



American  
**College**  
of Allergy, Asthma  
& Immunology



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



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September 21, 2016

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

**RE: *Docket No. FDA-2016-D-2268 DRAFT GUIDANCE “Insanitary Conditions at Compounding Facilities”***

To Whom It Concerns:

The Advocacy Council of the American College of Allergy, Asthma and Immunology (the AC), the American College of Allergy, Asthma and Immunology (ACAAI), the American Academy of Otolaryngic Allergy (AAOA) and the Asthma and Allergy Network (AAN), are writing to express their very serious concerns regarding the FDA Draft Guidance on *Insanitary Conditions at Compounding Facilities* (hereafter “the Draft Guidance”). The AC is sponsored by the American College of Allergy, Asthma and Immunology (ACAAI), a national specialty organization of over 3,500 physicians who are board-certified or board-eligible in allergy and immunology. The AAOA represents approximately 2500 board-certified otolaryngologists. AAN is a multidisciplinary, patient-centered network with over two million members that is dedicated to ending needless death and suffering due to asthma, allergies, and related conditions.

Our organizations strongly support FDA’s mission of protecting human health by ensuring that drugs and biologics are prepared under conditions that are safe and sanitary. However, we are concerned that certain requirements in the Draft Guidance do not take into consideration the unique characteristics of preparation of prescription sets of allergenic extracts.<sup>1</sup> Although we agree with most of the conditions set forth in the Draft

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<sup>1</sup> A “prescription set” has been defined by FDA 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

Guidance, the conditions related to preparation in an ISO Class 5 environment would seriously limit the ability of physicians, including the vast majority of our members, to prepare allergenic extracts in their offices for subcutaneous administration to their patients. As discussed in detail below, allergists having been preparing allergenic extracts in their offices for over 100 years under general aseptic conditions but outside of an ISO Classified environment with no evidence of sterility problems or patient harm.

The Draft Guidance also appears to diverge from FDA policy as set forth in its February 2015 Draft Guidance on *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* (hereafter “Draft Guidance on Mixing, Diluting or Repackaging”). As proposed, the Draft Guidance would drastically limit patient access to effective care for asthma and other allergic diseases and carries significant public health consequences. It also sets more stringent standards and is thus at cross purposes with FDA’s careful intent, in the Draft Guidance on Mixing, Diluting or Repackaging, to ensure that patients continue to have access to allergenic extract prescription sets compounded in their physicians’ offices.

For these reasons, and as more fully explained below, we ask that the Draft Guidance be amended to exempt from enforcement allergenic extract prescription sets that are prepared outside of an ISO Classified environment. The specifics of our Request and suggested draft language are set forth in Section 4 below.

## 1. Background

In its Draft Guidance on “Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application,” issued in February of 2015, FDA took special care to recognize the unique circumstances surrounding the preparation of “prescription sets” of licensed allergenic extracts and states that the agency will not take action for violations of § 351 of the Public Health Service (PHS) Act or § 502(f)(1) of the Food Drug and Cosmetic (FD&C) Act (“the Act”) if prescription sets are prepared in accordance with the ten conditions set forth in that Draft Guidance. We support those requirements and believe that the vast majority of our members are already in compliance.

One of the ten conditions is that allergenic extracts be prepared “in accordance with USP Chapter <797> . . .” 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 USP’s Sterile Compounding Committee to address safety concerns surrounding compounding of allergen extracts. As a result of these collaborative efforts, when the final USP Ch. <797> rules were issued, allergenic extracts were exempted from the stringent standards applicable to other compounded sterile products as long as certain standards specific to allergenic extract preparation were met. These rules have been in effect since 2008 and have been widely adopted by the majority of practitioners in the allergy community. Significantly, those standards do not require that allergenic extracts be prepared in an ISO Classified environment.<sup>2</sup>

In contrast, under this Draft Guidance, prescription sets of allergenic extracts subject to the provisions of the FD&C Act (including the provisions regarding adulteration), would have to meet the same stringent environmental and engineering controls and sterility testing requirements applicable to compounding facilities making high risk sterile preparations intended for intravenous, spinal, or other systemic means of administration.

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instructions from a prescription or order by a licensed physician for an individual patient.” FDA Draft Guidance on “Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application,” Feb. 2015, page 12.

<sup>2</sup> In September 2015, the United States Pharmacopeia (USP) proposed revisions to Chapter <797> that would eliminate its special treatment of allergenic extracts and would be counter to the intent of FDA’s Draft Guidance on Mixing, Diluting or Repackaging with respect to preparation of allergenic extracts. See [http://www.usp.org/sites/default/files/usp\\_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf). The AC vigorously opposes the USP proposal and has communicated its concerns to USP. It is our understanding that USP intends to re-issue its proposed Ch. <797> revisions for additional comment sometime before the end of 2016 and that additional changes are likely. The AC has also communicated its concern to FDA in comments on the Draft Guidance on *Mixing, Diluting or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* because that Guidance proposes to incorporate future USP Ch. <797> provisions by reference.

Although we understand the importance of these requirements for most sterile compounded products, the more than 100 years of clinical practice and lack of reports of patient harm in the medical literature are clear evidence that such requirements are not necessary for preparation of allergen extract prescription sets using standard aseptic technique.

## 2. Safety and Efficacy of Allergenic Extracts Prepared in Physicians' Offices

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.<sup>3</sup>

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.<sup>4</sup> Allergists have been preparing allergen immunotherapy extracts in their offices for over 100 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 100-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 safe and sterile. This conclusion is supported by several studies, both retrospective and prospective.<sup>5</sup>

### A. Preparation of Allergenic Extracts

The mixing of allergenic 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 Practice Parameters<sup>6</sup> developed by the Allergy and Immunology national specialty societies is followed and the vials are labeled and stored in refrigerated conditions. Those standards do not require preparation in an ISO Class 5 environment and thus are different from USP standards applicable to other compounded sterile products. Beyond Use Dates (BUDs) are assigned based on the most recent expiration date of any of the component antigens.

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<sup>3</sup> 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/>

<sup>4</sup> 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.

<sup>5</sup> 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.

<sup>6</sup> See <http://www.allergyparameters.org/published-practice-parameters/alphabetical-listing/immunotherapy-download/>.

A typical multi-dose vial of maintenance extract contains enough doses to last over a 10- to 12- month period.<sup>7</sup> Dilutions, which are given at the onset of treatment, are also prepared in ten-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.

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, allergenic 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.

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

Several recent studies support the safety of allergenic extracts prepared under aseptic technique but outside of an ISO Class 5 environment. A report by allergists at Lackland Air Force Base described ten 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.<sup>8</sup> 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-controlled 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.<sup>9</sup> 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 eight-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.<sup>10</sup>

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.<sup>11</sup> Nor did any of the

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<sup>7</sup> The Medicare program allows for payment of up to 12 months of antigens at a time. *See* 42 C.F.R. § 410.68

<sup>8</sup> 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.

<sup>9</sup> 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.

<sup>10</sup> 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.

<sup>11</sup> 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.

patients, who were seen every one to three 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.<sup>12</sup>

A pilot study has recently been completed at two 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 five days) was examined over a ten-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 five-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.<sup>13</sup>

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.<sup>14</sup> 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.<sup>15</sup> None of the vials showed microbial growth and no difference was found between hood or bench top preparations.

These studies support the current safety and sterility of allergenic extracts prepared in physicians' offices using standard aseptic technique. We do not believe that preparation of prescription sets outside of an ISO Class 5 environment should be considered preparation in insanitary conditions in violation of Section 501(a)(2)(A) of the Act.

### **3. Public Health Impact**

#### **A. Impact on Access to Care**

Respiratory allergies affect more than 50 million Americans. The most common respiratory allergy, allergic rhinitis, represents the 5<sup>th</sup> leading chronic disease overall, and the third leading chronic disease among children

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<sup>12</sup> *Id.*

<sup>13</sup> Balekian DS, *et al.* *J Allergy Clin Immunol.* 2016. DOI: <http://dx.doi.org/10.1016/j.jaci.2016.03.021>

<sup>14</sup> 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.*

<sup>15</sup> 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.

under age 18.<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup>

Survey data from the American Academy of Allergy Asthma and Immunology and the American College of Allergy, Asthma and Immunology of their members suggest 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.<sup>19</sup>

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. If the provisions of the FDA Draft Guidance related to use of ISO Class 5 environments and related monitoring provisions are enforced with respect to prescription sets of allergenic extracts, it will be virtually impossible for allergists to safely prepare allergen immunotherapy for their patients without being at risk of violating the PHS Act and the FD&C Act.

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.<sup>20</sup> Randomized controlled studies also show that it is effective in preventing the development of asthma in individuals with allergic rhinitis.<sup>21</sup> In fact, allergen-specific immunotherapy is the only treatment known to provide long-term benefit and alter the course of allergic disease.<sup>22</sup>

Allergen immunotherapy also reduces health care costs. In a groundbreaking study involving an analysis of ten 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 patient.<sup>23</sup> 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.<sup>24</sup>

If, as a result of this Draft Guidance, prescription sets must be prepared in an ISO Class 5 environment, patient access to allergen immunotherapy will be severely threatened, if not eliminated, because the vast majority of

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<sup>16</sup> 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 21<sup>st</sup> Century, November 1999. See <http://www.agingsociety.org/agingsociety/pdf/chronic.pdf>.

<sup>17</sup> 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.

<sup>18</sup> *Id.*

<sup>19</sup> These numbers are based on more current information that numbers cited in our comment letter dated April 28, 2015. They reflect 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.

<sup>20</sup> 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/>.

<sup>21</sup> *Id.*

<sup>22</sup> Cox L, Atwater S. *Allergen immunotherapy for allergic rhinitis and asthma*. Drug Benefit Trends 2008;20:1-6.

<sup>23</sup> 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).

<sup>24</sup> *Id.*

allergists will be unable to comply with the extremely costly and resource intensive requirements that go along with establishing and maintaining an ISO Class 5 environment. Nor is moving allergenic extract preparation to large compounding laboratories or pharmacies 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. In addition, any requirement for sterility testing prior to revised extract release introduces an unsustainable delay in treatment, as well as patient safety and efficacy concerns.

Furthermore, for those few large groups or laboratories that might be able to meet the ISO Class 5 and related conditions in the Draft Guidance, 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 § 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*.<sup>25</sup> We believe that the Draft Guidance could make access to care for these vulnerable populations a significant issue negatively impacting their health with no offsetting safety benefits.

## **B. 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. Thus, it is not simply a matter of moving preparation of prescription sets to large commercial laboratories or outsourcing facilities with ISO Class 5 environments because preparation of allergenic extracts in such environments, away from the treating physician's direct oversight and supervision, would not meet applicable coverage rules. This would directly and negatively impact the health care of hundreds of thousands of Medicare recipients and others and could transfer the cost of a previously covered benefit to the beneficiary.

## **4. Request**

We do not believe FDA intended that the Draft Guidance would have this result; rather it seems clear from prior Industry Guidance that FDA has taken care to ensure that access to allergenic extracts prepared in physicians' offices is preserved, as reflected in the enforcement safe harbor for allergenic extracts established in the Draft

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<sup>25</sup> 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](http://www.epa.gov/sites/production/files/2014-08/documents/federal_asthma_disparities_action_plan.pdf).


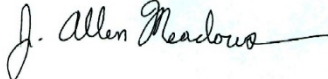
Guidance on Mixing, Diluting or Repackaging. For this reason, we ask that FDA amend the Draft Guidance so that the requirements related to preparation in an ISO Class 5 environment do not apply to preparation of allergenic extract prescription sets. Draft language for such a policy is set forth in Attachment A. This modification to the Draft Guidance will preserve patient access without jeopardizing patient safety and will allow the hundreds of thousands of patients who receive allergen immunotherapy to continue to do so.

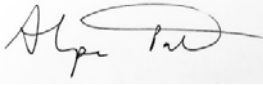
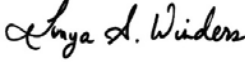
## 5. Conclusion

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.

We appreciate your consideration of our views on this important issue. We can be reached through the AC's Director of Advocacy Administration, Susan Grupe at [SueGrupe@acaai.org](mailto:SueGrupe@acaai.org) or 847-427-1200.

Sincerely,

 Brian L. Martin, DO President American College of Allergy, Asthma & Immunology		 J. Allen Meadows, MD Chairman Advocacy Council of the ACAAI
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	 Alpen Patel, MD- Socio-economic Chair- American Academy of Otolaryngic Allergy	 Tonya Winders Chief Executive Officer Allergy & Asthma Network
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cc: Michael Nelson, MD, PhD  
Chair, FDA Allergenic Products Advisory Committee

Jay E. Slater, MD  
Division of Bacterial, Parasitic and Allergen Products, FDA



**Attachment A**  
**Suggested Revision to Draft Guidance (Line 326)**

**C. Licensed Allergenic Extracts**

FDA recognizes that there are circumstances in which licensed allergenic extracts would be mixed and diluted in a physician office or similar setting to provide subcutaneous immunotherapy to an individual patient. Such combinations are commonly referred to as prescription sets.<sup>26</sup> 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.

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 settings that do not meet the requirements of section III.A related to maintaining an ISO Class 5 area. FDA would not consider such products to have been prepared in insanitary conditions in violation of 501(a)(2)(A) of the Act. Further, FDA would not expect that entities engaged in preparing prescription sets of allergenic extracts conduct the routine environmental monitoring set forth in section III.B. with respect to testing required for ISO Class 5 areas.

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<sup>26</sup> 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.