

Due to a publication error, portions of the following article (Vol. 136 Iss. 4, April 2007, pp 658-659) were not printed in the issue. The article is reprinted in this issue in entirety. The publisher sincerely apologizes for the oversight.

SHORT SCIENTIFIC COMMUNICATION

The implications of regulatory guidelines on allergen vial mixing for the practicing otolaryngologist

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OBJECTIVES: To introduce otolaryngologists to proposed standards regarding allergen vial mixing, to identify clinical implications, and to recommend efforts to address the issue of vial mixing standards.

STUDY DESIGN AND METHODS: A policy review.

RESULTS: The Institute of Medicine report on medical errors increased awareness of medication errors, spurring efforts to improve patient safety. One example is the United States Pharmacopoeia's (USP) Chapter 797, a standard for sterile medication compounding. This standard requires the use of a dedicated clean room, ventilation hood, air sampling, surface sampling, and formal testing of mixing personnel. Regulatory agencies may include allergy vial mixing under USP 797. Formal allergy vial mixing guidelines are presented as a standard created by the American Academy of Otolaryngic Allergy taskforce on allergen vial mixing.

CONCLUSION/SIGNIFICANCE: Otolaryngologists must be involved the discussion regarding vial mixing standards to ensure that the standards developed are reasonable, safe, preserve patient access, and are based on evidence based medicine.

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After the Institute of Medicine released its report on medical errors in 1999,¹ there has been greater awareness of the scope of the problem of medical errors in the United States, as well as efforts to improve patient safety. An example is the United States Pharmacopoeia (USP), a non-

profit, volunteer, nongovernmental, standard setting organization that is composed of a majority of pharmacists. The USP issued standard 797 on pharmaceutical compounding of sterile preparations in 2003.²

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) considers USP 797 a valuable guideline but will not survey for compliance with the details of USP 797.³ However, organizations being inspected by JCAHO must have a standard based on expert advice, review of literature, or local organizational studies. Institutions may develop their own safe standards for compounding if there is no specific state law.⁵ The State of Virginia's Board of Medicine has moved to adopt USP 797 with a temporary exemption for allergen immunotherapy, but it is unclear if this exemption will be permanent. If regulatory agencies that adopt USP 797 as a standard choose to include allergen immunotherapy under that standard, the costs to the practitioner and patient will significantly increase, perhaps with the unintended consequence of ultimately decreasing patient access to immunotherapy. An estimated 7 to 10 million annual allergy immunotherapy injections administered in the United States could be affected.⁴

DISCUSSION

The standards set forth in USP 797 for medication compounding include risk levels, employee training, written

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procedures, facility standards, and storage time after compounding. USP 797 divides risk levels into low, medium, and high, assigned according to the potential for microbial contamination during compounding. Allergen immunotherapy would most likely be considered medium risk. USP 797 requires extensive personnel training, documentation, and testing (practical and written). Under 797, a written procedure manual must be kept. Required facility standards would include a dedicated mixing clean room with laminar flow hood or pharmacy isolator. Air sampling would be required monthly, surface and glove sampling weekly. Medium risk compounds would be discarded after 7 days, unless specifically exempt.

What would it mean for the practicing otolaryngologist and his or her patients if the otolaryngologist's office were to adopt USP 797 medium-risk standards for their office? Current vial mixing is now typically performed on a dedicated surface in a room that has no food, specimens, or contaminated items such as instruments. A dedicated space would need to be converted into a clean room, at a significant cost, as well as the purchase of a laminar flow hood. Vials currently are remixed approximately once every 10 weeks per patient while in the escalation phase for inhalant allergen desensitization, during which patients typically receive weekly subcutaneous injections. Vials are also diluted on site if the vial is too potent and incites a local allergic reaction with a test dose. Therefore, if adopting medium-risk class standards, the vial would need to be remixed every week⁵ instead of once every 10 weeks, increasing the time needed by the allergy nurse solely for vial mixing by 10-fold, as well as increasing supplies by 10-fold. One likely, unintended effect of adopting these standards would likely be a significant decrease in the number of physicians offering vial mixing and immunotherapy due to the prohibitive cost of meeting the standards of USP 797.

Current mixing practices have focused on the avoidance of anaphylaxis and systemic reactions after immunotherapy. The overwhelming majority of offices have guidelines such as new vial testing on the patient with a small test dose and observing the patient for 20–30 minutes after injection for signs and symptoms local and systemic allergic reactions. Mixing personnel typically undergo rigorous training to understand correct vial mixing and dosing in order to prevent anaphylaxis, and detailed mixing logs are kept, as well as records of injections and adverse reactions. Current mixing practices do use aseptic technique. However, most offices probably do not emphasize formal documentation of training or have a written guideline of practices implemented in order to prevent infection.

Recommendations

What can an otolaryngologist do when being faced with the possibility of increasing regulation of allergen vial mixing? We must educate ourselves regarding the issue, so that we can become informed participants. Practitioners also need to inform their state and national medical societies about their concerns regarding this issue, so grass roots efforts can be organized. There is also a real need for evidence-based medicine to examine the effects of mixing conditions on contamination and risks of infection for the immunotherapy patient. And, finally, the creation of USP 797 does certainly encourage otolaryngologists to formalize and examine our current practice of allergen vial mixing. Currently, the American Academy of Otolaryngic Allergy (AAOA) has created a taskforce that is working with the Joint Council of Allergy, Asthma and Immunotherapy (JCAAI) to create suggested standards for mixing. These standards are based on the input and past experience of practitioners, so that reasonable standards to ensure patient safety are followed (AAOA/JCAAI Taskforce Suggested Allergen Immunotherapy Extract Preparation Guidelines [Table 1; see journal website at <http://journal.entnet.org>]). The task force will continue to refine these guidelines based on scientific evidence and expert opinion.

CONCLUSION

There is a push to regulate allergen immunotherapy on both the state and federal level, so otolaryngologists must be involved to ensure that the standards that are developed are reasonable, promote patient safety, and preserve patient access and are based on evidence-based medicine.

REFERENCES

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ADDENDUM A

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 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.

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Table 1
AAOA/JCAAI Taskforce Suggested Allergen Immunotherapy Extract Preparation Guidelines

1. Qualifications of Extract Preparation Personnel:
 - Compounding personnel must pass a written test on aseptic technique and extract preparation.
 - Compounding personnel must be trained in preparation of allergenic products.
 - Compounding personnel must annually pass a media-fill test, as described in Addendum A.
 - Compounding Personnel who fail written or media-fill test would be re-instructed and re-evaluated.
 - Compounding Personnel must be able to demonstrate understanding of antiseptic hand cleaning and disinfection of mixing surfaces.
 - 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 must contain phenol concentrations 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 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 (eg., 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 to be performed for physical integrity of vial.
10. Labeling: Immunotherapy vials are 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.