
CME review article

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Comparison of allergen immunotherapy practice patterns in the United States and Europe

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Objective: To discuss important differences and similarities in the allergen specific immunotherapy (SIT) treatment practices for aeroallergen sensitivity in the United States and Europe.

Data Sources: Information on regulation and standardization in the United States and Europe was obtained from a Food and Drug Administration Allergenic Products Advisory Committee meeting, published literature, personal communications, and information obtained from the extract manufacturers.

Study Selection: Information from the published literature included articles known to the authors and acknowledged consultants, textbooks, and PubMed, with search terms dependent on the particular subtopic.

Results: Key differences between Europe and the United States include allergen extract regulation, standardization, formulation, types of allergen extracts, routes of administration, and reimbursement. Most SIT is formulated in US allergists' offices, whereas virtually all SIT is formulated by extract manufacturers in Europe. Sublingual immunotherapy represents a significant percentage of SIT treatment in Europe (approximately 45%), but only a small percentage of US allergists (approximately 5.9%) prescribe sublingual immunotherapy. Similarities between European and US allergist specialists lie in their perception of SIT and approach to providing optimal SIT care, which is detailed in their practice guidelines.

Conclusion: Significant differences and similarities exist in SIT practice patterns of US and European allergy specialists. The differences lie primarily in the availability of allergen extracts and how these extracts are formulated. A key similarity is that both recognize the need for ongoing research focused on developing safer and more effective SIT.

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INTRODUCTION

The practice of allergen specific immunotherapy (SIT) has been used in the treatment of allergic rhinitis and asthma in Europe and the United States for many years, since the first

description by Noon in 1911, almost a century ago.¹ In the 1900s, research focused on desensitizing patients with seasonal allergic rhinitis with pollen extract injections was conducted on both sides of the Atlantic, beginning with Noon and Freeman in London, England, and Lowdermilk in Galena, Kansas. Despite similar beginnings and many similarities in the practice principles of SIT, there have also been developments over the years that have resulted in considerable differences in how SIT is currently practiced in Europe and the United States.

The purpose of this review is to highlight and discuss important differences and similarities in SIT treatment practices for aeroallergen sensitivity in the United States and Europe. By expanding the respective knowledge and under-

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standing of the developments and decisions made for the treatment, we can facilitate future exchange of experiences and research in the field of SIT. This will benefit the continuously increasing number of patients with respiratory allergic symptoms because SIT is the only treatment for respiratory allergic diseases that has the potential to change the natural course of the disease and prevent further exacerbations.^{2,3}

Key differences between Europe and the United States include allergen extract regulation, standardization, formulation, available types of allergen extracts, routes of allergen administration, and reimbursement. Differences among European countries also exist in many of these areas, and some of the information on European SIT practice in this review is not specific to countries (Table 1).

Because no official statistics covering all European SIT markets are available, the figures in this article illustrating the distribution of different treatment options and different products for SIT represent a best estimate based on personal information provided by the manufacturers present in the European market. This article is limited to aeroallergen SIT and will not include venom immunotherapy.

DIFFERENCES

Standardization and Regulation in the United States

In the United States, allergen extracts are regulated by the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research (CBER). The specific regulations regarding allergen extract are primarily found in part 680 of Title 21 of the Code of Federal Regulations.⁴ US allergen extracts are manufactured in 2 forms: standardized and nonstandardized. Nonstandardized extracts have no US

standard of potency and report content as either weight/volume, which is the weight of the source material extracted with a given volume of extracting fluid or protein nitrogen units. Neither method confers any direct or comparative information about an extract's biological potency or composition.

The extraction processes for standardized and nonstandardized extracts are essentially the same. However, although nonstandardized extracts are defined by their method of manufacture, standardized extracts have additional quality control requirements that encompass source material, in-process, and finished product testing with lot-release by regulatory authorities to improve product consistency.

The CBER directs the US standardization program, determining for which allergens they will establish standards of potency for use by industry. For standardized allergen extracts, the potency of the manufacturer's extract is established by comparing the extract with the CBER's reference control using an in vitro assay, such as an enzyme-linked immunosorbent assay (ELISA) for grass and mites. As an exception to the comparison based on biological potency, cat and short ragweed extracts were originally standardized based on the estimate of major allergen content, Fel d 1 and Amb a 1, respectively. The concentrations of Fel d 1 and Amb a 1 were shown to correlate with the overall biological activity of the cat and short ragweed extracts as determined by quantitative skin testing.^{5,6}

The biological potency of the CBER reference control is most commonly based on titrated intradermal skin testing of highly allergic individuals with 3-fold dilutions of the candidate extract (ID₅₀EAL method).⁷ The sum of the longest and

Table 1. Comparison of the Differences Between US and European Allergen Extracts and Specific Immunotherapy Practice Patterns

Variable	United States	Europe
Regulatory agency	FDA	EMA
Standardization		
Method	ID ₅₀ EAL	Nordic
Test technique	Intradermal	Percutaneous
End point	Extract dilution that produces sum of erythema of 50 mm	Extract dilution that produces a wheal equal to the histamine control
Potency determination	Comparison with CBER reference control	Compared with in-house reference
Future focus	Overall allergenicity	Major allergen content
Potency units	BAU, wt/vol, PNU, milligrams of major allergen for ragweed and cat	Varies; each company essentially has its own potency units, some provide milligrams of major allergen
Extract formulation		
Location	Prepared in physicians offices	Prepared at extract manufacturer site
No. of allergens	Multiple	Generally 1
Allergen extract types	Aqueous and glycerinated unmodified extracts, alum-precipitated depot extracts	Approximately 100% depot extract, 20% allergoid, <5% adjuvants
SLIT	Approximately 5.9% of allergists, no FDA-approved formulation	Approximately 45% of prescribed SIT, solution and tablets available, some are registered
Reimbursement	Covered as a medical service by government and private insurers, prices can be negotiated but private insurers often use government schedule	Varies, extract companies negotiate coverage with each country

Abbreviations: BAU, bioequivalent allergy units; CBER, Center for Biologics Evaluation and Research; EMA, European Medicinal Agency; FDA, Food and Drug Administration; PNU, protein nitrogen units; SIT, specific immunotherapy; SLIT, sublingual immunotherapy.

midpoint diameters of erythema (ΣE) is measured. The log dose producing a 50-mm ΣE response is referred to as the D_{50} . Extracts with a mean D_{50} of 14, which falls between the 13th and 15th 3-fold serial dilution of the reference extract, are arbitrarily assigned the value of 100,000 bioequivalent allergy units (BAU).⁸ An extract with a mean D_{50} falling between the 11th and 13th dilutions is labeled 10,000 BAU. A formula has been developed that can be applied to determine the number of highly allergic individuals required for a particular allergen.⁹ If the variability is higher than the established limit, additional patients need to be included in the study.

Future Directions for Allergen Standardization in the United States

Establishing extract potency by comparison with pooled sera from an allergic population provides information about overall allergenicity. An advantage of this approach is that it provides an estimate of potency even if all of the relevant allergens are not known. The disadvantage is that it cannot detect the presence of specific and potentially important allergens. Data from the CBER laboratory have shown that the overall potency approach may be insensitive to clinically significant changes in specific allergens.¹⁰ Another problem with determining an allergen extract's total potency is that all the relevant allergens in a particular extract may not have been identified.

Appreciating that the need to develop an assay that can measure known allergens and recognize important allergens not yet identified, the CBER is developing a multiplex antibody-based method for profiling complex allergen mixtures.¹⁰ The CBER plans to apply this technique to cat, ragweed, and the standardization of German cockroach. Earlier versions of this assay, using multiplex microbead technology with specific recombinant antibody fragments (scFv) generated by the avian immunoglobulin system and selected by phage technology, demonstrated accuracy similar to that of the current standardized methods in the measurements of Fel d 1 and Amb a 1.¹¹⁻¹³

In a multiplex microbead array, each bead can be bound to recombinant antibodies with different specificities and a single well of a 96-well plate can contain up to 100 beads. The future experiments of CBER include the binding of soluble scFv to bead-bound allergens, inhibition assays using known allergens, analysis of scFv binding patterns in Western blots, and identification of scFv-recognized antigens by N-terminal sequencing (Jay Slater, MD, data presented at an FDA Allergenic Products Advisory Meeting, March 18, 2009).

Standardization and Regulation in Europe

The European Union, which is composed of 27 member states, is currently working on establishing a uniform, well-integrated system for the regulation of medicine and medical care. Marketing authorizations in the current European system are based on pharmaceutical and clinical documentation of the products and provided by the respective national com-

petent authority of a member state. The legal framework for medicinal products includes both EU and national regulations and the competent authorities, who represent the national health authority (member state) and the European Medicinal Agency (EMA). A national application procedure exists, which only gives marketing authorization (approval) in the country to which it has been submitted.¹⁴ After the application is approved by the national procedure, the medicinal product (eg, allergen extract) can be marketed in only that 1 country. For an allergen product to enter more than 1 country in the European Union, the applicant can use the mutual recognition procedure (see Figure 1 for a summary of the procedures for new marketing authorizations in the European Union). This procedure can be used to expand the approval of the application to other EU member states based on submission of identical dossiers to these countries. Essential for the future EU regulation is the centralized procedure for registration and acceptance of marketing authorization. In the centralized procedure, an application dossier is submitted to the EMA, which coordinates the evaluation process. Two member states are selected as rapporteur and co-rapporteur to evaluate the application dossier as representatives for all of the EU member states. If marketing authorization is granted through the centralized procedure, it is valid throughout all of the EU member states. This procedure is mandatory for medicinal products fulfilling 1 of the following criteria: based on biotechnological processing, containing a new active substance, being innovative or orphan, or intended as medications for the following diseases: AIDS, cancer, neurodegenerative disorders, diabetes mellitus, autoimmune diseases, immune dysfunctions, and viral diseases.¹⁴ The mutual recognition procedure will continue to apply to allergen extracts. However, the registration of future products, such as recombinant allergens, will have to go through a centralized procedure, which means these products will be immediately available in all EU member states after approval.

Guidelines based on state of the art in the medical field are integrated parts of the regulatory system of the EMA. Although not legally binding, these guidelines are accepted as strong recommendations, meaning that exemptions from the guidelines must be scientifically justified for the competent authority to accept the product. Two important guidelines have recently been developed: Guideline on Allergen Products: Production and Quality Issues¹⁵ and Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases.¹⁶

Only a few allergen products have passed the European regulatory procedures (eg, tablet-based form for SIT containing grass pollen). Most products for allergen-specific diagnosis and SIT have been on the market before the new European regulations, and the national marketing authorizations continue to apply. Many SIT products are sold on a named-patient basis, which are allergen extracts formulated for individual patients. The recently developed guidelines on allergen products^{15,16} do not always apply to named-patient

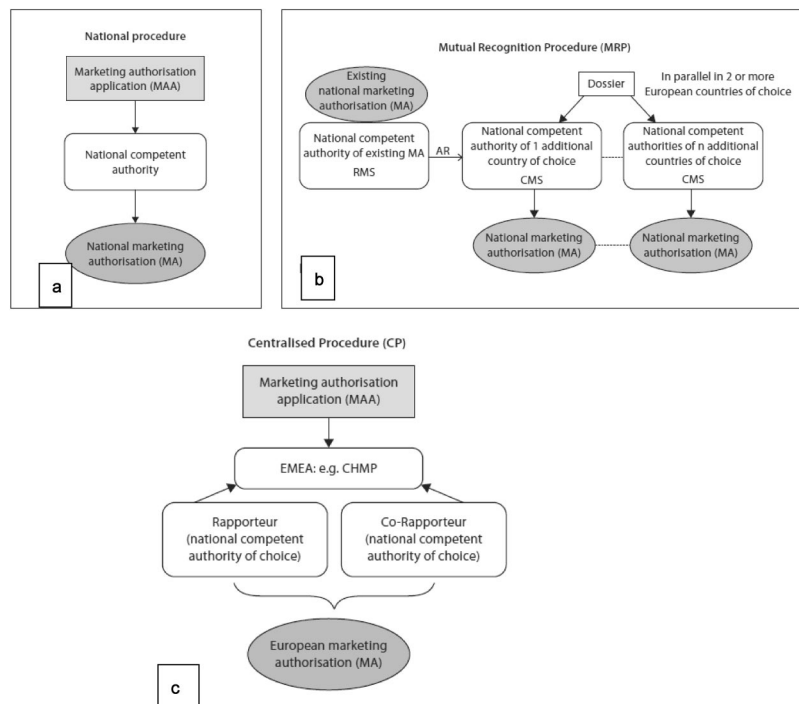


Figure 1. Summary of the 3 different regulatory procedures to apply for a marketing authorization (approval) in Europe. (a) Single member state approval: successful marketing authorization application (MAA) in 1 European member state results in a marketing authorization (MA) valid in only that 1 member state. (b) Additional EU member states: MA can be expanded to additional member states via the mutual recognition authorization (MRA). (c) Centralized procedure (CP): an MA granted by the CP is valid in all European member states after 1 single regulatory procedure. The procedure is mandatory for medicinal products fulfilling 1 of the following criteria: based on biotechnological processing containing a new active substance, being innovative or orphan, or intended as medications for the following diseases: AIDS, cancer, neurodegenerative disorders, diabetes mellitus, autoimmune diseases, immune dysfunctions, and viral diseases. AR indicates evaluation report; RMS, reference member state; CMS, concerned member state; and CHMP, Committee for Medicinal Products for Human Use. National Procedure. Adapted from Lorenz et al.¹⁴ Reprinted with permission from S. Karger AG Medical and Scientific Publishers.

products. In some EU member states, these products comprise the major part of SIT treatments.

As in the United States, the EMEA also requires detailed documentation of the allergen product and manufacturing process. The EMEA provides guidelines for manufacturing and handling of source material, allergen product production, identification of protein and allergen profile, potency evaluation, and establishment of the clinical documentation.^{16,17}

Most allergen extracts are not yet regulated by the EMEA but rather by local country-specific authorities. As in the United States, both standardized and nonstandardized product forms are found on the market in Europe. European extract manufacturers currently use an in-house reference for standardization and report their allergen extract's potency in their company's unique units, making comparisons of extract potency among companies difficult.¹⁸

In Europe, allergen standardization is primarily based on titrated skin prick testing of allergic individuals, for example, comparing the wheal size with a histamine control (Nordic method). This method established the first proposal for a regulatory demand for allergen extracts introducing a biological unit (BU) as a measure of potency; an extract producing

a wheal size the same size as a 10-mg/mL histamine control was assigned the value of 10,000 BU or 10 HEP (histamine equivalent potency). Manufacturers were instructed to produce an in-house reference, adjust the potency in BU, and use the in-house reference for extract lot-to-lot control.¹⁹

With the goal of improving allergen extract standardization, the European Union funded a project called the CREATE project from 2001 to 2005.²⁰ The CREATE project's primary focus was allergen extract standardization based on major allergen content. Major and minor allergens are defined by the percentage of the allergic population who recognize them by producing allergen specific IgE. A protein is considered a major allergen if it is recognized by more than 50% of the allergic population, whereas minor allergens are recognized by less than 50% of the allergic population. The term *minor*, however, does not mean it is clinically unimportant to some allergic individuals. However, the major allergen content appears to correlate well with the overall biological potency of the extract.^{21,22} The CREATE project evaluated ELISAs for major allergen measurements and the use of recombinant allergens as reference materials with goals of producing certified reference materials and validated assays for their quan-

tification. Three recombinant allergens displayed sufficient structural and immunologic similarity to their natural counterparts to be selected for a follow-up project (rBet v 1, rPhl p 5a, and rDer p 2). One or 2 ELISAs were identified that showed comparable dose response curves for the recombinant and natural allergens.

Extract Formulation

In Europe, many of the treatments are prepared by the extract manufacturer and provided as named-patient products. Named-patient products are, in principle, prescription-based medications that include a package insert with guidelines for use. In most countries they are sold to patients through pharmacies. Named-patient products are regulated based on the manufacturer's production process and controls. On average, 60% of SIT medications in Europe are patient-named products, with great differences among countries: Northern Europe, almost none; Germany, 25%; Italy and France, almost 95%; and Spain, more than 50%.

Some European extracts are registered as pharmaceuticals based on either earlier registrations or new registrations in accordance with the EMEA regulations and guidelines. In some countries (ie, Denmark, Sweden, Norway) allergen extracts have only been available as pharmaceutical products for several decades, and in these countries no market for named-patient products exists. No final allergen extract formulation is prepared by physicians. In contrast, most allergen extract formulations in the United States are prepared in physicians' offices. More than 95% of the 1.9 million to 2.7 million immunotherapy prescriptions each year are estimated to be formulated in approximately 5,000 physician offices in the United States.²³

One of the significant differences between European and US SIT practice patterns is the use of single vs multiallergen formulations. Most of the US allergen extract formulations contain multiple allergens. On the basis of patient prescriptions formulated for US allergists in 2002 at Greer (Lenoir, North Carolina), the mean number of component extracts was 8.²³ The reimbursement value for compounding a patient's prescription is based on the average cost of using 6 allergens in an allergen extract preparation (Gary Gross, MD, written communication, May 31, 2009). In contrast, less than 10% of European formulations contain more than 1 non-cross-reacting allergen. For many years, there has been a longstanding debate between the US and European allergy communities regarding the efficacy of multiallergen SIT. The use of multiallergen immunotherapy is likely because most allergic patients in the United States are polysensitized. The mean number of positive prick-puncture skin responses was 3.5 in a study of 10,508 individuals in the US general population tested to 10 allergens (National Health and Nutrition Examination Survey III).²⁴ The 3 most frequent responses were dust mite (27.5% of the tested population), perennial rye (26.9%), and German cockroach (26.1%). In a study of 1,338 patients with mild to moderate asthma, who were skin prick tested to 12 allergens or allergen mixes, 81% had 3 or more

positive skin test responses (Asthma Clinical Research Network trials).²⁵ The limited number of multiallergen SIT clinical trials has produced conflicting results. A recent review of the literature on subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) identified 13 studies that used 2 or more unrelated allergen extracts: 11 SCIT, 2 SLIT, and 1 both.²⁶ Four of the 7 studies that used 2 non-cross-reacting allergens reported superior efficacy compared with placebo and comparable efficacy when compared with single-allergen extract treatment. However, the other 3 studies failed to report the results between single and multiple allergens separately. In the 5 studies that used multiple allergens, the practice most commonly used by US allergists, 3 demonstrated efficacy,^{27–29} whereas 2 did not.^{30,31}

The considerable heterogeneity in the design of these studies and the failure to provide results specific to each allergen make it difficult to evaluate the efficacy of multiallergen SIT. Further research is clearly needed before firm conclusions about the efficacy (*or lack of*) multiallergen SIT can be made. It is also important to treat the patients only with relevant allergens (ie, allergens that the patient is exposed to produce symptoms with exposure).

Allergen Extract Types: Depot, Allergoids, and Adjuvants

In Europe, virtually all of the extracts used for aeroallergen SCIT are absorbed to depot materials, such as aluminum hydroxide or L-tyrosine, which is intended to facilitate slow-release presentation of the allergen. In contrast, aqueous or glycerinated extracts are used in most US formulations. There are a limited number of alum-precipitated (Center-Al) extracts available in the United States, and none of these products are related to an FDA standard reference. It is estimated that approximately 75,000 to 150,000 patients are receiving SIT with alum-precipitated (Center-Al) extracts in the United States (Greg Plunkett, PhD, ALK-Abello, written communication, May 8, 2009), which is approximately 5% of the population with allergic rhinitis, asthma, or both in the United States receiving SCIT (approximately 2.5 million persons).

Allergoids are allergen extracts that have been chemically modified to reduce IgE-binding capacity. These extracts are based on the concept of potentially reducing the allergenicity of the allergens but retaining the antigenicity. Allergoids are used in an average of 20% of SCIT treatments prescribed in Europe, but the percentage varies by country (eg, almost none in Northern Europe and 35% in Germany). There are no FDA-approved allergoids in the United States. The pollen allergoid products are for the most part used only as short-term preseasonal treatment. Most other treatments are with house dust mites.

The mechanism of effective SIT involves basic changes in the cellular immunologic response to allergen challenge. A shift from a T_H2 response to a more prominent T_H1 response, along with the induction of T regulatory cells, is an important component of the immunologic changes associated with effective SIT. Adjuvants may enhance the effectiveness of allergen immunotherapy by shifting the immune response

toward T_H1 production. The 2 adjuvants that have been most extensively studied in the treatment of allergic rhinitis are an immunostimulatory oligonucleotide sequence of DNA containing a CpG motif (CpG) and 3-deacylated monophospholipid A (MPL), both of which target toll-like receptors. MPL is used in an allergen vaccine product composed of a glutaraldehyde-modified allergen absorbed to tyrosine (Pollinex Quattro; Allergy Therapeutics Ltd, West Sussex, England) that is administered as an ultrashort course of 4 injections before the season. To date this product is available in Europe for grass and trees, but it is only used in a small percentage (<5%) of SCIT treatments and primarily in Germany.

Clinical trials with CpG and MPL have been conducted in the United States.^{32,33} The development of CpG ragweed was discontinued by the company after analysis of interim 1-year data from the 2-year phase 3 study (Dynavax Allergic Rhinitis TOLAMBA Trial) indicated that there was no measurable disease during the ragweed season in either the placebo or the CpG groups, making it impossible to measure the therapeutic effect of CpG ragweed.³⁴

Several clinical trials designed to study the efficacy and safety of MPL in the treatment of grass pollen or ragweed-induced allergic rhinitis have been conducted in the United States. However, the FDA placed a clinical hold on all of the MPL-related vaccine studies in the United States while investigating an adverse event reported in the grass pollen study.³⁵

Route of Delivery: SCIT vs SLIT

One of the greatest differences between Europe and US SIT practices lies in the use of SLIT. In Europe, named-patient products can be produced for different routes of administration, and these allergen extracts are not specifically approved for a particular route of delivery. In the past 25 years, there has been a substantial and growing increase in the use of SLIT in Europe. The convenience and safety of SLIT are likely factors for the increase in SLIT use in Europe in recent years.

In some countries, SLIT represents most of the new immunotherapy prescriptions. Currently, approximately 45% of SIT treatments in Europe are SLIT, but there is a wide regional difference: Northern Europe, almost none and only the new EMEA registered products (no market for named-patient products in Scandinavia); Germany, approximately 25%; and Southern Europe, up to 80%. SLIT is the focus of the most recent and ongoing European SIT studies, and new products are approved in accordance with the mutual recognition procedure in the European Union. In contrast, there is little use of SLIT in the United States. This is likely because there is currently no FDA-approved formulation for SLIT. According to an electronic survey of US allergists conducted in early 2007, the most commonly cited reason for not prescribing SLIT was lack of FDA approval (471 of the 763 respondents [61.7%]).³⁶ The second most common reason was unknown effective dose (27.5%).

A small percentage of US physicians, 45 of 766 respondents (5.9%) in this survey, prescribe SLIT. The US SLIT prescribers primarily used the commercially available extracts used for SCIT (79%) (ie, off-label use). Off-label implies that an FDA-approved product is being used for treatment that is not indicated in the product information (ie, the package insert). An example of off-label use would be prescribing an antihistamine medication approved for seasonal allergic rhinitis to a patient who has chronic urticaria. This is not an uncommon practice in the United States. Allergen extract package inserts licensed in the United States specify subcutaneous or intradermal use. The package insert also includes a black box warning, which is the highest level of 5 possible warning categories found in US pharmaceutical package inserts.³⁷ The black box warning states that allergen extracts may elicit a severe life-threatening systemic reaction and emergency measures and personnel must be immediately available. Considering the fact that SLIT is a treatment administered at home with no direct supervision and the medicolegal climate in the United States, this black box warning may discourage US allergists from prescribing SLIT with FDA-approved products for SCIT.

Currently, several US clinical trials are in progress intended to seek FDA approval for new SLIT products (ie, tablets) or a change in the package insert of existing US-licensed SCIT products. To date, none of the US SLIT trials have met their primary outcome. Several factors may account for this failure, including low pollen counts and patient selection.

Reimbursement for SIT

Reimbursement for medical services, including SIT, varies by country in Europe. Extract manufacturers must negotiate with the regulatory health authorities of each country to establish the prices and reimbursement for their SIT products. If negotiations are successful and the regulatory health authority approves coverage for the product, the amount of coverage may vary significantly across borders. For example, ALK's grass-tablet product, which was registered in 27 EU member states by the mutual recognition procedure in 2006, was offered national reimbursement status on the level of prescription drugs in Spain in 2008.³⁸ By the end of 2008, many European countries offered public reimbursement for the tablet: Sweden, Norway, Finland, Germany, the Netherlands, Ireland, Austria, Switzerland, Spain, Greece, certain regions in Italy, and the United Kingdom. However, some countries do not provide reimbursement yet.

The cost-effectiveness of a particular treatment has become more important for the decision makers on health care coverage on both sides of the Atlantic. Along with the usual outcomes, reduced symptoms and medication use, improvement in quality of life has also been factored into cost-effectiveness assessments in some recent SLIT cost-effectiveness studies.⁸ In the United Kingdom, the National Institute for Health and Clinical Excellence determined that a drug can generate 1 quality-adjusted life-year for less than €29,200, compared with an

Table 2. Comparison Between EAACI and the US Joint Task Force on Practice Parameters Indications for Specific Allergen Immunotherapy

Joint Task on Practice Parameters on Allergen Immunotherapy ⁹	EAACI standards for practical allergen specific immunotherapy
Symptoms of allergic rhinitis or asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND 1 of the following: Poor response to pharmacotherapy, allergen avoidance, or both Unacceptable adverse effects of medications Wish to reduce or avoid long-term pharmacotherapy and the cost of medication Coexisting allergic rhinitis and asthma Possible prevention of asthma in patients with allergic rhinitis	Indications in rhinoconjunctivitis and asthma in patients with symptoms induced predominantly by allergen exposure Patients in whom antihistamines and moderate dose topical glucocorticoids insufficiently control symptoms Patients in whom pharmacotherapy induces undesirable side effects Patients who do not want to be on constant or long-term pharmacotherapy Patients with rhinitis and symptoms from the lower airways during peak allergen exposure Patients with a prolonged season or with symptoms induced by succeeding pollen seasons Patients with clinical symptoms due to a single or few allergens

Abbreviation: EAACI, European Academy of Allergy and Clinical Immunology.

alternative, and is therefore considered cost-effective.³⁹ The National Institute for Health and Clinical Excellence is more than twice as likely to recommend a drug when it considers it cost-effective, underscoring the importance of establishing cost-efficacy.

Although cost-efficacy is important in the United States, it has yet to become a factor in a medication or treatment approval process. One study that compared pre-SCIT and post-SCIT treatment costs in children with allergic rhinitis receiving Florida Medicaid, the US government health insurer for low-income individuals, demonstrated a significant reduction in treatment costs in those who received SCIT despite a low compliance rate (16% completed 3 years of SCIT).⁴⁰ In a subsequent study, the investigators compared health care costs during an 18-month period in the children who received SCIT with a matched control group.⁴¹ There were significantly lower total per patient health care costs (\$3,244 vs \$4,962; $P < .001$), pharmacy costs (\$1,108 vs \$1,324; $P < .0001$), and outpatient costs exclusive of immunotherapy-related care (\$1,109 vs \$2,706; $P < .0001$), which became evident after 3 months of initiating SCIT.

In the United States, SIT is generally covered as a medical service by government and private insurers provided the medical service is approved by the FDA and not considered investigational. Reimbursement rates for SIT can vary with private insurers, but many base their reimbursement rates on the government's pay schedule (Medicare). Currently, the *Current Procedural Terminology (CPT)* code, 95165, which is a billing code for allergen immunotherapy extract preparation, defines allergen immunotherapy as "parenteral administration of allergenic extracts."⁴² Medicare has specifically issued a warning that code 95165 is to be used only for parenteral administration (Don Aaronson, MD, JD, MPH, written communication, July 11, 2009). Services that do not have a CPT code, such as SLIT, will generally not be reimbursed by the government or private insurers. A new CPT

code for reimbursement for an alternative immunotherapy approach or product would not be approved until the new product had obtained FDA approval. Once a product has been approved by the FDA, an application for a new CPT code can be submitted to the American Medical Association. The application is then referred to an advisory board and specialty societies for feedback and comments. If the CPT application is approved, it is referred to the Relative Value Update Committee, who determines the relative value units for the new CPT code, which influences the government's reimbursement fee. The timeline from submission of the CPT application to insurers' adoption of the new code is approximately 2 to 3 years. An application for a new code can be submitted during the FDA approval process, but, if granted, it will be contingent on approval.

SIMILARITIES

Similarities between European and US allergists likely lie in the perception of SIT as a disease-modifying agent and the established practice guidelines that provide recommendations. Although there may be an ongoing debate between Europe and US allergists regarding the number of allergens to include in an allergen extract formulation, there is virtually no disagreement that this treatment can provide long-lasting clinical improvement after discontinuation and potentially prevent the progression of the allergic disease and development of new allergen sensitizations.

Practice guidelines have been published by organizations on both continents. Recently, published guidelines include the European Academy of Allergy and Clinical Immunology Immunotherapy Task Force Standards for practical allergen SIT published in 2006⁴³ and the American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology/Joint Council of Allergy, Asthma and Immunology Joint Task Force on Practice Parameter's Allergen Immunotherapy: A Practice Parameter

Second Update published in 2007.⁴⁴ The goal of both documents is to provide recommendations that will optimize the safety and efficacy of allergen immunotherapy. Similarities lie in many areas, including the indications (Table 2) and contraindications for SIT, recommended postinjection wait period (30 minutes), guidelines regarding pregnancy, β -blocker use, staff supervision, recommended office equipment, and documentation guidelines.

Another similarity between Europe and the United States is the underuse of SIT. Although it is recognized by US and European allergy specialists as the only disease-modifying treatment for allergic rhinitis and asthma, only a small percentage of allergic patients are prescribed this treatment on both continents (approximately 5% of the population). Inconvenience was the most commonly cited reason for discontinuing SCIT,^{45–47} and it is probably the most common reason for the low use of SCIT. The inconvenience is primarily due to the time involved in receiving the treatment in a supervised medical facility (eg, patient travel, wait period). SLIT offers the convenience of home administration because of its better safety profile, and this is likely why this approach is being used with increased frequency in Europe. However, the lack of an approved FDA formulation limits the use of this method in the United States.

CONCLUSIONS

Significant differences and similarities exist in the allergen immunotherapy practice patterns of US and European allergy specialists. The differences lie primarily in the availability of allergen extracts and how these extracts are formulated, and both of these factors are influenced by regulatory guidelines. In Europe, extract manufacturers prepare the final finished allergen formulation, often provided as named-patient products, whereas this role is played by allergy specialists in the United States. New allergen extracts or formulations must prove efficacy and safety in appropriately controlled studies before being approved by the FDA. A similar approval process is required for existing approved products seeking a new indication (ie, a SCIT extract seeking a new package insert indication for SLIT use).

Similarities between European and US allergist specialists lie in their perception of SIT and their approach to providing optimal SIT care, which is detailed in their practice guidelines. Another unfortunate similarity is that only a small percentage of allergic individuals subscribe to this disease-modifying treatment on both sides of the Atlantic. However, allergy specialists on both continents recognize the need for ongoing research focused on developing safer and more effective SIT.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Cox LS. 2009;103:451–460.

CME Test Questions

1. An allergen extract standardization procedure that establishes extract potency by comparison with pooled sera from an allergic population, such as the ID₅₀EAL method:
 - a. can determine if a relevant allergen is missing
 - b. provides information about the overall allergenicity of the extract
 - c. will ensure that the allergen extracts with the same labeled potency have similar compositions

-
- d. correlates with the weight of the source material extracted with a given volume of extracting fluid (wt/vol)
- e. will determine the major allergen content
2. The following is considered a contraindication for allergen immunotherapy in both the US Allergen Immunotherapy Practice Parameters and the European Academy of Allergy and Clinical Immunology Practice Guidelines.
- pregnancy
 - poorly controlled asthma
 - hypertension
 - autoimmune disease
 - children younger than 5 years
3. Allergen extracts are complex heterogeneous mixtures of allergenic and nonallergenic protein, glycoproteins, and polysaccharides. The major allergen:
- content does not correlate with the extract's overall biological potency
 - is defined as an allergen to which at least 50% of the allergic population produces allergen specific IgE
 - is defined by the severity of the reaction it produces in the allergic population
 - is the basis for grass standardization in the United States
 - is not the basis for short ragweed standardization in the United States
4. Allergen extracts can be modified to improve efficacy and/or safety. All of the following are examples of modified allergen extracts except:
- allergoids, which are extracts that have been chemically modified to reduce IgE-binding capacity with the concept of potentially reducing the allergenicity of the allergens but retaining the antigenicity
 - adjuvants, such as 3-deacylated monophospholipid A, which target toll-like receptors and may enhance the effectiveness of allergen immunotherapy by shifting the immune response toward T_H1 production
 - absorption to depot materials, such as aluminum hydroxide or L-tyrosine, which may facilitate slow-release presentation of the allergen
 - recombinant allergens, which can be modified to reduce IgE reactivity and improve specific immunotherapy safety or use as reference material for assays measuring major allergen because they can have sufficient structural and immunologic similarity to their natural counterparts
 - glycerinated-saline allergen extracts administered by the sublingual route
5. Which of the following statements regarding allergen extracts in Europe and the United States is not correct?
- Standardized allergen extracts are compared with the Food and Drug Administration's Center for Biologics Evaluation and Research's reference control and labeled in bioequivalent allergy units or allergy units or major allergen content (Amb a 1), which provides for consistency among lots from different manufacturers.
 - Allergen extracts are compared with manufacturer's in-house reference in Europe and labeled in manufacturer-specific units, which provides for consistency with different lots within a manufacturer but makes comparisons of extract potency between companies difficult.
 - The future focus of allergen extract standardization in the United States is measurement of overall potency using multiplex bead array technology.
 - The future focus of allergen extract standardization in Europe is major allergen content using recombinant allergens as reference materials and validated assays for their quantification.
 - Most allergen extract formulations are prepared in the allergy specialist's office in Europe.

Answers found on page 495.