in this chapter that are applicable to other sterile CSPs. The standards for compounding allergenic extracts, which are described in 21. Compounding Allergenic Extracts, are applicable only when:

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances; and
2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

21. COMPOUNDING ALLERGENIC EXTRACTS

Licensed allergenic extracts are mixed and diluted into prescription sets for an individual patient, even though these allergenic extract combinations are not specified in the approved licenses for the licensed biological products (e.g., Biological License Applications [BLA]). Allergenic extract prescription sets must follow standards at least as stringent as those in this section as follows:

21.1 Personnel Qualifications for Compounding Allergenic Extract Prescription Sets

- A designated person(s) with training and expertise in allergen immunotherapy is responsible for ensuring that personnel who will be preparing allergenic extract prescription sets are trained, evaluated, and supervised.
- Before beginning to independently prepare allergenic extracts, all compounding personnel must complete training and be able to demonstrate knowledge of principles and skills for sterile compounding.
- Annual personnel training and competency must be documented. Personnel must demonstrate knowledge and competency in these procedures by passing written or electronic testing before they can be allowed to compound allergenic extract prescription sets.
- Before being allowed to independently compound, all compounders must successfully complete gloved fingertip and thumb sampling on both hands (see Box 1 and Table 1) no fewer than 3 separate times. Each fingertip and thumb evaluation must occur after performing separate and complete hand hygiene and garbing procedures. After the initial competency

evaluation, compounding personnel must successfully complete gloved fingertip and thumb sampling on both hands at least every 12 months thereafter.
- Compounding personnel must have their sterile technique and related practices evaluated at least every 12 months as demonstrated by successful completion of a media-fill test (see Box 2). If compounding outside of a PEC, the post-media-fill surface sample is not required.
- Personnel who fail competency evaluations must successfully pass reevaluations in the deficient area(s) before they can resume compounding of allergenic extract prescription sets. The designated person(s) must identify the cause of failure and determine appropriate retraining requirements.
- Personnel who have not compounded an allergenic extract prescription set in more than 6 months must be evaluated in all core competencies before resuming compounding duties.

21.2 Personnel Hygiene and Garbing for Compounding Allergenic Extract Prescription Sets
- Before beginning compounding of allergenic extract prescription sets, personnel must perform hand hygiene (see Box 3) and garbing procedures according to the facility's SOPs.
- The minimum garb requirements include:
    - A low-lint garment with sleeves that fit snugly around the wrists and an enclosed neck (e.g., gowns)
    - A low-lint, disposable head cover that covers the hair and ears and, if applicable, a disposable cover for facial hair
    - Face mask
    - Sterile powder-free gloves
- Throughout the compounding process, personnel must apply sterile 70% IPA onto all surfaces of the gloves and allow them to dry thoroughly.

21.3 Facilities for Compounding Allergenic Extract Prescription Sets
- The compounding process must occur in an ISO Class 5 PEC or in a dedicated allergenic extract compounding area (AECA). The PEC or AECA used to compound allergenic extract prescription sets must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality. Neither a PEC nor an AECA may be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality. The PEC or the work surfaces in the AECA must be located at least 1 m away from a sink. The impact of activities that will be conducted around or adjacent to the PEC or AECA must be considered carefully when designing such an area.
- If used, the PEC must be certified at least every 6 months
- If used, a visible perimeter must define the AECA.
    - Access to the AECA during compounding must be restricted to authorized personnel.
    - During compounding activities, no other activity is permitted in the AECA.
    - The surfaces of walls, floors, fixtures, shelving, counters, and cabinets in the AECA must be cleanable.
    - Carpet is not allowed in the AECA.
    - Surfaces should be resistant to damage by cleaning and disinfecting agents.

    - The surfaces in the AECA upon which the allergenic extract prescription sets are prepared must be smooth, impervious, free from cracks and crevices, and non-shedding to allow for easy cleaning and disinfecting.
    - Dust-collecting overhangs such as utility pipes, ledges, and windowsills should be minimized. If overhangs or ledges are present, they must be easily cleanable.
    - The AECA must be designed and controlled to provide a well-lighted working environment, with temperature and humidity controls for the comfort of compounding personnel wearing the required garb.

21.4 Cleaning and Disinfecting for Compounding Allergenic Extract Prescription Sets

- In a PEC, all interior surfaces of the PEC must be cleaned and disinfected each day of use before compounding begins and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.
- In an AECA, all work surfaces in the AECA where direct compounding is occurring must be cleaned and disinfected each day of use before compounding begins and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface between each prescription set.
    - If present, walls, doors, and door frames within the perimeter of the AECA must be cleaned and disinfected monthly and when surface contamination is known or suspected.
    - Ceilings within the perimeter of the AECA must be cleaned and disinfected when visibly soiled and when surface contamination is known or suspected.
- Vial stoppers on packages of conventionally manufactured sterile ingredients must be wiped with sterile 70% IPA to ensure that the critical sites are wet and allowed to dry before they are used to compound allergenic extract prescription sets.

21.5 Establishing BUDs for Allergenic Extract Prescription Sets

The BUD for the prescription set must be no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set, and the BUD must not exceed 1 year from the date the prescription set is mixed or diluted.

21.6 Labeling for Allergenic Extract Prescription Sets

The label of each vial of an allergenic extract prescription set must display the following prominently and understandably:

- Patient name
- Type and fractional dilution of each vial, with a corresponding vial number
- BUD
- Storage conditions

21.7 Shipping and Transporting Allergenic Extract Prescription Sets

- If shipping or transporting allergenic extract prescription sets, compounding personnel must select modes of transport that are expected to deliver properly packed prescription sets in an undamaged, sterile, and stable condition. Inappropriate transport can adversely affect the quality of allergenic extract prescription sets.

- When shipping or transporting allergenic extract prescription sets that require special handling, personnel must include specific handling instructions on the exterior of the container.

21.8 Documentation for Compounding Allergenic Extract Prescription Sets
All facilities where allergenic extract prescription sets are prepared must have and maintain written or electronic documentation to include, but not limited to, the following:

- SOPs describing all aspects of the compounding process
- Personnel training records, competency assessments, and qualification records including corrective actions for any failures
- Certification reports of the PEC, if used, including corrective actions for any failures
- Temperature logs for refrigerator(s)
- CRs for individual allergenic extract prescription sets (see Box 10)
- Information related to complaints and adverse events including corrective actions taken
- Investigations and corrective actions

Glossary

Allergenic extract: A biological substance used for the diagnosis and/or treatment of allergic diseases such as allergic rhinitis, allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy.

Allergenic extract compounding area (AECA): A designated space, area, or room that is not required to be classified, with a visible perimeter that is suitable for preparation of allergenic extract prescription sets.

Allergenic extract prescription set: Combinations of licensed allergenic extracts that would be mixed and diluted to provide subcutaneous immunotherapy to an individual patient, even though these allergenic extract combinations are not specified in the approved BLAs for the licensed biological products.

Box 1. Gloved Fingertip and Thumb Sampling Procedures

- Use one sampling media device (e.g., plates, paddles, or slides) per hand, containing general microbial growth agar (e.g., trypticase soy agar [TSA]) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) as this agar supports both bacterial and fungal growth.
- Label each media device with a personnel identifier, right or left hand, and the date and time of sampling.
- Do not apply sterile 70% isopropyl alcohol (IPA) to gloves immediately before touching the media device because this could cause a false-negative result. Using a separate media device for each hand, collect samples from all gloved fingertips and thumbs from both hands by rolling fingertip pads and thumb pad over the agar surface.
- Incubate the media device at 30°–35° for no less than 48 h and then at 20°–25° for no less than 5 additional days. Samples must be incubated in an incubator. Handle and store media devices to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).
- Record the number of cfu per hand (left hand, right hand).
- Determine whether the cfu action level is exceeded by counting the total number of cfu from both hands.

Box 2. Media-Fill Testing Procedures

- If all of the starting components are sterile to begin with, manipulate them in a manner that simulates sterile-to-sterile compounding activities, and transfer the sterile soybean–casein digest media into the same types of container closure systems commonly used at the facility. Do not further dilute the media unless specified by the manufacturer.
- If some of the starting components are nonsterile to begin with, dissolve a commercially available nonsterile soybean–casein digest powder in nonbacteriostatic water to make a 3% nonsterile solution. Manipulate it in a manner that simulates nonsterile-to-sterile compounding activities. Prepare at least 1 container as the positive control to demonstrate growth promotion, which is indicated by visible turbidity upon incubation.
- Once the compounding simulation is completed and the final containers are filled with the test media, perform a gloved fingertip and thumb sample on each hand and surface sample of the direct compounding area inside the PEC. Take the samples prior to disinfecting gloves and PEC. Handle and store samples to avoid contamination and prevent condensate from dropping onto the agar during incubation and affecting the accuracy of the cfu reading (e.g., invert containers).
- Incubate the final containers at 20°–25° and 30°–35° for a minimum of 7 days at each temperature band to detect a broad spectrum of microorganisms. The order of the incubation temperatures must be described in the facility's SOPs. Final containers must be incubated in an incubator.
- Failure is indicated by visible turbidity or other visual manifestations of growth in the media in one or more container closure unit(s) on or before 14 days

Box 3. Hand Washing Procedures
• Clean underneath fingernails under warm running water using a disposable nail cleaner. • Wash hands and forearms up to the elbows with soap and water for at least 30 seconds. • Dry hands and forearms up to the elbows completely with low-lint disposable towels or wipes.

Box 10. Compounding Records
CRs must include at least the following information: • Name, strength or activity, and dosage form of the CSP • Date and time of preparation of the CSP • Assigned internal identification number (e.g., prescription, order, or lot number) • A method to identify the individuals involved in the compounding process and individuals verifying the final CSP • Name of each component • Vendor, lot number, and expiration date for each component for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredient(s) • Weight or volume of each component • Strength or activity of each component • Total quantity compounded • Final yield (e.g., quantity, containers, number of units) • Assigned BUD and storage requirements • Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing) If applicable, the CR must also include: • MFR reference for the CSP • Calculations made to determine and verify quantities and/or concentrations of components

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https://www.usp.org/compounding/general-chapter-797