

The potential impact of USP 797 and what the JCAAI is doing about it

The Joint Council of Allergy, Asthma, and Immunology continues to provide its members through *New News You Can Use* with socioeconomic information to improve practice management. This section in *Allergy and Asthma Proceedings* reaches out to a larger allergy audience and is useful to expand on specific issues or concerns that may have a considerable impact on the allergist's practice. This section is not meant to eliminate the importance of joining the JCAAI, which informs its membership weekly on critical rapidly changing issues facing medicine and allergy in particular, and what the JCAAI, made up of leaders from both the AAAAI and ACAAI, is doing to find solutions.

One such issue is United States Pharmacopeia's (USP) proposed revision to Chapter 797 on sterile compounding. The recommended change is that all compounded substances be prepared under sterile conditions to insure patient safety. The JCAAI has previously alerted its membership in its *New News You Can Use* (October 26, 2005 and January 26, 2006) on the potential applicability of this change to the practicing allergist. If USP 797 Sterile Compounding Rules are enforced there could be implications for all allergists who prepare allergy vaccines for their patients. This rule change would require that allergy vaccines be mixed under sterile hoods in a "clean room", an environment supplied with HEPA filtered air, in addition to other criteria. Once a product is compounded, it may only be stored and used for nine days, unless an extension is granted.

It is clear that, if applied to allergy vaccines, these rules would create a severe hardship on allergy practices. However, the FDA will only enforce USP standards for compounded products if a specific USP monograph exists for the product. Thus far, this does not exist for allergy vaccines prepared for individual patients. Although USP 797 states that it applies to all settings in which products are compounded, including physician's offices, the USP has no enforcement power and therefore cannot compel physicians to comply. However, certain large medical practices or those connected with hospitals may have to meet USP 797 as a condition of accreditation by JCAHO. Many state boards of pharmacy are requiring licensed pharmacies to follow USP rules.

The JCAAI has already taken initial steps to defer the implementation of draconian rules governing the manufacture of sterile allergy extracts. Representatives of JCAAI have met with USP staff to discuss this issue. They seemed to agree it might be reasonable for USP's Sterile Compounding Committee to review whether USP 797 should apply to allergy immunotherapy. They asked JCAAI to submit its request in writing. In response to our appeal, they suggested we develop an alternative proposal for the safe preparation of allergenic extracts. Consequently, a working group of the JCAAI, AAAAI, ACAAI, and American Academy of Otolaryngic Allergy (AAOA), developed joint standards for allergy extract preparation, which addresses product sterility to ensure patient safety. The recommendations outlined below will be reviewed by the AAAAI and ACAAI Joint Task Force on Practice Parameters on Allergy Immunotherapy and then go back to the boards of the AAAAI and ACAAI for final approval. A written test on aseptic technique and allergy extract preparation is being developed by the College and Academy Immunotherapy Committees and, if approved by their respective boards, we would recommend allergists start implementing them as soon as possible.

Allergen Immunotherapy Extract Preparation Guidelines as Proposed by the JCAAI, AAAAI, ACAAI, and AAOA

1. Qualifications of Extract Preparation Personnel:
 - a. Compounding personnel must pass a written test on aseptic technique and extract preparation.
 - b. Compounding personnel must be trained in preparation of allergenic products.
 - c. Compounding personnel must annually pass a media-fill test, as described below.
 - d. Compounding personnel who fail written or media-fill test would be re-instructed and re-evaluated.
 - e. Compounding personnel must be able to demonstrate understanding of antiseptic hand cleaning and disinfection of mixing surfaces.
 - f. Compounding personnel must be able to correctly identify, measure, and mix ingredients.

2. **Physician Responsibility:** A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in preparation of immunotherapy using aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis:** Allergen extract dilutions must be bacteriostatic, meaning that they just contain phenol concentration of at least 0.25% or if phenol concentration is less than 0.25%, the extract must have a glycerin concentration of at least 20%.
4. **Dilutions Prepared in Accordance with Manufacturer's Instructions:** Allergen extracts must be diluted in accordance with antigen manufacturer's instructions.
5. **Potency:** The manufacturer's expiration dates must be followed. Beyond-use dates for allergy extract dilutions should be based upon best available clinical data.
6. **Mixing of Extracts with High and Low Proteolytic Enzymes. Cross-Reactivity of Antigens:** Separation of aqueous extracts with high proteolytic enzyme activities from other extracts is recommended.
7. **Storage:** Extracts should be stored at 4°C to reduce the rate of potency loss, or according to manufacturer's directions. Extracts beyond expiration date of the manufacturer are to be discarded. Storage must be in a designated refrigerator for medications, not one used for food or specimens.
8. **Subcutaneous Injection:** Allergen extracts may only be administered intradermally or through subcutaneous injection unless FDA-approved package insert or accepted standards of clinical practice permit another route of administration.
9. **Aseptic Technique:** Preparation of allergy immunotherapy shall follow aseptic manipulations defined as:
 - a. The physician must designate a specific site, such as a countertop, in an area of the practice facility where personnel traffic is restricted and activities that may contribute to microbial contamination (e.g., eating, food preparation, placement of used diagnostic devices and materials, and soiled linens) are prohibited.
 - b. The extract preparation area must be sanitized with 70% isopropanol that does not contain added ingredients, such as dyes and glycerin.
 - c. Extract preparation personnel must thoroughly wash hands to wrists with detergent or soap and potable water. Substitution of hand washing by treatment with sanitizing agents containing alcohol and/or 70% isopropanol is acceptable.
 - d. Necks of ampules to be opened and stoppers of vials to be needle-punctured must be sanitized with isopropanol.
 - e. Direct-contact contamination of sterile needles, syringes, and other drug-administration devices and sites on containers of manufactured sterile drug products from which drugs are administered must be avoided. Sources of direct contact contamination include, but are not limited to, touch by personnel and nonsterile objects, human secretions, blood, and exposure to other nonsterile materials.
 - f. After mixing is complete, visual inspection is to be performed for physical integrity of vial.
10. **Labeling:** Immunotherapy vial is to be clearly labeled with patient's name and beyond-use date of the vial.
11. **Mixing Log:** A mixing log is to be kept with information on the patient's name, extract used for mixing, mixing date, and expiration date and lot numbers.
12. **Policy and Procedure Manual:** Practices preparing allergy extracts must maintain a policy and procedure manual for the procedures to be followed in mixing, diluting, or reconstituting of sterile products and for the training of personnel in the standards described above.

Example of a Media-Fill Test Procedure

This or an equivalent test is performed at least annually by each person authorized to compound allergen immunotherapy extracts. The test needs to be performed under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of allergen immunotherapy extracts. Once begun, this test is completed without interruption.

A double-concentrated media such as from Valiteq is transferred, in ten (10) 0.5-mL increments with a sterile syringe to a sterile 10-cc vial. Five (5) mL of sterile water (preservative free) is added. This is the "concentrate." The vial is incubated within a range of 20–35°C for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

Finally, the JCAAI pointed out that the preparation of allergy extracts in the physician's office for his or her own patients, based on a prescription established by the physician, is quite different from pharmacy compounding. The main difference is that the pharmacist may not see the patient at all, is often not involved in the ongoing care of the patient, and thus may not be in a position to quickly learn of problems associated with a compounded product.

I hope this update is helpful and if you are facing problems associated with USP 797 Sterile Compounding Rules, please contact the JCAAI office.