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Immunotherapy Preparation Guidelines, Rules, and Regulation

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Abstract Allergen immunotherapy has been used to treat allergic diseases for more than 100 years. In the U.S., the preparation of diagnostic and therapeutic extracts requires the cooperation of the extract manufacturer, who provides the individual allergen concentrates, and the practicing physician who formulates, dilutes, and administers the final patient-specific treatment extract. The guidelines, rules, and regulations for these activities have been established and continue to be developed as progress is made. The molecular characterization and standardization of allergenic extracts has allowed for improvements in defining the potency of these products. In turn, these advances have led to improved dosing regimens and formulation practices. This review will describe in detail some of these interactions and will identify issues that require more attention.

Keywords Allergen immunotherapy · Allergenic extracts · Standardization · Immunotherapy dosing · Formulation guidelines · Practice parameters · Preparation · Regulation

Introduction

Allergen immunotherapy is the practice of diagnosing and treating patients using allergen products derived from substances that can cause allergic symptoms after exposure. Following the diagnosis of allergic disease and determining the relevant allergen or allergens for each patient, a treatment regimen is formulated. The methods used for choosing allergens for treatment can be varied, but are based on the clinical significance of regional aeroallergens, the cross-reactivity patterns between allergens, the availability of standardized allergen products, and the need to target the optimal concentration for each constituent [1••]. Treatment vials formulated for polysensitized patients frequently contain multiple allergen extracts, therefore potential deleterious interactions between products need to be considered. Finally, allergenic extracts that are formulated in multiple-dose vials must contain a preservative unless it contains 50 % or more volume in volume (v/v) glycerin [under 21 CFR 610.15(a)]. There are distinct differences in immunotherapy treatment in the U.S. compared to Europe [2]. In Europe, all the therapeutic products are compounded by the manufacturers in pharmaceutical compliant facilities. In contrast, the treatment vials in the U.S. are mostly compounded in physician offices, laboratories, or hospital pharmacies using manufacturers' bulk concentrates. The manufacturers' products are regulated by the Food and Drug Administration (FDA), but generally, the patient-specific formulations are not. Given the complexity of the formulations that can contain 10 or more individual allergen extracts, it is important to establish controls and standards for compounding immunotherapy mixtures.

Principles of Formulating Allergen Immunotherapy Extracts

Allergen immunotherapy guidelines have been developed by the Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology (JCAAI). The objective of the allergen immunotherapy practice parameter [1••] is to establish a safe and effective use of allergen immunotherapy while reducing

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unnecessary variation in immunotherapy practice. Mixing, labeling, and dosing recommendations for immunotherapy vials are recommended. The parameter also addresses the use of diluents, allergen stability, compatibility, and expiration dating. Other topics relevant to allergen immunotherapy extract preparation, and use have also been recently reviewed by Cox et al. [3•] and Nelson [4].

Allergenic Extracts

Nearly 500 different allergenic extracts derived from pollens, fungi, stinging insects, mites, and animal danders are marketed in the U.S. by six licensed manufacturers for immunotherapy. These extracts are complex natural biomaterials containing proteins, carbohydrates, lipids, glycoproteins, enzymes, and other substances that may or may not be allergenic. The characterization and analysis of allergen extracts has played an important role in the standardization of 19 of these products, but still most extracts in use today are not standardized [5].

Standardized allergenic extracts include the pollens from short ragweed, 7 northern pasture grasses, and Bermuda grass, cat hair/epithelia, the house dust mites, *Dermatophagoides farinae* and *D. pteronyssinus*, and the Hymenopteran venoms from the honey bee, yellow jackets, hornets, and paper wasps. (Table 1) Standardized extracts are labeled in various units depending on the product and type of testing done to determine potency. Skin testing is an essential component in determining the biological activity of allergen extracts and in assigning the potency unit used in the U.S., the bioequivalent allergy unit (BAU). The FDA has developed a method using quantitative intradermal skin testing with serially diluted extracts in highly allergic subjects. This method, referred to as the ID50EAL or intradermal dilution for 50-mm sum of erythema, determines the bioequivalent allergy units and has been applied to the standardization of the extracts derived from house dust mites, cat hair/epithelia, and grass pollen extracts. Because the procedure is time consuming and requires human subjects, it cannot be routinely used for lot release testing. In vitro potency assays that are predictive of the extracts' biological activity have been developed for quality control purposes by the manufacturers and the FDA. The grass pollen and house dust mite extract potencies are determined by comparing the relative inhibition of the binding of specific IgE antibodies from pooled allergic sera to a reference preparation with a defined BAU or AU. When data supporting the correlation of the overall biological activity of an extract to the concentration of a single allergenic component are available, then the measurement of the major allergens content is used. For example, cat hair and epithelia extracts are labeled as 10,000 BAU/mL if they have between 10 and 19.9 FDA Units Fel d 1 /mL. Short ragweed pollen extracts are labeled on the basis of their Amb a 1 (Antigen E) content and the extraction ratio (w/v) used for their manufacture. In addition, one manufacturer provides a short ragweed pollen extract that is labeled on the basis AU/mL. For Hymenopteran venom extracts, the total protein content and the presence of the major allergens, hyaluronidase and phospholipase is verified by enzymatic tests for each lot.

There are no FDA validated methods or requirements for testing the potency of non-standardized extracts. Lot-to-lot consistency of these extracts relies on controlled source material collection, processing, and storage, and by the use of reproducible extraction and sterile filtering procedures. Non-standardized extracts are labeled in terms of their w/v extraction ratio, such as 1:10 w/v or 1:20 w/v; or in terms of their Protein Nitrogen Units per mL, such as 10,000 PNU/mL. Many of the more important offending allergen species have been characterized and proteins identified that are sensitizers in various populations. At this time, except in a few cases, these important allergens are not measured in individual lots. The assays and reference standards used in these cases are specific to the manufacturer and may or may not be comparable to other manufacturer's assays [6, 7].

Continued progress with allergen identification, characterization, and assay development is needed to expand the list of standardized extracts. For example, no fungal extracts have been standardized to date. The lack of a single allergen standardization approach as well as problems specific to fungal allergens has impeded progress [8]. Future studies targeting those allergens that have the greatest impact on public heath could also help to optimize our efforts and to set priorities. For example, it has been proposed [9] that future standardization efforts should focus on products that meet criteria to maximize the public health benefit. This could be done by targeting extracts that (1) are in widespread use in the U.S., (2) are produced by a majority of manufacturers, and (3) have greater public health impact from correct diagnosis or treatment. Selecting those products that meet one or more of these criteria should be a priority for the future.

Effective Dosing

An advantage to using standardized allergenic extracts is that dose regimens employed in controlled trials can be directly and safely applied to clinical practice. For example, there are well-controlled clinical trials proving the efficacy and safety of short ragweed pollen and cat hair allergenic extracts that were conducted with U.S. standardized allergenic extracts [10–13].

The studies with standardized products have provided guidance for efficacious and safe immunotherapy. The immunotherapy practice parameter recommends maintenance target doses for U.S.-licensed allergenic extracts [1••]. The

Table 1 Standardized allergenic extracts licensed in the U.S.

Allergenic extract	Labeled unitage	Lot release testing
Short ragweed (*Ambrosia artemisiifolia*)	w/v or AU/mL, and Amb a 1 U/mL	Amb a 1 - Radial immunodiffusion (200–400 Amb a 1 U=100,000 AU; 1 U≈1 μg)
Bermuda grass (*Cynodon dactylon*)	BAU/mL	Competition ELISA, total protein
Perennial ryegrass (*Lolium perrene*)	BAU/mL	Competition ELISA, total protein
Timothy grass (*Phleum pretense*)	BAU/mL	Competition ELISA, total protein
June (Kentucky bluegrass) (*Poa pratensis*)	BAU/mL	Competition ELISA, total protein
Orchard grass (*Dactylis glomerata*)	BAU/mL	Competition ELISA, total protein
Meadow fescue grass (*Festuca elatior*)	BAU/mL	Competition ELISA, total protein
Red top grass (*Agrostis alba*)	BAU/mL	Competition ELISA, total protein
Sweet vernal grass (*Anthoxanthum odoratum*)	BAU/mL	Competition ELISA, total protein
House dust mite (*Dermatophagoides farinae*)	AU/mL	Competition ELISA, total protein
House dust mite (*Dermatophagoides pteronyssinus*)	AU/mL	Competition ELISA, total protein
Cat pelt (*Felis domesticus*)	BAU/mL	Fel d 1 – Radial immunodiffusion (10–19.9 Fel d 1 U/mL=10,000 BAU/mL; 1 U≈3–4 μg)
Cat hair (*Felis domesticus*)	BAU/mL	Fel d 1 – Radial immunodiffusion (10-19.9 Fel d 1 U/mL=10,000 BAU/mL; 1 U≈3–4 μg)
Yellow hornet (*Dolichovespula arenaria*)	μg protein	Total protein, hyaluronidase and phospholipase activity
White-faced hornet (*Dolichovespula maculata*)	μg protein	Total protein, hyaluronidase and phospholipase activity
Yellow jacket (*Vespula* spp.)	μg protein	Total protein, hyaluronidase and phospholipase activity
Paper wasp (*Polistes* spp.)	μg protein	Total protein, hyaluronidase and phospholipase activity
Mixed vespid (*Vepula* spp. + *Dolichovespula* spp.)	μg protein	Total protein, hyaluronidase and phospholipase activity
Honey bee (*Apis mellifera*)	μg protein	Total protein, hyaluronidase and phospholipase activity

recommendations are based on doses shown to be effective in clinical studies conducted world-wide. Table 2 summarizes the probable effective dose ranges for U.S. standardized and non-standardized allergenic extracts as recommended in the practice parameter.

For studies using products not available in the U.S., the study extract potency was compared, when possible, with U.S. extracts. Doses for ragweed pollen and cat extracts were based on studies employing U.S. standardized extracts, and are, therefore, essentially interchangeable to those available from U.S. manufacturers. Short ragweed pollen immunotherapy with a dose of 6-12 Amb a 1 Units was shown to be effective [12, 13]. Similarly, immunotherapy trials with cat hair extract showed that 15ug Fel d 1 showed the best efficacy for symptom improvement [10, 11], though 5ug also showed a positive effect [14]. The Amb 1 (Antigen E) concentration is available on the label of each lot of standardized short ragweed allergenic extract, so the volume needed in a maintenance vial can be calculated. Based on the estimated Fel d 1 content of 20–50 μg/mL for a U.S. standardized cat extract, 5–15 μg of Fel d 1 would be equivalent to about 1,000–4,000 BAU.

There have been no double-blind, placebo-controlled injection immunotherapy trials in the U.S. for standardized grass or house dust mite extracts. Therefore, recommending doses for grass and mite allergy must rely on studies done outside the U.S. with European extracts. Clinical investigations for grass allergy [15, 16] and for dust mites [17, 18] used alum-adsorbed allergy vaccines and described doses in terms of units unique to the manufacturer of the extracts. These studies reported specific allergen microgram concentrations of the allergenic extracts, so a comparison to the specific allergen content of U.S. extracts can be made. The study by Frew et al. [15] described effective doses of the alum-adsorbed timothy grass pollen extract in ALK SQ units, but also reported that the extract contained approximately 20 μg Phl p 5. Based on the estimated Phl p 5 content of 425–1,100 μg/mL for a U.S. standardized 100,000 BAU/mL timothy grass pollen extract, 20 μg Phl p 5 would be equivalent to about 1,000–4,000 BAU.

In the Haugaard study [17], the effective dose was determined to be equivalent to approximately 7 μg of Der p 1 and shown to be a good balance between efficacy and safety. For many U.S. extracts, the Der 1 content of 10,000 AU/mL dust mite extracts is approximately 70 μg/mL. Attaining an effective dose of 7 μg would then be equivalent to about 1,000 AU. The European studies used mite extracts with a high ratio of Der 1 to Der 2, whereas some U.S. extracts can have higher relative Der 2 concentrations [19]. In addition, U.S. mite extracts are manufactured with

Table 2 Probable effective dose ranges for U.S. standardized and non-standardized extracts

Allergen extract	Allergen content	Probable effective dose range		Volume to 10-mL maintenance vial
		μg Allergen	Labeled potency	
Standardized northern pasture grass pollens (timothy, perennial rye, orchard, meadow fescue, red top, sweet vernal)	425–1,100 μg/mL Group 5 500–2,300 μg/mL Group 1	5–20 μg Group 5	1,000–4,000 BAU	0.2–0.8 mL 100,000 BAU/mL
Standardized Bermuda grass	140–420 μg/mL Cyn d 1	N/A	300–1,500 BAU	0.3–1.5 mL 10,000 BAU/mL
Standardized short ragweed	300–600 μg/mL Amb a 1	6–12 μg Amb a 1	1,000–4,000 AU 1: 500–1,000 w/v	0.2–0.8 mL 100,000 AU/mL or 1:10 w/v
Standardized house dust mites (*D. farinae*, *D. pteronyssinus*)	20–200 μg/mL Group 1 2–180 μg/mL Group 2	7–12 μg Group 1	500–2,000 AU	1.0–2.0 mL 10,000 AU/mL
Standardized cat hair, cat pelt	20–50 μg/mL Fel d 1 30–2,000 μg/mL Fel d 2 (albumin)	5–15 μg Fel d 1	1,000–4,000 BAU	2–8 mL 10,000 BAU/mL
Non-standardized AP dog hair	80–400 μg/mL Can f 1 <12 μg/mL Can f 3 (albumin)	5–15 μg Can f 1	1:500–2,000 w/v	0.7–2.0 mL 1:100 w/v
Non-standardized dog epithelia	0.5–10 μg/mL Can f 1 12–1,500 μg/mL Can f 3 (albumin)	5–15 μg Can f 1	1:10–1:20 w/v	Full strength 1:10–1:20 w/v
Non-standardized pollen extracts	Variable	N/A	1:50–200 w/v	0.5–2.0 mL 1:10–20 w/v
Standardized Hymenopteran venoms	100–300 μg/mL total protein	50–200 μg	50–200 μg	Full strength concentrate
Non-standardized imported fire ant extract	Variable	N/A	1:10–1:100 w/v	Full strength–1.0 mL

different cultivation, purification, and manufacturing methods, and therefore can have significant differences in allergen protein composition, despite being labeled with the same AU potency [20]. For these reasons, a dose range of 500–2,000 AU has been selected for the practice parameters recommendations.

For non-standardized extracts, extract doses may not be interchangeable and target doses must be extrapolated from studies using potency units that are arbitrary or specific to a manufacturer. Thus, there is a wide range of doses still used in immunotherapy maintenance vials. In these cases, a general result is that higher doses or maximally tolerated doses produce more effective results than lower doses. However, higher doses also have higher risk for adverse events. In a study with concentrated dog hair extract, positive outcomes were achieved with 15 μg Can f 1 [21]. Other non-standardized dog extracts used in the U.S. are derived from different source materials and have a different composition, with high levels of Can f 3 (dog albumin) and lower Can f 1 levels, making it difficult to reach comparable doses of Can f 1 used in this study.

Although dose-ranging studies for most extracts are lacking and individual patient sensitivities and responses need to be considered, these guidelines have provided useful targets for clinical practice [22•, 23]. The dosing recommendations are also based on monotherapy trials and do not take into account the possible combined effect from combining allergen extracts. Treating with the recommended amount of extract can limit the number of species that can be mixed together. This is demonstrated in Table 2 where the volume of extract needed for a 10-mL maintenance vial can be a significant percentage of the total volume. This is especially the case for cat and dog epithelial extracts which have low concentrations of allergenic protein.

Progress is being made in defining effective maintenance doses for specific allergens, but other questions related to multi-allergen immunotherapy, dose-escalation, and dose-adjustment protocols, compliance to dosing schedules, and duration of treatment need to be addressed in the future [24].

Stability and Expiration Dating

Allergen extract manufacturers conduct potency testing as part of their stability studies to support expiration dating on the standardized extracts. Depending on the product, expiration dates will vary from 6 to 12 months for Hymenopteran venom extracts reconstituted to 100 μg/mL in albumin saline and stored at 2–8 °C to 3 years for

manufacturers' stock concentrates of 50 % glycerinated grass pollen, house dust mite, short ragweed, and cat extracts stored at 2–8 °C. In contrast, non-standardized extracts, which have no standard of potency, rely on generalized dating periods specified in 21 CFR 610.53: Extracts with 50 % or more glycerin content stored at 2–8 °C are given 36 months in manufacturer's storage and 36 months after leaving manufacturer's storage. Extracts with less than 50 % glycerin content stored at 2–8 °C are given 18 months in manufacturer's storage and 18 months after leaving manufacturer's storage.

It is important to point out that the potency testing and stability studies are conducted on single allergen products packaged in the manufacturer's container-closure system. Once the products leave the manufacturer and enter the clinic or pharmacy, the products are diluted, combined with other products, and repackaged into new containers. The stability of these mixtures is difficult to predict because the final product and storage conditions vary from clinic to clinic. Several studies have been conducted with various combinations of extracts and these studies have shown that enzymes, especially proteases, have the greatest impact on the stability of mixtures [25–28]. For this reason, it is recommended that fungal and insect extracts that contain high levels of protease activity be separated from susceptible pollen extracts. This separation means many patients receive injections from 2 or more vials. The degradation of proteins may be slowed or inhibited in mixes that are used for non-injection immunotherapy that are mixed with 50 % glycerin. More studies are needed to determine the degree of inhibition in 50 % glycerin as well as how enzymes in fungal and insect allergens affect each other.

The FDA specifies that extracts in multi-dose vials must contain a preservative. Phenol at a concentration of 0.4 % is the most common preservative used throughout the industry for preserving aqueous extracts. This preservative at this concentration is ideally suited for allergen extracts based on the safety, antimicrobial activity, and minimal effect on the allergen extract proteins. Alternatively glycerin at concentrations of at least 50 % v/v can be used as a preservative. In addition to its antimicrobial activity, glycerin can also improve the time the allergen proteins maintain their potency.

Diluents for Mixing

Conventional injection immunotherapy regimens include an initial build-up phase, when the dose and concentration of the allergenic extracts are increased up to the maintenance dose. Various sterile diluents are used to prepare extract dilutions and depending on the build-up schedule, these dilutions may be stored for varying times. There are several options for diluents each with their advantages and disadvantages. The most common diluent used in extract formulations is normal saline with phenol (NSP), which is composed of physiological saline, 0.9 % NaCl and 0.4 % phenol. Various substances such as buffers, human serum albumin, or glycerin can be added to NSP to preserve the potency of extracts after dilution [29]. It has long been known that glycerin is the most effective preservative for allergenic extracts. Glycerin at 10–50 % v/v is an effective inhibitor of protease activity that may have a deleterious effect on extract potency and stabilizes extracts when they are exposed to temperature fluctuations, including freezing and thawing. For these reasons, glycerinated diluents have been widely used to maximize the shelf-life of manufacturer's bulk concentrates and maintenance vials formulated in the clinic. The disadvantage is that they can produce pain and discomfort at the injection site [30]. Decreasing the glycerin content may reduce the pain, but is less effective as a preservative. Human serum albumin at a concentration of 0.03 % is used to provide stability to the very dilute solutions produced for build-up vials, presumably by reducing allergen absorption to the glass vial wall. Thus, the optimal use of diluents in preparing maintenance vials and dilutions for build-up vials will depend on the extract dilution as well as the anticipated storage conditions and duration.

Composition of Immunotherapy Extract Mixtures: Cross-Reactivity and Compatibility

The presence of allergenic cross-reactivity among extracts can have a significant impact on formulating immunotherapy mixtures [31]. This is likely to occur with the northern pasture grasses, the Chenopod–Amaranth families of weeds, and the birch and oak families of trees, as well as other botanically related pollens (Table 3). In these cases where extensive cross-reactivity has been established, treatment with a single representative pollen extract or mixture would suffice. Knowledge of these and other clinically relevant cross-reactivity could reduce adverse events and would reduce the total number of extracts needed for effective diagnosis and immunotherapy.

In general, patterns of allergenic cross-reactivity closely follow their taxonomic relationships. For pollen allergens, these relationships are relatively well established. Studies with non-pollen allergen sources have been variable [32]. Extensive cross-allergenicity has been observed among the Glycyphagidae mites, the family to which the important house dust mites *Dermatophagoides farinae*, *D. pteronyssinus*, and *Euroglyphus maynei* belong. Both cross-reactive and unique

allergens of clinical importance have been identified in cockroach extracts, which has led to the recommendation for using locally relevant species for testing and treatment. Similarly, Hymenopteran venoms show variable cross-reactivity. The venoms from the members of the subfamily Vespinae (yellow jackets and hornets) have the strongest cross-reactivity, a lesser degree of cross-reactivity exists between the *Polistes* (paper wasps) and Vespinae venoms, while the cross-reactivity between *Apis* (honey bee) and the vespids is limited to minor allergens. Cross-reactivity among the fungi is highly variable and often contradictory. This could be explained by the differences in the selection of fungal strains, and the cultivation and manufacturing methods used by different manufacturers of fungal extracts, which lead to their qualitative differences [8]. In some cases, even different manufacturers' products labeled as the same fungal species do not guarantee allergenic cross-reactivity.

Fungal extracts also have varying enzymatic activities, especially proteases that have deleterious effects on the potency of other extracts when mixed. Cockroach and other whole-body insect extracts can have significantly higher protease activities. Depending on the combinations and the diluents used, the destabilizing effect can range from undetectable to a loss of more than 90 % potency after less than 3 months of storage [33•, 34]. Grass pollen allergenic extracts were the most susceptible to the effects of fungal and insect proteases, while ragweed pollen and cat allergens were more resistant. Fungal proteins seem to be resistant to the action of endogenous proteases in these extracts. By comparison, proteases in cockroach extracts are capable of degrading prominent allergens in the extracts unless stored in the presence of at least 50 % glycerin.

Increased information and knowledge regarding allergenic cross-reactivities between related and unrelated allergens have allowed for optimizing treatment formulations and reducing the number of extracts used. However, both unique and cross-reacting allergen proteins can be present in extracts and resolving which ones are relevant in any given patient is difficult if not impossible using crude extracts. Cross-reactivity among minor allergens such as profilin and lipid transfer proteins can also be very extensive in some patients, but may have varying degrees of clinical relevance. More precise molecular diagnostic approaches will have to be developed in order achieve the level of specificity desired for selecting allergens for immunotherapy, especially with polysensitized patients [35, 36].

USP 797 Rules for Compounding Sterile Preparations

The U.S. Pharmacopeia (USP) provides practice and quality standards for the compounding of sterile products [37]. These rules apply to many more situations than are subject to the FDA definition of compounding. For example, compounding, by FDA's definition, does not include reconstituting, mixing, or dilution that is performed using directions in the approved labeling provided by the manufacturer. Beyond-use dates for sterile products that have been opened, mixed, or diluted for administration are not specified in the package inserts for allergenic extracts. The USP <797> addresses these practices that are rarely described in the manufacturer's directions as well as environmental quality, personnel garbing and gloving, and other aseptic precautions by which sterile products are to be

Table 3 Examples of cross-reacting allergen groups

	Cross-reacting groups	Representative extracts
Grass pollens	Pooideae	*Poa* (bluegrass), *Dactylis* (orchard), *Festuca* (fescue), *Lolium* (perennial rye), *Agrostis* (redtop), *Anthoxanthum* (vernal), *Phleum* (timothy)
	Chloridoideae	*Cynodon* (Bermuda)
	Panicoideae	*Paspalum* (Bahia), *Sorghum* (Johnson)
Tree pollens	Aceraceae	*Acer* (maples and box elder)
	Betulaceae	*Alnus* (alder), *Betula* (birches), *Corylus* (hazelnut)
	Fagaceae	*Quercus* (oaks), *Fagus* (beech)
	Juglandaceae	*Carya* (hickory, pecan), *Juglans* (walnut)
"Weed" pollens	Chenopodiaceae	*Atriplex* (saltbush), *Chenopodium* (lamb's quarter), *Salsola* (Russian thistle), *Kochia* (firebush), *Allenolfea* (iodine bush)
	Amaranthaceae	*Amaranthus* (pigweeds)
House dust mites	Pyroglyphideae	*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Euroglyphus maynei*
Hymenopteran venoms	Vespinae (Vespids)	*Vespula* (yellow jackets), *Dolichovespula* (hornets)
	Polistes	*Polistes* (paper wasps)
	Apis	*Apis* (honey bee)

prepared for administration. The potential impact of these rules was assessed and recommendations were made by a working group of the JCAAI, AAAAI, ACAAI, and the American Academy of Otolaryngic Allergy (AAOA) [38]. Although the USP <797> rules specifically exempt allergen vaccines from many of the requirements, the current immunotherapy practice parameter incorporated those that were deemed critical for immunotherapy extract compounding. These include establishing qualifications for extract preparation personnel, the use of appropriate environmental controls to limit unintended contamination, and the use of sterile manufacturer's extracts and sterile diluents containing appropriate preservatives. An annual process validation by performing a media-fill test procedure is also recommended for each person authorized to compound allergen immunotherapy extracts. Adherence and compliance to these guidelines would be especially important in light of recent incidents resulting in adverse events and deaths at sterile compounding facilities in the U.S. [39], and as the FDA seeks more oversight and regulatory authority on compounding. The USP Expert Panel on General Chapter <797> will be reconvening this year to strengthen USP's relationship with the FDA and to harmonize their efforts to develop, maintain, and promote quality standards of compounded medicines [40].

Conclusions

The safety, efficacy, and outcomes of allergen immunotherapy in the U.S. have been shaped by the activities of practicing allergists, medical scientists, allergen extract manufacturers, regulatory agencies, and healthcare insurance providers. These groups represent a complex network of overlapping interests and goals that have provided for the decades of progress made in treating allergic patients. The standardization of allergen products and the development of the immunotherapy practice parameters are two activities that have made a significant impact toward improving allergy treatment outcomes. Continued improvements and evolution of these standards will be required as health care reform is implemented in the coming years and as the cost-effectiveness of allergen immunotherapy is critically examined.

Compliance with Ethics Guidelines

Conflict of Interest Robert E. Esch is an employee of Greer Laboratories, Inc.

Greg A. Plunkett is an employee of ALK-Abello Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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