January 28, 2016

United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790

**Re: Revisions to General Chapter <797> Pharmaceutical Compounding – Sterile Preparations as published in Pharmacopeial Forum 41(6) November/December 2015**

Submitted electronically to CompoundingSL@USP.Org

Dear Sir or Madam:

The American College of Allergy, Asthma and Immunology (ACAAI), together with the Advocacy Council of the ACAAI, the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Otolaryngic Allergy (AAOA), the American Rhinologic Society (RHS), the American Academy of Otololaryngology – Head and Neck Surgery (AAOHNS) Foundation, and the Asthma and Allergy Network (AAN) appreciate this opportunity to submit comments on proposed revisions to *USP General Chapter* <797> on sterile compounding as published in the Pharmacopeial Forum. Together, our organizations represent approximately 13,500 physicians who provide care to millions of patients suffering from asthma and allergic diseases. The AAN is a multidisciplinary, patient-centered network dedicated to ending needless death and suffering due to asthma, allergies, and related conditions and reaches over 10 million people each year with its magazine *Allergy & Asthma Today*. Our organizations are writing to request that the USP maintain the current Chapter <797> rules applicable to allergen extracts pending completion of a full and fair review that includes collaboration with affected stakeholders and an analysis of the profound and serious consequences on the future use of well-established safe and effective treatment for patients with allergic diseases. Facts supporting this request are set forth below in detail.

**Executive Summary**

Our organizations, representing physicians and patients, strongly oppose the USP's proposed revision to Ch. <797> that would remove the special rules for preparation of allergen extracts for the following reasons:

- Allergen extracts have been safely prepared by physicians using aseptic technique for over one hundred years.
- The sterility record of allergen extracts prepared under current Ch. <797> rules is well-established in both the medical literature and clinical practice.
- There is no evidence that current Ch. <797> rules pose any threat to patient safety.
- The proposed rules were developed without an analysis of their impact on public health and costs to our health care system.
- The process did not follow USP Convention resolutions.
- The proposed rules are inconsistent with recently proposed Food and Drug Administration (FDA) Industry Guidance which recognizes special treatment for allergen extracts.
- If the proposed rules are adopted, access to allergen immunotherapy, a proven treatment for asthma and allergic diseases, would be severely curtailed, costs of care would rise dramatically, disparities in health care would be increased, and overall patient health would suffer.

We strongly urge that the current USP <797> rules applicable to allergen extracts be maintained and that any future changes to USP <797> applicable to allergen extracts be developed through an open and fair process that includes full participation of patients and other affected stakeholders and a thorough analysis of the impact on public health and costs of care.

## I. Introduction

Our organizations are extremely concerned by the Compounding Expert Committee's (the Committee's) proposal to eliminate the special rules for allergen extracts adopted by this same Committee and by the USP less than 10 years ago.[1] Those rules provide that allergen extracts are not subject to the personnel, environmental, and storage requirements applicable to other compounded sterile products (CSPs) if the eleven criteria set forth in Tab 1 are met.

The safety record of allergen immunotherapy extract preparation using aseptic technique is well-established in both the medical literature and in clinical practice going back over one hundred years. We are aware of no reports in the medical literature of infections resulting from non-sterile allergen immunotherapy administration. We estimate that over 16 million subcutaneous allergy immunotherapy injections are given annually in the United States to over 2.6 million people. Yet, out of the many millions of injections administered to millions of patients over several decades, there are no reported infections. This is clear evidence of the safety of current practice. Yet, with no explanation, and in a complete reversal of policy adopted only ten years ago, the USP now proposes that allergen extracts intended for subcutaneous injection must be subject to the same restrictive and extremely costly environmental and engineering controls, sterility testing requirements, and drastically shortened beyond use dates (BUDs) applicable to high risk preparations intended for intravenous, spinal, or other systemic means of administration. If adopted, these standards will make it virtually impossible for allergists to safely prepare allergen immunotherapy for their patients.

[1] USP standards for allergenic extracts is attached, *see* Tab 1.

Allergen immunotherapy is the only proven therapy for asthma, allergic rhinitis, and allergic conjunctivitis that is disease modifying and offers patients a possibility for cure. Other currently available therapies provide symptomatic relief and control while on treatment but withdrawal inevitably leads to disease reoccurrence. Therefore, the public health consequences if this proposal is adopted are enormous.

We are especially concerned about the lack of transparency in the USP's revision process. Although USP is a non-governmental organization, it is well aware that its standards are enforced by the FDA as well as state legislatures, state boards of pharmacy, and private accrediting bodies such as The Joint Commission. Thus, changes to its standards have far-reaching effects and, consequently, the lack of transparency is especially troubling. For example, the Committee has offered no explanation for the major changes to its sterile compounding guidelines for allergen extracts and no rationale for the replacement of the current allergen extract rules. Nor is there any analysis of the impact of its revisions on public health or financial implications for our health care system. Although the public is given an opportunity to provide written comments, that process is limited by USP's failure to provide any rationale for its proposed changes. Thus, there is very little opportunity for meaningful public input.

The Committee's proposal is also inconsistent with many of the Resolutions adopted by the USP Convention membership at its April 25, 2015 meeting.[2] Resolution VIII states that

> USP will collaborate with stakeholders to develop, strengthen, revise and promote adoption of health care quality standards that address quality and safety related to the use of medications and that are of value to patients and practitioners. (with emphasis)

However, the Committee has failed to make the case for how its elimination of the current allergen extract rules will be "of value to patients and practitioners." In fact, just the opposite is true. As discussed below in more detail, the new rules will have the effect of drastically reducing, if not eliminating, patient access to allergen immunotherapy – a proven treatment for patients with asthma and other allergic diseases.

The proposed rules also ignore Resolution XI which states that USP "will increase its commitment to global public health" by, among other things, strengthening systems "that ensure access to quality foods and medicine." The proposed revisions will, instead, reduce access.

Also troubling is the Committee's failure to provide for an open process in which those impacted by its proposed rules, including physicians and patients, can meet and discuss their concerns. Resolution VI specifically calls upon USP to "promote alignment with stakeholders to develop quality standards for biological medicines, ensuring that innovation and availability are facilitated and complemented."

Even more significant, the USP's proposal is also inconsistent with the position taken by the FDA in its draft Industry Guidance, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved*

[2] U.S. Pharmacopeial Convention, *2015-2020 Resolutions* (April 25, 2015), http://www.usp.org/about-usp/2015-2020-resolutions.

*Biologics License Application* (Draft Guidance).[3] In the Draft Guidance, the FDA allows physicians to continue to prepare allergen extracts for their patients provided certain conditions are met. The FDA states its intent to continue to allow compounding of "prescription sets," defined as a "vial or set of vials of premixed licensed standardized and non-standardized allergenic extracts for subcutaneous immunotherapy diluted with an appropriate diluent prepared according to instructions from a prescription or order by a licensed physician for an individual patient." Physicians who prepare prescription sets that meet FDA criteria would not be subject to enforcement actions for violations of the Public Health Service Act or the Food Drug and Cosmetic Act. Those criteria include the current USP <797> rules for allergen extracts which the Draft Guidance accepts as reasonable.

Resolution 1 of the USP Convention states that the "USP will increase communication and collaboration with the FDA to promote alignment with the FDA's regulatory and scientific policies from the inception of the standards planning and development process." However, it does not appear that the USP has communicated with the FDA on this issue. Resolution 1 also states that "USP will work with FDA, industry, and other stakeholders throughout the process to increase understanding of the regulatory impact of such proposals." Yet, the proposed rule changes, and in particular the elimination of the allergen extract rules, seems to have been developed in complete disregard of their public health impact.

The USP proposal also fails to take into account the serious impact on public health that would result if allergy immunotherapy is no longer available because the costs of allergen extract preparation are prohibitively expensive. The new standards would require, among other things:

- Redesign of office space to meet the stringent engineering controls necessary to maintain an ISO Class 5 environment for compounding, an ISO Class 8 ante-area, and an ISO Class 7 buffer area;
- Environmental sampling for viable and non-viable airborne particulates;
- Ongoing sterility testing requiring culturing of vials in accordance with USP specifications and delaying distribution to patients;
- Discarding of all preparations after either 28 or 42-days regardless of manufacturer BUD dates.

Especially important is the last item - the significantly shorter BUD. This would require more frequent mixing of allergen extracts which would actually increase the risk of an adverse event due to an allergic reaction because of extract lot variability with respect to content and potency which can cause allergic reactions. We strongly object to these additional requirements that would jeopardize patient safety.

In addition to safety concerns, these shorter BUD requirements would impact efficacy of therapy. This potential lack of efficacy relates to immunotherapy induction of tolerance developed when maintenance dosing is achieved, and the linkage to the timing of injections that are typically given monthly once the maintenance dose is reached. If the allergen preparation for maintenance therapy must be remade every month, it would

[3] FDA, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* (Draft Guidance) (Feb. 2015), http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434176.pdf; *see* Tab 2.

prevent the patient from reaching the maintenance dose (and desensitization) because the schedule would have to be restarted with each newly prepared allergen extract material.

Furthermore, for those few large groups or laboratories that are able to meet USP rules, the additional costs of compliance will be substantial and will inevitably have to be passed on to patients and insurers, including Medicare, Medicaid and other governmental payers. We are especially concerned about the impact of higher costs and resultant lack of access this would have on vulnerable populations, especially in underserved inner cities and rural America where access and coverage of allergen immunotherapy for individuals with asthma and allergic rhinitis already presents a challenge. This will increase disparities of care in direct opposition to the goals of the National Strategy for Quality Improvement in Health Care as set forth in Section 3011 of the Affordable Care Act which call for reducing "health disparities across health disparity populations . . ." It also undermines the specific goals of the 2012 *Coordinated Federal Action Plan to Reduce Racial and Ethnic Asthma Disparities*.[4] We believe that the proposed changes will make access to care for these vulnerable populations a significant issue negatively impacting their health.

In summary, the Committee's proposed revisions were not developed in a manner consistent with the USP Convention's resolutions and policies. Nor are they supported by scientific or clinical evidence. In fact, as discussed below, existing studies demonstrate just the opposite – that allergen extract preparation is safe and presents no infectious risk to public health.

We believe the Committee needs to withdraw the proposed revisions, start this process anew, and ensure that any future revisions proposed for Ch. <797> follow the policies established by the USP Convention. Specifically, the USP must engage in a full and fair process with affected stakeholders and conduct a public health analysis of the impact of its proposal on patients with asthma and allergic diseases.

We therefore request that the current standards applicable to allergenic extracts be maintained and that any proposed revisions to those standards be developed in collaboration with affected stakeholders and based on a complete analysis of the public health ramifications.

## II. Development of the 2007 USP Sterile Compounding Standards

The USP's reversal of its position is especially bewildering in view of the extensive discussions and dialogue the allergy specialty organizations had with the USP prior to adoption of the current rules. In 2006, during the development of the current USP Ch. <797> sterile compounding standards, the allergy specialty organizations worked closely with USP staff and members of the Sterile Compounding Committee to address safety concerns surrounding compounding of allergen extracts. This included a meeting with USP staff in December 2005 and a presentation made at the USP Compounding Stakeholder Forum held on June 16th, 2006.

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[4] *See* President's Task Force on Environmental Health Risks and Safety Risks to Children, *Coordinated Federal Action Plan to Reduce Racial and Ethnic Disparities* (May 2012), http://www.epa.gov/sites/production/files/2014-08/documents/federal_asthma_disparities_action_plan.pdf.

We understood, at that time, that the Sterile Compounding Committee had concerns about the safety of allergen extract preparations. Although allergenic extracts had been made by allergists in their offices since the early part of the 20th century using aseptic technique, there was, at that time, no set of uniform safety guidelines. Consequently, our organizations worked to develop a set of guidelines for allergen extract preparation that addressed product sterility and patient safety. The guidelines included proper training of personnel mixing extracts, oversight by physicians, inclusion of proper concentrations of glycerin and phenol for bacteriostasis, use of an aseptic technique, and refrigerated storage. They also specified that allergen immunotherapy is only intended for subcutaneous injection. Those standards, which were approved by the boards of each organization, were published as part of the Allergen Immunotherapy Practice Parameters Third Update.[5] They were also provided to USP as part of the 2006 revision process.

We intended that these guidelines would be viewed by allergists as an example of best clinical practice and used in the same way as practice parameters and asked that USP either adopt them or incorporate them by reference. The USP did not adopt these guidelines but did exclude allergenic extracts from the stringent standards applicable to other compounded sterile products as long as certain standards specific to allergenic extract preparation were met. These standards have been in effect since 2008 and have been widely adopted by the majority in the allergy community. The proposed revisions to Ch. <797> would eliminate these standards and treat allergen immunotherapy extracts the same as all other compounded sterile products. This would require, among other things, the use of a dedicated clean room, ventilation hood, air sampling, frequent testing of personnel, ongoing culturing of vials for sterility testing, and discarding of multi-dose patient vials after 28 to 42 days.

## III. Safety and Efficacy of Allergen Immunotherapy

Allergen immunotherapy, administered through subcutaneous injections, is a proven clinically effective treatment for individuals with allergic rhinitis, allergic asthma, and hypersensitivity to insect stings. The efficacy of allergen immunotherapy is well-established in the medical literature.[6]

There are approximately 5,300 physicians in the United States who prepare and provide allergen immunotherapy extracts to their patients and it is estimated that over 16 million allergen immunotherapy injections are administered annually in the United States.[7] Allergists have been preparing allergen immunotherapy extracts in their offices for over one hundred years. Patients are closely monitored for reactions to the injections and cases of anaphylaxis have been reported as well as lesser reactions. However, a medical literature search we conducted of the over one hundred year history of this treatment found no reported cases of endotoxicity, abscesses, or sepsis. Nor do we see such events in our clinical practice. This

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[5] Cox L, Nelson H, Lockey R. *Allergen Immunotherapy: A practice parameter third update. Joint Task Force Report.* (2010) J. Allergy Clin Immunol. *See* http://www.allergyparameters.org/published-practice-parameters/alphabetical-listing/immunotherapy-download/.

[6] *Id.*

[7] Extrapolation from Medicare data and AAAAI/ACAAI surveillance study: Epstein T, Liss G, Murphy-Berendts K, Bernstein D. *The impact of asthma control and higher maintenance doses on immunotherapy safety: year 5 of the AAAAI/ACAAI surveillance study. (Abstract)* J. Allergy Clin Immunol. 2015; 135(2): Supplement, AB215. Medicare utilization data indicates that Medicare alone paid for approximately 6.7 million doses of allergy immunotherapy in 2014 and it is reasonable to estimate, assuming monthly injections, that this represents approximately half a million individual patients in the Medicare population alone.

gives us assurance that allergen extracts prepared in physician offices are safe and sterile. This conclusion is supported by several studies, both retrospective and prospective.[8] (See discussion below)

### A. Preparation of Allergen Immunotherapy Extracts

Allergen extracts are prepared based on the allergist's written order specifying the content, concentration, and dosing schedule. When a patient begins immunotherapy, he or she typically begins with diluted doses and the concentration gradually increases over time. Usually, by the end of a year, a patient is on a maintenance dose and receives injections once or twice every month. Injections are typically between 0.5 and 1.0 mL and are administered subcutaneously.

The mixing of allergen extracts begins with FDA approved allergenic extracts. Most, but not all, commercial allergenic extracts are 50% glycerinated. The allergenic extracts or "concentrates" are combined in a sterile vial using sterile syringes. Serial 5-fold or 10-fold dilutions are then made from the vial of concentrate using sterile saline (either normal saline or HSA saline) typically containing 0.4% phenol. Aseptic technique based on current USP Ch. <797> guidelines or the standards set forth in the Practice Parameters[9] is followed and the vials are labeled and stored in refrigerated conditions. BUDs are assigned based on the most recent expiration date of any of the component antigens.

A typical multi-dose vial of maintenance extract contains 10 doses designed to last over a 10-12 month period.[10] Dilutions, which are given at the onset of treatment, are also prepared in 10 dose vials but storage time is less because the injections are given more frequently (*e.g.*, weekly to bi-weekly).

Patients often experience reactions to their immunotherapy extracts that are generally addressed by the treating allergist through dosage adjustments or changes to the allergenic extracts themselves. Furthermore, patient history and physical well-being are assessed before each injection and modifications are implemented to protect patients, such as dose reductions or no administration, for example, when a patient has an asthma flare. It is important that the allergist be able to make these changes on a timely basis so that the course of treatment is appropriate and not delayed.

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[8] *See* Lay PC, Bass R, Lin S. *Allergen vial mixing and immunotherapy: Risks of infections and vial contamination*. Otolaryngology-Head and Neck Surgery 2007; 137, 243-245 (Tab 3); Lin SY, Lay PC, Hughes LF, Bass R. *The safety of multi-dose vials in allergy immunotherapy*. Otolaryngology-Head and Neck Surgery 2008; 139, 195-197 (Tab 4); Gilbert KC, Sundrarehsan V, Bass RM, Lin SY. *Antibacterial properties of additives used in injection immunotherapy*. International Forum of Allergy & Rhinology 2012; 2(2): 135-138 (Tab 5); Letz AG, Tankersley MS, Dice JP, England RW. *Monitoring bacteriostasis in allergen extract mixing: 10 years of culture data.* J. Allergy Clin Immunol 2009; 123(5): 1175-1176. Letter to the Editor. (Tab 6); Lay PC. *Injectable immunotherapy: recommendations for safe allergen vial preparation in the office setting*. Current Opinion in Otolaryngology and Head and Neck Surgery 2009, 17:223-225 (Tab 7); Lay PC, Bass R, Hughes LF, Lin SY. *Risks of allergy vial contamination: comparison of mixing in-office versus under ventilation hood*. Otolaryngology-head and Neck Surgery 2008; 139: 364-365 (Tab 8); Rossow K, Butler MA, Lowe D, Li JT. *Bacteriostatic agents and sterility requirements for allergen immunotherapy*. Annals of Allergy, Asthma and Immunology 2011; 106:76-77 (Tab 9).

[9] *See* note 5.

[10] The Medicare program allows for payment of up to 12 months of antigens at a time. *See* 42 C.F.R. § 410.68

Preparation of allergen extracts in the allergist's office for their own patients, based on a prescription established by the allergist, is quite different from pharmacy compounding in a number of important ways. First, patients who receive allergen immunotherapy in the physician's office are closely monitored by the physician for reactions for at least 30 minutes post-injection. Further, patients receiving immunotherapy come to the physician's office at least monthly for injections. Before the patient receives his or her next injection, the patient is queried by the nurse regarding any reactions to the last injection. The injection site is also physically examined. Any problems are reported to the physician. In contrast, in the pharmacy environment the pharmacist may never see the patient and is often not involved in his or her ongoing care and thus may not be in a position to quickly learn about problems associated with a compounded product.

In summary, allergen extract injections are only administered subcutaneously and in small volumes of 0.5 to 1.0 mL. They are never injected intravenously or into body cavities or the central nervous system. Thus, they present significantly less risk compared to CSPs administered through intravenous or spinal injection. We believe the unique aspects of the doctor/patient relationship should be considered in the development of compounding standards for allergen extracts.

### A. Studies Supporting Sterility of Allergenic Extracts Prepared Using Aseptic Technique

Several recent studies support the safety of allergenic extracts prepared under aseptic technique. A report by allergists at Lackland Air Force Base described 10 years of bacterial cultures performed on allergen immunotherapy vials and found that of the 2,085 cultures completed between 1998 and 2009, 2,084 cultures were negative.[11] No information was available on whether the single positive culture was administered to a patient, but the authors reported no known cases of infections at their institution.

Another single-blinded, prospective, case-control study performed in 2008 that compared mixing of allergenic extracts in the office using aseptic technique with preparation under an ISO Class 5 vacuum ventilated hood also supports the conclusion that the risk of bacterial contamination in immunotherapy prepared in the office under aseptic conditions is extremely rare.[12] A second prospective study supports sterility of allergenic extracts over several months. In that study, 136 vials of allergenic extract were cultured at the time of expiration over an 8-month period after multiple doses were given from each vial. All culture results were negative. The authors concluded that immunotherapy vials are at low risk for contamination when prepared in the office using aseptic technique.[13]

A 2007 retrospective study of 272 patients given 26,795 injections from January 2000-June 2006 at a university clinic showed no documented skin or systemic infections as a result of allergen injections.[14] Nor did

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[11] Letz AG, Tankersley MS, Dice JP, England RW. *Monitoring bacteriostasis in allergen extract mixing: 10 years of culture data.* J. Allergy Clin Immunol 2009; 123(5): 1175-1176. Letter to the Editor (Tab 6).

[12] Lay PC, Bass R, Hughes LF, Lin SY. *Risks of allergy vial contamination: comparison of mixing in-office versus under ventilation hood*. Otolaryngology-head and Neck Surgery 2008; 139: 364-365; *see* note 8, Tab 8.

[13] Lin SY, Lay PC, Hughes LF, Bass R. *The safety of multi-dose vials in allergy immunotherapy*. Otolaryngology-Head and Neck Surgery 2008; 139, 195-197; *see* note 8, Tab 4.

[14] Lay PC, Bass R, Lin S. *Allergen vial mixing and immunotherapy: Risks of infections and vial contamination.* Otolaryngology-Head and Neck Surgery 2007; 137, 243-245 (Tab 3).

any of the patients, who were seen every 1 to 3 weeks in follow-up, experience fever, discharge from the injection site, or cellulitis. None required antibiotics or medical treatment for infection. Although there was incidence of both systemic and local allergic reactions, they all related to reactions to the antigens themselves and not the presence of contaminants in the antigen preparations.[15]

A pilot study has recently been completed at 2 major academic medical centers in Boston (Massachusetts General Hospital and Brigham and Women's Hospital) in which an association between episodes of administration of allergen immunotherapy using extracts prepared with aseptic technique and subsequent evidence of skin or soft tissue infection (within 5 days) was examined over a 10-year time frame. CPT codes 95115 and 95117 identified episodes of allergen immunotherapy administration, and ICD-9 codes (680, 681.00, 681.01, 681.10, 681.90, 682, 684, 704.8, 705.83, 771.5, 675.1, 675.2) were used to identify dermatitis and skin/soft tissue infection. In this study 145,930 separate episodes of administration of allergen immunotherapy were identified, in which there were 46 episodes of dermatitis or skin/soft tissue infection occurring in the same patient within a 5 day period. Chart review of those 46 episodes of documented dermatitis or clinical infection was undertaken to identify the precise clinical process prompting utilization of the ICD-9 code. All dermatitic or clinical infectious episodes were identified as being remote from the site of immunotherapy administration and included the following clinical descriptors: folliculitis (15), dermatitis with or without superinfection (14), pustule, abscess or cellulitis (9), seborrheic dermatitis (3), hidradenitis (2) and pityriasis rosea, paronychia and inclusion cyst (1 each). The conclusion was that no infectious complications of administration of allergen immunotherapy, with extracts prepared using aseptic technique, were identified among these 146,930 administrations (unpublished data Aidan Long et al).

The absence of reported sterility problems is due in large part to the antibacterial properties of additives used in preparation of allergenic extracts. A 2012 *in vitro* study examined microbial growth in allergen immunotherapy vials prepared with varying concentrations of glycerin, phenol, and a combination of both. This study demonstrated the role of these additives in inhibiting bacterial growth and concluded that based on results of this study and analysis of other data, that current standards of immunotherapy vial mixing using aseptic technique without the need for a ventilation hood are supported by the literature.[16] Another study at the Mayo Clinic compared the effects of microbial growth by using lower than recommended concentrations of phenol and glycerin in two experiments in which one group of vials was prepared using a laminar flow hood and appropriate attire, including gown, mask, and sterile gloves and the other set were prepared on the bench top and included alcohol wipes of the vials and reagent bottles.[17] None of the vials showed microbial growth and no difference was found between hood or bench top preparations.

We believe the implementation of the current Ch. <797> standards in 2008 and the standards developed by our specialties which began in 2007 has helped ensure sterility in allergenic extracts. The proposed changes will have a negative impact on public health and increase the overall cost of medical care in the United States.

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[15] *Id.*

[16] Gilbert KC, Sundrarehsan V, Bass RM, Lin SY. *Antibacterial properties of additives used in injection immunotherapy*. International Forum of Allergy & Rhinology 2012; 2(2): 135-138 (Tab 5); *see* note 8.

[17] Rossow K, Butler MA, Lowe D, Li JT. *Bacteriostatic agents and sterility requirements for allergen immunotherapy*. Annals of Allergy, Asthma and Immunology 2011; 106:76-77 (Tab 9).

If the current published data are insufficient, the task of undertaking a prospective study to prove a negative at the clinical level (*i.e.* lack of infectious complications associated with allergen immunotherapy), would require massive data gathering. The need for the extraordinarily large sample size is related to the extremely low event rate and the need to power the study appropriately to achieve acceptable scientific rigor in terms of study design. However, at a minimum, the allergy community should be allowed to assess the feasibility of embarking on a surveillance project that would further substantiate the safety of allergen immunotherapy prior to any changes to the current Ch. <797>. At the same time, we would ask that any data the USP has regarding safety concerns relative to allergen immunotherapy be shared in a timely way with the allergy community so that we can work together to resolve them (if they exist).

## IV. Public Health Impact if Proposed Standards are Adopted

### A. Impact on Access to Care

Respiratory allergies affect more than 50 million Americans. The most common respiratory allergy, allergic rhinitis, represents the 5th leading chronic disease overall, and the third leading chronic disease among children under age 18.[18] Those with allergic rhinitis can experience disturbed sleep, decreased energy, depressed mood, poor concentration, decrements in performance at school and work, and millions of lost work and school days annually.[19] In 2005, estimated total direct U.S. costs of allergic rhinitis exceeded $11 billion and in 2011 the direct costs were estimated to exceed $14 billion.[20]

Survey data suggests that there are approximately 2.6 million individuals in the United States that receive approximately 16 million allergen immunotherapy subcutaneous injections for allergic diseases and conditions each year.[21] Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is effective in the treatment of allergic rhinitis as well as such life-threatening conditions as asthma and stinging insect hypersensitivity.[22] Randomized controlled studies also show that it is effective in preventing the development of asthma in individuals with allergic rhinitis.[23] In fact, allergen-specific immunotherapy is the only treatment known to provide long-term benefit and alter the course of allergic disease.[24]

Allergen immunotherapy also reduces health care costs. In a groundbreaking study involving an analysis of 10 years of Medicaid claims (1997-2007) in Florida, evidence showed that over an 18-month period, children with allergic rhinitis who received allergen-specific immunotherapy incurred 42 percent lower per-patient health care costs than those who did not receive allergen-specific immunotherapy, or a savings of $3,865 per

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[18] The American Academy of Allergy Asthma and Immunology (AAAAI). *The Allergy Report*. Milwaukee, WI. AAAAI, 2000. National Academy on an Aging Society. Chronic Conditions. A Challenge for the 21st Century, November 1999. *See* http://www.agingsociety.org/agingsociety/pdf/chronic.pdf.

[19] Hankin CS, Cox L, Wang Z, Bronstone A. *Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis.* J Allergy Clin Immunol 2013; 131:1084–1091 (Tab 10).

[20] *Id.*

[21] *See* note 7.

[22] Allergen Immunotherapy: A practice parameter third update (*See* note 5).

[23] *Id.*

[24] Cox L, Atwater S. *Allergen immunotherapy for allergic rhinitis and asthma*. Drug Benefit Trends 2008;20:1-6.

patient.[25] A similar analysis involving claims data for adult patients was equally compelling. Over 18 months, health care costs for adults with allergic rhinitis who received allergen-specific immunotherapy were 30 percent lower than those who did not – a savings of $4,397 per patient.[26]

If the proposed USP Ch. <797> rules are finalized, patient access to allergen immunotherapy will be drastically reduced, if not eliminated, because allergists will no longer be able to prepare allergen immunotherapy vials for their patients. Moving allergen extract preparation to large compounding laboratories or pharmacies is not a viable alternative due to safety considerations. This is because patients often have allergic reactions to their immunotherapy injections that require the allergist to change the content or dilution of the vials before they can receive the next injection. For example, if a patient comes in for an injection and reports that after the last injection they experienced a reaction to his or her last shot, depending on the nature of the reaction, this would require the allergist to change the dilution or possibly even change the specific allergens in the vial in response to specific sensitivities. Failure to do so could result in a life-threatening systemic allergic reaction. These adjustments would need to be done while the patient is in the office if the patient's treatment schedule is not to be interrupted or delayed. Compounding pharmacies, located off-site from the allergist's office, would not be able to make these adjustments in a timely fashion. Furthermore, any requirement for sterility testing prior to revised extract release introduces an unsustainable delay in treatment, as well as patient safety and efficacy concerns.

### A. Impact on Coverage

Medicare does not cover allergen immunotherapy manufactured by a third party vendor. CPT code 95165, which is recognized by Medicare, is for the direct physician supervision of the making of allergen immunotherapy extract. This code would not be applicable for allergen immunotherapy manufactured by an outside source and the use of this code, by a physician or beneficiary to be reimbursed for allergen immunotherapy could be considered Medicare fraud.

In addition, commercial insurers recognize CPT Code 95165 for reimbursement for allergen immunotherapy and, as with Medicare, it is not clear that there are any alternative CPT codes that would be recognized for reimbursement of allergen immunotherapy that is compounded outside of a physician's office. The direct consequence of the USP eliminating the special rules for allergen immunotherapy compounding is that Medicare recipients, and potentially Medicaid and commercially insured patients, would no longer have allergen immunotherapy as a covered service. USP would be effectively making a medical policy decision that would directly and negatively impact the health

care of hundreds of thousands of Medicare recipients and others. This potential change could transfer the cost of a previously covered benefit to the beneficiary.

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[25] Hankin CS, Cox L, Wang Z, Bronstone A. *Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis.* J Allergy Clin Immunol 2013; 131:1084–1091 (Tab 10).
[26] *Id.*

Finally, even if Medicare and other payers did reimburse for allergen extracts prepared by outside laboratories or compounding pharmacies, based on data obtain from third party vendors, charges for antigens prepared using current USP 797 standards are already as much as five times the cost per dose recognized by Medicare. If those vendors had to implement the more stringent rules proposed by the Committee, it is certain that those costs would be significantly higher.

## V. Conclusion

Although we strongly support the USP's mission of protecting patients from harm caused by contaminated compounded products, we cannot help but think that applying the proposed USP <797> standards to allergen extracts is a solution in search of a problem. Our goal as physicians is to ensure that the care we provide is both safe and effective. Decades of clinical experience plus several recent studies indicate that allergenic extracts prepared in the allergist's office under aseptic technique and administered through subcutaneous injection do not present a risk of infection. As such, the proposed Ch. <797> standards, as applied to allergenic extracts, are not supported by the science. Nor do they take into consideration the very serious public health impact that would result from reduced access to effective immunotherapy for hundreds of thousands of Americans who rely on or are in need of this treatment. We strongly urge you to retain the current USP <797> standards for allergenic extracts. In the alternative, we ask that you work with our organizations to develop workable standards that are supported by scientific evidence. The health of our patients is at risk.

Sincerely,

Brian L. Martin, DO
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# TAB 1

and CACIs; counter tops where finished preparations are placed; areas adjacent to BSCs and CACIs, including the floor directly under the working area; and patient administration areas. Common marker hazardous drugs that can be assayed include cyclophosphamide, ifosfamide, methotrexate, and fluorouracil. If any measurable contamination (cyclophosphamide levels greater than 1.00 ng per $cm^2$ have been found to cause human uptake) is found by any of these quality assurance procedures, practitioners shall make the decision to identify, document, and contain the cause of contamination. Such action may include retraining, thorough cleaning (utilizing high-pH soap and water), and improving engineering controls. Examples of improving engineering controls are (1) venting BSCs or CACIs 100% to the outside, (2) implementing a CSTD, or (3) re-assessing types of BSCs or CACIs.

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.

## RADIOPHARMACEUTICALS AS CSPs

In the case of production of radiopharmaceuticals for positron emission tomography (PET), general test chapter *Radiopharmaceuticals for Positron Emission Tomography—Compounding* ⟨823⟩ supersedes this chapter. 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.

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 (see *Injections* ⟨1⟩) shall be designated as, and conform to, the standards for *Low-Risk Level CSPs.*

These radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO Class 5 (see *Table 1*) PEC located in an ISO Class 8 (see *Table 1*) or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements.

Radiopharmaceutical vials designed for multiuse, compounded with technetium-99m, exposed to ISO Class 5 (see *Table 1*) environment, and punctured by needles with no direct contact contamination may be used up to the time indicated by manufacturers' recommendations. Storage and transport of properly shielded vials of radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO class designation.

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 (see *Table 1*) or cleaner air environment to permit special handling, shielding, and air flow requirements. To limit acute and chronic radiation exposure of inspecting personnel to a level that is as low as reasonably achievable (ALARA), direct visual inspection of radiopharmaceutical CSPs containing high concentrations of doses of radioactivity shall be conducted in accordance with ALARA.

Radiopharmaceuticals prepared as *Low-Risk Level CSPs with 12-Hour or Less BUD* shall be prepared in a segregated compounding area. A line of demarcation defining the segregated compounding area shall be established. Materials and garb exposed in a patient care and treatment area shall not cross a line of demarcation into the segregated compounding area.

## ALLERGEN EXTRACTS AS CSPs

Allergen extracts as CSPs are single-dose and multiple-dose *intradermal or subcutaneous injec-*

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*tions* that are prepared by specially trained physicians and 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. Nonpreserved 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 nonantimicrobial 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 nonsterile 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.

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.*

## VERIFICATION OF COMPOUNDING ACCURACY AND STERILITY

The compounding procedures and sterilization methods for CSPs correspond to correctly designed and verified written documentation in the compounding facility. Verification requires planned testing, monitoring, and documentation to demonstrate adherence to environmental quality requirements, personnel practices, and procedures critical to achieving and maintaining sterility, accuracy, and purity of finished CSPs. For example, sterility testing (see *Test for Sterility of the Product To Be Examined* under *Sterility Tests* ⟨71⟩) may be applied to specimens of low- and medium-risk level CSPs, and standard self-contained biological indicators (BI) shall be added to nondispensable specimens of high-risk level CSPs before terminal sterilization for subsequent evaluation to determine whether the sterilization cycle was ade-

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# TAB 2

# Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application

## Guidance for Industry

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Leah Christl (CDER) at 301-796-0869 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-7800.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**February 2015**
**Compliance**

# Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application

## Guidance for Industry

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
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# TABLE OF CONTENTS

**I. INTRODUCTION AND SCOPE ..... 1**
**II. BACKGROUND ..... 3**
**A. Biological Products ..... 3**
**B. Legal Framework for FDA's Regulation of Biological Products ..... 5**
**C. Sections 503A and 503B of the FD&C Act Do Not Exempt Biological Products from the Premarket Approval Requirements of the PHS Act or from Provisions of the FD&C Act ..... 5**
**D. Hospital and Health System Repackaging of Drugs In Shortage For Use in the Health System (Section 506F of the FD&C Act) ..... 6**
**III. POLICY ..... 7**
**A. General Conditions ..... 7**
**B. Mixing, Diluting, or Repackaging Licensed Biological Products ..... 7**
**C. Licensed Allergenic Extracts ..... 12**
**APPENDIX 1 — MICROBIAL CHALLENGE STUDY DESIGN ..... 16**

# Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application Guidance for Industry[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. INTRODUCTION AND SCOPE

This guidance sets forth FDA's policy regarding the mixing,[2] diluting, and repackaging[3] of certain types of biological products that have been licensed under section 351 of the Public Health Service Act (PHS Act) when such activities are not within the scope of the product's approved biologics license application (BLA) as described in the approved labeling for the product.[4] This guidance describes the conditions under which FDA does not intend to take action for violations of sections 351 of the PHS Act and sections 502(f)(1) and where specified, section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when a state-licensed pharmacy, a Federal facility, or an outsourcing facility[5] dilutes, mixes or repackages certain biological products without obtaining an approved BLA.

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[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] For purposes of this guidance, mixing means combining an FDA-licensed biological product with one or more ingredients. Not covered by this guidance is diluting or mixing a biological product at the point of care for immediate administration to a single patient after receipt of a patient specific prescription or order for that patient (e.g., diluting or mixing into a syringe to administer directly to the patient).

[3] For purposes of this guidance, repackaging means taking a licensed biological product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. As used in this guidance, the terms mixing, diluting, and repackaging describe distinct sets of activities with respect to a biological product.

[4] This guidance does not apply to blood and blood components for transfusion, vaccines, cell therapy products, and gene therapy products

[5] *"Outsourcing facility"* refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the FD&C Act. *See* FDA's draft guidance, *"Guidance for Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act."*

This guidance **does not address** the following:

- Biological products not subject to licensure under section 351 of the PHS Act (i.e., biological products for which a marketing application could properly be submitted under section 505 of the FD&C Act (see section 7002(e) of the Affordable Care Act)). The repackaging of biological products not subject to licensure under section 351 is addressed in a separate draft guidance document. [6]
- Products intended for use in animals. FDA will consider addressing this issue in a separate guidance document.
- Mixing, diluting, or repackaging biological products (other than allergenic extracts) by entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities; and preparation of allergenic extracts by entities that are not state-licensed pharmacies, Federal facilities, outsourcing facilities, or physicians (See additional information in section III.A. of this draft guidance document).
- Removing a biological product from the original container at the point of care for immediate administration to a single patient after receipt of a patient-specific prescription or order for that patient (e.g., drawing up a syringe to administer directly to the patient). FDA does not consider this to be "repackaging," for purposes of this guidance document.
- Upon receipt of a patient-specific prescription, a licensed pharmacy removing from one container the quantity of solid oral dosage form biological products necessary to fill the prescription and placing it in a smaller container to dispense directly to its customer.
- Mixing, diluting, or repackaging a licensed biological product when the product is being mixed, diluted, or repackaged in accordance with the approved BLA as described in the approved labeling for the product. FDA considers this to be an approved manipulation of the product.
- Mixing, diluting, or repackaging of blood and blood components for transfusion,[7] vaccines, cell therapy products, or gene therapy products (see footnote 4). The guidance does not alter FDA's existing approach to regulating the collection and processing of blood and blood components. In addition, FDA intends to consider regulatory action if licensed vaccines, cell therapy products, and gene therapy products are subject to additional manufacturing, including mixing, diluting, or repackaging, in ways not specified in the product's approved BLA as described in the approved labeling for the product.

As stated above, this guidance does not address the mixing, diluting, or repackaging of a biological product for which a marketing application could properly be submitted under section 505 of the FD&C Act (see section 7002(e) of the Affordable Care Act). Accordingly, the term

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[6] The repackaging of biological products approved under section 505 is addressed in a separate draft Guidance, "*Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities.*"

[7] The guidance does apply to licensed biological products that are plasma derived products, including recombinant and transgenic versions of plasma derivatives, mixed, diluted, or repackaged outside the scope of an approved BLA.

*"biological product"* as used in this guidance does not include products for which a marketing application can be or has been submitted under section 505 of the FD&C Act.

Section II of this guidance provides background on biological products and the legal framework for FDA's regulation of these products, and explains that sections 503A and 503B of the FD&C Act do not provide exemptions for mixing, diluting, or repackaging of biological products. Section III describes FDA's policy on mixing, diluting, or repackaging of certain licensed biological products that is not within the scope of the product's approved BLA as described in the approved labeling for the product.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## II. BACKGROUND

### A. Biological Products

The term "biological product" is defined in section 351(i)(1) of the PHS Act to mean:

> a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Biological products can be complex chains or combinations of sugars, amino acids, or nucleic acids, or living entities such as cells and cellular therapies. Biological products include therapeutic proteins, monoclonal antibodies, allergenic extracts, blood and blood derivatives, cell therapy products, and gene therapy products, preventive vaccines, and therapeutic vaccines. Generally, biological products have a complex set of structural features (e.g., amino acid sequence, glycosylation, folding) essential to their intended effect, and are very sensitive to changes to their manufacturing process, including, but not limited to, any manipulation outside of their approved container-closure systems. In addition, many biological products are particularly sensitive to storage and handling conditions and can break down or aggregate if exposed to heat and/or light, if dropped, or if shaken during storage and handling. Accordingly, diluting or mixing a biological product with other components, or repackaging a biological product by removing it from its approved container-closure system and transferring it to another container-closure system, is, in the absence of manufacturing controls, highly likely to affect the safety and/or effectiveness of the biological product.

Nevertheless, certain licensed biological products may need to be mixed or diluted in a way not described in the approved labeling for the product to meet the needs of a specific patient. For example, for some biological products there is no licensed pediatric strength and/or dosage form, so the product must be diluted for use in pediatric patients. In addition, there may be certain

circumstances where a person would repackage a licensed biological product by removing it from its original container and placing it into a different container(s), in a manner that is not within the scope of the approved BLA as described in the approved labeling for the product. Like other drugs, biological products are sometimes repackaged for various reasons including for pediatric or ophthalmic use. For example, a pediatric dialysis unit may repackage a larger quantity of a product into smaller aliquots so that the optimal dose may be administered to each pediatric dialysis patient being treated at that particular time.

Repackaging a drug or biological product could change its characteristics in ways that have not been evaluated during the approval process and that could affect the safety and effectiveness of the product. Improper repackaging of drug and biological products can cause serious adverse events. Of particular concern is the repackaging of sterile drugs, which are susceptible to contamination and degradation. For example, failure to properly repackage a sterile drug under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death. Repackaging practices that conflict with approved product labeling have led to product degradation resulting in adverse events associated with impurities in the product or lack of efficacy because the active ingredient has deteriorated. These risks are often even more acute for biological products due to their complex composition and sensitivity to variations in storage and handling conditions.

Cell and gene therapy products often contain viable cells or intact/active viral vectors. The manufacturing process for these products is complex and includes multiple controls to assure the purity or potency of the product and its safety and effectiveness. Many cell therapy products are cryopreserved, and the procedures for thawing and handling in preparation for administration described in the approved labeling must be followed to maintain the safety and effectiveness of the product. In addition, because these products are frequently implanted or administered intravenously and are not typically amenable to terminal sterilization, their microbiological safety is dependent largely on facility design, aseptic technique, and manufacturing protocols that are best controlled by robust quality systems.

Vaccines are manufactured using biological systems and supplied by manufacturers in single dose or multi-dose presentations. Unlike most other drugs and biological products, vaccines are administered to healthy individuals, including infants, to prevent disease. Vaccines may contain live attenuated organisms, inactivated organisms, or components of bacteria or viruses such as polysaccharides, inactivated toxins, or purified proteins. The manufacturing process for vaccines is complex and includes multiple controls to assure safety and effectiveness. Each single dose of a vaccine is formulated to deliver the correct quantity of active ingredient(s) to the recipient.

The policies in this guidance do not cover cell therapy products, gene therapy products, and vaccines. Because of the particularly sensitive nature of these products as described above, these categories of products must be prepared, and if applicable to that product's use, repackaged, under an approved BLA, in accordance with section 351 of the PHS Act.

The policies in this guidance also do not cover or alter FDA's existing approach to regulating the collection and processing of blood and blood components for transfusion. These activities are

currently conducted in FDA licensed or registered blood collection establishments and in hospital-based transfusion services regulated in part by the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments of 1988. In all instances, blood collection and processing is already subject to current good manufacturing practices (CGMP) under the existing statutory and regulatory framework for blood and blood components and will not be subject to the policies described here.

### B. Legal Framework for FDA's Regulation of Biological Products

Section 351(a)(1) of the PHS Act prohibits the introduction into interstate commerce of any biological product unless "a biologics license…is in effect for the biological product." For FDA to approve a BLA, the BLA must contain data to demonstrate that the biological product is safe, pure, and potent and that the facility in which the biological product will be manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe, pure, and potent. Because manufacturing controls are so important to ensuring the safety and effectiveness of biological products, FDA licensing of a biological product is based, in part, on an extensive review of chemistry and manufacturing controls data submitted by the applicant. This includes a thorough evaluation of the raw materials, drug substance, and drug product to ensure consistency in manufacturing and continued safety and effectiveness. In addition, other data are submitted and reviewed (e.g., stability and compatibility testing results) to establish the storage and handling conditions appropriate to ensure the safety, purity, and potency of the biological product.

A biological product that is mixed, diluted, or repackaged outside the scope of an approved BLA is an *unlicensed biological product* under section 351 of the PHS Act. For example, if a licensed biological product is diluted or mixed with components other than those described in the approved labeling for the product, or if it is removed from its original container-closure system and placed in a new container-closure system that is not described in the approved labeling for the product, these additional manufacturing steps would create a new, unlicensed biological product. To be legally marketed, the new biological product would have to be licensed on the basis of an approved BLA that includes, among other things, chemistry and manufacturing controls data.

### C. Sections 503A and 503B of the FD&C Act Do Not Exempt Biological Products from the Premarket Approval Requirements of the PHS Act or from Provisions of the FD&C Act

Section 503A of the FD&C Act exempts compounded drugs from sections 505 (concerning new drug approval of human drugs products), 502(f)(1) (concerning labeling of drug products with adequate directions for use), and 501(a)(2)(B) of the FD&C Act (concerning CGMP) provided that certain conditions are met, including that the drug is compounded pursuant to a prescription for an individually-identified patient from a licensed practitioner.

The Drug Quality and Security Act added a new section 503B to the FD&C Act. Under section 503B(b) of the FD&C Act, a compounder can register as an outsourcing facility with FDA. Drug products compounded under the direct supervision of a licensed pharmacist in an

outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act and the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act if the conditions in section 503B are met. Drugs compounded in outsourcing facilities are not exempt from the CGMP requirements of section 501(a)(2)(B).

Although sections 503A and 503B provide an exemption for certain compounded drugs from the requirement to obtain premarket approval under section 505 of the FD&C Act, they do not provide an exemption from the requirement to obtain premarket approval under section 351 of the PHS Act. Manufacturers of biological products must obtain an approved license under section 351(a) or (k) of the PHS Act. Thus, for purposes of sections 503A and 503B, a *drug* does not include any biological product that is subject to licensure under section 351 of the PHS Act. Accordingly, such biological products are not eligible for the exemptions for compounded drugs under sections 503A and 503B of the FD&C Act. In other words, the FD&C Act does not provide a legal pathway for marketing biological products that have been prepared outside the scope of an approved BLA.

### D. Hospital and Health System[8] Repackaging of Drugs In Shortage For Use in the Health System (Section 506F of the FD&C Act)

The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law in July, 2012, added section 506F to the FD&C Act. This section exempts certain hospitals within a health system from registration requirements in section 510 of the Act provided certain conditions are met, including that the drugs (including biological products) are, or have recently been, listed on FDA's drug shortage list[9] and are repackaged for the health system. Section 506F of the FD&C Act defines "repackaging," for purposes of that section only, as "divid[ing] the volume of a drug into smaller amounts in order to—(A) extend the supply of a drug in response to the placement of the drug on a drug shortage list under section 506E; and (B) facilitate access to the drug by hospitals within the same health system."

Section 506F of the FD&C Act has a termination clause that states "This section [506F] shall not apply on or after the date on which the Secretary issues a final guidance that clarifies the policy of the Food and Drug Administration regarding hospital pharmacies repackaging and safely transferring repackaged drugs [including drugs that are licensed biological products] to other hospitals within the same health system during a drug shortage." [10] These issues are addressed and clarified by this guidance, and the guidance on *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*. Therefore, when these guidances become final, section 506F of the FD&C Act will no longer apply.

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[8] For purposes of this guidance, the term *"health system"* refers to a collection of hospitals that are owned and operated by the same entity and that share access to databases with drug order information for their patients.

[9] See section 506F(b) (providing that the exemption may be available if, among other factors, the drug is repackaged (1) during any period in which the drug is listed on the drug shortage list under section 506E; or (2) during the 60-day period following any period described in paragraph (1)).

[10] See section 506F(d) of the FD&C Act.

## III. POLICY

Because biological products sometimes need to be mixed, diluted, or repackaged in ways not addressed in labeling approved for the product under section 351 of the PHS Act, but do not qualify for the exemptions in sections 503A or 503B of the FD&C Act, FDA has developed this guidance to explain the conditions under which FDA does not intend to take action when certain biological products are mixed, diluted, or repackaged in a manner not described in their approved labeling.

### A. General Conditions

This guidance addresses the mixing, diluting, or repackaging of a licensed biological product, not a biological product licensed for further manufacturing use only, or a bulk drug substance. The policies expressed in this guidance do not extend to any person or entity that mixes, dilutes, or repackages a biological product from any other starting material. Consistent with section 351 of the PHS Act, a manufacturer seeking to mix, dilute, or repackage a biological product licensed for further manufacturing use only, or a bulk drug substance, must first submit a BLA and obtain a license for the product.

Furthermore, the policies expressed in this guidance apply only to the mixing, diluting, or repackaging of certain licensed biological products, in accordance with the conditions specified in sections III.B and III.C of this guidance. Except as described in sections III.B and III.C, the agency will consider regulatory action if a licensed biological product is subject to additional manufacturing, including mixing, diluting, or repackaging, outside of the conditions specified in the approved labeling for the licensed product.

As described in section B, a biological product that is mixed, diluted, or repackaged outside the scope of an approved BLA is an unlicensed biological product under section 351 of the PHS Act. To be legally marketed, the new biological product would have to be licensed on the basis of an approved BLA, have labeling with adequate directions for use, and be made in accordance with biological product standards and CGMP requirements. Therefore, biological products that do not meet the conditions in this guidance, including 1) biological products that are mixed, diluted, or repackaged by entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities or 2) prescription sets of allergenic extracts that are not prepared by state-licensed pharmacies, Federal facilities, outsourcing facilities, or licensed physicians, must comply with requirements in the PHS Act, FD&C Act, and FDA regulations applicable to biological products manufactured by "conventional" manufacturers, including, but not limited to, biological product license requirements, and compliance with applicable standards and CGMP requirements.

### B. Mixing, Diluting, or Repackaging Licensed Biological Products

FDA does not intend to take action for violations of sections 351 of the PHS Act or 502(f)(1) of the FD&C Act if a state-licensed pharmacy, a Federal facility, or an outsourcing facility[11] mixes, dilutes, or repackages a biological product in accordance with the conditions described below, and any applicable requirements.[12] In addition, FDA does not intend to take action for violations of section 501(a)(2)(B) of the FD&C Act when a state-licensed pharmacy or a Federal facility mixes, dilutes, or repackages a biological product in accordance with the conditions described below, and any applicable requirements. Outsourcing facilities remain subject to applicable CGMP requirements.

The conditions referred to in the preceding paragraph are as follows:

1. The biological product that is mixed, diluted, or repackaged is an FDA-licensed biological product, not a biological product licensed for further manufacturing use only or a bulk drug substance.

2. The biological product is mixed, diluted, or repackaged in a state-licensed pharmacy, a Federal facility, or an outsourcing facility.

3. If the biological product is mixed, diluted, or repackaged in a state-licensed pharmacy or a Federal facility (but not an outsourcing facility), it is mixed, diluted, or repackaged after (a) the receipt of a valid prescription for an identified, individual patient directly from the prescribing practitioner, patient, or patient's agent; or (b) a written order in a patient's chart in a healthcare setting,[13] unless it is mixed, diluted, or repackaged (but not distributed) in advance of receipt of such a prescription or a written order in a patient's chart in a quantity that does not exceed the expected demand for the biological product within the beyond use date (BUD) on the product, based on a history of receipt of prescriptions or orders for such a biological product for that time period.

4. The biological product is mixed, diluted, or repackaged by or under the direct supervision of a licensed pharmacist.

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[11] As we discuss in section II of this guidance, biological products licensed under section 351 of the PHS Act are not eligible for the statutory exemptions offered by sections 503A or 503B of the FD&C Act, and if a facility registers as an outsourcing facility but only mixes, dilutes, or repackages such biological products, none of the products made at the facility will be eligible for the exemptions under section 503B. However, this guidance describes the conditions under which FDA does not intend to take action for violations of section 351 of the PHS Act and sections 501(a)(2)(B) and 502(f)(1) of the FD&C Act if such biological products are mixed, diluted, or repackaged at a state-licensed pharmacy, a Federal facility, or an outsourcing facility that compounds drug products in accordance with section 503B.

[12] Applicable requirements include, for example, the requirement that manufacturers not adulterate a biological product by preparing, packing , or holding the drug under insanitary conditions. See section 501(a)(2)(A) of the FD&C Act.

[13] Drugs produced by outsourcing facilities, including drugs that are also biological products, remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, a prescription drug, including a biological product, cannot be dispensed to a patient without a prescription.

5. Except as provided below for a single dose vial, the biological product is mixed, diluted, or repackaged in a way that does not conflict with the approved labeling for the licensed biological product.[14]

   For a biological product packaged in a single dose vial that is mixed, diluted, or repackaged into multiple units, the biological product is mixed, diluted, or repackaged in a way that does not conflict with the approved labeling, except for the statements designating the product as a single dose or single use product, and related language (e.g., discard remaining contents).[15]

6. As described in section II of this guidance, biological products are very susceptible to product quality concerns when mixed, diluted, or repackaged. For example, because biological products provide a rich media for microbial growth, they are particularly susceptible to microbial proliferation over time, if contaminated. Therefore, the mixed, diluted, or repackaged biological product is given a BUD that is not longer than the applicable BUD[16] below:

   a. If the biological product is mixed, diluted, or repackaged by a state-licensed pharmacy or a Federal facility, it is given a BUD that
      - is not longer than 4 hours, or is equal to the time within which the opened product is to be used as specified in the approved labeling, whichever is shorter; [17] or

      - is up to 24 hours if microbial challenge studies performed on the formulation of the diluted, mixed, or repackaged biological product in the type of container in which it will be packaged demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD. (See Appendix 1 for a description of microbial challenge study design.)

   b. If the biological product is mixed or diluted by an outsourcing facility, it is given a BUD that

[14] For example, if the approved labeling for the licensed biological product contains instructions for handling or storage of the product, the mixing, diluting, or repackaging is done in accordance with those instructions. Otherwise, it would be considered to be in conflict with the approved labeling for the licensed biological product.

[15] For example, Avastin (bevacizumab) is packaged in a single dose vial. This condition could be satisfied even if Avastin is repackaged into multiple single dose syringes despite the fact that the label of the approved product states, "Single-use vial…Discard unused portion." However, this condition would not be satisfied if Avastin is mixed, diluted, or repackaged in a manner that conflicts with other language in the approved labeling (e.g., regarding the appropriate diluent and storage conditions).

[16] The BUD timeframes in this condition begin from the time in which the container of the original biological product to be repackaged or to be used for mixing or diluting is punctured or otherwise opened ("opened product").

[17] The 4 hour BUD timeframe in this guidance is consistent with the labeling of many licensed biological products, which require the disposal of any product not used within 4 hours after the product has been reconstituted or the container has been entered. Where another timeframe is provided in the labeling, it is based on data generated under specific conditions by the product's manufacturer and submitted with the BLA. Such data are not available for products mixed, diluted, or repackaged outside the scope of a BLA, as described in this guidance.

- is not longer than 4 hours, or is equal to the time within which the opened product is to be used as specified on the approved labeling, whichever is shorter; or

- is up to 24 hours if microbial challenge studies performed on the formulation of the mixed or diluted biological product in the type of container in which it will be packaged demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD. (See Appendix 1 for a description of microbial challenge study design.)

c. If the biological product is repackaged by an outsourcing facility, it is given a BUD that
   - is not longer than 4 hours, or is equal to the time within which the opened product is to be used as specified on the approved labeling, whichever is shorter; or

   - is up to 24 hours if microbial challenge studies performed on the formulation of the repackaged biological product in the type of container in which it will be packaged demonstrate that microbial growth will not progress to an unacceptable level within the period of the BUD. (See Appendix 1 for a description of microbial challenge study design); or

   - does not exceed 5 days or the expiration date of the biological product being repackaged, whichever is shorter, provided that the outsourcing facility conducts adequate compatibility studies on the container-closure system (e.g., the syringe) of the repackaged biological product to demonstrate compatibility and ensure product integrity. (*See* Title 21, section 211.94 of the Code of Federal Regulations for regulations on drug product containers and closures). [18]

7. If the biological product is mixed, diluted, or repackaged in a state-licensed pharmacy or a Federal facility, it is done in accordance with the United States Pharmacopeia (USP) Chapter <797>, except the BUD is as specified in condition 6; if the biological product is mixed, diluted, or repackaged in an outsourcing facility, it is done in accordance with CGMP requirements, except the BUD is as specified in condition 6.

8. The biological product is not sold or transferred by an entity other than the entity that mixed, diluted, or repackaged the biological product. For purposes of this condition, a sale or transfer does not include administration of a biological product in a health care setting.

[18] This longer BUD reflects that outsourcing facilities must comply with CGMP requirements and are subject to FDA inspections on a risk-based schedule. Conditions maintained to comply with CGMP requirements provide greater assurance of the quality of manufacturing operations and the products that are produced at the facility. This longer BUD is not provided for mixed or diluted biological products because these activities are more likely to alter the characteristics of the biological product in ways that could harm patients, even if performed under CGMP conditions. To provide a sufficient basis for FDA to conclude that a longer BUD on a mixed or diluted product was justified, an outsourcing facility would need to submit a BLA that included data on the impacts of diluting or mixing the specific product.

9. The mixed, diluted, or repackaged biological product is distributed only in states in which the facility mixing, diluting, or repackaging the biological product meets any applicable state requirements.

10. If the biological product is mixed, diluted, or repackaged by an outsourcing facility:

    a. The label on the immediate container (primary packaging, e.g., the syringe) of the mixed, diluted, or repackaged biological product includes the following:
        i. The statement "This biological product was mixed/diluted by [name of outsourcing facility]," or "This product was repackaged by [name of outsourcing facility]", whichever statement is appropriate
        ii. The address and phone number of the outsourcing facility that mixed, diluted, or repackaged the biological product
        iii. The proper name of the original biological product that was mixed, diluted, or repackaged
        iv. The lot or batch number assigned by the outsourcing facility for the mixed, diluted, or repackaged biological product
        v. The dosage form and strength of the mixed, diluted, or repackaged biological product
        vi. A statement of either the quantity or the volume of the mixed, diluted, or repackaged biological product, whichever is appropriate
        vii. The date the biological product was mixed, diluted, or repackaged
        viii. The BUD of the mixed, diluted, or repackaged biological product
        ix. Storage and handling instructions for the mixed, diluted, or repackaged biological product
        x. The National Drug Code (NDC) number of the mixed, diluted, or repackaged biological product, if available[19]
        xi. The statement "Not for resale," and, if the biological product is distributed by an outsourcing facility other than pursuant to a prescription for an individual identified patient, the statement "Office Use Only"
        xii. If included on the label of the FDA-licensed biological product from which the biological product is being mixed, diluted, or repackaged, a list of the active and inactive ingredients, unless such information is included on the label for the container from which the individual units are removed, as described below in 10.b.i; and if the biological product is mixed or diluted, the label of the mixed or diluted product includes any ingredients that appear in the mixed or diluted product in addition to those ingredients that are on the original FDA-licensed biological product.

    b. The label on the container from which the individual units are removed for administration (secondary packaging, e.g., the bag, box, or other package in which the mixed, diluted, or repackaged biological products are distributed) includes:

[19] The NDC number of the original licensed biological product should not be placed on the mixed, diluted, or repackaged biological product.

i. The active and inactive ingredients, if the immediate product label is too small to include this information
ii. Directions for use, including, as appropriate, dosage and administration, and the following information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.

c. Each mixed, diluted, or repackaged biological product is also accompanied by a copy of the prescribing information that accompanied the original FDA-licensed biological product that was mixed, diluted, or repackaged.

d. The mixed, diluted, or repackaged biological product is included on a report submitted to FDA each June and December identifying the drug products made by the outsourcing facility during the previous 6-month period, including: a notation that this is a mixed, diluted, or repackaged biological product; the active ingredient; the source of the active ingredient; NDC number of the source ingredient, if available; strength of the active ingredient per unit; the dosage form and route of administration; the package description; the number of individual units mixed, diluted, or repackaged[20]; and the NDC number of the final product, if assigned.[21]

e. The outsourcing facility reports serious adverse events to FDA that may be associated with its mixed, diluted, or repackaged biological products.

### C. Licensed Allergenic Extracts

FDA recognizes that there are circumstances in which licensed allergenic extracts 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. Such combinations are commonly referred to as prescription sets.[22] For the purpose of this guidance a *prescription set* is defined as a vial or set of vials of premixed licensed standardized and non-standardized allergenic extracts for subcutaneous immunotherapy diluted with an appropriate diluent prepared according to instructions from a prescription or order by a licensed physician for an individual patient.

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[20] Currently, FDA's electronic drug reporting system is not configured to accept additional information that is specific to biological products, such as license number. In the future, FDA intends to modify the system to accept this information.

[21] FDA has issued a draft guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* , which prescribes how human drug compounding facilities are to submit drug product reports to FDA. Although this guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the biological products they mixed, diluted, or repackaged.

[22] Under 21 CFR 610.17, licensed biological products must not be combined with other licensed biological products; either therapeutic, prophylactic or diagnostic, except as covered by a license obtained for the combined product. All mixes of allergenic extracts that are not prescription sets must be the subject of an approved BLA, or have in effect an investigational new drug application.

FDA does not intend to take action for violations of section 351 of the PHS Act or section 502(f)(1) of the FD&C Act if a physician, state-licensed pharmacy, a Federal facility, or outsourcing facility prepares prescription sets of allergenic extracts in accordance with the conditions described below, and any applicable requirements.[23]

In addition, with respect to a prescription set prepared in accordance with the following conditions and any applicable requirements, FDA does not intend to take action for violations of section 501(a)(2)(B) of the FD&C Act when the prescription set is prepared by a physician, state-licensed pharmacy, or a Federal facility in accordance with the conditions described below; outsourcing facilities remain subject to applicable CGMP requirements.

The conditions referred to in the preceding paragraph are as follows:

1. The prescription set is prepared from FDA-licensed allergenic extracts and appropriate diluents.

2. The prescription set is prepared in a in a physician's office, state-licensed pharmacy, a Federal facility, or outsourcing facility.

3. If the prescription sets are prepared in a physician's office, state-licensed pharmacy, or a Federal facility (but not an outsourcing facility), each set is prepared after (a) the receipt of a valid prescription for an identified, individual patient directly from the prescribing practitioner, patient, or patient's agent; or (b) a written order in a patient's chart, unless it is prepared in advance of receipt of such a prescription or a written order in a quantity that does not exceed the expected demand for that prescription set within the BUD for the product, based on a history of receipt of prescriptions or orders for such a prescription set for that time period. If the prescription sets are prepared in an outsourcing facility, those sets are prepared either after, or in anticipation of, receiving valid prescriptions for an identified, individual patient or a written order in a patient's chart.

4. The prescription set is distributed to a physician or to a health system for use within the health system only after the receipt of a valid prescription for an identified, individual patient or a written order in a patient's chart.

5. The prescription set is prepared in a way that does not conflict with approved labeling of the licensed biological products that are part of the prescription set.[24]

6. The BUD for the prescription set is no later than the earliest expiration date of any allergenic extract or any diluent that is part of the prescription set.

[23] See note 12.
[24] See note 15.

7. If the prescription set is prepared in a state-licensed pharmacy or a Federal facility, or in a physician's office, it is prepared in accordance with USP Chapter <797>, except the BUD is as specified in condition 6; if the prescription set is prepared in an outsourcing facility, it is prepared in accordance with applicable CGMP requirements, except the BUD is as specified in condition 6.

8. The prepared prescription set is not sold or transferred by an entity other than the entity that prepared the prescription set. For purposes of this condition, a sale or transfer does not include administration of a prescription set in a health care setting.

9. The prescription set is distributed[25] only in states in which the facility preparing the prescription set meets any applicable state requirements.

10. If the prescription set is prepared by an outsourcing facility:

    a. The label on the immediate container(s) (primary packaging) of the prescription set includes the following:
        i. The patient's name as identified on the prescription
        ii. The statement "This prescription set was prepared by [name of outsourcing facility]"
        iii. The address, and phone number of the outsourcing facility that prepared the prescription set
        iv. The identity of each allergenic extract in the prescription set, and the quantity of each
        v. The dilution of each dilution vial
        vi. The lot or batch number of the prescription set
        vii. The date the prescription set was prepared
        viii. The BUD of the prescription set
        ix. Storage and handling instructions for the prescription set
        x. The statement "Not for resale"

    b. The label of the container from which the individual units of the prescription set are removed for administration (secondary packaging) includes the following information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.

    c. Each prescription set also is accompanied by instructions for use and the FDA approved package insert for each allergenic extract.

    d. The prescription set is included in a report submitted to FDA each June and December identifying the drug products made by the outsourcing facility during the previous 6-month period, including: a notation that this is a biological product; the active ingredient(s); source of the active ingredient(s); NDC number of the source ingredient(s), if available; strength of the active ingredient(s) per unit; the dosage

[25] *Distribution* means that the prepared prescription set has left the facility in which it was prepared.

form and route of administration; the package description; the number of individual units produced; and the NDC number of the final product, if assigned.[26]

e. The outsourcing facility reports serious adverse events to FDA that may be associated with its prescription sets.

[26] FDA has issued a draft guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* , which prescribes how human drug compounding facilities are to submit drug product reports to FDA. Once finalized, that guidance will represent the Agency's thinking on that topic. Although this guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the prescription sets they prepared.

## APPENDIX 1 – MICROBIAL CHALLENGE STUDY DESIGN

The following design recommendations for product growth promotion studies should be followed to extend the BUD to up to 24 hours for a mixed, diluted, or repackaged biological product as referenced in Section II. B.

Microbial challenge studies are designed to demonstrate that the product in question does not support adventitious microbial growth under the proposed storage conditions. Each facility would conduct a microbial challenge study at least once for each mixed, diluted, or repackaged biological product, to demonstrate that the microbial quality of the biological product mixed, diluted, or repackaged by that facility can be ensured. The microbial challenge study should be repeated if the formulation or the container-closure system is changed. The studies should be accurately documented and records maintained for inspection.

The challenge microbes should include the panel provided in USP<51> Antimicrobial Effectiveness Testing.[27] These strains represent the species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus brasiliensis* (formerly *Aspergillus niger*). It should also incorporate typical skin microflora and nosocomial agents to simulate the types of flora that may contaminate a drug product in a healthcare setting. Finally, the challenge should include strains of the tribe *Klebsielleae*, as they have been shown to proliferate in infusion products.[28]

Individual containers of the mixed, diluted, or repackaged biological product should be inoculated with each challenge organism, with each container receiving one type of organism. The inoculum size should be small but also measurable and repeatable. For example, if a membrane filtration method is used to quantify the number of organisms, an inoculum size of fewer than 100 CFU/mL is appropriate.

Following inoculation of the final product with the challenge organisms, the test units should be stored at the temperature(s) described in the biological product's labeling. Samples should be removed periodically throughout the duration of the study for determination of microbial count for up to 72 hours (3 times the maximum BUD). To support a BUD of 24 hours, each challenge organism should demonstrate no increase from the initial count (where *no increase* is defined as not more than 0.5 log10 unit higher than the initial inoculum at any time point up to 72 hours) and no evidence of growth. As explained in the example below, data from a study of 72 hours' duration should be examined for trending and to establish a maximum storage time of up to 24 hours at a specified temperature.

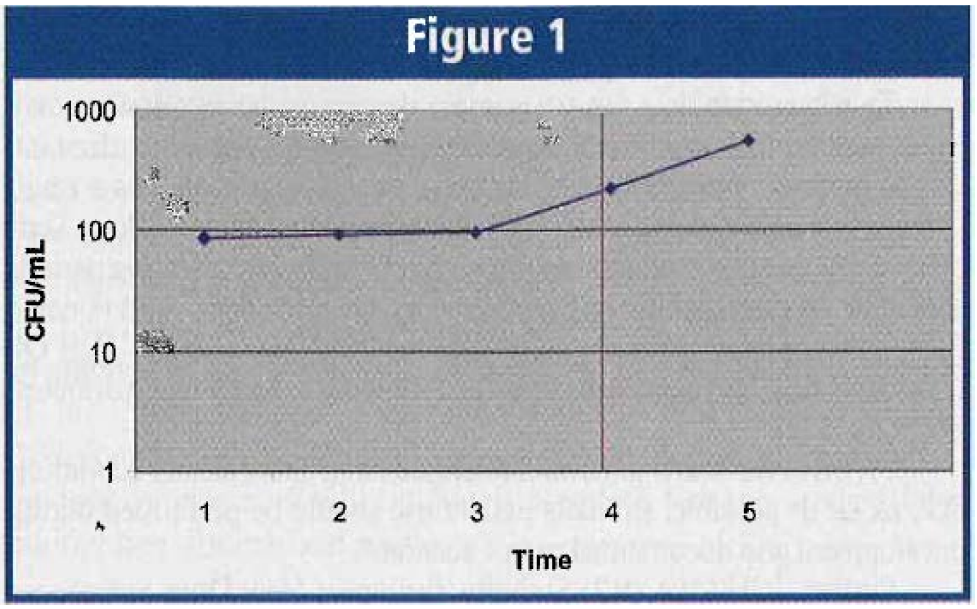
**Example: Determination of Microbial Growth**

[27] USP51/NF26. United States Pharmacopeial Convention, 2008.
[28] See, Mahl, M.C., et al. Nitrogen Fixation by Members of the Tribe *Klebsielleae*, *J. Bacteriol.*, 1965, 89(6): 1482; Maki, D., et al., Infection Control in Intravenous Therapy, *Annals of Internal Medicine*, 1973, 79: 867.

574 The following table represents data from a hypothetical microbial challenge experiment where
575 the inoculum is less than 100 CFU/mL, and the requested maximum hold time is equivalent to
576 Time Point 4.
577

| Time | Microbial Count (CFU/mL) | Log of Microbial Count |
|---|---|---|
| 1 | 88 | 1.9 |
| 2 | 95 | 2 |
| 3 | 98 | 2 |
| 4 | 220 | 2.3 |
| 5 | 552 | 2.7 |

578
579
580 These data reflect *no increase* from the initial count through Time Point 4. However, as
581 illustrated in Figure 1 below, the semi-logarithmic graph of CFU/mL vs. Time shows clear
582 evidence of growth of the challenge organism at Time Point 4.
583




584
585
586 Thus, a maximum hold time equivalent to that of Time Point 4 would pose potential risk to the
587 microbiological quality of the hypothetical mixed, diluted, or repackaged biological product, and
588 the acceptable BUD would be set at one-third of Time Point 3. It is also important to note that, if
589 the experiment were concluded at Time Point 4, the ability to predict the trend of the data would
590 be lost. As presented in the graphic, the growth trend appears to signal the start of log-phase
591 growth, which could occur earlier or later with different strains of a given species. Such growth
592 would produce exponential increases in the microbial population that pose significant risk to
593 patients. This concern is the reason for periodic sampling when determining microbial
594 concentration.

# TAB 3

Otolaryngology–Head and Neck Surgery (2007) 137, 243-245

ORIGINAL RESEARCH

# Allergen vial mixing and immunotherapy: Risks of infections and vial contamination

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**OBJECTIVE:** To study the risks of vial contamination and infection associated with immunotherapy vial mixing and injection.
**STUDY DESIGN:** Retrospective review of patient immunotherapy records from January 2000-June 2006.
**SETTING:** Tertiary care outpatient otolaryngology clinic.
**RESULTS:** Two hundred seventy-two patients were given 26,795 injections (average of 98.5 injections per patient). Three hundred ninety-nine total local reactions were reported by the subjects (1.49%; 95% CI 1.34%-1.63%). The majority (82%) of the local reactions occurred during escalation dosing. There were 23 episodes of wheezing or shortness of breath after injections (9.6 of 10,000). No patients experienced anaphylaxis. There was no documented skin or systemic infections as a result of the allergy injections. None of the patients experienced fever, discharge from the injection site, cellulitis, or required antibiotics.
**CONCLUSION:** This review of immunotherapy records revealed no complications of infection from the preparation and administration of immunotherapy performed in an outpatient clinic.
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An estimated 7 to 10 million allergy immunotherapy injections are administered annually in the United States,[1] and typically the immunotherapy vials are prepared and administered in a physician's office. Immunotherapy has been widely practiced for decades, with the majority of practitioners performing immunotherapy vial mixing in office without the use of a hood or a clean room. However, medical practitioners are being held to increasingly stringent standards of practice by regulatory agencies, including allergy vial mixing. There have been recent attempts to put forth new guidelines that may impact allergen vial immunotherapy on both the federal and state level. The United States Pharmacopeia (USP), a nonprofit, volunteer, nongovernmental, standard-setting organization with pharmacists comprising the majority of its volunteers, issued USP <797>, a standard on medication compounding of sterile preparations in 2003.[2] This standard requires the use of a dedicated clean room, ventilation hood, air sampling, surface sampling, and formal testing of mixing personnel. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) considers USP <797> a valuable guideline for safe practices that describe a best practice of establishing safe compounding of sterile medications.[3] The Virginia 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.

Standardization guidelines to ensure patient safety that are based on scientific evidence are welcomed by both patient and physician. However, there is a lack of scientific literature that discusses the risk of local or systemic infections from allergen immunotherapy, or the need for a clean room or a hood. The purpose of our study is to determine the risks of vial contamination and infection associated with immunotherapy vial mixing and injection from current mixing practices. To the authors' knowledge, this is the first study to examine, in particular, risks of infection from current vial mixing and administration practices.

## STUDY DESIGN

We performed a retrospective review of the immunotherapy injection records of all patients receiving immunotherapy injections at the Southern Illinois University otolaryngology clinic from January 2000-June 2006 after receiving approval from the local human subjects institutional review board. The immunotherapy records contained information regarding antigens contained in the vial, date of vial mixing, as well as date of injection, amount of injection, and location of injection (left or right arm). Reactions from injections were also recorded in the immunotherapy records. The injections were administered from vials mixed at the clinic in a dedicated mixing space. These vials were mixed by using sterile technique, but without the use of a sterile hood or a clean room, as described by King et al.[4] Charts were reviewed with particular attention to possible local or systemic reactions from immunotherapy. Information was also reviewed from the patient's clinic chart and hospital records regarding possible sequelae from immunotherapy.

Received September 18, 2006; accepted February 9, 2007.

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doi:10.1016/j.otohns.2007.02.012

## RESULTS

Over a 6-year period, 272 patients were given 26,795 injections (average of 98.5 injections per patient). Of these injections, 23,981 were subcutaneous injections of immunotherapy varying in volume from 0.05 to 0.5 mL. The remaining 2814 injections were vial tests, in which a small volume from a newly mixed vial was injected intradermally to form a 4-mm wheal. Immunotherapy patients were given instructions when starting immunotherapy to report local reactions, which are defined as "an area of firmness (not necessarily redness) at the injection site larger than a 50 cent piece persisting for at least 24 hours"[5]; instructions were also given to report any respiratory or systemic reactions. Patients were observed for 20 minutes postinjection in the office. Three hundred ninety-nine total local reactions were reported by the subjects (1.49%; 95% CI 1.34%-1.63%). One hundred thirty-three of the 272 subjects (49%) had reported at least one local reaction. Sixty-one percent of the local reactions were described as being larger than a half-dollar in size; in 39 percent of local reactions patients were unable to clearly quantify size and recorded the reaction as local reaction of unknown size. The majority (82%) of the local reactions occurred during escalation, with 18 percent occurring during maintenance dosing. There were 23 episodes of wheezing or shortness of breath after injections (9.6 of 10,000). There were no reports of anaphylaxis. In 1 patient with multiple local reactions, the immunotherapy serum was sent for bacterial culture. The culture was negative and the patient continued to receive injections from that vial without further difficulty after dose adjustment. There were no documented skin or systemic infections as a result of the allergy injections.

Follow-up of these patients ranged from 5 to 60 months, during which time the patient was seen every 1 to 3 weeks. In the escalation phase, during which 82 percent of local reactions occurred, patients were seen weekly. None of the patients experienced fever, discharge from the injection area, or cellulitis. No patients required antibiotics or medical treatment for infection.

## DISCUSSION

Many papers do exist that discuss the safety of immunotherapy from the standpoint of anaphylaxis and systemic reactions.[6-9] Other papers discuss the use of glycerin as a preservative in allergen extracts and immunotherapy vials, but do not discuss the possible bacteriostatic properties of glycerin or phenol, which are included in the immunotherapy vials.[10-12] None of these papers discuss risk of infection, local or systemic. Our retrospective review of our immunotherapy injection records revealed no evidence of local or systemic infection transmitted by our clinic's current method of immunotherapy mixing and administration.

Our clinic mixes vials using sterile technique, but without the use of a sterile hood or a clean room, as described by King et al.[4] Commercially available stock vials of antigen from Antigen Laboratory (Liberty, MO) are stored in a refrigerator at 4°C. These vials contain antigen in 50 percent glycerin. The vial rubber stopper is cleaned with a 70 percent isopropyl alcohol pad, and then an aliquot of antigen is removed from this stock bottle with a 1-mL syringe and 26-gauge needle. Commercially available sterile injection vials with rubber tops are used for individual patient immunization preparations. These vials are cleaned with fresh 70 percent isopropyl alcohol pads. The previously removed antigen is then injected into the sterile patient vial. Several different antigens may be injected into these vials and diluted with sterile 0.4 percent phenolated saline buffered to pH 7.4 in a similar manner. Then 25 percent or 50 percent glycerin may be injected into the patient vial to bring the glycerin content to 10 percent. The injection is then drawn into a small-gauge (27-gauge) syringe and administered subcutaneously after the skin is prepped with 70 percent isopropyl alcohol. Doses range in volume from 0.05 to 0.5 mL. Vials are typically remixed once every 10 weeks while in the buildup phase of immunotherapy, with all vials marked with a 3-month expiration date. A small test dose, the vial test, is given from a newly mixed vial intradermally to form a 4-mm wheal prior to administration of a dose of immunotherapy from the vial. The vial is diluted 5-fold if there is a vial test in which the wheal increases in size to greater than 13 mm in 10 minutes, or discarded and remixed if there is a systemic reaction with the test dose. Patients are seen very frequently during immunotherapy, so there is repeated, short-term follow-up. Patients typically receive weekly injections during the first year of immunotherapy, every other week injections the second year, and monthly injection from years 3 to 5. Patients are monitored in the clinic for 20 minutes after injection. Patients are instructed to report local reactions, an area of induration the size of a half-dollar or greater and persisting for greater than 24 hours; they are also told to report any systemic reactions and given an EpiPen (DEY Napa, CA) with directions on use. Local and systemic reactions are typically treated by dose adjustment in the immunotherapy to a previously tolerated dose by decreasing the volume of injection from the same vial, and then increasing doses on an escalation schedule or back to a maintenance dose at subsequent visits.

Our review found local reactions greater than a half-dollar in size in 0.91 percent (245 of 26,795) and another 0.57 percent in which there were local reactions in which patients were unable to quantify the size (154 of 26,795). Wheezing or shortness of breath was reported in 0.086 percent (23 of 26,795). There were no reports of anaphylaxis in our review. Previous recent studies report local reactions in 3.16 percent and 8.3 percent; systemic reactions were present in 0.13 percent and 2.2 percent.[13,14]

As background for this project, the authors performed a PubMed search of the English medical literature to see if data existed on infection rates for any series of intradermal

or subcutaneous injections. The assistance of a medical reference librarian was also enlisted in searching the medical and nursing literature as well. The infection control departments of 2 hospitals were contacted, and 1 hospital's regulatory affairs office to see if any internal data existed. These efforts yielded no published or internal data on infections rates following repeated subcutaneous or intradermal injections in healthy individuals.

The current series is limited in that it is a retrospective review. Reports of local reactions relied on patient self-reporting at the next visit after the reaction occurred. Self-reporting of patients may distort the true incidence of significant local reactions. Also, there were no details available on time of onset of local reactions or physical examination of local reactions, because information reviewed was from patient self-reporting of reactions that occurred in between regular immunotherapy intervals. However, the fact remains that no patient required medical treatment for infection from immunotherapy in this series. Future, prospective studies would be helpful to further study the risks of infection transmission from allergy immunotherapy and vial mixing.

The immunotherapy method used by our clinic is typical of many practitioners. The lack of reports of infectious complications from immunotherapy in the literature and in our current study suggests that infection from immunotherapy is not a clinically significant problem.

## CONCLUSION

This retrospective review of immunotherapy records reveals no complications of infection from the preparation and administration of immunotherapy performed in an outpatient clinic.

## ACKNOWLEDGMENT

The authors would like to acknowledge Larry Hughes, PhD, for his statistical support for this project.

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## FINANCIAL DISCLOSURE

None.

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# TAB 4

Otolaryngology–Head and Neck Surgery (2008) 139, 195-197

ORIGINAL RESEARCH—ALLERGY

# The safety of multi-dose vials in allergy immunotherapy

**Sandra Y. Lin, MD, P. Chase Lay, MD, Larry F. Hughes, PhD,** and **Richard Bass, MD,** Baltimore, MD; and Springfield, IL

**OBJECTIVE:** To prospectively evaluate the risks of vial contamination after routine clinical use of multiple-dose vials for immunotherapy.

**STUDY DESIGN:** Prospective observational study of immunotherapy vial cultures from June 2007 to January 2008.

**SETTING:** Tertiary care outpatient otolaryngology clinic.

**RESULTS:** Over an 8-month period, 136 consecutive vials were cultured for aerobic and anaerobic bacteria at the 3-month expiration date after regular use in an outpatient allergy clinic and dispensation of multiple doses of injection immunotherapy from each vial. All vials had negative cultures.

**CONCLUSION:** Immunotherapy vials are at low risk to undergo contamination in routine use. Important factors include aseptic technique, bacteriostatic agents, and expiration dating.

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Nosocomial infections are one of the serious concerns facing health care today, with increasing resources devoted to infection-control programs. Multiple-dose vials for injectable medications are a potential source of infection. In the allergy office, multidose immunotherapy vials are prepared for a specific patient, with numerous doses administered from that vial to that same patient over a period of several weeks to months. The vials are refrigerated between use, and the injections withdrawn with a sterile syringe after prepping the rubber stopper top with isopropyl alcohol. The injections are administered subcutaneously to patients by health care personnel after preparing the skin with alcohol. Current recommendations for vial mixing emphasize the importance of listing the name of one specific patient, with a beyond-use date and storage temperature range that is assigned based on manufacturers' recommendations or peer review publications (www.usp.org); the addition of bacteriostatic substances to the vials such as 0.25 percent phenol or 20 percent glycerin is also recommended.[1]

Although an estimated 10 million immunotherapy injections are administered annually in the United States, very little in the scientific literature had been published addressing the infection control risks of immunotherapy. One retrospective review of 272 patients over 6 years receiving 26,795 immunotherapy injections found no complications of infection from the administration of immunotherapy injection performed in an outpatient clinic.[2] However, to the authors' knowledge, there are no prospective studies looking at the possible infection risks associated with the multidose use of immunotherapy vials. The purpose of this current study was to prospectively evaluate the risks of vial contamination after the repeated use of multiple-dose vials for immunotherapy. One hundred thirty-six consecutive vials were cultured at the 3-month expiration date after regular use in an outpatient allergy clinic and dispensation of multiple doses of injection immunotherapy from each vial.

## STUDY DESIGN

A prospective study of immunotherapy vials prepared and administered at the Southern Illinois University otolaryngology clinic from June 2007 to January 2008 was performed after approval from the local human subjects' institutional review board. Immunotherapy vials were prepared in the otolaryngology clinic in standard fashion by using an aseptic technique as described by King et al.[3] A custom vial is prepared for each patient based on allergy skin or in vitro testing results. Several different antigens may be injected into these vials and diluted with sterile 0.4 percent phenolated saline buffered to pH 7.4 in a similar manner. Then, 25 percent or 50 percent glycerin is injected into the patient vial to bring the glycerin content to a minimum of 10 percent. The injection is then drawn into a small-gauge syringe (27 G) after prepping the rubber stopper top with 70 percent isopropyl alcohol and administered subcutaneously after the skin is prepped with 70 percent isopropyl alcohol. Doses range in volume from 0.05 to 0.5 mL. Vials are typically remixed once every 10 weeks while in the buildup phase of immunotherapy, with all vials marked in this clinic with a 3-month expiration date.

One hundred thirty-six consecutive vials were cultured at the time of expiration over an 8-month period after multiple doses were given from each vial per patient in routine clinic

Received April 8, 2008; revised April 29, 2008; accepted May 6, 2008.

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doi:10.1016/j.otohns.2008.05.013

use for immunotherapy. Expired vials were cultured by using standard culture techniques and transported to the microbiology laboratory in a hermetically sealed ACT II tube (Remel, Lenexa, KS; ACT II collection vial, catalog # 12402) with aerobic-anaerobic culture medium. A total of 136 vials were prepared, cultured, and examined by a single-certified microbiology laboratory staff member. The results were reported after 5 days of incubation in a polymicrobial sheep, chocolate, and brucella media that facilitates both aerobe and anaerobe growth (Remel, Lenexa, KS; tryptic soy agar plates with 5% sheep blood, catalog # R01202). Anaerobic plates were incubated at 37°C in a closed container with a gas-generating pouch system (Becton Dickinson, Franklin Lakes, NJ; GasPak EZ Gas Generating Pouch System, catalog # 260683) to create an anaerobic environment.

## RESULTS

One hundred thirty-six consecutive expired immunotherapy vials were cultured after routine use for immunotherapy. All culture results were negative. The smallest proportion of positive vials with a 95 percent confidence interval that excludes 0 would be 0.037 (5/136). Although it is impossible to prove a 0 percent contamination rate, we can conclude with 95 percent confidence that the true proportion of contaminated vials would be equal to or less than 3.7 percent given the sample size of 136. To increase the precision (decrease the 95% confidence interval) to 2 percent would require a sample size of 315, 1.5 percent would require 500, 1 percent would require 1500, and 0.5 percent a sample size of 4425. The sample size of 136 was chosen because of its proximity to the inflection point in the sample size, alluded to earlier, and what was thought to be a clinically significant contamination rate. The calculations were performed with the assistance of Pass 2005 (NCSS, Kaysville, Utah).[4]

## DISCUSSION

Multidose vials, or multiple-use containers of injectable medications, can be found throughout hospitals and clinics in the United States. Multidose vials describe a vial in which antibacterial preservatives are present and in which the vial may be used more than once. They are commonly used in patient care but can be a source of serious infections when these vials become infected. For example, there are reports of hepatitis C transmission[5] from multidose vial use for general anesthesia and in saline flushes.[6] *Serratia marcescens* bloodstream infections were reported in a surgical ward from contaminated multidose vials[7] and an outbreak of streptococcal abscesses after the administration of diphtheria-tetanus toxoid-pertussis vaccines from contaminated multidose vials.[8]

An outpatient setting in which multidose vials are used frequently is the allergy clinic in which patients receive multiple injections from a multidose vial mixed specifically for that single patient to use repeatedly. A retrospective review of over 26,000 immunotherapy injections showed no evidence of infectious complications.[2] However, this current study differs in that vials are cultured for evidence of contamination after routine use with multiple doses withdrawn for immunotherapy, with all 136 expired vials negative for aerobic and anaerobic contaminants.

Previous studies have examined the risks of multidose vial contamination in the patient-care setting. Studies of multidose vial contamination rates range from 0.4 percent to 1.4 percent.[9-11] Factors thought to be important in contamination risks include the number of punctures, rubber closure characteristics, use of aseptic technique, injection of air into the vial before removal of the solution, length of storage, and antimicrobial activity of bacteriostatic agents.[12] In our study, there was emphasis on the aseptic technique, the addition of 0.4 percent phenol and 10 percent glycerin added for bacteriostasis, and clearly marked expiration dates. None of the 136 multiple-dose vials in our study had positive cultures.

## CONCLUSION

Our results suggest that multiple-dose immunotherapy vials have a low risk of contamination in routine use; in fact, none of the vials cultured at the time of expiration were positive in this study. Important factors to consider in decreasing potential contamination include the use of the aseptic technique for mixing, aseptic-injection techniques, the addition of bacteriostatic agents, and a clear expiration date.

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## AUTHOR CONTRIBUTIONS

**Sandra Y. Lin,** study design, data, writer; **P. Chase Lay,** study design, data, writer; **Larry F. Hughes,** study design, writer, statistics; **Richard Bass,** study design, writer.

## FINANCIAL DISCLOSURE

None.

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# TAB 5

# Antibacterial properties of additives used in injection immunotherapy

Kevin C. Gilbert, MD[1], Vidya Sundareshan, MD[2], Richard M. Bass, MD[1], Sandra Y. Lin, MD[3]

***Background:*** Previous studies have reviewed the safety of preparing and administering allergy injection immunotherapy in a physician's office, and showed no evidence of infectious complications. The current study examines the antimicrobial properties of the common additives used in preparation of multidose immunotherapy vials.

***Methods:*** Vials were prepared with varying concentrations of glycerin (0-25%), phenol (0-0.4%) and combinations of glycerin with phenol. A standard inoculum of *Staphylococcus aureus* was introduced in each vial and incubated. Optical densities were measured and colony counts were performed at 24 and 48 hours. Follow-up broth microdilution assays were performed using varying inocula of bacteria and the highest concentrations of additives to determine the number of bacteria for which these solutions were bacteriostatic and/or bactericidal. Optical densities were measured and colony counts were performed as in the vial assays.

***Results:*** All vials with varying dilutions of glycerin, phenol, and their combination showed bacterial growth with the standard inoculum of *Staphylococcus aureus*. Visible turbidity and optical density were inversely related to additive concentration. Follow-up microdilution assays with differing concentrations of bacteria demonstrated bactericidal activity with inocula of $1 \times 10^3$ colony forming units (CFU) of *Staphylococcus aureus* at clinically used concentrations of glycerin and phenol.

***Conclusion:*** Higher concentrations of additives show better inhibition of bacterial growth. Solutions containing glycerin showed superior bactericidal activity than those containing only phenol. At concentrations of additives used in preparing allergy immunotherapy vials, antibacterial effects were observed with inoculation of $1 \times 10^3$ CFU or less of *Staphylococcus aureus*. © 2011 ARS-AAOA, LLC.

*Key Words:*
cutaneous drug administration; drug preparation; immunologic densitization; immunotherapy; in vitro; risk assessment

***How to Cite this Article:***
**Gilbert KC, Sundareshan V, Bass RM, Lin SY. Antibacterial properties of additives used in injection immunotherapy. *Int Forum Allergy Rhinol*, 2012; 2:135–138**

An estimated 7 to 10 million allergy immunotherapy injections are administered annually in the United States.[1] Immunotherapy vials are typically mixed and administered in a physician's office in this country. Allergy immunotherapy in injection form has been practiced for close to a century. Injection immunotherapy enjoys a long history as an effective tool in treating allergic disease.

Approximately 5 years ago, immunotherapy multidose vials came under greater scrutiny in regard to possible risks of transmission of infection and the safety of immunotherapy prepared and dosed in an office setting was questioned. Three studies have subsequently examined the risk of infection and vial contamination associated with immunotherapy vial mixing and injection performed in a physician's office. These studies have shown no evidence of increased infection risk from injection immunotherapy prepared in an otolaryngic allergy clinic.[2–4] The first study retrospectively reviewed 26,795 injections and showed no evidence of infection.[2] The second and third studies were prospective, controlled, single-blinded studies looking at vials prepared in the office using sterile technique vs those prepared under a ventilation hood for any microbiological evidence of contamination. These studies found no significant risk to patients with either preparation method.[3,4]

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Presented at the American Academy of Otolaryngic Allergy Annual Meeting, September 10, 2011, San Francisco, CA.
Funding sources for the study: American Academy of Otolaryngic Allergy Foundation.
Potential conflict of interest: None provided.

Received: 22 August 2011; Revised: 4 October 2011; Accepted: 11 October 2011
DOI: 10.1002/alr.20105
View this article online at wileyonlinelibrary.com.

**TABLE 1.** Protocol showing concentrations of additives used in vials*

| | 1 (no additive) | 2 | 3 | 4 | 5 | 6 | 7 (no bacteria) |
|---|---|---|---|---|---|---|---|
| Glycerin | 0 | 1.0 | 2.5 | 6.25 | 12.5 | 25 | 25 |
| Phenol | 0 | 0.016 | 0.04 | 0.1 | 0.2 | 0.4 | 0.4 |
| Glycerin + | 0 | 1.0 | 2.5 | 6.25 | 12.5 | 25 | 25 |
| Phenol | 0 | 0.016 | 0.04 | 0.1 | 0.2 | 0.4 | 0.4 |

*Concentrations of each additive in percent by volume (vol/vol). Positive controls in column headed "1" and negative controls in column headed "7."

In the current study, we evaluate the bacteriostatic and bactericidal properties of the additives used in the compounding of immunotherapy vials. Glycerin and phenol are the most commonly used immunotherapy vial additives in the United States. Glycerin is used to preserve antigenic potency, and phenol is contained in the saline used as a diluent in preparing injection immunotherapy vials. Previous work has shown bactericidal properties of phenol and glycerin at singular concentrations of 0.22% and 1.27% (vol/vol), respectively.[5] Our study builds upon this previously published study by varying concentrations of phenol from 0% to 0.4% and glycerin from 0% to 25%, representative of concentrations used in clinical practice when mixing vials.

## Materials and methods

### Study vial preparation

Glycerin, phenol, and a combination of these 2 immunotherapy additives were prepared in varying concentrations in 1.5-mL vials. The vials were then inoculated with *Staphylococcus aureus*, which was selected because it is a primary pathogen causing skin infections and is a skin-colonization organism.

Glycerin solutions were prepared with the following concentrations in the vials: 0%, 1.0%, 2.5%, 6.25%, 12.5%, and 25% (vol/vol). The concentrations of phenol used were 0%, 0.016%, 0.04%, 0.1%, 0.2%, and 0.4% (vol/vol). Combinations of glycerin/phenol were included at varying concentrations as follows: 0/0%, 1.0/0.016%, 2.5/0.04%, 6.25/0.1%, 12.5/0.2%, and 25/0.4% (vol/vol). Preparation of the vials took place in the allergy clinic, under clean conditions without the use of ventilation hoods. Negative control vials without bacterial inoculation were made of 25% glycerin, 0.4% phenol, and 25/0.4% glycerin/phenol (Table 1.)

The glycerin and phenol were obtained from Antigen Laboratories, Inc. (Liberty, MO). The glycerin set was prepared from a solution of 50% glycerin, 0.5% NaCl, 0.075% sodium citrate, 0.036% potassium phosphate, and 0.0567% sodium phosphate, which expired 4 years from the time of this study. The phenol set was prepared from a stock solution of 0.9% NaCl and 0.4% phenol, with an expiration date 2 years after the completion of our study. The glycerin/phenol set was prepared from a solution of 25% glycerin, 0.5% NaCl, 0.4% phenol, 0.075% sodium citrate, 0.036% potassium phosphate, and 0.0567% sodium phosphate that expired 2 years from the time of our study. These solutions were diluted with phosphate buffered saline to achieve the desired concentrations for the study.

### Bacteria

The vials were inoculated with 1 mL of a solution containing $5 \times 10^5$ CFU/mL bacteria of *Staphylococcus aureus* (American Type Culture Collection [ATCC] strain #25923) and the vials were incubated at 37.4°C for 24 and 48 hours. At 24 hours, the vials were examined for visible turbidity, and optical densities were measured with a spectrophotometer (Genesys 200; Thermo Fisher Scientific, Waltham, MA). The negative control solutions containing 25% glycerin, 0.4% phenol, and 25/0.4% glycerin/phenol without bacteria were used to calibrate the spectrophotometer. The study was done in triplicate, and colony counts of selected vials were made at 24 hours on Mueller-Hinton agar. The same was repeated at 48 hours, and the solutions in these vials were then examined for bacterial growth to determine bacteriostatic and bactericidal properties of the additives.

### Microdilution assay

The second set of experiments was performed in which the single highest concentrations of glycerin (25%), phenol (0.4%), and glycerin/phenol (25/0.4%) were used in a broth microdilution assay. Log dilutions of *Staphylococcus aureus* were prepared and introduced into wells of the plate containing the additives. The bacterial inocula used varied from 1 to $1 \times 10^5$ CFU per well. The test was performed in quadruplicate. At 24 hours the optical densities were measured and colony counts were performed on Mueller-Hinton agar. The same was repeated at 48 hours.

## Results

### Vials

All inoculated vials showed visible turbidity. The optical densities and observed turbidity increased as the concentrations of additives decreased (Fig. 1.) The negative control solutions showed no visible turbidity, and the colony counts showed no growth. The highest concentration of the additives (glycerin, phenol, and their combination) had minimal visible turbidity, but demonstrated growth on subculture (Table 2).

**TABLE 2.** Colony forming units from vials*

| | 24 hours | 48 hours |
|---|---|---|
| Positive control (no additive) | $4.5 \times 10^4$ | TNTC |
| 1.0% glycerin | $7.2 \times 10^4$ | TNTC |
| 0.016% phenol | $7.9 \times 10^4$ | $1.05 \times 10^5$ |
| 1.0% glycerin + 0.016% phenol | $7 \times 10^4$ | $1.44 \times 10^5$ |
| 25% glycerin | $5 \times 10^4$ | $5.1 \times 10^4$ |
| 0.4% phenol | $2 \times 10^2$ | $5.1 \times 10^4$ |
| 25% glycerin + 0.4% phenol | $1 \times 10^3$ | $1.2 \times 10^4$ |
| Negative controls (no bacteria) | | |
| 25% glycerin | 0 | 0 |
| 0.4% phenol | 0 | 0 |
| 25% glycerin + 0.4% phenol | 0 | 0 |

*Colony counts for selected vials at 24 and 48 hours after inoculation with $5 \times 10^5$ CFU of *S. aureus*. Positive controls contained only phosphate buffered saline with inoculum. Negative controls included vials of glycerin, phenol, and glycerin + phenol without inoculum.

CFU = colony-forming units; TNTC = too numerous to count.

## Microdilution assay

Log dilutions of the bacteria were used in a broth microdilution assay and added to the single highest concentration of the additives, which had none or minimal visible turbidity during the vial experiment. From the broth microdilution assay, none of the wells showed visible turbidity, but some of the optical densities were above zero (Table 3.) At bacterial inocula of $1 \times 10^3$ CFU/well or less, bactericidal effects were noted. Glycerin alone and the combination of glycerin and phenol showed bactericidal activity at inocula of $1 \times 10^3$ CFU/well or less. Phenol alone showed bactericidal activity at $1 \times 10^2$ CFU/well or less (Table 4.)

# Discussion

The results of the current study suggest that glycerin and phenol, common additives used in immunotherapy vial preparation, have bactericidal effects against *Staphylococcus aureus*, a common skin contaminant. These effects were seen at concentrations of glycerin 25% after inoculation with $1 \times 10^3$ CFU and phenol 0.4% after inoculation with $1 \times 10^2$ CFU *Staphylococcus aureus*. Higher concentrations of additive exhibited increased antimicrobial activity.

In clinical practice, the concentrations of glycerin and phenol in immunotherapy vials varies based on the number of allergens present and the patient's status in the dose escalation process. Glycerin could conceivably range from as low as 0.0004% to 40%. Phenol content in mixed vials

**TABLE 3.** Microdilution assay optical densities*

| *S. aureus* inoculum (CFU/well) | 25% Glycerin | 0.4% Phenol | 25% Glycerin + 0.4% phenol |
|---|---|---|---|
| $1 \times 10^5$ | 0 | 0.001 | 0.015 |
| $1 \times 10^4$ | 0 | 0.01 | 0 |
| $1 \times 10^3$ | 0 | 0.02 | 0.047 |
| $1 \times 10^2$ | 0.014 | 0.001 | 0.037 |
| $1 \times 10^1$ | 0 | 0.001 | 0 |
| $1 \times 10^0$ | 0 | 0 | 0 |
| Control | 0 | 0 | 0 |

*Optical densities of microdilution assay. The control wells received no inoculum.

CFU = colony-forming units.

**TABLE 4.** CFU from microdilution assay*

| *S. aureus* inoculum (CFU/well) | 25% Glycerin | 0.4% Phenol | 25% Glycerin + 0.4% phenol |
|---|---|---|---|
| $1 \times 10^5$ | $4 \times 10^4$ | $7 \times 10^3$ | $4 \times 10^4$ |
| $1 \times 10^4$ | $2 \times 10^3$ | $1.8 \times 10^4$ | $4 \times 10^2$ |
| $1 \times 10^3$ | 0 | $3 \times 10^3$ | 0 |
| $1 \times 10^2$ | 0 | 0 | 0 |
| $1 \times 10^1$ | 0 | 0 | 0 |
| $1 \times 10^0$ | 0 | 0 | 0 |
| Control | 0 | 0 | 0 |

*Colony counts at 48 hours from the microdilution assay. The control wells received no inoculum.

CFU = colony-forming units.

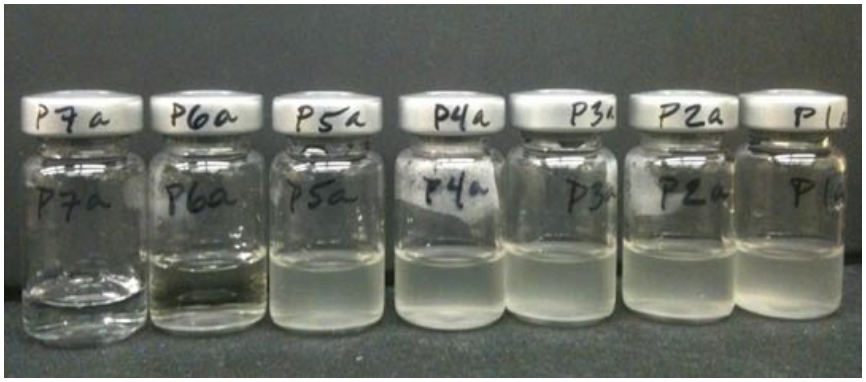



**FIGURE 1.** Allergy vials inoculated with bacteria. Turbidity increases as additive concentration decreases.

ranges from 0.08% to 0.4%, though the majority contain 0.35% or higher. A common practice is to add glycerin to increase total glycerin content to a minimum of 10% in order to maintain potency of the allergens. However, increasing the glycerin content in immunotherapy vials to very high levels for bactericidal purposes might not be practical, as levels of glycerin above 10% may provoke local site reactions after injection. While this would not affect the safety of the patient, local reactions at the injection site prematurely halt dose escalation for therapy and would prevent achieving an appropriate maintenance level.[6]

The questions that arise in light of the results of our study areas are as follows: How are the current study results applicable to clinical allergy immunotherapy vial mixing in the office? In particular, what bacterial load would typically be introduced into an immunotherapy vial from contamination and a break in aseptic technique? The authors performed a literature review in order to see if data was available to answer what type of contamination $1 \times 10^3$ CFU would represent, which is the level at which in our study bactericidal effects were noted. Unfortunately, the authors could locate no such data in the existing literature. However, 1 recent study may shed some insight into this matter. Brunetti et al.[7] cultured the palms and fingertips of healthcare personnel working in the surgical department and intensive care units. Imprints of healthcare workers' hands and fingertips were taken monthly during the morning shift. This study found 75 to 80 CFU from the palms, and 62 to 70 CFU from all 5 fingertips in surgical and intensive care workers. If these numbers are representative of those preparing immunotherapy vials in the clinic, this may represent an estimate of the skin contamination to the rubber stoppers on the vials. The number of bacteria actually introduced into the vial via a contaminated needle through the rubber stopper would likely be smaller than the amounts cultured directly from the hand of a healthcare worker. Therefore, bactericidal activity against inoculations from $1 \times 10^2$ to $1 \times 10^3$ CFU appears to be adequate activity against a reasonable skin contamination from the hands. This level of contaminant was shown in our study to be susceptible to the bactericidal properties of phenol and glycerin that were studied in the microdilution assays.

It appears that the current method of compounding immunotherapy vials in a physician's office using is safe. Previous retrospective and prospective studies demonstrated no evidence of infection from the current practice. These studies included clinical evaluation of patients as well as evaluation of vial contents both at the beginning and end of their use. Our current study supports the finding of these previous studies, by demonstrating antibacterial activity of commonly used additives against levels of *Staphylococcus aureus* expected from skin contamination. When combining the results of our current study with the aforementioned prior studies of vial contamination and mixing practices,[2–4] it appears that current recommendations that immunotherapy vial mixing be performed using aseptic technique without need for a ventilation hood are supported by the literature.[8]

## Conclusion

Glycerin and phenol independently demonstrated antimicrobial effects against *Staphylococcus aureus* in this study. Glycerin-containing solutions exhibited better antibacterial properties than phenol alone. Higher concentrations of additive had improved bactericidal effects. The concentration of glycerin that showed the best bactericidal activity in our study may not be tolerated by some patients. At concentrations of additive used clinically, bactericidal effects are noted against $1 \times 10^3$ CFU and lower of *Staphylococcus aureus*.

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# TAB 6

of the results to all AAAAI members. With that caveat, the survey data demonstrate variability among AAAAI members with interest in urticaria. The data presented show that clinicians are indeed prescribing thyroid hormone in some cases when increases of antithyroid antibody levels are found during diagnostic work-up, despite the lack of consensus regarding possible mechanism and conflicting data to date on the clinical effectiveness of thyroid hormone in this situation. Furthermore, there are minimal data on what dose of thyroid hormone to use in these patients (who are often clinically euthyroid) and no consensus as to what should be the target TSH level. Our findings underscore a significant need for further large-scale research in this area.

We thank the members of the Urticaria and Angioedema Committee of the AAAAI from 2006-2008 who assisted with the development and conduct of this study: Aleena Banerji, MD; Vincent Beltrani, MD; Jonathan A. Bernstein, MD; Mark Davis-Lorton, MD; Maria C. di Prisco, MD; Kerry Drain, MD; David Dreyfus, MD; Marta Ferrer, MD; Luz S. Fonacier, MD; Roger Fox, MD; El Desouki Fouda, MD; Evangelo Frigas, MD; Mario Geller, MD; Carla Irani, MD; Douglas T. Johnston, DO; Young-Mok Lee, MD; Huamin Henry Li, MD; Arvind Madaan, MD; Alejandro Malbran, MD; Yoseph Mekori, MD; Lenor Pagtakhan-So, MD; Donald Russell, MD; W. Carrock Sewell, MD; Meir Shalit, MD; Saba Sharif, MD; Thomas J. Shen, MD; Shaz Siddiqi, MD; David Weldon, MD; and Wei Zhao, MD.

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Disclosure of potential conflict of interest: J. Sheikh has received honoraria from Alcon, Genentech, Meda, Novartis, Sanofi-Aventis, UCB; research support from GlaxoSmithKline; has provided legal consultation on the topic of adverse drug reactions; and has served on the executive boards of the Massachusetts Allergy Society and the New England Society of Allergy. S. S. Saini has received research support from Genentech. A. Kulczycki has received honoraria from Sanofi-Aventis, and UCB. S. C. Dreskin has received honorarium from Genentech; received research support from the National Institutes of Heath, the American Health Insurance Plans, and the Johns Hopkins School of Public Health; has provided legal consultation on the topic of allergic bronchopulmonary aspergillosis; and serves on the board of directors for the Aspen Allergy Conference.

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Available online March 2, 2009.
doi:10.1016/j.jaci.2008.12.1130

## Monitoring bacteriostasis in allergen extract mixing: 10 years of culture data

*To the Editor:*

There has been recent controversy regarding the safety of current allergen extract mixing practices for immunotherapy prescriptions.[1] Allergen extract vials are often mixed in physicians' offices by transferring stock extract into multidose patient-specific vials with an aseptic technique. Similar methods have been used safely for nearly 100 years, going back to the time of Noon and Freeman.[2] There are no reports in the medical literature of infections caused by immunotherapy injections.[3] A retrospective study of immunotherapy records of 272 patients who received 26,795 injections over 6 years showed no evidence of infections caused by allergen immunotherapy injections.[4]

The United States Pharmacopeia regulates compounded sterile preparations and in January 2004 issued regulations that would include stringent requirements for allergen immunotherapy mixing (use of a laminar flow biologic safety cabinet, positive-pressure room, and storage limited to 7-14 days after immunotherapy mixing).[1] These requirements would have rendered immunotherapy impractical for the majority of patients.

The Joint Council of Allergy, Asthma and Immunology responded to these concerns, and standards for safely mixing allergen immunotherapy preparations were published in "Allergen immunotherapy: a practice parameter second update"[3] and recently finalized.[5] These standards include proper training of mixing personnel, oversight by physicians, inclusion of proper concentrations of glycerin or phenol for bacteriostasis, use of an aseptic technique, and refrigerated storage and that allergen immunotherapy is only intended for subcutaneous injection. Importantly, vials can be discarded according to the manufacturer's expiration dates (not 7-14 days after mixing), and there is no specific requirement for a flow hood or positive-pressure environment. The United States Pharmacopeia considered these guidelines during a public comment period and excluded allergen extracts from the more stringent standards of other compounded sterile preparations as long as certain standards are met, including sterile needle transfer of commercial allergen preparations, inclusion of appropriate bacteriostatic agents, use of patient-specific multidose vials, use of an aseptic technique with handwashing, and use of gloves, hair covers, gowns, face masks, and disinfection with alcohol.[6]

To provide further reassurance supporting the safety of our profession's current immunotherapy preparation mixing practices, we report the results of 10 years of bacterial cultures performed on allergen immunotherapy vials. At our institution, allergen extracts are mixed by using an aseptic technique in a laminar flow hood in a room without positive-pressure ventilation. Gloves are worn during mixing, and vials are wiped with alcohol pads. As part of quality assurance monitoring, 20 vials are cultured each month. At the time of mixing, 0.5 mL is removed from a patient's 1:1 vol/vol and 1:1,000 vol/vol vials and injected into separate collection tubes (6-mL sterile BD Vacutainer red-top blood collection tubes; BD, Franklin Lakes, NJ) by using an aseptic technique. These are stored at 4°C for up to 30 days and submitted to the laboratory in a batch for culture. The clinical microbiology laboratory then transfers the contents of each tube to both a chocolate agar plate and a thio broth culture medium; therefore the sample collected from 1 vial is cultured by using 2 different methods. Both culture media are obtained from BD. The

chocolate agar plates are cultured in a 5% $CO_2$ environment, the thio broth is cultured in a non–$CO_2$-enriched environment for 3 days at 35°C, and then results are reported. The chocolate agar is intended to culture for only aerobic organisms, whereas the thio broth cultures for both aerobic and anaerobic organisms.

A total of 2,085 cultures were done between 1998 and the present, and 2,084 cultures were negative. Only 1 culture from 1999 grew *Enterococcus* species (representing <0.05% of all cultures). No information was available on whether the positive culture extract had been administered to the patient. There have been no known cases of infections caused by allergen immunotherapy injections at our institution.

The frequency of positive cultures at our center is even lower than that reported by Lay et al.[7] In this study bacterial contamination was compared between vials prepared either in an office setting by using an aseptic technique without a ventilation hood or under an International Organization of Standardization classification 5 vacuum-ventilated hood in the hospital pharmacy. Three hundred twenty vials were prepared in the office, and 217 vials were prepared in the pharmacy (total = 537 vials). Two (0.6%) of 320 office-prepared vials and 1 (0.5%) of 217 pharmacy-prepared vials showed positive cultures for bacterial contamination. The 3 patients who received injections from the contaminated vials experienced no clinical infection. Our rate of contamination (1/2085 [0.048%]) compares favorably with their overall rate (3/537 [0.56%]).

Mixing personnel at our center use an aseptic technique with gloves and alcohol pads under a laminar flow hood after proper handwashing but thus far have not worn gowns, face masks, or hair covers. Because our flow hood is conveniently available, we will continue to use it. However, a flow hood, gowns, face masks, and hair covers are not required by the present guidelines.[5] Cultures are also not necessarily recommended but were begun 10 years ago at our center as a reasonable means of quality assurance. The current guidelines recommend that mixing personnel qualify at least annually by performing a media-fill test.

In conclusion, our nearly completely negative culture results over 10 years support the safety of our office-based allergen immunotherapy mixing practices at a tertiary referral center. Although most practicing allergists presumably do not use a flow hood for preparing allergen extracts, our data, combined with those of Lay et al[7] (who demonstrated a very low rate of bacterial contamination without a flow hood), support the current allergen immunotherapy preparation guidelines in use by the allergy community.[5] The allergen extract cultures are an imperfect (because of unknown *in vivo* correlation) but reasonable and practical marker for bacteriostatic safety. Periodic cultures could be considered by any office or center preparing allergen extracts for subcutaneous immunotherapy as a method of ensuring quality assurance but are not required by the present guidelines (which recommend a media-fill test). Further studies performing cultures without a flow hood would further confirm the safety of mixing without a flow hood. It is especially reassuring that no clinical infections caused by allergen immunotherapy injections have ever been reported in the literature.

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Disclosure of potential conflict of interest: J. P. Dice has received research support from AstraZeneca, GlaxoSmithKline, and Genentech. The rest of the authors have declared that they have no conflict of interest.

Disclaimer: The views presented in this work are those of the authors and do not necessarily represent the views of the U.S. Government.

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Available online March 2, 2009.
doi:10.1016/j.jaci.2009.01.048

## Current use of room disinfectants and allergic symptoms at the age of 4 years

*To the Editor:*

Epidemiologic studies suggest an association of occupational domestic cleaning with asthma.[1,2] More recently, a correlation of nonprofessional use of cleaning sprays with adult asthma has also been reported for private households.[3] In this study application of commonly used cleaning and air-refreshing sprays was found to be a major risk factor for asthma, but the relevance of these findings for children remains to be understood. Because of their small airway diameters, young children are particularly susceptible to respiratory symptoms. In addition, allergic diseases are frequently primed in early childhood, and potential risk factors need to be avoided. For these reasons, we wished to analyze potential associations between current use of room disinfectants in private homes and respiratory, cutaneous, and allergic symptoms in young children. To this end, we performed an observational study in 4-year-old offspring from pregnant women participating in a multicenter, randomized, double-blind, placebo-controlled clinical trial described in detail elsewhere.[4] Briefly, the effects of increased intakes of a fish oil preparation (0.5 g of docosahexaenoic acid and 0.15 g of eicosapentaenoic acid), 400 μg of 5-methyl-tetrahydrofolate, both, or placebo from the 22nd week of gestation until delivery and birth outcomes were assessed in the main trial. Thus a selection bias with respect to allergic diseases and use of room disinfectants would not be expected.

Study centers were the University Hospital of Granada (Spain), the University of Pecs (Hungary), and the University of Munich (Germany). Three hundred eleven healthy women between 18 and 40 years of age with uncomplicated singleton pregnancies completed the study until delivery. Mothers who dropped out had a higher body mass index in the 20th week of gestation ($P < .02$, Mann-Whitney $U$ test) compared with mothers who completed the study. This difference was no longer seen in the 30th week of gestation. From 270 women completing the study, 176 offspring (all white; 43% total dropout rate) attended the clinic at

# TAB 7

# Injectable immunotherapy: recommendations for safe allergen vial preparation in the office setting

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**Current Opinion in Otolaryngology & Head and Neck Surgery** 2009, 17:223–225

**Purpose of review**

To review the proper technique for preparing allergen vials to be used in subcutaneous immunotherapy in the office setting, examine the potential for bacterial contamination during mixing and handling and associated risk factors and review the data relevant to contamination during vial mixing.

**Recent findings**

Existing literature on the subject of safe vial preparation suggests that the incidence of bacterial contamination of allergen vials is very low. Historically, there is no report of bacterial infection for subcutaneous immunotherapy using vials prepared in the office setting or otherwise when using the proper sterile technique.

**Summary**

In-office compounding of vials is a safe practice with literature to support continuing this practice of preparation.

**Keywords**

allergen, contamination, preparation, sterile, vial

Curr Opin Otolaryngol Head Neck Surg 17:223–225
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1068-9508

## Introduction

The diagnosis and treatment of allergy in the field of otolaryngology is important. Many of the disease processes seen in otolaryngology clinics such as otitis media, chronic rhinitis, chronic sinusitis, and even Ménière's disease have allergies as an exacerbating factor. The best chance for cure of allergies is immunotherapy, which in the United States is usually subcutaneous injectable immunotherapy (SCIT). There are no reported cases of infection from SCIT, though the possibility exists. It is essential that proper preparation and handling techniques be employed when administering injectable immunotherapy. This article reviews the literature examining safe practices of injectable immunotherapy.

## Current in-office immunotherapy practices

The last several years have shown a surge of activity in otolaryngic allergy practices across the country. Allergen-specific immunotherapy (SIT) is implemented usually in the form of SCIT. When attempts at medical management with avoidance, oral antihistamines, nasal irrigations, and nasal steroids are inadequate or only partially successful, allergen-SIT significantly improves a patient's symptom profile and is the only intervention which can potentially cure the patient making it an essential part of any allergy physician's practice. The otolaryngologist can identify patients with potential allergy, who may not know they have allergy and save the patient the expense of traveling to another physician's office for allergy management. By offering allergy evaluation and therapy, the otolaryngologist provides a maximum value, 'a one stop shop' for many patients with ear, nose, and throat disorders, which have an allergic component. The demand is quite high and growing in the field of otolaryngology. Some 10 million patients are treated annually with SCIT in the United States alone [1•].

Chronic rhinosinusitis, Eustachian tube dysfunction, and chronic otitis media are just a few of the diseases seen in otolaryngology clinics associated with environmental allergies [2]. Safe allergy management is as important as effective allergy management. Safety of allergy immunotherapy requires not only that the antigen dosage be appropriate, but also that the vial and the administration be sterile. This article will review safe and sterile allergy vial preparation.

The incidence of anaphylaxis is 0.005% of allergy shots among otolaryngic allergists. The presentation and treatment algorithm for anaphylaxis is well described in the literature [2]. A less frequently considered adverse event following an allergy shot is infection. The issue of sterility in the preparation of allergen vials has been discussed nationally among pharmacists, otolaryngologists, and medical allergists for the last several years. In 2003, United States Pharmacopeia (USP) made recommendations regarding the compounding of medications that

 DOI:10.1097/MOO.0b013e32832b376f

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would place onerous burdens on the practices of the physicians treating allergy patients. In the Pharmacopeial Forum, chapter 797, the guidelines for medication compounding in office recommended clean rooms, ventilated hoods, air sampling, and other safety measures. While it did not specifically cite allergen vial preparation, a translation to vial preparation was easily apparent. In 2006 the USP, after weighting the input of various allergy societies, undertook a revision that stated allergen vial preparation in the office setting was reasonable and did not require the ventilated hoods and air sampling required of compounding medications in a hospital or pharmacy. This revision is now in print in the updated 2007 version of chapter 797 [3]. So then, what is considered proper handling of materials and sterile technique for preparing vials?

## What is sterile preparation?

King and Mabry [4] outlined a practical protocol for mixing allergen vials in an office setting. This same protocol was used in prospective studies looking for rates of bacterial contamination. The steps are as follows:

(1) A counter top in the allergy clinic is designated as the mixing space and is prepped topically with 70 isopropyl alcohol or clinical germicide.
(2) When prepping the mixing area and arranging vial materials, nonsterile gloves are worn. Proper hand washing occurs prior to gloving.
(3) Vials of hermetically sealed allergen are mixed in vials using hermetically packaged syringes and diluent.
(4) Several different antigens may be injected into these vials and diluted with sterile 0.4 percentage phenolated saline buffered to pH 7.4. Then, 25 or 50% glycerin is injected into the patient vial to bring the glycerin content to a minimum of 10%.
(5) Once the vials are prepared, they are stored in refrigerator at approximately 38°F for no longer than 3 months.
(6) For administration, the allergen is drawn into a small-gauge syringe (27 G) after prepping the rubber stopper top with 70% isopropyl alcohol and administered subcutaneously after the skin is prepped with 70% isopropyl alcohol.
(7) All disposable materials, such as syringes and needles, are handled and used only once, then discarded in the appropriated receptacles.
(8) Vials are typically remixed once every 5–10 weeks while in the buildup phase of immunotherapy, and all vials are marked in with a 3-month expiration date.
(9) Vials are discarded after the 3-month storage period.

A custom vial is prepared for each patient based on allergy skin or in-vitro testing results. Doses range in volume from 0.05 to 0.5 ml. The injections are administered subcutaneously to patients by trained healthcare personnel after preparing the skin with alcohol while wearing gloves. Current recommendations for vial mixing emphasize the importance of listing the name of one specific patient, with a beyond-use date and storage temperature range that is assigned based on manufacturers' recommendations or peer review publications (www.usp.org). The addition of bacteriostatic substances to the vials such as 0.25% phenol or 20% glycerin is also recommended [5•]. Although glycerin has shown some bateriostatic properties, it has not been clearly quantified, so it is used largely as a preservative [6]. The concentrations of phenol and glycerin vary depending on manufacturer, physician preference, and desired shelf life of the vial being used. The above method was used in three studies recently published on safe vial preparation and bacterial contamination [1•,7••,8••].

## Factors that may increase the risk of infection when handling vials in the clinic

Longfield, Bawden, Melnyk, and Thompson [9–12] in four separate studies cited handling techniques that increase risk of infection. These included increased number of punctures, a lack of resealability of rubber closure, lack of aseptic technique, injection of air into the vial before removal of the solution, prolonged length of storage, and reduced antimicrobial activity of bacteriostatic agents used in preparation and administration. The antimicrobial and preservatives used in these studies were variable, including 0.4% phenol, 0.9% benzyl alcohol, 0.1% methylparaben, 0.01% propylparaben, and others. The conclusion of these articles uniformly was that the incidence of contamination was quite low, from 0.004 to 0.5% [11]. These studies were not on allergen vials specifically; however, their conclusions are applicable to allergy vials.

## Commercial preparation

In 2001, Wohlfarth *et al.* [13] of Antigen Laboratories, Inc., described the advantages of commercially produced vials such as assured sterility. In the article, the conditions for compounding included clean room environs, air sampling, vial sampling with cultures, and preparation under a ventilated hood. These measures, though undoubtedly very effective, were duplicated in a recent study conducted at Southern Illinois School of Medicine. Vials prepared under ventilated hoods in a pharmacy were cultured and compared with vials prepared in the office setting with no significant difference in rates of bacterial contamination. Of the vials cultured in the pharmacy under the ventilated hood, one tested positive for *Escherichia coli*, and those prepared in the office revealed two cultures that were positive for

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coagulase-negative Staphylococcus and an alpha-Streptococcus. Repeat cultures of these vials revealed no bacteria suggesting that these were simply handler contaminants rather than originating from the vials themselves. In Wohlfarth *et al.*'s article, positive cultures were found in random sampling of the vials prepared in the setting of a clean room under ventilated hood and disposed of appropriately. A long safety record with no documented infections strongly suggests that there is no difference in overall sterility of vials for SCIT whether prepared in the traditional manner in the office without a hood or in the hospital setting clean room with a hood.

## Comparison of commercial and office preparation of vials

In Lay *et al.*'s retrospective study and literature review, there were no cases of bacterial infection from SCIT [1•]. In a recent prospective study by the same authors, vials were prepared in the office setting and under a ventilated hood in a microbiology lab, and no significant difference in contamination rates was found between the two arms. A total of 537 vials were prepared and cultured; 320 vials were arbitrarily assigned to in-office preparation and 217 to under-hood preparation. A total of two (0.6%) positive cultures occurred in vials prepared in-office and one (0.5%) from under-hood preparation. This outcome yielded an odds ratio of 1.36 with a 95% confidence interval of 0.12–15.08 ($P = 0.8$). The sample size (537) used in this experiment was large enough detect a significant difference of 4% (13 of 320) versus 0.5% (one of 217) with a power of 80%, which was judged to be within clinically acceptable limits [7••].

Preparing allergy vials in the physician allergist office is convenient and cost-effective. Each patient has his or her own unique combination of allergens and dosing requirements, which can be changed in real time in the office setting.

## Conclusion

SCIT has enjoyed a long and apparently infection-free history of treatment. Allergy patients rely on us as allergy physicians to maintain this track record of safe preparation and administration of SCIT. Using simple sterile technique in the office setting with appropriately prepared areas by trained staff is the standard.

## Acknowledgements

I would like to thank Dr Richard Bass and Dr Stephen Chadwick for their guidance in writing this article.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 247).

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**7** •• Lay PC, Lin S, Bass R. Risks of allergy vial contamination: comparison of mixing in-office versus under ventilation hood. Otolaryngol Head Neck Surg 2008; 139:364–366.

A prospective analysis of vials prepared under a ventilated hood versus those compounded in the office setting. Positive cultures occurred in both arms but appeared to be contaminants. Sample size was limited but suggests no significant difference between two means of preparation.

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# TAB 8

Otolaryngology–Head and Neck Surgery (2008) 139, 364-366

ORIGINAL RESEARCH—ALLERGY

# Risks of allergy vial contamination: Comparison of mixing in-office versus under ventilation hood

**P. Chase Lay, MD, Richard Bass, MD, Larry F. Hughes, PhD,** and **Sandra Y. Lin, MD,** Carbondale, IL; and Baltimore, MD

**OBJECTIVE:** Compare the risk of bacterial contamination of allergy immunotherapy vials prepared in-office versus those mixed under a ventilation hood.
**STUDY DESIGN:** Prospective single-blinded study.
**SETTING:** Tertiary otolaryngology outpatient clinic.
**RESULTS:** Five hundred thirty-seven vials were prepared and cultured for aerobes and anaerobes over an 11-month period. Three hundred twenty vials were arbitrarily assigned to in-office preparation and 217 to under-hood preparation. A total of two positive cultures occurred in vials prepared in-office and one from under-hood preparation. Follow-up cultures of these three vials were all negative. No patients receiving injections had signs or symptoms of skin or systemic infections from the injections.
**CONCLUSION:** Our results suggest that the risk of bacterial contamination in immunotherapy vials in both groups is rare.
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In-office preparation of allergen vials for the practicing otolaryngologist is a key component in the armamentarium of the physician treating allergic rhinitis. With greater scrutiny of physician practice standards and with guidelines being developed to improve patient safety, it is important that physicians are proactive in creating safety standards—and in this case—immunotherapy vial preparation.[1] As reported in our previous retrospective article examining the risk of infection and vial contamination from those prepared in the office using aseptic technique, there were no cases of infections, skin or systemic, in 272 patients who received over 26,000 injections.[2] Seven to 10 million allergy immunotherapy injections are administered annually[3] and are most often prepared in the office without the use of a ventilation hood or clean room. However, as physicians and their practices are held to ever stricter standards of safety, regulatory agencies may adopt new guidelines that could significantly impact what is now a cost-effective, safe, and efficient means of providing allergy immunotherapy.

For example, in 2003, the United States Pharmacopeia (USP), a standard-setting organization, issued USP its first standard on medication compounding of sterile preparations.[4] This standard required the use of a dedicated clean room, ventilation hood, air sampling, surface sampling, and formal testing of mixing personnel. Furthermore, although USP is not a governmental organization, regulatory agencies such as the Joint Commission consider USP a valuable guideline for establishing safe practices guidelines for compounding of sterile medications. In 2006, the USP undertook a revision of its original Chapter 797 after soliciting comments; during this time several allergy societies contributed their expert advice and commentary. In December 2007, the USP released a revision to 797 (currently available on the USP Web site: www.usp.org) that suggests their panel now agrees that mixing of allergen vials in the office without use of a ventilation hood is a reasonable practice.[5]

As these guideline are further revised and developed in the future to improve patient safety, it is of utmost importance that they are based on experience, expert opinion, and scientific data. The authors undertook this current project to look at any potential differences in vial safety in different mixing environments. This prospective single-blinded control study was undertaken to scientifically evaluate the risks of infection and vial contamination when mixing occurs in the office versus in a dedicated clean room with ventilation hood.

## STUDY DESIGN

We performed a single-blinded prospective case-control study with the consent of our institutional review board at the Southern Illinois University otolaryngologic allergy clinic. Newly prepared vials were mixed by the same two trained clinic nurse staff members between January and November 2007. Two groups of vials were compared: One group was prepared in the office using aseptic technique in the clinic, and the second group under an International Organization of Standardization classification 5 vacuum ventilated hood in our hospital pharmacy. While working under the hood, the preparer wore mask and gloves. Details

Received April 15, 2008; revised June 10, 2008; accepted June 10, 2008.

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doi:10.1016/j.otohns.2008.06.016

of vial mixing using aseptic technique that have been previously described by King et al[6] were used in this study.

Once prepared, vials were cultured according to standard culture techniques after completion of the mixing and transported to the microbiology laboratory in a hermetically sealed ACT II tube (ACT II collection vial, catalog # 12402; Remel, Lenexa, KS) with aerobic-anaerobic culture medium. A total of 537 vials were prepared, cultured, and examined by a single certified microbiology laboratory staff member who was blinded to the site of vial preparation. The results were reported after 5-day incubation in a polymicrobial sheep, chocolate, and brucella medium that facilitates both aerobe and anaerobe growth (tryptic soy agar plates with 5% sheep blood, catalog # R01202; Remel). Anaerobic plates were incubated at 37°C in a closed container with a gas-generating pouch system (GasPak EZ Gas Generating Pouch System, catalog # 260683; Becton Dickinson, Franklin Lakes, NJ) to create an anaerobic environment. For any positive culture, a repeat culture of the same vial was performed as well as an examination of the patients' medical record for possible signs and symptoms of local or systemic infection. NCSS 2007 (NCSS, Kaysville, UT) and PASS 6.0 (NCSS) were used to analyze the data (odds ratio and differences between proportions) and conduct the power analyses.[7]

## RESULTS

A total of 537 vials were prepared and cultured over an 11-month period; 320 vials were arbitrarily assigned to in-office preparation and 217 to under-hood preparation (Table 1). A total of two (0.6%) positive cultures occurred in vials prepared in-office and one (0.5%) from under-hood preparation. This outcome yielded an odds ratio of 1.36 with a Mantel-Haenszel 95 percent confidence interval of 0.12 to 15.08 ($P = 0.8$). With the sample size (537) used in this experiment, it would have been possible to detect a significant difference of 4 percent (13 of 320) versus 0.5 percent (1 of 217) with a power of 80 percent, which we judged to be within clinically acceptable limits. Within these limits, we were unable to detect a significant difference in contamination when comparing the two groups. A power of 80 percent would require a sample size of 862 for 3 percent, 1722 for 2 percent, and 9346 for 1 percent versus 0.5 percent.

**Table 1**
**Culture results**

| | Under hood | In-office |
|---|---|---|
| No. of cultures | 217 | 320 |
| No. of positive cultures | 1 | 2 |
| Organism | *E coli* | *Staphylococcus, Streptococcus* |
| Repeat culture | Negative | Negative<br>Negative |

Of the positive cultures in the office-prepared vials, the organisms were a rare coagulase-negative *Staphylococcus*, and rare alpha *Streptococcus*. The one under-hood positive vial culture showed rare *Escherichia coli*. Each of these vials was sampled and recaptured; all follow-up second cultures revealed negative results. The two vials from the office group were recultured at 9 days and 57 days after mixing, and the positive hood sample was recultured 5 days after the initial positive culture.

For the three vials with positive cultures, medical records or the patients receiving immunotherapy injections from these vials were reviewed to see if any of the patients reported adverse effects or symptoms. The three patients who received injections from these three positive vials did not show any signs or symptoms of local or systemic infections, such as local edema, erythema, purulence, or fever.

## DISCUSSION

The need for safe compounding of immunotherapy vials is clear, and our data suggest there is little risk of bacterial contamination of allergen vials that are mixed according to aseptic technique in the office versus under a ventilation hood. In our study, the risks of vial contamination were very rare in both groups, follow-up cultures were all negative, and there were no signs or symptoms of infections in the patients receiving injections from the immunotherapy vials. The data in this paper support the idea that vials can be prepared in an aseptic fashion in the office by trained staff using proper technique, and can be administered with very little risk of bacterial contamination and subsequent infection of the patient. Indeed, to date no report has shown a systemic infection from injectable allergy therapy that required antibiotics. Furthermore, the follow-up cultures taken from those three vials that first tested positive were all negative. One reason for this result may be that glycerin and phenol used as preservatives may have mild bacteriostatic properties. Some clinical studies have suggested that glycerin may have some antiseptic attributes, particularly against *Staphylococcus aureus* and *Streptococcus pyogenes*.[8] Another reason for the negative repeat cultures is that these bacteria were simply handler contaminants in the setting of the laboratory. The patients receiving subcutaneous injections from the vials that had positive cultures in our studies exhibited no signs or symptoms of infection after the injections.

Although the risk of anaphylaxis and systemic reactions from allergen vial injections has been determined to be acceptably low, it is important that physicians who practice allergy medicine make continued efforts to safeguard their patients

from potential harm.[9-12] Currently, there has been increasing awareness of the importance of medication errors and safety, including the area of allergen immunotherapy mixing. A recent publication outlines suggested guidelines for mixing immunotherapy vials to minimize the risk of vial contamination and improve patient safety[1]; our current paper supports the recommendations of mixing in a dedicated area using aseptic techniques but not requiring the use of a ventilation hood. However, one of the limitations of the current study is the relatively small sample size for detecting the very uncommon events of vial contamination. Further studies with larger sample size would be useful to definitively investigate any potential differences in contamination in comparisons of vial mixing with and without a ventilation hood.

## CONCLUSION

On the basis of these results, it is reasonable to say that mixing vials in the clinic using standardized aseptic technique appears to be safe for patients. The long history of injectable immunotherapy and the absence of any reports of systemic infections further support this determination. Proper handling and preparation of the allergens and vials are paramount, and continued diligence in our practices as physicians safeguards our patients and our practices.

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**Sandra Lin:** study design, data, writer; **Richard Bass:** study design, writer; **P. Chase Lay:** study design, data, writer; **Larry Hughes:** study design, statistics, writer.

## FINANCIAL DISCLOSURE

This study was funded by an American Academy of Otolaryngology Foundation research grant.

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## BACTERIOSTATIC AGENTS AND STERILITY REQUIREMENTS FOR ALLERGEN IMMUNOTHERAPY

Phenol and glycerin are common bacteriostatic preservatives added to allergen extracts. United States Pharmacopeia guidelines, Immunotherapy 2007 Practice Parameters, and the American Academy of Allergy Asthma & Immunology/American College of Allergy, Asthma and Immunology/Joint Council of Allergy, Asthma and Immunology (JCAAI) guidelines do not specify recommended concentrations of phenol or glycerin.[1–3] The Joint Council of Allergy, Asthma and Immunology and the American Academy of Otolaryngic Allergy (AAOA) have recommended that "allergen extract dilutions must be bacteriostatic, meaning 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] To our knowledge, no published studies support the use of phenol concentrations of at least 0.25%, or if less than that, glycerin concentrations of at least 20%. Limited studies have been published on the sterility of immunotherapy.[5] Immunotherapy vials are multidose vials kept for up to 1 year, with the potential for multiple manipulations over that time. To our knowledge, no reports have been made of patients developing infections from immunotherapy injections. We investigated the potential for microbial growth in expired allergenic extracts previously used in patient care and studied the effects of using recommended and lower than recommended concentrations of phenol and glycerin on microbial growth in allergenic extracts.

Fifty expired immunotherapy vials from one institution were collected from patients undergoing immunotherapy. The phenol and glycerin concentrations in each expired vial were calculated. Albumin saline with 0.4% phenol (Allergy Laboratories, Oklahoma City, OK) was used for diluent. Phenol concentrations ranged from 0.12% to 0.4%, and glycerin concentrations ranged from 0% to 35% (Fig. 1). Forty-four vials contained greater than 0.25% phenol. Six vials contained less than 0.25% phenol but at least 20% glycerin. An additional 50 expired immunotherapy vials, from a different institution, were collected for culture purposes only. All 100 expired vials were sent for bacterial culture in thioglycolate broth, as well as in blood agar and anaerobic plates.

**Disclosures:** Authors have nothing to disclose.
**Funding Sources:** Financial support was provided by the Mayo Clinic Allergy Division discretionary funds.
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doi:10.1016/j.anai.2010.10.024

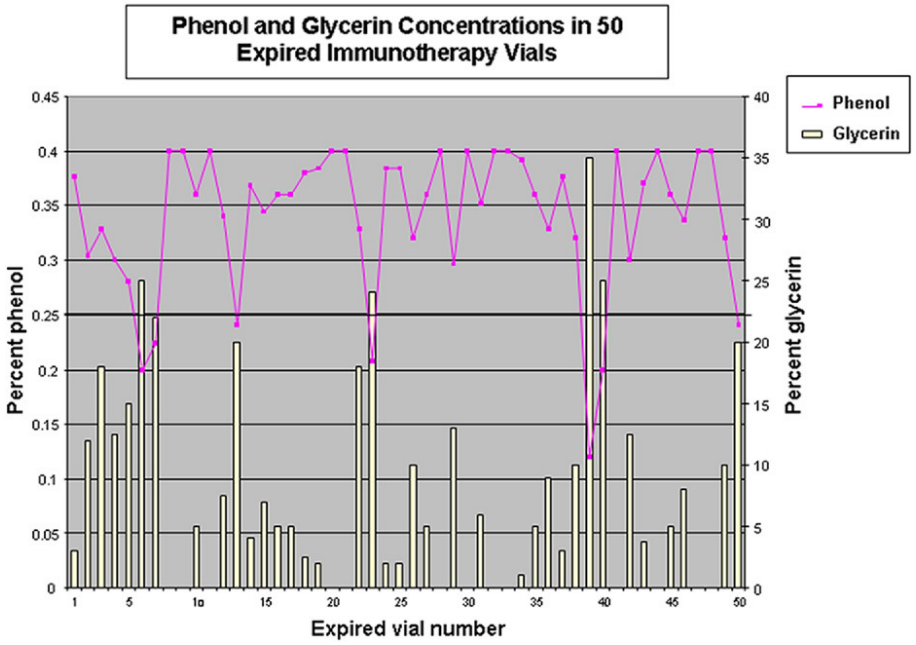



Figure 1. Phenol and glycerin concentrations in 50 of the expired patient immunotherapy vials. All expired immunotherapy vials met the JCAAI and AAOA recommendations of the use of at least 0.25% phenol, or if the phenol concentration was less than 0.25%, the extracts contained glycerin concentrations of at least 20%.

To study the effects on microbial growth of using lower than recommended concentrations of phenol and glycerin, two sets of experiments were set up in parallel with and without a laminar flow hood (Nuaire Biologicals, Class II type AZ, Plymouth, MN). The first experiment was conducted with the use of a laminar flow hood with appropriate attire, including gown, mask, sterile gloves, and sterile alcohol. The second experiment was prepared on the bench top and included alcohol wipes of the vials and reagent bottles, with dilutions performed on the bench top. For each experimental setup, a sterile, 5-mL vial was prepared with 5 mL of preservative-free (Allergen Extract Diluent Injection preservative free, sterile, nonpyrogenic, isotonic, Mayo Pharmacy Services, Rochester, MN) diluent with the addition of varying concentrations of phenol from 0%, 0.05%, 0.1%, and 0.25% (albumin saline with phenol: NaCl 0.9%, normal serum albumin 0.03%, phenol 0.4%, from Allergy Laboratories Inc., Oklahoma City, OK) or glycerin from 0%, 1%, 5%, 10%, and 20% (sterile diluent for allergenic extract with glycerin 50% (wt/vol), sodium bicarbonate 0.091%, NaCl 0.166%, from ALK-Abelló, Inc., Round Rock, TX) with or without 1 mL of cat hair (1,000 bioequivalent allergy units) allergen extract (Standardized Cat Hair 5,000 bioequivalent allergy units/mL, ALK-Abelló, Inc., Round Rock, TX), for a total of 36 vials (18 using the hood, 18 on the bench top). The vials were stored at 4°C for a 1-month period. During this 1-month period, a total of 10 manipulations were performed to each vial on the bench top. An alcohol pad was swiped across the top of each vial, and a 27-gauge needle plus 1-mL syringe was used to puncture the tops of the vials and was allowed to contact the solution, simulating an allergy shot withdrawal. These punctures were performed every 3 to 5 days over 1 month.

The results showed that none of the 100 total expired immunotherapy vials showed microbial growth, and none of the 4 different concentrations of phenol or the 5 different concentrations of glycerin tested showed microbial growth. No difference was found between hood or bench top preparation. Only the spiked positive control vials developed bacterial growth.

Based on our study, we conclude that one institution's 50 expired immunotherapy vials met the JCAAI and AAOA recommendations of at least 0.25% phenol or glycerin concentrations of at least 20%, and that current immunotherapy practice is highly effective at preventing microbial growth. Second, a sterile hood may not be necessary to ensure the sterility of allergenic extracts, and the sterility of immunotherapy extracts is preserved even with low concentrations of phenol or glycerin over a period of 1 month.

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# TAB 10

# Allergy immunotherapy: Reduced health care costs in adults and children with allergic rhinitis

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**Background: Research demonstrates significant health care cost savings conferred by allergen-specific immunotherapy (AIT) to US children with allergic rhinitis (AR).**

**Objective: We sought to examine whether AIT-related cost benefits conferred to US children with AR similarly extend to adults.**

**Methods: A retrospective (1997-2009) Florida Medicaid claims analysis compared mean 18-month health care costs of patients with newly diagnosed AR who received *de novo* AIT and were continuously enrolled for 18 months or more versus matched control subjects not receiving AIT. Analyses were conducted for the total sample and separately for adults (age ≥18 years) and children (age <18 years).**

**Results: Matched were 4,967 patients receiving AIT (1,319 adults and 3,648 children) and 19,278 control subjects (4,815 adults and 14,463 children). AIT-treated enrollees incurred 38% ($6,637 vs $10,644, $P < .0001$) lower mean 18-month total health care costs than matched control subjects, with significant savings observed within 3 months of AIT initiation. Compared with control subjects, significantly lower 18-month mean health care costs were demonstrated overall (38%; $6,637 for patients receiving AIT vs $10,644 for control subjects, $P < .0001$), and for both AIT-treated adults (30%; $10,457 AIT vs $14,854 controls, $P < .0001$) and children (42%; $5,253 AIT vs $9,118 controls, $P < .0001$). The magnitude of 18-month health care cost savings realized by AIT-treated adults and children did not significantly differ ($4,397 vs $3,965, $P = .435$).**

**Conclusions: Patients with newly diagnosed AR initiating AIT incurred significantly lower health care costs than matched control subjects beginning 3 months after AIT initiation and continuing throughout the 18-month follow-up period. The significant cost benefits achieved by children with AR diagnoses who initiated AIT were also observed for adults with AR diagnoses who initiated AIT. (J Allergy Clin Immunol 2013;131:1084-91.)**

***Key words:*** *Allergic rhinitis, allergy immunotherapy, allergy immunotherapy, costs, health care use, Medicaid, matched cohort, retrospective, administrative claims*

Allergic rhinitis (AR), which affects approximately 1 in 5 persons in the United States, is associated with significant clinical and economic burden.[1] Those with AR can experience disturbed sleep, decreased energy, depressed mood, low frustration tolerance, poor concentration, decrements in performance at school and work, and millions of lost work and school days annually.[2,3] In 2005, estimated total direct US costs of AR exceeded $11 billion ($14 billion in 2011[1]), with 60% of expenditures for prescription medications (the cost of over-the-counter medications was not assessed).[4] Additional billions of dollars are reportedly spent to treat conditions for which AR is a predisposing risk factor, such as asthma, sinusitis, and otitis media.[5]

Subcutaneously administered allergen-specific immunotherapy (AIT), which has just commemorated its centennial anniversary since its first use to treat allergies,[6] is indicated in the US for the treatment of AR in patients with symptoms not adequately controlled by medications and avoidance measures, or those experiencing unacceptable adverse effects of medications, or who wish to reduce the long-term use of medications.[7] AIT is distinguished from symptomatic drug treatments by its unique potential to alter the course of allergic disease and thereby mitigate progression to asthma[8-11] and development of new allergen sensitivities,[12-18] as well as to maintain efficacy after discontinuation of treatment.[12,18-25]

The significant cost savings conferred by AIT to US children with AR are well documented.[26-28] In a 7-year (1997-2004) retrospective claims analysis of Florida Medicaid-enrolled children (age <18 years) who were given new diagnoses of AR (with or without asthma) and who were naive to AIT, use and costs of pharmacy, outpatient, and inpatient services were significantly reduced in the 6 months after versus preceding AIT initiation.[27] In a subsequent study, investigators examined 10 years (1997-2007) of Florida Medicaid claims data to compare health services use and costs between children with newly diagnosed AR who subsequently received AIT versus matched control subjects who did not receive AIT.[26] Compared with their matched counterparts, children who received AIT incurred significantly lower median total, outpatient, and pharmacy costs during the 18 months after AIT initiation. These significant health care savings were evident within the first 3 months of treatment initiation.

The present analysis examined whether AIT-related cost benefits demonstrated for children with AR extend to adults with AR diagnoses. To this effect, we examined 12 years of Florida Medicaid data as follows.

1. First, we compared health care use and costs of all targeted patients (adults and children) with newly diagnosed AR who received *de novo* AIT with matched control subjects with newly diagnosed AR who did not receive AIT.

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Support for this research was provided by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology.

Disclosure of potential conflict of interest: C. S. Hankin, A. Bronstone, and Z. Wang have been supported by one or more grants from the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology and have consultancy arrangements with Teva Pharmaceuticals and ALK-Abelló. L. Cox has consultancy arrangements with Teva Pharmaceuticals, Genentech, Stallergenes, Baxter Pharmaceuticals, and Ista and has received one or more grants from or has one or more grants pending with Stallergenes.

Received for publication December 9, 2011; revised December 7, 2012; accepted for publication December 10, 2012.

Available online January 30, 2013.

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0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2012.12.662

*Abbreviations used*
AIT: Allergen-specific immunotherapy
AR: Allergic rhinitis
CCI: Charlson Comorbidity Index
GEE: Generalized estimating equations
ICD-9: International Classification of Disease, ninth edition

2. Next, we conducted the same analyses described above for the adult (age ≥18 years) and child (age <18 years) subgroups to determine:
   A. whether previously reported AIT-related cost savings achieved by children with AR diagnoses (based on 10 years of data) held in this larger sample of children (based on 12 years of data);
   B. whether there were significant differences in health care use and costs between adults with newly diagnosed AR who received *de novo* AIT versus matched control subjects with newly diagnosed AR who did not receive AIT; and
   C. whether the magnitude of cost benefits differed between AIT-treated adults and children.

# METHODS

## Florida Medicaid dataset

To expound on the findings of our previous study in children enrolled in Florida Medicaid,[26] we examined Florida Medicaid claims data for both children and adults from July 1, 1997, to June 30, 2009. Florida Medicaid provides access to health care for more than 2 million low-income children and adults annually. The Florida Medicaid Bureau of Medicaid Program Analysis provides researchers with claims data that are patient deidentified and fully compliant with the Health Insurance Portability and Accountability Act Privacy Rule. Each patient-specific claim identifies the date and type of health service provided, such as prescription drug fills (per National Drug Codes) or medical, surgical, or diagnostic procedures (Current Procedural Terminology). Each claim also includes patients' demographics (eg, sex, age, and race/ethnicity) and clinical information (primary and secondary diagnoses according to the International Classification of Disease, ninth edition [ICD-9]). Because our research was restricted to the use of existing and Health Insurance Portability and Accountability Act–compliant patient-deidentified claims data, it was exempt from institutional board review.

## Definition of terms

ICD-9 codes 477.X identified the diagnosis of AR. Current Procedural Terminology codes 95115, 95117, 95120, 95125, 95144, 95165, 95180, and 95199 identified the administration of AIT. Comorbid allergy-related illnesses were identified by the following ICD-9 codes: 493.X for asthma, 691.8 for atopic dermatitis, and 372.X for conjunctivitis. Patients with newly diagnosed AR were those who had no AR diagnoses in the year preceding their first ("index") AR diagnosis. Patients who received *de novo* AIT were characterized as those whose first documented AIT claim followed (rather than preceded) their index AR diagnosis and who received 2 or more administrations of AIT.

## Identification of matched samples

Participants were Florida Medicaid enrollees who had a paid claim between July 1, 1997, and June 30, 2009. To identify the pool of eligible AIT-treated patients, we first selected subjects with a diagnosis of AR. In subsequent steps, we retained only those who had newly diagnosed AR, received at least 2 administrations of *de novo* AIT, and had at least 18 months of continuous enrollment after AIT initiation. To identify the pool of eligible control subjects, we selected subjects with newly diagnosed AR who had not received AIT at any time during the study. As described in greater detail below, each eligible AIT-treated patient was matched with up to 5 control subjects. We required that AIT-treated patients match to at least 1 control patient on all of the following 8 variables: demographics (age at first AR diagnosis ±6 months, sex, and race/ethnicity), comorbid illness burden (the Charlson Comorbidity Index),[29] date of AIT initiation ("match date"), and diagnoses of comorbid atopic conditions (asthma, atopic dermatitis, and conjunctivitis) during the year prior to AIT initiation (or match date). Matched control patients also were required to have at least 18 months of follow-up data from their match date. If an AIT-treated patient did not match to at least 1 control patient on all 8 matching variables, then that AIT-treated patient was excluded from further analysis. Because Florida Medicaid claims data do not provide information regarding the type of allergen or allergens to which patients had positive test results, we were not able to match on type of allergy.

To ensure that any observed differences in outcomes were unattributable to differences in disease burden not associated with AR, we matched patients on the Charlson Comorbidity Index (CCI) in the year before AR diagnosis.[29] The CCI has been widely used by researchers to measure burden of disease and has been adapted for use with ICD-9-CM administrative claims databases.[30] Although originally designed to predict risk of 1-year mortality in hospitalized patients,[29] the CCI also significantly predicts health care use and costs in primary care populations.[31,32] The CCI is comprised of 19 conditions that are assigned weights according to 1-year risk of mortality.[29] The total score (range, 0-37) is calculated as the sum of the weighted items.[29] A score of 0 denotes no comorbid illness burden.[29] The developers of the CCI noted that, in most clinical studies, it will not be possible to stratify patients into more than 2 comorbidity groups.[29] They further recommended that the selection of cut points should vary depending on the disease under investigation: if the disease investigated is associated with a low likelihood of mortality, a cut point of 1 or greater might be appropriate; if disease-related mortality is high, a cut point of 2 or greater or 3 or greater might be appropriate.[29] We used a score of 0 to 1 to characterize patients with no or mild comorbid disease burden and a score of 2 or greater for those with moderate-to-severe comorbid disease burden.

Because the CCI might not sufficiently assess the illness burden of IgE-mediated allergic illness, we further identified AIT-treated patients who had a diagnosis of other well-recognized atopic conditions (asthma, atopic dermatitis, and conjunctivitis) in the year before their first AIT administration. These AIT-treated patients were matched to control subjects with similar diagnoses of atopy during a comparable period, as follows. We first examined the AIT-treated patient sample to determine the date of each patient's index AR diagnosis and time elapsed until receiving administration of their index AIT. From the pool of matched control subjects, we established comparable periods from the dates of each control subject's index AR diagnosis. We then assessed for the presence of comorbid atopy in the year preceding this "match date." Excluded were control subjects who did not have at least 18 months of continuous enrollment after their match date and eligible AIT-treated patients who had no appropriate control group matches.

In summary, we required that each patient in the AIT-treated group match with at least 1 patient in the control group on all 8 of the following variables: age at index AR, sex, race/ethnicity, CCI 1 year prior to first AR diagnosis, date at AIT initiation, and comorbid atopic conditions (asthma, conjunctivitis, and atopic dermatitis) during the year prior to AIT initiation. Control patients who were matched on these variables also had to have at least 18 months of data after their match date. If an AIT-treated patient could not be matched on all 8 variables to at least 1 control patient, then that AIT-treated patient was excluded from further analysis. Overall, there were 3 matched cohorts of AIT-treated patients and control subjects: all patients, adults (age ≥18 years) only, and children (age <18 years) only.

## Data analyses

The Florida Medicaid Program provided data in 36 compressed text files, which we decompressed and imported for analysis by using SAS/STAT (version 7; SAS Institute, Cary, NC). We compared groups on matching variables and health care use and outcomes by using pairwise comparisons

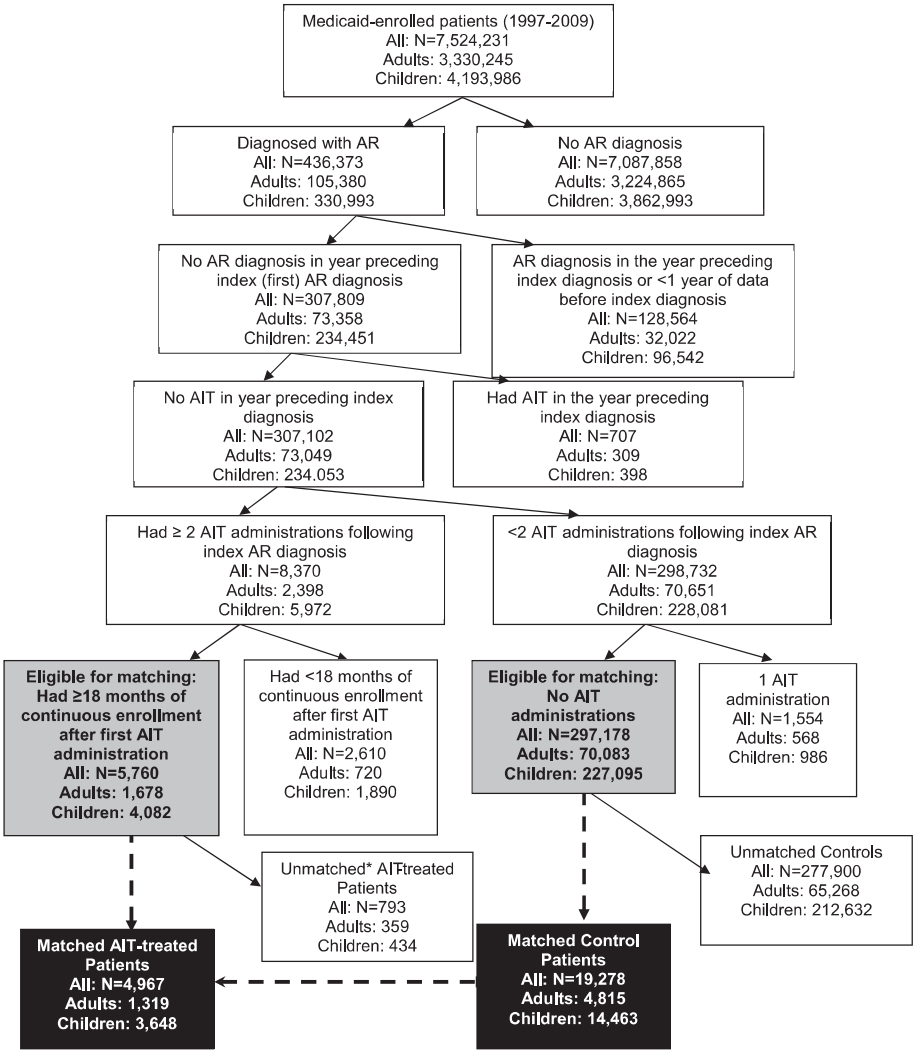



**FIG 1.** Identification of matched samples. *Seven hundred ninety-three AIT-treated patients (359 adults and 434 children) could not be matched on all 8 variables to at least 1 control patient and were therefore excluded from further analysis. Note: The 8 matching variables were: age at index AR diagnosis (±6 months), sex, race/ethnicity, CCI, date at AIT initiation, and 3 comorbid atopic conditions (asthma, atopic dermatitis, and conjunctivitis).

within cohorts. Components of total health care use and costs included inpatient care, outpatient visits (inclusive and exclusive of AIT-related care), and prescription medication use. In general, health care use data are not normally distributed and tend to be heavily skewed to the right (ie, a few patients might have unusually high rates of health care use and costs that skew the aggregated data). To withstand violations in normal distribution, we used the generalized linear model with log link and gamma variance functions to compare mean per-patient health care use and costs in patients with newly diagnosed AR who subsequently received *de novo* AIT and matched control subjects who did not receive AIT.[33] The SAS/STAT GENMOD procedure with generalized estimating equations (GEE) was used to fit the model, with correlated response for comparisons of health care outcomes between AIT-treated patients and matched control subjects. Because comparisons of the magnitude of cost savings for AIT-treated adults versus children did not involve correlated data, we used the GENMOD procedure without GEE for these analyses. Outcomes for AIT-treated patients and matched control subjects were compared for all patients, adults only, and children only. Generalized linear model with GEE also compared mean 18-month per-patient AIT-related cost savings (with positive values indicating lower mean costs for AIT-treated versus control patients) for adults versus children.

## RESULTS

### Characteristics of samples

Fig 1 displays the results of the sample identification procedures. Among all Florida Medicaid enrollees (n = 7,524,231), among whom there were 3,330,245 adults and 4,193,986 children, 5.8% (436,373/7,524,231) received a diagnosis of AR; among the 307,809 enrollees with newly diagnosed AR, 2.7% (8,370) received *de novo* AIT. Adult Medicaid enrollees were 62% less likely than child Medicaid enrollees to receive a diagnosis of AR (odds ratio, 0.38; 95% CI, 0.379-0.384; $P < .0001$) and 1.3 times more likely to initiate *de novo* AIT (odds ratio, 1.29; 95% CI, 1.23-1.36; $P < .0001$).

Overall, there were 5,760 AIT-treated patients and 297,178 control subjects eligible for matching; from this pool, 4,967 AIT-treated patients were matched to 19,278 control subjects (793 did not match to control subjects on all 8 of the requisite matching variables and were therefore excluded from further analysis). Among adults, 1,678 AIT-treated patients and 70,083 control

**TABLE I.** Comorbid disease and respiratory illness burden in the year before AIT initiation in AIT-treated adults and children and matched control subjects

| Characteristic | Adults | | | Children | | |
|---|---|---|---|---|---|---|
| | AIT group (n = 1,319) | Control group (n = 4,815) | *P* value | AIT group (n = 3,648) | Control group (n = 14,463) | *P* value |
| Comorbid disease burden: CCI, no. (%)* | | | .0007 | | | <.0001 |
| 0-1 (none, mild) | 1,244 (94.3) | 4,404 (91.5) | | 3,622 (99.3) | 14,125 (97.7) | |
| ≥2 (moderate to severe) | 75 (5.7) | 411 (8.5) | | 26 (0.7) | 338 (2.3) | |
| Respiratory illness burden, no. (%) | | | | | | |
| Acute respiratory tract infections (ICD-9 460-466) | 414 (31.4) | 1,775 (36.9) | .0002 | 2,064 (56.6) | 8,587 (59.4%) | .0022 |
| Other diseases of the URT (ICD-9 codes 470, 472, 474-476, 478) | 678 (51.4) | 2,113 (43.9) | <.0001 | 2,915 (79.9) | 9,662 (66.8%) | <.0001 |
| Nasal polyps (ICD-9 code 471.0) | 14 (1.1) | 14 (0.3) | .0002 | 36 (1.0) | 25 (0.2%) | <.0001 |
| Chronic sinusitis (ICD-9 code 473) | 208 (15.8) | 437 (9.1) | <.0001 | 718 (19.7) | 1,384 (9.6%) | <.0001 |
| Pneumonia and influenza (ICD-9 code 480-488) | 56 (4.3) | 205 (4.3) | .985 | 349 (9.6) | 1,417 (9.8%) | .675 |
| COPD and allied conditions (ICD-9 codes 490-496) | 424 (32.2) | 1,334 (27.7) | .0016 | 1,983 (54.4) | 7,223 (49.9%) | <.0001 |
| Other respiratory system diseases (ICD-9 codes 510-519) | 87 (6.6) | 315 (6.5) | .944 | 483 (13.2) | 1,345 (9.3%) | <.0001 |

*COPD*, Chronic obstructive pulmonary disease; *URT*, upper respiratory tract.
*The CCI includes 19 conditions assigned weights from 1 to 6, with a total score calculated by adding the weights.[30] A total score of 0 to 1 indicates no or mild comorbid disease burden, and a score of 2 or greater indicates moderate-to-severe comorbid disease burden.

subjects were eligible for matching, and 1,319 AIT-treated patients were matched to 4,815 control subjects (359 AIT-treated adults did not match to control subjects on all 8 of the requisite matching variables and were therefore excluded). Eligible children included 4,082 AIT-treated patients and 227,095 control subjects; of these 3,648 AIT-treated children were matched to 14,463 control subjects (434 did not match to control subjects on all 8 of the requisite matching variables and were therefore excluded).

The majority of the 1319 adults in the AIT-treated matched sample were female (86.2%) and of nonwhite race/ethnicity (53.7%); mean age at initial AR diagnosis was 47.3 (SD, 17.3) years. In the year before their initial AR diagnoses, most (96%) of these adults experienced no or mild comorbid disease burden, and rates of asthma, atopic dermatitis, and conjunctivitis were 23%, 0%, and 5.3%, respectively. The 3648 children in the AIT-treated matched sample were predominantly male (57.3%) and of nonwhite race/ethnicity (74.5%); mean age at initial AR diagnosis was 7.6 (SD, 3.9) years. In the year before their initial AR diagnoses, the majority (99.8%) of these children experienced no or mild comorbid disease burden, and rates of asthma, atopic dermatitis, and conjunctivitis were 51.1%, 5.7%, and 14.0%, respectively.

We conducted supplementary analyses to examine whether the demographic and comorbid illness characteristics of the 4967 matched AIT-treated adults and children differed from those of 793 AIT-treated patients for whom we found no matches and who were therefore excluded. Matched AIT-treated patients were significantly ($P < .0001$) more likely to be female and non-Hispanic white and to have less comorbid illness burden (CCI) in the year before their AR diagnosis and in the year before AIT initiation than unmatched subjects (data not shown). With regard to pre-existing atopy, although matched AIT-treated patients were significantly ($P < .0001$) less likely to receive a diagnosis of comorbid asthma, they were significantly more likely to receive diagnoses of atopic dermatitis or conjunctivitis compared with AIT-treated patients who could not be matched.

We returned to our primary research question to examine the overall comorbid disease burden (CCI) and specific respiratory illness burden experienced by the adult and child AIT-treated and matched control groups in the year before AIT initiation (or a comparable period for control subjects). As shown in Table I, compared with matched control subjects, adults and children who subsequently received AIT experienced significantly less overall comorbid disease burden in the year before AIT initiation. Whereas acute respiratory tract infections occurred significantly more frequently among matched controls, rates of other diseases of the upper respiratory tract, such as sinusitis, nasal polyps, chronic obstructive pulmonary disease, allied conditions, and other respiratory system diseases, such as pleurisy (in children), were significantly higher among AIT-treated patients.

**TABLE II.** Mean 18-month per-patient health care resource use and costs in AIT-treated patients and matched control subjects: all patients

| | All patients | | | |
|---|---|---|---|---|
| | AIT group | | Control group | |
| | No. | Mean ± SD | No. | Mean ± SD |
| Inpatient stays, no. | 192 | 1.9 ± 2.3* | 286 | 3.2 ± 8.2 |
| Outpatient visits (including AIT), no. | 4,954 | 40.5 ± 38.9 | 18,794 | 39.3 ± 46.0 |
| Outpatient visits (excluding AIT), no. | 4,777 | 23.6 ± 33.8§ | 18,145 | 39.9 ± 46.3 |
| AIT visits, no. | 4,967 | 21.3 ± 20.4 | — | — |
| Pharmacy fills, no. | 4,669 | 41.8 ± 48.4‡ | 17,000 | 39.7 ± 41.3 |
| Inpatient cost ($) | 192 | 8,834 ± 18,480* | 286 | 13,372 ± 27,801 |
| Outpatient (total) cost ($) | 4,954 | 2,718 ± 5,216§ | 18,794 | 4,653 ± 11,951 |
| Outpatient cost (excluding AIT [$]) | 4,777 | 2,252 ± 5,214§ | 18,145 | 4,728 ± 12,060 |
| AIT cost ($) | 4,967 | 547 ± 567 | — | — |
| Pharmacy cost ($) | 4,669 | 2,733 ± 4,312† | 17,000 | 3,039 ± 5,167 |
| Total health care cost ($) | 4,960 | 6,637 ± 1,218§ | 18,952 | 10,644 ± 18,143 |

*$P < .05$.
†$P \leq .01$.
‡$P \leq .001$.
§$P < .0001$.

## Patterns of AIT use (among patients receiving AIT)

Among all enrollees with newly diagnosed AR who initiated AIT, the median number of AIT administrations over 18 months

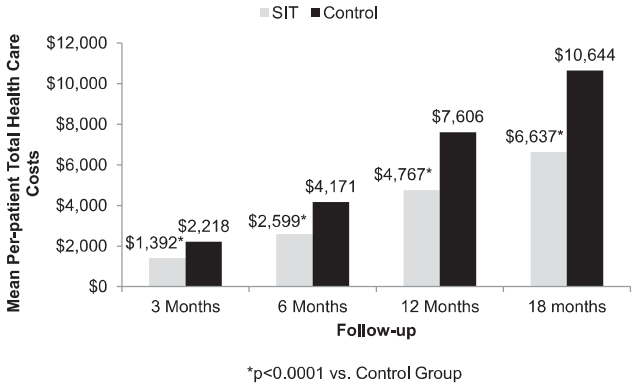



**FIG 2.** Mean total health care costs for AIT-treated patients and matched control subjects by duration of follow-up.

**TABLE III.** Mean 18-month per-patient health care use and costs in AIT-treated adults and matched control subjects

| | Adults | | | |
|---|---|---|---|---|
| | AIT group | | Control group | |
| | No. | Mean ± SD | No. | Mean ± SD |
| Inpatient stays, no. | 121 | 2.0 ± 2.6 | 194 | 2.6 ± 3.5 |
| Outpatient visits, no. | 1,315 | 34.0 ± 39.3 | 4,765 | 34.0 ± 41.5 |
| Outpatient visits (excluding AIT), no. | 1,238 | 24.0 ± 34.5* | 4,506 | 34.5 ± 41.9 |
| AIT visits, no. | 1,319 | 14.2 ± 18.3 | — | — |
| Pharmacy fills, no. | 1,203 | 83.8 ± 69.1 | 4,202 | 83.3 ± 55.3 |
| Inpatient cost ($) | 121 | 9,231 ± 21,899 | 194 | 13,152 ± 28,348 |
| Outpatient (total) cost ($) | 1,315 | 2,544 ± 4,298* | 4,765 | 3,355 ± 5,144 |
| Outpatient cost (excluding AIT [$]) | 1,238 | 2,372 ± 4,175* | 4,506 | 3,439 ± 4,805 |
| AIT cost ($) | 1,319 | 311 ± 442 | — | — |
| Pharmacy cost ($) | 1,203 | 5,336 ± 5,921 | 4,202 | 5,395 ± 4,603 |
| Total health care cost ($) | 1,319 | 10,457 ± 1,649* | 4,791 | 14,854 ± 16,557 |

*$P < .0001$.

was 13. Adults with newly diagnosed AR who initiated AIT received significantly fewer AIT administrations and experienced a shorter course of treatment than their child counterparts who initiated AIT (median number of AIT administrations was 6 for adults vs 18 for children, $P < .0001$; median duration of AIT [number of days between first and last AIT administration during 18-month follow-up] was 210 days for adults vs 271 days for children, $P < .0001$). The mean 18-month per-patient cost of AIT was $547 for the combined sample; these costs were significantly lower for adults than children ($311 vs $632, $P < .0001$) because of the higher number of AIT administrations received by children.

## Health care use and costs: Combined sample

Table II shows the 18-month mean health care use and costs for the combined (adult and child) sample. Patients with newly diagnosed AR who initiated AIT had significantly fewer inpatient stays and outpatient visits excluding AIT but more pharmacy fills over 18 months. These patients also incurred 38% lower total 18-month health care costs ($6,637 vs $10,644, $P < .0001$), as well as significantly lower costs for inpatient, outpatient, and pharmacy services (34%, 52%, and 10%, respectively).

**TABLE IV.** Mean 18-month per-patient health care use and costs in AIT-treated children and matched control subjects

| | Children | | | |
|---|---|---|---|---|
| | AIT group | | Control group | |
| | No. | Mean ± SD | No. | Mean ± SD |
| Inpatient stays, no. | 71 | 1.8 ± 1.7* | 92 | 4.2 ± 12.6 |
| Outpatient visits, no. | 3,639 | 42.8 ± 38.5 | 14,029 | 41.2 ± 47.3 |
| Outpatient visits (excluding AIT), no. | 3,539 | 23.5 ± 33.5† | 13,639 | 41.7 ± 47.6 |
| AIT visits, no. | 3,648 | 23.8 ± 20.5 | — | — |
| Pharmacy fills, no. | 3,466 | 27.3 ± 25.9† | 12,798 | 24.5 ± 18.7 |
| Inpatient cost ($) | 71 | 8,157 ± 10,441 | 92 | 13,747 ± 27,038 |
| Outpatient (total) cost ($) | 3,639 | 2,781 ± 5,509† | 14,029 | 5,123 ± 13,567 |
| Outpatient cost (excluding AIT [$]) | 3,539 | 2,209 ± 5,506† | 13,639 | 5,179 ± 13,632 |
| AIT cost ($) | 3,648 | 632 ± 583 | — | — |
| Pharmacy cost ($) | 3,466 | 1,829 ± 3,118† | 12,798 | 2,221 ± 5,101 |
| Total health care cost ($) | 3,641 | 5,253 ± 9,818† | 14,161 | 9,118 ± 18,451 |

*$P < .05$.
†$P < .0001$.

**TABLE V.** Magnitude of AIT-related cost savings in adults versus children

| | Mean 18-month AIT-related cost savings* | | |
|---|---|---|---|
| | Adults | Children | *P* value |
| Inpatient cost ($) | 3,921 ± 35,014 | 5,590 ± 28,661 | .745 |
| Total outpatient cost ($) | 811 ± 6,234 | 2,342 ± 14,231 | <.0001 |
| Outpatient cost excluding AIT ($) | 1,066 ± 6,393 | 2,970 ± 14,298 | <.0001 |
| AIT cost ($) | −311 ± 442 | −632 ± 583 | <.0001 |
| Pharmacy cost ($) | −59 ± 6,487 | 392 ± 5,868 | .092 |
| Total health care cost ($) | 4,397 ± 21,426 | 3,965 ± 20,181 | .435 |

*AIT-related cost savings calculated as the mean cost for matched control group minus the mean cost for the AIT-treated group. Positive numbers indicate that AIT resulted in cost savings.

Fig 2 compares the mean per-patient total health care costs for the combined sample of AIT-treated patients and their matched control subjects at 3-, 6-, 12-, and 18-month follow-up. Compared with matched control subjects, patients who received AIT incurred significantly lower mean per-patient total health care costs within 3 months of treatment initiation; this significant effect persisted over the 18-month follow-up period.

## Health care use and costs: Adult and child samples

Tables III and IV provide the 18-month mean per-patient health care resource use and costs for adults and children separately. Relative to matched control subjects, AIT-treated adults and children incurred 30% ($10,457 vs $14,854, $P < .0001$) and 42% ($5,253 vs $9,118, $P < .0001$) lower mean 18-month total health care costs, respectively. Both AIT-treated adults and children had significantly fewer outpatient visits excluding AIT and lower overall outpatient costs compared with their respective matched control subjects. Although AIT-treated adults did not differ from control subjects in terms of the number of inpatient stays over the 18-month period, AIT-treated children had significantly fewer

inpatient stays than their matched counterparts. AIT-treated adults did not differ from control subjects in the number of pharmacy fills and costs, but AIT-treated children incurred significantly lower pharmacy costs (despite a significantly higher number of prescription fills) than their matched counterparts. Similar to findings noted for the combined sample, significant differences ($P < .0001$) in mean total health care costs among adults and children separately occurred at 3-, 6-, 12-, and 18-month follow-up.

### Magnitude of cost savings: AIT-treated adults versus children

Table V compares mean 18-month AIT-related cost savings for adults and children. The mean 18-month total per-patient health care cost savings achieved by AIT-treated adults did not significantly differ from that observed for children ($4,397 vs $3,965, $P = .435$). The mean 18-month per-patient cost savings for outpatient visits achieved by AIT-treated children was almost 3 times greater ($2,342 vs $811, $P < .0001$) than that achieved by AIT-treated adults.

## DISCUSSION

Recent research using retrospective administrative claims data to examine the real-world outcomes of AR has consistently documented the significant economic benefits of AIT for children. In the present study we sought to extend this research to US adults with AR. Most notably, we found compelling cost benefits for AIT among US adults with AR that paralleled the benefits seen in children. Significant AIT-related cost savings were observed within 3 months of treatment initiation and persisted throughout the 18-month follow-up for the combined sample, as well as for adults and children separately. Findings demonstrated at 3 months in our study are consistent with research showing significantly reduced allergy symptoms within 12 to 14 weeks of AIT initiation.[34-36]

As a well-established, effective, and safe treatment for AR, AIT offers the potential for long-term effectiveness and preventive effects. Notwithstanding these potential benefits and despite evidence of patient dissatisfaction with symptomatic drug treatments for AR,[2,37] only 2% to 9% of US patients with an AR diagnosis receive AIT,[27,37-39] and a preponderance of patients who initiate AIT are likely to prematurely discontinue treatment.[27,39-43] Such underuse of AIT might result in suboptimal health outcomes among patients with AR.

Barriers to AIT access, which likely contribute to its underuse, include the disinclination of primary care providers, who are usually the initial point of contact for adults and children with AR,[37] to refer potential AIT candidates to allergy specialists. Lack of training in allergy/immunology during residency[44] and concerns regarding the loss of autonomy of patient care[45] have been identified as barriers to generalists' use of allergy specialist referral. On the basis of the superior outcomes seen among patients with respiratory allergy treated by allergy specialists versus generalists,[46-53] interventions that encourage collaboration between generalists and specialists could foster wider use of AIT.

Several limitations of our research should be mentioned. First, despite the matching procedures used, groups might have differed in ways other than exposure to AIT that affected observed cost differences. Although we matched patients on the presence of allergy-related comorbid disease, including asthma, before AIT initiation, it is possible that patients who received AIT had more poorly controlled asthma, which might have increased costs because of more frequent use of asthma-related emergency visits and hospitalizations. However, this seems unlikely because poorly controlled asthma is a relative contraindication for AIT because of the risk of anaphylaxis.[7] In addition to our primary, matched cohort analysis, we subsequently examined whether the AIT-treated and control groups, each in aggregate, differed by overall disease and respiratory illness burden in the year preceding AIT initiation (or comparable period for controls). This supplementary analysis showed that, compared to the control group, the AIT-treated group experienced significantly less overall comorbid disease burden, but greater respiratory illness burden, in the year preceding AIT initiation. How these differences might have affected cost outcomes is unknown, but AIT might have indirectly improved clinical and cost outcomes because the regimen requires regular and ongoing health care visits, which afford opportunities to address other health issues, including nonallergic respiratory conditions. In addition, although the validity of the CCI has been more extensively studied than other comorbidity measures[54] and was used as a measure of comorbidity in a cost study of children's asthma,[55] it has not been validated in a pediatric population. Therefore despite attempts to control for illness burden, the health status of groups might have differed and influenced use and cost outcomes.

Second, the retrospective nature of this study prohibits definitive conclusions about causality and introduces the possibility of bias. Regarding the latter, patients who elect to engage in the demands of AIT might be a more compliant group than those who do not elect to receive AIT. Given this proclivity, AIT-treated patients who receive allergy medications or recommendations for allergen avoidance might have derived greater clinical benefit and incurred lower costs than their counterparts who do not elect to receive AIT. We are currently conducting follow-up research to examine these complex issues more fully. We also acknowledge that many AIT-treated patients received fewer administrations than required to achieve maximum and long-lasting clinical benefit. Studies have demonstrated significant reductions in allergy symptoms after only 12 to 14 weeks of AIT, even though the greatest benefits are seen after the maintenance dose is achieved and maintained for at least 1 year. We are currently conducting additional analyses to examine the relationship between the frequency and duration of AIT and health outcomes.

Third, there are limitations regarding the generalizability of findings. Because this study involved Medicaid enrollees, findings might not apply to broader patient populations. In addition, excluded unmatched cases had a greater comorbid illness burden and higher prevalence of comorbid asthma than matched cases. Therefore findings might not generalize to populations that are comprised of more seriously ill patients with AR who initiate AIT.

Fourth, although pollen seasons in southern states, such as Florida, tend to begin earlier and last longer than those in northern states, a recent study demonstrated that the ragweed pollen season has lengthened in northern states while remaining stable in southern states, most likely because of climate change.[56] Because of the longer pollen season in southern states, mean medical costs for patients with AR in this study might be higher than those for similar patients living in cooler climates; however, the length of the pollen season should not influence the magnitude of cost differences observed between AIT-treated and control patients.

Fifth, claims data might include missing, imprecise, or incorrect codes, although it is unlikely that such errors would systematically differ across cohorts.

Sixth, because the follow-up period was limited to 18 months, results might underestimate the long-term clinical and economic benefits associated with AIT, considering its potential to reduce the risk of asthma,[10,11,57] one of the most common and costly chronic US childhood and adult diseases.[58]

Finally, given the limitations of claims data, we were unable to estimate the societal burden of AR associated with lost productivity and patients' out-of-pocket expenditures (eg, for over-the-counter medications) to treat AR. In light of its high prevalence and significant effect on job and school performance, the indirect costs of AR are substantial and exceed those of other costly chronic diseases, including asthma, diabetes, and coronary heart disease.[59]

This study constitutes the first demonstration of significant cost benefits associated with AIT among US adults, who experienced comparable overall AIT-related cost savings compared with those seen in children. Our research approach is consistent with the call for comparative effectiveness research that reflects real-world interventions and provides public health guidance regarding the effective care of high-cost, widely prevalent, and preventable diseases.[60] Because new and likely more expensive symptomatic drug treatments for AR and asthma proliferate, it might be wise to first benchmark the clinical and cost benefits offered by AIT. On the basis of the growing evidence of the efficacy, safety, and cost benefits of AIT, implementation of coordinated efforts to remediate modifiable barriers to AIT access, adoption, and adherence could increase appropriate use of this disease-modifying treatment and ultimately reduce the public health burden of AR and AR-related disease progression.

We thank Drs David Lang and Richard Lockey for their valuable comments on a draft of this manuscript.

**Clinical implications: Comparable, statistically significant health care cost benefits were achieved by children and adults with a diagnosis of AR who initiated AIT. Benefits appeared within 3 months of treatment initiation and continued through the 18-month follow-up.**

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