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Comparison of allergen immunotherapy practice patterns in inhalant allergies in the United States of America and Europe: Similarities and differences 2023

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ABSTRACT

IgE-mediated atopic diseases such as allergic rhinitis and rhinoconjunctivitis are common chronic diseases in the western world. Allergen immunotherapy (AIT) plays a fundamental role in the treatment of allergic patients by modulating the underlying immune mechanisms. Though this treatment is integrated in practice-patterns globally, many differences are found in the application of AIT on the national or international level due to heterogeneous methods, and clinical recommendations are given in different parts of the world.

This review from authors in Europe and the United States highlights differences and similarities in important aspects of AIT application in the 2 global regions. First, the regulatory situation differs regarding marketing authorization and licensing. Secondly, differences are elaborated in manufacturing practices, marketing distribution and formulations of AIT products. Thirdly, clinical administration patterns in the current guidelines show similarities in indications and contraindications of AIT, but also are divergent in some practical aspects.

Informing the readership on similarities, as well as differences of standards in AIT in the United States and Europe, the authors highlight the unmet need of thorough harmonization of standards of AIT, as it is the only disease modifying treatment option available for patients with allergic rhinitis and rhinoconjunctivitis.

Keywords: Allergen immunotherapy, Allergic rhinitis, House dust mite, Sublingual immunotherapy, Tablet, Total combined rhinitis score, Symptom score, Medication score, EU data, Quality of life, SCIT, SLIT, AIT

INTRODUCTION

Allergic reactions of the upper (allergic rhinitis) and lower airways (allergic asthma) affect more than one fifth of the general population and put a high socioeconomic burden on health care systems around the globe.[1] Symptom control can be achieved by allergen avoidance and pharma

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cotherapy with a variety of different drug classes.[1-3] However, only allergen immunotherapy (AIT) via subcutaneous (SCIT) or sublingual (SLIT) application routes has the capacity to achieve long-lasting disease-modifying effects by targeting the underlying pathophysiological mechanisms.[4,5] Although AIT looks back on a more than 100 year history since the first publication by Leonard Noon in 1911,[6,7] there is still an immense underutilization of AIT in moderate to severely affected patients worldwide. National and international allergy societies such as the American Academy of Allergy Asthma & Immunology (AAAAI), the European Academy of Allergy and Clinical Immunology (EAACI) and others developed guidelines to improve decision making in diagnostics and application of AIT in patients with inhalant allergies.[5,8-11] However, a high level of heterogeneity is found in national guidelines around the world regarding practical recommendations.[12]

Early AIT guidelines published in the last decade of the previous century were mainly consensus-based documents provided by highly experienced leaders in the field.[12] Based on the concept of Evidence-based-Medicine (EBM), the Grading of Recommendations, Assessment, Development and Evaluations system (GRADE) and the Appraisal of Guidelines for Research and Evaluation tool (AGREE II) have enabled comprehensive and more consistent guidelines.[13,14] These tools have been increasingly applied to AIT guidelines.[15]

In 1989 the AAAAI and the American College of Allergy, Asthma and Immunology (ACAAI) formed the Joint Task Force on Practice Parameters (JTFPP). They develop documents that establish recommendations for evidence-based patient care. Although practice parameters describe generally accepted practices as well as boundaries for appropriate patient care, they are not intended to define a standard of care. However, they have become the "de facto" standard of practice for AIT in North America. Similar to other practice parameters the JTFPP developed this document after performing a thorough review of the medical literature, paying particular attention to the strength of the evidence used to make recommendations, followed by review and input from other organizations such as the American Academy of Otolaryngic Allergy, and governmental agencies such as the US Food and Drug Administration (FDA). The parameters are finalized after a thorough invited review and public comment period by all stakeholders, members of ACAAI, and AAAAI. The latest Practice Parameters on AIT were published in 2011,[16] with an update in 2017 focusing especially on SLIT.[17] In 2020, a practice parameter update on Rhinitis was also developed by this group.[9]

In 2015 EAACI initiated the AIT guideline project based on systematic evaluation of the current evidence in AIT[18,19] and the involvement of multidisciplinary and multiprofessional groups, and made recommendations centered around patient care while balancing the benefits versus risks of AIT.[11] Multiple guidelines of EAACI have been formulated in line with the AGREE II approach.[13] As one out of this series, the "EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis" aimed to provide evidence-based recommendations for the use of AIT for patients of all ages with allergic rhinitis with or without conjunctivitis. The guidelines also incorporate guidance for other health care professionals (eg, physicians from other disciplines, nurses and pharmacists) in managing allergic rhinitis.[20] More recently, the EAACI has published a guideline on house-dust mite allergic asthma based on a systematic review following the GRADE methodology.[21]

Though the clinical development of AIT products is harmonized throughout European Union (EU) member states by the European Medicines Agency (EMA),[22] differences on available AIT products on the market exist in the these states. Aiming to provide recommendations on best practice of AIT in the German-speaking countries, the German, Austrian, and Swiss allergological societies have very recently published a guideline document and put emphasis on the product-specific evaluation of efficacy and safety.[5,15] Linked to this guideline is an online table with product-specific information of currently marketed AIT products, outlining their registration status, their published clinical documentation, and clinical development programs.[23]

In the light of AIT as the only disease-modifying treatment of IgE-mediated allergic diseases and

aimed to optimize standard of care internationally, the following review outlines principles and features of different (United States of America and European) guidelines with a special focus on similarities and differences. Therein, the authors are aware of a certain lack of definition of the term "Europe/European", but intent to avoid a limitation of this review to the member states of the European Union where possible, although some statements might not apply to every single European country.

THE REGULATORY ENVIRONMENT IN THE UNITED STATES AND EUROPE

Pharmaceutical companies are increasingly focused on global strategies to develop and market their products[24] and regulatory agencies in both Europe and the United States recognize the need for continued research focused on developing safe and effective AIT.[25,26] However, there are major differences in regulation of products for AIT between Europe[15] and the United States[26] (Table 1). These concern the marketing authorization (MA) in the European Union, licensure in the United States, and standardization. Differences in availability of product formulations, manufacturing, standardization, routes of application and differences in regulation and practise patterns are noted. As an example, while ready-to-use alum-precipitated, and/or further modified aeroallergens have been more commonly adapted into clinical practice in European countries, practitioners in the United States have nearly exclusively used aqueous or glycerinated products.

The regulations in the United States and European Union have evolved independently.[27,28] In the European Union, since 1989, allergen products are defined as medicinal products according to legislation. Directive 2001/83/EC[29] which provides the main regulatory framework, dictates that allergen preparations are considered medicinal products as they are substances or combination of substances presented for treating or preventing disease in human beings. The directive applies to allergen products produced industrially or manufactured by a method involving an industrial process and intended to be marketed in a member state. Generally, sufficient data proving quality, safety and efficacy of the concerned product is required to obtain a MA approval. There is one exception to this requirement. It is stated that the directive shall not apply to any medicinal product prepared in a pharmacy with a medicinal prescription for an individual patient. These products are considered "named patient products" (NPPs).

Despite the unification according to the directive, the regulatory landscape governing the approval of these products is enormously heterogeneous within the European Union and even more when viewed globally.[24] In Germany, the Therapy Allergen Ordinance (TAO) has been implemented with the aim to ensure tested and proven quality, efficacy, and safety of AIT-products for frequent allergens such as pollen of the birch-homologous group (*birch, alder, hazel*) and sweet grasses except maize, house dust mites, bee venom, and wasp venom.[30] This has led to a tremendous reduction of allergen products on the German market. A further consequence was that numerous randomized, double-blind, placebo controlled clinical trials were and are conducted[5,23,31] in accordance with Good Clinical Practise (GCP) guidelines as European countries started to implement GCP into national law since 2004.

The EU has a unique combination of national regulatory agencies that work together in a network to regulate market access of medicinal products. While the EMA with the Committee for Medicinal Products for Human Use (CHMP) is responsible for the guidance related to MA, the scientific assessment is actually done by the national competent authorities (NCAs) of the concerned countries.[32]

In contrast to allergen extracts, medicines derived from biotechnological processes have to go through the centralized procedure. However, the centralized procedure can also be used voluntarily if the product in question is based on a new active substance or if it can demonstrate a significant therapeutic, scientific, or technical innovation. This procedure is coordinated by the EMA and leads to a MA in the European Economic Area (EEA), which includes Norway, Iceland, and Liechtenstein in addition to all EU member states.[32]

So far, all inhalant allergens are authorized via a national authorization procedure. There are 2 different procedures possible depending on the origin of the initial application:

	United States	Europe
Regulatory Agency	FDA	EMA
	U.S. Food & Drug Administration	European Medicines Agency (EEA countries only)
	Center for Biologics Evaluation and Research (CBER)	National competent authorities (NCAs)
Regulatory status	Licensure	Products with Marketing Authorization
		Named patient products (NPPs)
Standardization	Standardized and non-standardized products (majority)	Product-specific standardization of single products cross-product comparability based on major allergen content in preparation
Most common standardization method	ID_{50}EAL, intradermal	Nordic, percutaneous initial standardization via in vitro methods also possible
Potency determination	Standardization based on FDA standards (CBER reference control)	Product-specific standardization based on in-house references
Standardization end point	Extract dilution producing sum of erythema of 50 mm	Extract dilution producing wheal equal to histamine control
Potency units	BAU, AU, wt/vol, PNU, mcg major allergen content	Each company has its own potency unit
Labelling	Potency related labelling	Manufacturer specific units, mostly based on IgE-binding capacity
Manufacturing	CBER	European Pharmacopeia (Ph. Eur.) by European Directorate for the Quality of Medicines & Healthcare (EDQM) (39 signatory states)
	US Pharmacopeia regulates mixing in doctor's offices	Monograph on allergen products[41]
		EMA Guideline on Allergen Products: Production and Quality Issues[62]
Regulations/Regulatory Guidance	No formal guidance for clinical development of AIT products. Each product under development is considered separately by the CBER.	CHMP Guidance Documents as *"Guideline on the Clinical Development of Products for Specific Immunotherapy for The Treatment of Allergic Diseases" (CHMP/EWP/18504/2006)*[22] and *"Guideline on the clinical investigation of medicinal products for the treatment of asthma" (CHMP/EWP/2922/01 Rev.1)*[63]
Use in children	Pediatric studies are encouraged; for example by PREA (Pediatric Research Equity Act) and pediatric exclusivity inducement	Products with proven efficacy and safety in parallel with products without clinical evidence Pediatric development monitored by PDCO

Table 1. Regulatory environment in the United States and Europe: similarities and differences

If a MA application is submitted to only one member state, the data are assessed under national timelines which vary among the countries. Once one national MA is obtained, each further application for MA in other member states will be performed via the mutual recognition procedure (MRP). Through MRP, the regulatory authorities of the new countries will be provided with the assessment report prepared by the authority which granted the first marketing approval. If the first MA application is submitted in 2 or more member states in parallel, the decentralized procedure (DCP) is followed and an authorization in several EU countries can be obtained with less effort and in a shorter time. With the successful closure of that procedure, national authorizations can be granted.[24]

The Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) is responsible for the examination and coordination of questions related to the MA of human medicines in accordance with the MRP or DCP. The CMDh is associated with the Heads of Medicines Agencies (HMA) which is a network of the heads of the NCAs responsible for regulation of medicinal products for use in the European Economic Area.

Furthermore, given AIT's strong potential for immunomodulatory effects, potential to prevent the progression of the atopic march and very little long-term data on efficacy in children, the Paediatric Regulation (EC) No 1901/2006[33] came into force in 2007 to ensure that medicines for use in children are of high quality, ethically researched, and authorized appropriately. The Paediatric Committee (PDCO) was established with the main role of determining the studies that companies must carry out on children as part of their paediatric investigation plans (PIPs).[34] PIP-compliance is a prerequisite for granting a MA not only for children, but also for the authorization for adults.

In comparison, in the United States, the FDA's Center for Biologics Evaluation and Research (CBER)[35] regulates allergenic products.[36] CBER has legal authority under two federal laws, the Food Drug and Cosmetic Act of 1938 and the Public Health Service Act of 1944, as amended. Specific regulations are primarily found in part 680 of Title 21. Extracts have been primarily regulated based on extraction methods. Extracts are divided into 2 types: Injectable allergen extracts out of which some are "*standardized*" with consistent biological potency and strength; others are "*not-standardized*" extracts which have more lot to lot variability. Specific sublingual allergen extract tablets have also been FDA approved.[37]

Licensing of allergen extracts has changed. In the United States, in the early 1970s, commercial allergenic extracts were classified into 3 different categories: Category I, approved; Category II, not approved; or Category III, data insufficient for classification and pending approval. Non-standardized products were placed in Category III pending approval. In the 1980s, licenses were issued based on safety and effectiveness data for standardized extracts, removing their non-standardized counterparts. The FDA in 2011 proposed classification of all 1200 species of extracts based on literature reviews up to this year.[36]

These procedures, formerly specified in regulations (21 CFR 601.25 and 601.26) and rendered obsolete in 2016, relate to allergenic extracts regulated by the National Institutes of Health (NIH) before transfer to the FDA in 1972. They are irrelevant to regulation of new products.[27]

At present, in the United States, the standards for licensure include a demonstration of safety, purity, and potency.[27] Clinical development includes a phase 1 protocol to support safety, phase 2 studies to determine proper dose range and to support efficacy and phase 3 studies. In the United States, for the biologics license application (BLA), an agreed upon pediatric study plan (PSP) detailing the data to support use in pediatric populations is required at the time point of submission of a BLA.[24,27]

AIT-PRODUCTS: PREPARATION/ MANUFACTURING AND DISTRIBUTION

Similarities and differences exist for both SCIT and SLIT on the extract formulation, the number of different allergen species included, potency and types of extracts mixed (Table 2, Fig. 1).

Overview of products

For biological medicinal products, the manufacturing process has a strong impact on the characteristics of the final drug product. Therefore, the process has to be well controlled and validated to ensure that each batch produced is of consistent and sufficient quality. These preconditions must be met before any further assessment of efficacy and safety becomes relevant.[38]

There are 4 US licensed companies who produce 19 standardized SCIT products, 4 standardized SLIT products, and a multitude of non-standardized SCIT products. Extracts have been primarily regulated based on extraction methods rather than collection methods. Most manufacturers use similar extraction methods among different source materials, using a slightly alkaline buffer with or without glycerin. Pollen extracts are manufactured similarly by each company and show little variability. Pollen source materials have minimal differences as collection methods are well established.[36] Molds are extracted similarly but use different strains and growing conditions.[39] Differences between fungal extracts can be significant as fungal strains, growth medium, source material processing methods, and harvesting techniques vary widely. Epithelial extracts (*cat, dog, etc.*) are concentrated through various methods, such as acetone precipitation and lyophilization.

All extracts must be sterile, which is completed by passing the extract through a sterilizing filter with a pore size 0.2 µm. All multiple-dose vials must contain a bacteriostatic and fungistatic preservative. Most manufacturers utilize phenol 0.4% (0.2–0.5%) with or without 50% glycerin. Extracts containing 50% of greater glycerin have longer expiration dates, up to a maximum of 6 years, including 3 years in manufacturer's storage and up to three years after the product is shipped. Mixtures are formulated in the Allergist's office or by the manufacturer under sterile conditions following US Pharmacopeia guidelines.[40]

In the European Union, manufacturing processes differ considerably, not only between manufacturers but partly also between allergen products from the same manufacturer. Therefore, the process has to be well controlled and validated to ensure that each batch produced is of consistent and sufficient quality. These preconditions must be met before any further assessment of efficacy and safety becomes relevant.[38] The European Pharmacopeia provides a regular framework for the manufacturers. It consists of monographs developed by the European Directorate for the Quality of Medicines and Healthcare (EDQM), describing common quality standards for the control of medicinal products. The central document for allergen extract quality control is the Monograph on Allergen Products.[41] In Europe, allergen extracts are manufactured in several member states by various companies. To date, allergens contained in marketed products are extracted from natural allergen sources. Extraction and production processes differ largely between

	United States	Europe
SCIT Extract formulation	Extract: Manufacturer Patient specific vials: Physician/Allergist offices	Allergen product manufacturer
No of allergens	Multiple	Generally 1, or mixture of similar allergens (eg, grass mix)
Potency units	BAU, AU, wt/vol, PNU, mcg major allergen	Each company has its own potency unit
Extract types	Aqueous and glycerinated unmodified extracts	Aqueous unmodified and modified extracts for SLIT, mostly alum-adsorbed extracts for SCIT
SLIT	Minority of prescriptions but increasing	More common than in United States, percentage varies between countries

Table 2. AIT products in the United States and Europe: similarities and differences

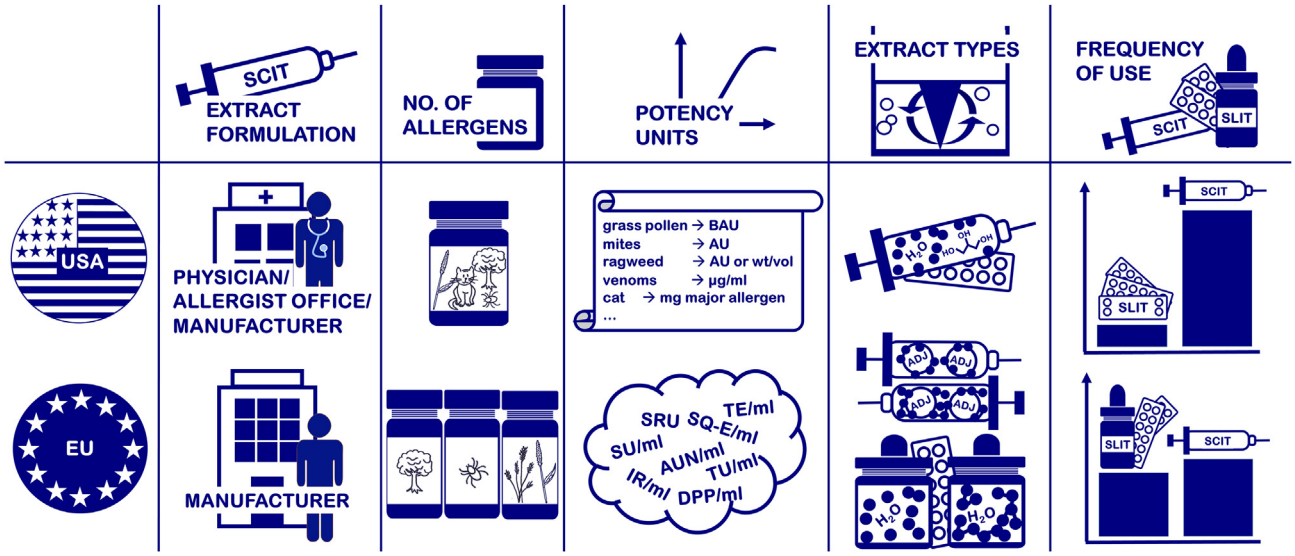

Fig. 1 AIT products in the United States and Europe: Overview of main similarities and differences. Products for AIT used in the United States and Europe differ in various aspects, including the site of extract formulation, the number of allergens commonly mixed in the preparations, and the units describing the strength of a product. Furthermore, the European market offers a more diverse range of extract types and the use of sublingual preparations is far more common compared to the United States

European manufacturers,[36] and allergen products, including extract mixtures, are generally prepared, formulated, and distributed by manufacturers only.

Standardization/extract potency standards

In the United States, standardization and extract potency is directed by CBER which maintains and distributes reference extracts and serum pools. Standardization refers to product specific standardization (batch to batch) and also refers to potency so that extracts from different manufacturers can be compared (cross-product).[25] They aim to provide labelling in a common potency unit, the bioequivalent allergy unit (BAU). Standardized extracts have additional quality control requirements encompassing source material and in-process and finished product testing with lot-release.

The potency of the manufacturer's extract is established by comparing the prepared extract with the CBER's reference control using an *in vitro* assay, such as ELISA for grass and dust mites.[26] These are labelled in BAUs for grass and AUs for dust mites. In contrast, cat and short ragweed extracts were originally standardized based on the estimate of major allergen content, *Fel d 1* and *Amb a 1*; these concentrations were shown to correlate with the overall biological activity of the extracts as determined by quantitative skin testing.

The CBER reference control is assessed for biological potency based on titrated intradermal skin testing of highly allergic individuals with 3-fold dilutions of the candidate extract (ID_{50}EAL method [IntraDermal dilution for 50 mm sum of Erythema determines the bioequivalent ALlergy units]).[25] The sum of the longest midpoint diameters of erythema is measured; a mean D50 of 14 (between #13 and 15 3-fold serial dilution) is assigned a potency of 1 000 000 BAU, whereas a mean D50 between #11 and 13 dilution is assigned a potency of 10 000 BAU.

The advantage of the current US methods includes an estimate of potency, and the ability to compare products between manufacturers. Disadvantages include that the United States has been slow to add to the list of standardized products, current methods cannot detect the presence of specific and potentially important allergens, and all relevant allergens may not have been identified. Future directions include development of multiplex antibody based methods and the use of mass spectrometry for profiling complex allergen mixtures.[42]

In Europe extraction and production processes differ largely between the manufacturers. So far, standardization in Europe mainly relates to homogeneity between batches (product-specific standardization) and is commonly based on in-house reference products (IHRP) and in-house

assays. Sometimes, products are additionally characterized based on major allergen content. The first IHRPs are usually biologically standardized by applying the Nordic method or the ID50EAL method,[36] while subsequent IHRP batches are established based on *in vitro* methods. The Nordic method compares the wheal size with a histamine control; the biological unit (BU) is the measure of potency; an extract producing a wheal size the same size as a 10-mg/mL histamine control was assigned 10 000 BU or 10 (histamine equivalent prick, HEP-units).[43] Most extracts are standardized for potency according to their capacity to bind IgE in human sera pooled from 10 to 15 donors.[25] There are no common extract-based European standards, and potency of extracts is expressed in arbitrary manufacturer-specific units relative to the IHRP. Different units based on biological activities are in use.[44] Thus, while the European system may lead to standardization of more products, it is not possible to compare extracts between manufacturers.[25]

The *"Development of certified reference materials for allergenic products and validation of methods for their quantification"* (CREATE) project was started in 2001 to support introduction of major allergen-based standardization for cross-product comparability by investigating and comparing ELISA systems for the quantification of allergens.[45] The Biological Standardisation Programme (BSP)090 project in 2006 was a follow-up project and established the recombinant major allergens rBet v 1 and rPhl p 5a as reference standards[46,47] and validated the corresponding Bet v 1- and Phl p 5-specific ELISAs.[25,48] The use of the resulting standard methods and declaration of allergen content will become mandatory in the European Union once the general texts describing the methods are implemented in the European Pharmacopeia (Jan 01, 2023 for Bet v 1 assay[49]) and the Monograph on Allergen Products has been updated accordingly.

Adjuvant products in AIT

In the United States SCIT products generally use aqueous or glycerinated extracts. Aqueous extracts are lyophilized and reconstituted prior to use. There are a limited number of alum-precipitated (Center-A1) extracts available.[16] In Europe most of the SCIT products are adsorbed to aluminum hydroxide. Only insect venoms are administered as aqueous extracts.[50] The use of chemically modified allergen extracts (so-called allergoids) is also common. Allergens in these products are treated by glutaraldehyde or formaldehyde to reduce IgE-binding epitopes and thereby decrease allergenicity and potential for systemic reactions while maintaining T-cell binding epitopes to preserve immunogenicity.[5]

SCIT formulations

In the United States, the majority of allergen extracts are provided by the manufacturer directly to the practitioner, and patient specific vials are formulated in the doctor's office or by the manufacturer under sterile condition as required by governmental regulations (Table 2, Fig. 1). Patient-specific vials can require mixing of aeroallergens and most patients receive multi-allergen immunotherapy. Aseptic conditions are maintained and personnel are required to follow guideline issued by the US Pharmacopoeia.[40] In Europe, AIT products are provided by the manufacturer as a single-allergen preparation or as compounded mixtures. Build-up and maintenance treatment vials are delivered pre-formulated in different vials of different allergen content.[26]

SLIT formulations

In the United States, there are 4 FDA approved SLIT tablets, including Oralair© (5-grass 300 IR), Grastek © (timothy grass, 2800 BAU), Ragwitek© (12 µg Amb a 1), and Odactra© (HDM 12 SQ units). These are prescribed by the Allergist and distributed by a specialty pharmacy to the patient after approval. The first dose is given in the Allergist's office.[37,51] Unlike other countries, US physicians are required to prescribe an epinephrine auto-injector to all patients receiving SLIT tablets. There are no FDA approved liquid SLIT products (ie, drops) in the United States. Allergists have started utilizing off-label SLIT more in their practices. They are using commercial aqueous allergen extracts that are marketed for SCIT. These are not approved for SLIT administration, as efficacy and safety studies are lacking. In Europe, an increasing number of SLIT products are authorized and used in daily practice with

differences on the national level throughout Europe.[5,20,23,36,50]

CLINICAL APPLICATION OF AIT: RECOMMENDATION FOR PRACTICAL AIT

Similar algorithms are taken for diagnosis of aeroallergen sensitivity in United States and Europe.[9,52] Detailed history and physical exam are strongly recommended. Definitive diagnosis is made with immediate skin prick test (SPT) and/or serum specific immunoglobulin E (IgE). Specific IgE levels are obtained when SPT cannot be performed due to skin disorders, such as severe eczema or dermatographism, or inability to discontinue antihistamine therapy. Intradermal skin test may be used when there is a strong clinical suspicion for patients with negative SPT.[36] Besides, organ specific allergen-challenge tests such as the nasal challenge test[53] are frequently used in Europe in case of contradicting diagnostic pattern outlined above aimed to confirm the clinical relevance of the underlying sensitization[5,20] (Table 3).

In the United States AIT is indicated for US patients with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and aeroallergen-driven atopic dermatitis, whose symptoms are not well-controlled on medications and/or avoidance measures[16] (Table 3). It is also indicated for patients who experience adverse reactions to medications or who wish to avoid or reduce medication use. Factors that should be considered prior to initiating AIT include patient preference, tolerability, adherence, medication requirements, response to avoidance measures, adverse effects of medication, and coexisting allergic rhinitis and/or asthma. There is no lower or upper age limit for AIT if indications are present without contraindications and the patient is adherent to the procedure. Contraindications for AIT include poorly controlled asthma and medical conditions that reduce patient's likelihood of surviving systemic allergic reaction or its treatment, such as poor lung function and significant cardiovascular disease.[16] Eosinophilic esophagitis, poorly controlled asthma, and history of severe systemic reaction are contraindications for SLIT tablets.[36] AIT can be continued during pregnancy, but it should not be initiated. If a patient becomes pregnant during build up, discontinuation of AIT and re-initiation of therapy after pregnancy should be considered. AIT can be considered in patients with immunodeficiency and autoimmune disorders if appropriate indications are present.[16] AIT should be prescribed by allergists who are adequately trained and all staff providing the AIT should be prepared to recognize and treat possible allergic reactions. AIT should only be administered where emergency medications are readily available.

In Europe AIT is recommended for patients with IgE-mediated allergic diseases supported by positive diagnostic test, inability to avoid allergen and inadequate control of symptoms (by pharmacotherapy) that interferes with daily activities or sleep (Table 3).[20,52] Absolute contraindications to AIT include uncontrolled asthma, active autoimmune disorders, and active malignant neoplasia. AIT can be continued during pregnancy but should not be initiated during pregnancy. Relative contraindications that require careful discussion of risks and benefits of AIT include partially controlled asthma, autoimmune disorders in remission, cardiovascular disease, children between age 2 and 5 years, HIV, psychiatric disorders, immunodeficiencies, use of immunosuppressives, and chronic infections.[54]

Dosing of AIT, premedication and observation time

The ACAAI/AAAAI recommend starting dose of SCIT to be 1000-fold or 10,000-fold dilution of the maintenance dose. During build up, SCIT dose is gradually increased with each visit over 8–28 weeks. For conventional build up, a single dose is given per visit, which ranges from 1 to 3 times a week.[16] With an accelerated schedule, multiple doses are given per visit to reach maintenance more rapidly than conventional schedule. For cluster schedule, 2 or more doses are given each visit, separated by 30 min monitoring time period, once or twice a week. During rush schedule, a patient receives 7 doses over 4 h, enabling the patient to reach maintenance faster than cluster immunotherapy.

Premedication with antihistamines can reduce the risk of systemic reactions to accelerated therapy. Combination therapy with prednisone, H1

	Overlapping aspects (similar in all the 3 guidelines/ Practice Parameters)	Modified to the practice Parameters of the United States (ACAAI/AAAAI)[16]	Modified to the Guideline of the EAACI[20]	Modified to Guideline of the German speaking countries Germany, Austria and Switzerland[5]
INDICATION	**=Clinically relevant allergic sensitization** **=Insufficient control by pharmacotherapy and/or avoidance** **=Also possible with intention to prevent asthma-progression/ prevention**	-Evidence of specific IgE antibodies to clinically relevant allergens -Factors which support to begin AIT: >Patients' preferences >Adherence >Medication requirements Response to avoidance measures >Coexisting asthma >Possible prevention of asthma >Atopic dermatitis, if associated with aeroallergen sensitivity	All three criteria should be met: -Symptoms strongly suggestive of AR, with or without conjunctivitis -Evidence of IgE-sensitization (positive SPT and/or serum-specific IgE) to one or more clinically relevant allergen -Moderate-to-severe-symptoms which interfere with usual daily activities or sleep despite regular and appropriate pharmacotherapy and/or avoidance strategies Note: AIT may also be indicated in less severe AR in view of (tertiary) preventive measures Product specific evaluation of the evidence for efficacy in the clinical documentation recommended Summary of Product Characteristics (SmPC) should be checked (licensed indications may differ between preparations)	-Moderate to severe intermittent and persistent allergic (also possible in case of milder symptoms) rhinitis/ rhinoconjunctivitis and/or at least partially controlled allergic asthma -Evidence of a corresponding clinically relevant allergic sensitization -Symptoms despite symptomatic therapy and/or allergen avoidance -Evidence of efficacy of the planned AIT for the respective indication and age group.
CONTRA-INDICATIONS	**=Uncontrolled asthma** **=Poor adherence and severe psychiatric disorders** **=initiation during pregnancy**	Relative: -Patients non-cooperative of non-compliant - Severe asthma uncontrolled by pharmacotherapy -Beta-blocker therapy -Significant cardiovascular diseases -AIT performed in a setting where prompt	Absolute: -Uncontrolled or severe asthma -Active, systemic autoimmune disorders (unresponsive to treatment) -Active malignant neoplasia -AIT initiation during pregnancy Relative: -Partially controlled asthma -Beta-blocker therapy (local or systemic)	-Uncontrolled asthma -History of severe systemic reactions -Malignant neoplastic diseases with current clinical significance -Severe systemic autoimmune diseases, immunodeficiencies, relevant immunosuppression -Insufficient adherence, severe psychiatric disorders -Untreated chronic infection (e.g.,

	recognition and treatment of anaphylaxis is not given.	-Severe cardiovascular diseases, for example, coronary artery disease -Systemic autoimmune disorders in remission or organ specific -Severe psychiatric disorders -Poor adherence -Primary and secondary immunodeficiencies -History of serious systemic reactions to AIT	HIV, hepatitis C) F-or SLIT: History of inflammatory gastrointestinal diseases (e.g., eosinophilic esophagitis), wounds of the oral cavity and others -Summary of Product Characteristics (SmPC) should be checked (licensed indications may differ between preparations)

Table 3. Indications and contraindications of AIT in the United States and in Europe[5,16,20,36,54,59]

and H2 antihistamines or use of omalizumab as premedication also has been shown to reduce risk of systemic reaction during accelerated therapy.[16] ACAAI/AAAAI and EAACI recommended at least 30 min of observation after SCIT. Dose adjustments after a systemic reaction, gap in therapy and new vial is commonly practiced by most.[55] Safety of dose adjustments for late injections, injection after refills and after systemic reaction has been studied.[56] However, more prospective data are needed to support recommendations for changes in dosing due to gaps.[57] Factors to consider include the concentration of the SCIT, history of systemic reaction and the length of the gap, with greater decrease in dose with longer gap in therapy. A decrease in dose after a systemic reaction and with new refill vial is recommended by ACAAI/AAAAI. However, there is insufficient data to support dose adjustment after a large local reaction. The common practice to decrease SCIT dose during peak pollen season is supported by a survey of US physician practices reporting an association between pollen seasons and systemic reactions.[58] However, this has not been confirmed in other systematic reviews.[59,60] After initiation therapy (updosing phase), maintenance dosages are usually given in intervals of 15–30 days.

In the European Union the EAACI guidelines recommend dosing in the initiation phase and maintenance phase in line with the information of the summary of product characteristics (SmPC) of the marketed products.[20,52] Accelerated schedules are also possible and in clinical use.[61] After initiation therapy (updosing phase), maintenance dosages are usually given in intervals of 4–6 weeks following the guidance in the SmPC. In case of local reactions under SCIT, premedication with an H1-antihistamine is also recommended aimed to reduce frequency and severity. This is in principle also given for severe local reactions under SLIT. However, it is also stated that these measures do not prevent the onset of severe systemic reactions such as anaphylaxis. Moreover, in case of recurrent severe adverse events the EAACI guideline recommends a re-evaluation of the prescribing physician on the benefits and risks for the decision for cessation of treatment, dose-adaption or continuation which

should always follow the SmPC of the applied single products.[20] Also, the EAACI guidelines underline the important role of thorough information and education of the patient regarding the procedures, adherence, and precautions in AIT.[20,52] This is also much highlighted in the recently published guideline of the German speaking countries providing the readership recommendable measures to improve treatment adherence in practical routine.[5]

CONCLUSION

More than one fifth of the general population in the western world is affected by IgE-mediated allergic diseases of the airways, and although allergen immunotherapy has been established as disease-modifying treatment option in these patients a significant underutilization is found. This may be related to the heterogeneous practices and clinical recommendations given in different parts of the world.

This review of European and US authors aimed to highlight differences and similarities in important aspects of AIT application on the 2 regions. First, the regulatory situation differs regarding MA and licensing. Secondly, differences exist in manufacturing practices, marketing distribution and formulations of AIT products. Thirdly, although clinical administration patterns in the current guidelines show similarities such as indications and contraindications of AIT, they are also divergent in some practical aspects.

There is an urgent need for thorough harmonization of these standards in AIT aimed to improve the care of allergic patients internationally.

Abbreviations

AAAAI, American Academy of Allergy Asthma & Immunology; ACAAI, American College of Allergy, Asthma and Immunology; AGREE-II, Appraisal of Guidelines for Research and Evaluation tool; AIT, allergen immunotherapy; BAU, bioequivalent allergy unit; BLA, biologics license application; BSP, Biological Standardisation Programme; BU, biological unit; CBER, Center for Biologics Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use; CMDh, Coordination Group for Mutual Recognition and Decentralized Procedures-Human; CREATE, Development of certified reference materials for allergenic products and validation of methods for their quantification; DP, decentralized procedure; EAACI, European Academy of Allergy and Clinical Immunology; EBM, Evidence-based-Medicine; EDQM, European Directorate for the Quality of Medicines and Healthcare; EEA, European Economic Area; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; GCP, Good Clinical Practise; GRADE, Grading of Recommendations, Assessment, Development and Evaluations system; HEP, histamine equivalent prick; HMA, Heads of Medicines Agencies; ID50EAL, IntraDermal dilution for 50 mm sum of Erythema determines the bioequivalent ALlergy units; IHRP, in-house reference products; JTFPP, Joint Task Force on Practice Parameters; MA, marketing authorization; MRP, mutual recognition procedure; NCA, national competent authorities; NPP, named patient products; PIP, paediatric investigation plans; PDCO, Paediatric Committee; PSP, pediatric study plan; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual allergen immunotherapy; SPT, skin prick test; TAO, Therapy Allergen Ordinance; US, United States of America.

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Ethics statement

Not applicable, as this is a review paper.

Consent

All authors agree to the publication of this work.

Declaration of competing interest

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