

**American Academy of Allergy, Asthma, & Immunology  
American College of Allergy, Asthma, and Immunology  
American Academy of Otolaryngic Allergy**

**Joint Statement for the Record  
Before the House Energy and Commerce Health Subcommittee  
Hearing Entitled  
*“Examining Implementation of the Compounding Quality Act”***

**Tuesday, January 30, 2018**

Chairman Burgess, Ranking Member Green, and members of the Subcommittee, on behalf of the American Academy of Allergy, Asthma, & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the American Academy of Otolaryngic Allergy (AAOA), thank you for the opportunity to share our views on the implementation of the Compounding Quality Act. We hope you will consider our comments regarding efforts to establish heightened safeguards for compounded medications. The AAAAI and the ACAAI are the premier specialty societies representing more than 6,000 allergist-immunologists and related professionals worldwide dedicated to advancing allergy and immunology health care. The AAOA is the premiere otolaryngology (ENT) society focused on diseases of the respiratory tract, including allergy, and represents over 2000 members impacting over 8000 otolaryngologists.

Our written statement will discuss the recent proposed changes by the U.S. Pharmacopeia (USP) and the Food and Drug Administration (FDA) that would transform allergen immunotherapy (AIT) – a currently proven safe and effective disease modifying therapy – into a higher risk and less accessible treatment option.

**Allergen Extracts and Allergen Immunotherapy**

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 begins with highly diluted doses and the concentration gradually increases over time. Injections are typically between 0.5 and 1.0 mL and are administered subcutaneously. Usually, by the end of a year, a patient is on a maintenance dose and receives injections once or twice every month. For some patients, such as those with life-threatening stinging insect allergies, this course of treatment can create a change in the body’s immune response that is potentially life-saving.

The mixing of allergen immunotherapy treatment sets 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 specialty-developed Practice Parameters is followed, and vials are labeled and stored in refrigerated conditions accordingly. Beyond-use dates (BUDs) are assigned based on the most recent expiration date of any of the component antigens. The inclusion of preservatives deters many infectious

concerns while allowing treatment to proceed safely by use of consistent extract over many months while the immune response to the allergens present increases.

A typical multi-dose vial of maintenance extract contains 10 doses designed to last over a 10-12 month period. 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).

Allergen extracts are uniquely situated compounded products. Allergen extracts require close monitoring at the time of the injection, and patients are closely monitored in the physician's office for reactions for at least 30 minutes post-injection. Additionally, patients receiving immunotherapy come to the physician's office at least monthly for injections. Before each new injection, patients are queried regarding any issues with the previous injection including any lesser reactions. The injection site is also physically examined. Any problems are reported to the physician. Based on the patient history and well-being, modifications are implemented to protect patients. For example, dose reductions or a postponed administration might be adopted if a patient has suffered 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 for the patient's current condition and not delayed. Anaphylactic reactions are always a possibility throughout immunotherapy treatment, and are the primary risk to allergen immunotherapy patients. The ability to compound and consistently monitor the use of allergen extract is fundamental to minimizing this risk.

Allergen immunotherapy has been safely compounded and administered in allergists' offices for over 100 years. This precision medicine technology is life altering and at times lifesaving. And unlike many other compounded treatments, AIT is administered subcutaneously and not parenterally or intrathecally, essentially eliminating any risk of systemic infection. Indeed, there is no documented evidence of an infectious risk from compounding allergen extracts in the office setting.

### **Current Standards**

Current U.S. Pharmacopeia (USP) <797> standards, which are recognized by the FDA in regulation and guidance as required by statute, distinguish the unique nature of allergen extracts from other compounded drugs and provide specific requirements for their use. However, allergen extracts as compounded sterile preparations (CSPs) are not subject to the personnel, environmental, and storage requirements.

### **FDA Guidance**

In February 2015, the Food and Drug Administration (FDA) issued draft guidance titled "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application Guidance for Industry." Those FDA draft guidelines suggest in-office allergen extract compounding should follow the USP <797> instructions specific to allergen extracts and specified policies which provided special exceptions recognizing the unique nature of AIT. We previously submitted comments generally in support of the FDA draft guidance, and we are pleased that the final guidance released in January 2018 retains the special exemptions for allergen extracts.

Given that Congress has statutorily required the FDA defer to the USP for some key regulatory questions, we urge you to maintain oversight not only over the FDA process but also the USP process. As you may be aware, USP is in the process of crafting a significant revision to the <797> chapter that, if approved as proposed, could significantly alter the process of AIT compounding and administration that could significantly decrease access to this treatment.

In the fall of 2015, USP published a proposed revision of Chapter 797 that significantly altered the standards for sterile compounding, moving from a risk assessment-based series of requirements to one that treated all sterile compounding as equally and inherently dangerous, regardless of the contents or administration site of the compounded material. The proposed changes to the USP for allergen compounding are not based on published scientific data in which any infectious clinical problem(s) with allergen extract compounding has occurred. However, these proposed changes have the potential to significantly decrease the safety of AIT and place patients at increased risk for adverse outcomes.

Under the proposed revisions, allergen extracts would no longer have specific requirements for their use but would instead be treated similar to all other CSPs. The proposal would require that all sterile compounding, including allergen extract compounding, be performed in an ISO Class 5 environment. This contradicts current USP <797> guidelines and current FDA guidelines, without providing any evidence that such an approach is necessary to avoid infectious risk from mixing and administration of AIT. Therefore, we reject that the current standards (as previously agreed to by the USP and FDA) are insufficient to safely provide these services in the physician's office.

The USP proposal would also require discarding of all preparations after either 28 or 42-days regardless of manufacturer beyond use dates (BUDs). This change would require more frequent mixing of allergen extracts, significantly increasing 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. In addition to safety concerns, shorter BUD requirements would impact the 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 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.

The proposed changes to USP <797> are not indicated by the medical literature, which supports the conclusion that allergen extract preparation following current <797> guidelines is safe and does not place patients at risk for infectious complications related to AIT. The over-reaching and dangerous USP proposal was met with almost 8,000 comments. The volume, intensity and extraordinary level of concern expressed in those comments reflects significant consideration from health care providers and patients, as well as an expectation that evidence supportive of this overreaching, "one-size-fits-all" approach should be provided before such draconian measures should be considered.

Recently, USP invited a private practicing allergist, Andrew Murphy, MD, FAAAAI, to serve as an expert consultant, providing important input as the USP Compounding Expert Committee (CEC) completes work on its second draft of USP <797> for public comment (expected September 4, 2018). However, there is no opportunity for ongoing feedback from the national specialty organizations while this work is underway.

#### **FDA Position**

In August 2016, the FDA issued draft guidance on insanitary conditions at compounding facilities. The draft guidance duplicates USP's inappropriate proposal that would require an ISO class 5 environment (among other things) or otherwise declare mixed products insanitary. This is a broad over-reach, given that these environmental standards have not previously been applied to the much-broadened category of "compounding facility" cited in the FDA's proposal.

Additionally, we are concerned that through this draft guidance, FDA is fundamentally attempting to undermine the processes in place at the USP regarding the Chapter 797 proposed revision.

Recently, the FDA announced as part of its 2018 Compounding Policies Priority Plan<sup>1</sup> that the Agency plans to revisit some of these key issues in light of concerns raised by providers. Specifically, the document states (with respect to the insanitary conditions guidance): “This guidance will address concerns raised by some providers who compound small quantities of drugs in their offices for patient use, and as part of their routine clinical practice. This came up in the setting of certain dermatological procedures, for example. The FDA plans to better define the circumstances under which we believe drugs are being mixed and applied in a manner that creates negligible patient risk, and therefore wouldn’t be subject to the same compliance policy under the agency’s risk-based approach to implementing these requirements.”

Therefore, we look forward to receiving more information from the FDA. Previously, we requested that the FDA withdraw this draft guidance, but we appreciate the FDA taking an initial step of recognizing the valid concerns we have presented. We urge Congress to continue to maintain oversight of the regulatory process to ensure that patient access is not unnecessarily hampered.

### **Impact of Proposed Changes**

If the USP and FDA proposals are finalized, as initially drafted, patient access to AIT will be drastically reduced, if not eliminated, because allergists will no longer be able to prepare AIT vials for their patients in their offices. Moving allergen extract preparation to large compounding laboratories or pharmacies is not a viable alternative due to safety considerations. Patients experiencing allergic reactions to their immunotherapy injections require the allergist to change the content or dilution of the vials before they can receive the next injection. Failure to do so could result in a life-threatening systemic allergic reaction. These adjustments need to be done while the patient is in the office if the patient’s treatment schedule is to continue without significant interruption or delay. Compounding pharmacies, located off-site from the allergist’s office, would not be able to make these adjustments in a timely fashion.

Again, anaphylaxis is the major risk in an AIT treatment. This risk is carefully managed under current requirements by having the extract mixed onsite by physicians and staff with a personal knowledge and experience with each and every patient. Outsourcing extract preparation removes this important safeguard and severely limits a physician’s ability to respond to any adverse allergic reactions to AIT or other considerations impacting treatment. The proposed revisions would require patients to start new extract vials every month, most likely changing source material in the extract, and thus significantly increasing risk for adverse and potentially fatal allergic reactions. These changes therefore decrease the safety and increase the risk to the patient, forcing physicians and patients to decide if the newly increased risk is actually worthwhile, all based on a hypothetical but undocumented risk of infection.

### **Conclusion**

To date, neither the FDA nor the USP has provided any scientific data, case reports or anecdotal evidence that AIT compounding, following current USP guidelines and in accordance with section 503A of the FD&C Act, has resulted in an infection.

Members of Congress have previously weighed-in on this issue, urging the Secretary of the Department of Health and Human Services (HHS) to carefully weigh proposed regulations and the impact that they

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<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm>

have on patient care. The FDA has recognized the important and vital role of allergen immunotherapy in managing patients with allergic diseases. In addition, proposed changes in USP <797> decrease the safety of allergen immunotherapy and increase documented risk of anaphylactic reactions, in an effort to prevent what is no more than a hypothetical risk. Proposed changes are overreaching, not based on any data suggesting a risk of infectious complication from allergen extract compounding, and ignore the scientific data that supports the safety of allergen extract compounding. Failure to keep the current USP <797> guidelines for allergen extract compounding will significantly increase the risk/benefit ratio of AIT and needlessly place patients in danger of medical complications and potential death.

We urge Members of this Subcommittee and the Congress to actively oversee FDA's efforts to revise its compounding guidance documents. Forthcoming revisions should recognize that AIT compounding is a safe and unique compounding procedure that can continue following current <797> guidelines.

Thank you again for taking into consideration our written comments. I encourage you to contact Sheila Heitzig, JD, MNM, CAE, AAAAI Director of Practice and Policy, at (414) 272-6071 or [sheitzig@aaaai.org](mailto:sheitzig@aaaai.org), Jim Sublett, MD, ACAAI Executive Director of Advocacy and Governmental Affairs, at [jsublett@familyallergy.com](mailto:jsublett@familyallergy.com), or Jami Lucas, AAOA Executive Director and CEO, at [lucas@aaof.org](mailto:lucas@aaof.org) if you have any questions. The American Academy of Allergy, Asthma, & Immunology, the American College of Allergy, Asthma and Immunology, and the American Academy of Otolaryngic Allergy look forward to working with the Subcommittee to address issues of importance to our patients and ways in which we can promote public health.