ADVOCACY COUNCIL
of the American College of Allergy, Asthma & Immunology

AMERICAN ACADEMY OF OTOLARYNGIC ALLERGY

March 23, 2016

J. Daniel Gifford, MD
Chair, Federation of State Medical Boards

Via email: MStaz@fsmb.org

Re: Compounding Medications by Physicians: FSMB Draft Position Paper

Dear Dr. Gifford:

The Advocacy Council of the American College of Allergy, Asthma and Immunology (the Advocacy Council) together with the American Academy of Otolaryngic Allergy (AAOA), are pleased to have this opportunity to comment on the Federation of State Medical Boards' Position Paper on *Compounding of Medications by Physicians.* The Advocacy Council and the AAOA together represent over 5,000 physicians board-certified or board-eligible in allergy and immunology or in otolaryngology.

Allergists have a long history of safe in-office compounding of allergen extracts that goes back over one hundred years. We commend the FMSB for initiating a discussion of safe compounding practices by physicians. However, we believe it is important for the FSMB's position paper to also acknowledge the longstanding safety of allergen extract preparation by physicians specially trained in allergy and immunology.

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.[1] In fact, 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.

[1] 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/

Background

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 subcutaneous injections are administered annually in the United States.

Allergists have been preparing allergen immunotherapy extracts in their offices for over one hundred years. Treatment of patients with allergic diseases with allergy immunotherapy is integral to our practice and is something we are specially trained to do. Because patients are being treated with small amounts of substances to which they have allergic reactions, there is always the potential for a systemic reaction, including anaphylaxis. Allergists and their clinical staff are specially trained to look for and treat such reactions. Their offices are equipped with everything needed to treat anaphylactic reactions including crash carts.

Sterility of allergen extracts is not, however, a problem. 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 gives us assurance that allergen extracts prepared in physician offices are sterile. This conclusion is supported by several studies, both retrospective and prospective.[2]

Preparation of Allergen Immunotherapy Extracts

Allergen extracts are prepared for individual patients based on the allergist's written order that specifies the content, concentration, and dosing schedule. When a patient begins immunotherapy, he or she typically begins with very diluted doses and the concentration gradually increases over time. Usually, by the end of 3-6 months, 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. They are never administered intravenously.

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

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[2] *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 ; 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; 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; 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 ; 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; 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; 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

0.4% phenol. The use of glycerinated extracts and the addition of phenol are extremely effective in ensuring that there is no bacterial growth. Aseptic technique based on current USP Ch. <797> guidelines or the standards set forth in the Allergy Immunotherapy Practice Parameters[3] is followed and the vials are labeled and stored in refrigerated conditions. Beyond use dates (BUDs) are assigned based on the most recent expiration date of any of the component antigens.

A typical multi-dose vial of maintenance extract lasts for a period of 10-12 months.[4] Dilutions, which are given at the onset of treatment, are also prepared in multi-dose vials but storage time is less because the injections are given more frequently (e.g., weekly to bi-weekly).

Patients may experience allergic 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.

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. <u>They are never injected intravenously or into body cavities or the central nervous system.</u> Thus, they present significantly less risk compared to other compounded sterile products administered through intravenous or spinal injection.

Discussion

The Position Paper sets forth a number of recommendations related to physician compounding. We agree with many of these; however we are concerned that some of the recommendations could be viewed as disapproving of compounding of allergen extracts.

First, the Position Paper notes that safety concerns exist if a pathogenic agent is introduced into a drug during the compounding process and that this can result in patient harm or even death. We agree that safety concerns exist whenever compounded materials are introduced into the human

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[3] *See* note 1.
[4] The Medicare program allows for payment of up to 12 months of antigens at a time. *See* 42 C.F.R. § 410.68

body as was tragically demonstrated several years ago in the case of New England Compounding Pharmacy. We also agree that compounding incorrectly has the potential to harm patients and that it should be performed according to specific protocols.

Allergists that prepare allergen extracts in their offices adhere to either the special protocol established by the USP in its chapter 797 on sterile compounding or to vaccine preparation guidelines developed by the allergy specialty and published as part of the Allergy Immunotherapy practice parameters. [5]As noted above, there are no reported adverse events or harm to patients resulting from sterility issues associated with allergen extract preparation.

The Position Paper states that physicians should limit compounding activity to non-sterile preparations. It also states that physicians should familiarize themselves with USP Ch. 795 (non-sterile compounding) and Ch. 797 (sterile compounding). We disagree with the statement that physicians should only engage in non-sterile compounding. Allergen extracts prepared in the office are considered sterile preparations and it is essential that patients continue to have access to this treatment. We believe this recommendation fails to properly take into consideration the established safety record of allergen extract preparation and its important role in treating patients with asthma and other allergic diseases.

The Position Paper also states that the decision to treat a patient with a compounded medication must be triggered by a specific need in an individual patient and that medications should not be compounded in bulk. We strongly agree with this statement. First, we agree that allergy immunotherapy should only be used for patients who meet the criteria for this treatment as set forth in the Practice Parameters.[6] Many patients with allergic rhinitis or asthma can be successfully treated with medication and/or environmental controls. However, once the physician, based on testing and a complete examination of the patient, concludes that allergy immunotherapy is appropriate for an individual patient, there is generally no other way to provide that treatment other than through a compounded product.

The Position Paper also states that the active ingredients included in a compound are necessary for treating the individual's specific medical condition which should be reflected in the patient's medical record. We also strongly agree with this statement. Each set of allergy immunotherapy vials should be based on the specific antigens to which the individual is reactive, based on the patient's history, skin testing and/or in vitro testing and this should be reflected in the patient's medical record. It would certainly not be appropriate to treat a patient with antigens to which a patient is not reactive or which are not present in the environment.

We also share the FSMB's concern that patients not be subject to excessive charges for compounded medications. Allergen extracts are not separately billed. Rather, they are covered as part of the physician's service which includes establishing the patient's dosage and schedule and supervising the

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[5] We note that the USP has recently proposed modifications to its Ch. 797 that would significantly modify current standards for allergen extract preparation. Our organizations are strongly opposed to these changes and are in discussions with USP to address our concerns. Our written comments to USP can be viewed here.

[6] See Note 1.

preparation. Medicare has set a fixed payment per dose that does not vary with the quantity or type of antigens include.

In summary, preparation of allergen extracts is a critical part of the practice of allergy and immunology and is something which our members are specially trained to do. We believe that any position the FSMB adopts on physician compounding must take into consideration the unique nature of allergen extract preparation by the treating physician.

Request

We are very concerned that the Position Paper, as currently worded, could be interpreted as expressing disapproval of preparation of allergen extracts by the physician in the office. We ask that the Position Paper be modified to include a section addressing the safety of allergen extracts when prepared in accordance with aseptic technique We suggest the following language:

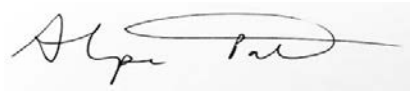
> *Sterile preparations of allergen extracts prepared by or under the supervision of specially trained physicians for their individual patients and delivered by subcutaneous injection have a long track record of safety and sterility. We believe physicians that prepare or supervise preparation of allergen extracts for their patients should follow aseptic technique and the protocols developed by the specialty and set forth in applicable published practice parameters.*

Conclusion

We appreciate the opportunity to comment on this Position Paper. This is a very important issue for our specialty. We would be happy to meet with you to further discuss this issue. If you have any questions, please do not hesitate to contact us through the Advocacy Council's Director of Advocacy Administration at suegrupe@acaai.org

Sincerely,

J. Allen Meadows, MD
Chair
Advocacy Council of ACAAI



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