

Understanding differences in allergen immunotherapy products and practices in North America and Europe



Vera Mahler, MD,^a Robert E. Esch, PhD,^b Jörg Kleine-Tebbe, MD,^c William J. Lavery, MD, PhD,^d Greg Plunkett, PhD,^e Stefan Vieths, PhD,^{a*} and David I. Bernstein, MD^{d*} *Langen and Berlin, Germany, Hickory, NC, Cincinnati, Ohio, and Mead, Wash*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the JACI Web site: www.jacionline.org. The accompanying tests may only be submitted online at www.jacionline.org. Fax or other copies will not be accepted.

Date of Original Release: March 2019. Credit may be obtained for these courses until February 29, 2020.

Copyright Statement: Copyright © 2019-2020. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1.00 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Vera Mahler, MD, Robert E. Esch, PhD, Jörg Kleine-Tebbe, MD, William Lavery, MD, PhD, Greg Plunkett, PhD, Stefan Vieths, PhD, and David I. Bernstein, MD (authors); Zuhair K. Ballas, MD (editor)

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: V. Mahler reports personal fees (prior to current position) from ALK-Abelló, Bencard/ATL, HAL, Novartis/Leti and other support from Allergopharma, Germany, and DBV, France, outside the submitted work and grants, personal fees, and other support from Novartis, Germany, and nonfinancial support from the European Academy of Allergy and Clinical Immunology outside the submitted work. J. Kleine-Tebbe reports personal fees from Allergopharma, ALK-Abelló, Bencard/Allergy Therapeutics, Circassia, HAL, LETI, Lofarma, Merck (USA), and Stallergenes Greer for lecturing, conduct of studies or consultancy; personal fees from AllergenOnline (University of Nebraska), AstraZeneca, Dr. Pfleger, German Society of Allergology and Clinical Immunology, Glaxo, Novartis, Paraxel International, Sanofi, ThermoFisher for lecturing or consultancy;

personal fees from Springer International and THIEME publishers outside the submitted work; and nonfinancial support from the American Academy of Allergy, Asthma & Immunology, European Academy of Allergy and Clinical Immunology, and WHO/IUIS Allergen Nomenclature Subcommittee. S. Vieths reports personal fees from Ärzteverband Deutscher Allergologen, the Swiss Society for Allergy and Immunology, Schattauer Allergologie Handbuch, Elsevier Nahrungsmittelallergien und Intoleranzen, Karger Food Allergy: Molecular Basis and Clinical Practice, and the American Academy of Asthma, Allergy & Immunology; nonfinancial support from the German Research Foundation, the European Directorate for the Quality of Medicines and Health Care, the European Academy of Allergy and Clinical Immunology, the German Chemical Society (GDCh), AKM Allergiekongress, the International Union of Immunological Societies; and personal fees from University Hospital Gießen/Marburg, the University of Bonn, and Pharmacon; and nonfinancial support from the Spanish Society for Allergy and Clinical Immunology (SEAIC) outside the submitted work. D. I. Bernstein reports grants and personal fees from ALK-Abelló and grants from Allergy Therapeutics, Merck, the American College of Allergy, and the American Academy of Allergy, Asthma & Immunology outside the submitted work. Z. K. Ballas (editor) disclosed no relevant financial relationships.

Activity Objectives:

1. To review the differences in allergen immunotherapy (manufacturing, regulatory requirements, and clinical administration) between the United States and Europe.
2. To understand the differences between European and American immunotherapy products and practices, including unique products available in each setting.
3. To describe the differing diagnostic and therapeutic approaches to allergen immunotherapy in Europe and the United States.

Recognition of Commercial Support: This CME activity has not received external commercial support.

List of CME Exam Authors: Ammara Ahmed, DO, Joan H. Dunlop, MD, Suzanne R. Kochis, MD, Jo Wilson, MD, and Robert A. Wood, MD.

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: The exam authors disclosed no relevant financial relationships.

From ^aPaul-Ehrlich-Institut, Langen; ^bthe School of Natural Sciences, Lenoir-Rhyne University, Hickory; ^cAllergy & Asthma Center Westend, Outpatient Clinic & Research Center, Berlin; ^dthe Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, Cincinnati; and ^eIndependent Contractor Allergy Immunotherapy Consultant, Mead.

*These authors contributed equally to this work.

Received for publication December 20, 2018; revised January 25, 2019; accepted for publication January 28, 2019.

Corresponding author: Stefan Vieths, PhD, Paul-Ehrlich-Institut, Paul-Ehrlich-Str. 51-59, D-63225 Langen, Germany. E-mail: stefan.vieths@pei.de. Or: David I.

Bernstein, MD, Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Rm 7507, Cincinnati, Ohio 45267-0563. E-mail: BERNSTDD@ucmail.uc.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2019.01.024>

Allergen immunotherapy (AIT) is thought to be clinically effective and safe in treating allergic rhinitis, asthma, and stinging insect allergy in Europe and North America. However, there are intercontinental differences in AIT therapeutic products in terms of their application and regulation. In North America unmodified standardized and nonstandardized aqueous aeroallergen extracts are approved and used almost exclusively for subcutaneous immunotherapy, whereas more product options are available in Europe, including adsorbed allergens, chemically modified allergens, or both. Both liquid extracts and tablets are approved for sublingual immunotherapy in Europe. Nevertheless, within the European Union, there are major differences in AIT products approved and used in individual countries. There are major differences in the clinical approach to subcutaneous immunotherapy in polysensitized patients; in the United States mixed extracts containing multiple aeroallergens are used, whereas European allergists preferably administer separate injections of single allergen sources or homologous groups deemed to be clinically relevant. Moreover, the regulatory approach differs between the European Union and United States. In contrast to the United States, where common allergen standards exist based on biologic activity, no common standards exist in Europe. In terms of development of new investigational products, the United States has followed the European example for phase II and III studies; no formal US Food and Drug Administration guidance has been issued. (*J Allergy Clin Immunol* 2019;143:813-28.)

Key words: Allergen immunotherapy, allergen, allergoid, diagnostic, European Medicines Agency, European Union, extracts, Food and Drug Administration, practices, regulatory, subcutaneous, sublingual, United States

Allergen immunotherapy (AIT) with grass pollen was first introduced by Noon and Freeman more than 100 years ago and has been used in clinical practice both in Europe and North America during the last century.¹ Subsequently, subcutaneous immunotherapy (SCIT) has been increasingly practiced on both sides of the pond for treating patients with seasonal and perennial allergic rhinitis, IgE-dependent asthma, and anaphylaxis caused by Hymenoptera insect venom. Placebo-controlled studies performed in both Europe and the United States have supported both the efficacy and safety of a variety of AIT modalities (<https://www.clinicaltrialsregister.eu> and <https://clinicaltrials.gov/>).^{2,3} Yet over the decades, routine clinical practices surrounding AIT used by allergists prescribing AIT in the United States and Europe have diverged substantially. For example, 2 key differences in AIT practice patterns have emerged. First, a limited number of therapeutic aeroallergen species are used, particularly in Central Europe (eg, a single tree, grass, and house dust mite species), versus allergen mixtures used in the United States, representing multiple species of pollens, mold spores, house dust mites and mammalian epidermal allergens. Second, ready-to-use, alum-precipitated, and/or further modified aeroallergens have been adapted into clinical practice in European countries versus the United States, where practitioners have nearly exclusively used aqueous standardized and nonstandardized aeroallergen extract products.

Because of clear intercontinental differences in aeroallergen sources and formulations, it is challenging to directly compare clinical efficacy and safety data derived from placebo-controlled

Abbreviations used

AIT: Allergen immunotherapy
CBER: Center for Biologics Evaluation and Research
EMA: European Medicines Agency
EU: European Union
FDA: US Food and Drug Administration
MA: Marketing authorization
MS: Member state
NPP: Named patient product
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
USP: United States Pharmacopeia

studies conducted in Europe and the United States. Although the US Food and Drug Administration (FDA) has defined the minimal detectable clinical effect by using a statistical approach, in the European Union (EU) statistical significance is the chosen primary end point, and a clinical justification of the relevance of the effect obtained in a pivotal clinical trial is requested.

Moreover, it is difficult to judge the effectiveness of the different AIT approaches in Europe and the United States under real-life conditions. There is likely a substantial lack of familiarity among European allergists of AIT products and practices in the United States and *vice versa*. The goals of this article are to compare differences between the United States and Europe in AIT practices related to:

1. manufacturing and development of therapeutic aeroallergen products;
2. regulatory requirements and clinical development of AIT products;
3. diagnostic approaches used to identify and select specific aeroallergens for AIT;
4. clinical administration of AIT, including build-up schedules and risk management; and
5. unmet needs and controversies.

ALLERGEN EXTRACT MANUFACTURING US practices

There are currently 4 United States–licensed companies that manufacture and market allergen extracts in the United States for clinical use. Together, they manufacture hundreds of extracts derived from diverse allergen sources. Before the 1970s, it was common practice for practicing allergists to manufacture their own extracts using allergen source materials provided by regional suppliers. Today, more stringent regulatory requirements have essentially eliminated this activity from the allergists' clinic and allowed for standardization of 19 products (Table I).⁴

FDA-approved tablet products standardized for allergenic potency are listed in Table II. However, most commercially available allergen extracts are not standardized. Extracts manufactured in the United States have been primarily regulated based on extraction methods used rather than the methods used to collect or produce allergen source materials. For this reason, most manufacturers of US products use similar extraction methods across

TABLE I. Summary of available SCIT products in the United States, including types of commercial products, available products standardized by allergenic potency, methods of preparation, and administration and risk

Commercial treatment allergen products	Specific allergens	Standardized allergen products	Allergen preparation	Compounding and preparing dilution vials	Administration	Risk of systemic reactions and anaphylaxis
Aqueous and glycerinated aeroallergen products	Used in all treated patients	Short ragweed, cat hair/pelt products, 7 temperate	Single- or multiple-allergen mixes prepared in patient-specific	Multiple- or single-allergen vials mixed in allergy clinics and vial dilutions by staff according to USP 797 compounding guidance [‡]	Slow or accelerated cluster build-up used to safely reach effective maintenance doses§	Systemic reactions in 0.1% of injections
Homogeneous liquid products*	Pollens, molds, house dust mites, mammalian epithelia and feathers, whole-body insect and miscellaneous items (eg, kapok)	subtropical grass Bermuda, 2 house dust mites (<i>D farinae</i> and <i>D pteronyssinus</i>)	vials diluted in normal saline and 0.4% phenol with or without buffer or 0.03% human serum albumin		Maintenance injections given every 2-4 wk for 3-5 y	Rare cases of fatal anaphylaxis
	Standardized and nonstandardized products are used together. [†]					Asthmatic patients at risk for fatal reactions
Lyophilized	Hymenoptera venom products	Yellow jacket, white-faced and yellow hornets, honey bee, <i>Polistes</i> species (wasp)	Venoms diluted in PBS with human serum albumin	NA	Venom build-up schedule achieves maintenance dose (100 µg per venom) by 9-15 wk Ultrarush build-up protocols for select patients	Well tolerated but high risk of severe anaphylaxis in patients with mastocytosis
Alum-absorbed products (rarely used)	Pollens, nonstandardized Grass extracts available and not standardized	None	Diluted in normal saline and 0.4% phenol	Same as aqueous Alum products not mixed with aqueous	Same as aqueous	Low risk
Allergoids, adjuvant or recombinant products	NA	NA	NA	NA	NA	NA

NA, Not applicable.

*Extraction is similar across the industry by using Coca solution (physiologic saline, bicarbonate buffer, and phenol) with or without glycerin. Pollen extracts are manufactured similarly by each company and show the least variability.

†Most allergen extracts in the United States are nonstandardized (no standard of potency). Commercial products must pass sterility and safety compendium tests (USP) but not a potency test. Strength by weight per volume or sometimes the protein nitrogen unit is used for labeling.

‡Manufacturers provide some allergen mixes (see text).

§See Table IX in Cox et al for effective maintenance aeroallergen doses.⁴

different allergen source materials, including those derived from pollens, foods, epithelia, fungi, mites, and insects.⁵ Allergen source materials are extracted in a slightly alkaline buffer, such as bicarbonate pH 8.4, to increase protein and allergen recovery.

Extraction is similar across the industry, using Coca solution (physiologic saline, bicarbonate buffer, and phenol) with or without glycerin. Pollen extracts are manufactured similarly by each company and show the least variability. Each company has its own source material departments, and therefore there can be some variability in purification of the pollen. The other categories have different manufacturing methods. Molds are extracted similarly but use different strains and growing conditions. Some foods are dialyzed. Epithelial extracts are concentrated through various methods, such as lyophilization, diafiltration, or acetone precipitation. Dust mites are grown on different media and use different purification techniques.

Some manufacturers perform dialysis, ultrafiltration, or other purification steps, but this is not common. All allergen extracts must be sterile, and this is accomplished by passing the bulk extract through a sterilizing filter with a nominal pore size of

0.2 µm. In addition, all extracts marketed in multiple-dose vials must contain a preservative that is bacteriostatic and fungistatic. Most manufacturers use phenol at 0.2% to 0.5% with or without 50% glycerin. When extracts are prepared with glycerin concentrations of greater than 50%, phenol is not required. The utility of glycerin in extracts as a stabilizer has been well established, and for this reason, the expiratory dating of nonstandardized extracts is assigned according to FDA regulations 21 Code of Federal Regulations 610.53, which states that extracts should be stored in final containers with 50% or greater glycerin and stored at 2°C to 8°C. The dating period is up to a maximum of 6 years but no more than 3 years in manufacturer's storage and no more than 3 years after the product is shipped by the manufacturer. For extracts in final containers with less than 50% glycerin and for alum-precipitated extracts, the period is up to a maximum of 3 years but no more than 18 months in manufacturer's storage and no more than 18 months after the product is shipped by the manufacturer.

Qualitative differences between manufacturers' products are based on differences used to collect or produce allergen source

TABLE II. Summary of commercially available products used for SLIT in the United States including FDA-approved sublingual allergen products, approved indications, advantages, and limitations

Commercial tablet products	FDA-approved indication for allergic rhinitis	Standardized products (effective allergen dose)	Level of evidence supporting efficacy in patients with allergic rhinitis	Advantages	Limitations
Grass, ragweed, house dust mite* tablets	Seasonal or perennial	Five-grass (300 IR) Timothy grass (2800 BAU, 15 µg of Phl p 5) Ragweed (12 µg of Amb a 1) HDM (12 SQ units, 30 µg of major allergens, including equal amounts of <i>D farinae</i> and <i>D pteronyssinus</i> group 1 and group 2 allergens)	High	Convenient self-dosing and low risk of anaphylaxis Safe treatment option for patients unwilling to receive SCIT Minimal treatment duration (12-16 wk) required to achieve efficacy	Persistent site application reactions, <5% of patients might require cessation Cost barriers in some patients and low adherence rates
Off-label sublingual use of commercial glycerinated aqueous allergen products	None	Effective dose not established	Low	Convenient self-dosing	Unproved efficacy and safety with sublingual aqueous drops administered in the United States No reimbursement

*No asthma indication for house dust mites in the United States, as in Europe.

materials. These differences are minimal with pollen source materials because their collection methods are well established across manufacturers and independent collectors or suppliers. Regional and annual variations in specific allergen content have been attributed to genetic and environmental factors, but manufacturers can adjust for this through in-process testing and controls.⁶ In contrast, differences between fungal extracts manufactured in the United States are great. This is because the fungal strains, growth medium, harvesting techniques, and source material processing methods vary widely.

The US approach to allergen standardization aims to provide labeling in a common potency unit, the bioequivalent allergy unit, to facilitate the use of common dose regimens for the large number of products available for clinical use. Some allergen extracts, particularly those derived from fungal source materials, might require creative solutions to achieve this. A major regulatory challenge is to define how hundreds of nonstandardized products should be prioritized for standardization and how to implement the program in a timely fashion. Most allergen extracts in the United States are nonstandardized (no standard of potency). Commercial products must pass sterility and safety compendium tests (United States Pharmacopeia [USP]) but not a potency test. Strength by weight per volume or sometimes the protein nitrogen unit is used for labeling. The FDA classifies extracts into approved or not approved.

EU manufacturing practices

Allergen extracts for AIT (Table III) are manufactured in several EU member states (MSs), including Spain, Italy, France, Denmark, The Netherlands, and Germany, as well as in Great Britain. The first sublingual immunotherapy (SLIT) product was authorized in Germany in 2004, whereas the first SCIT products were authorized in 1976, and most currently available SCIT products were authorized in the 1990s. Most of the SCIT products

in Europe are adsorbed to aluminum hydroxide. Only insect venoms are administered as aqueous extracts. Approved SLIT products are available as liquid formulations and as tablets or oral lyophilisates. Use of chemically modified allergen extracts (so-called allergoids) is also common: allergens in these products are treated (ie, by glutaraldehyde or formaldehyde) to reduce IgE-binding epitopes and thereby decrease allergenicity and the potential for systemic allergic reactions while maintaining T-cell binding epitopes to preserve immunogenicity. Standardization and quality control of allergoids is more complex than quality control of native allergens.⁷ Some allergen mixture products are used in Europe after preparation by manufacturers and not after compounding in allergists' clinics.

To date, all allergens contained in marketed products are based on natural allergen sources. Extraction and production processes differ largely between European manufacturers. Standardization is mainly based on in-house references and in-house assays, and sometimes these are based on major allergens. Because no common European standards exist, different units based on biological activities are used (see Table E1 in this article's Online Repository at www.jacionline.org).⁸ The first in-house reference is usually biologically standardized by applying the Nordic Method⁹ or the ID50 EAL Method.¹⁰

Unfortunately, different in-house references and units do not facilitate comparison of different products. Therefore, in 2001, an EU-funded project, the CREATE project, was started to support introduction of major allergen-based standardization for cross-product comparability. The aim of the project was to evaluate use of recombinant allergens as reference materials and of ELISA systems for major allergen measurements (reviewed by Kaul et al¹¹). Based on the results of the CREATE project and the BSP090 project (the follow-up to CREATE) in 2014, Supplement 8.2 to the European Pharmacopeia Monograph on Allergen Products established the recombinant major allergens rBet v 1 and rPhl p 5a as reference standards, although still for optional use to this

TABLE III. Overview on characteristics of AIT products used in the EU (exemplarily demonstrated for Germany)

Commercial treatment allergen products with MAs	Native allergens								Modified allergens (allergoids)								No. of products
	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/ grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)	Bee and wasp venom	Other	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/ grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)	Bee, wasp venom	Other			
SCIT																	
Aqueous extracts	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	
Lyophilized	—	—	—	—	—	Eight products from 3 pharmaceutical companies (A, C, D)		—	—	—	—	—	—	—	—	8	
Alum adsorbed	Six products from 1 pharmaceutical company (A)	Four products from 1 pharmaceutical company (A)	—	Six products from 2 pharmaceutical companies (A, B)	—	Two products from 1 pharmaceutical company (A)	—	Seven products from 2 pharmaceutical companies (B, D)	Seven products from 2 pharmaceutical companies (B, D)	Four products from 2 pharmaceutical companies (B, D)	Two products from 1 pharmaceutical company (E)	Nine products from 1 pharmaceutical company (B)	—	—	47		
Tyrosine adsorbed	—	—	—	—	—	—	—	One product from 1 pharmaceutical company (C)	One product from 1 pharmaceutical company (C)	—	—	—	—	—	2		
Tyrosine adsorbed and MPL adjuvanted	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
SLIT																	
Drops, liquid	Four products from 2 pharmaceutical companies (D, H)	—	—	—	—	—	—	—	—	—	—	—	—	—	4		
Tablets	—	Two products from 2 pharmaceutical companies (A, H)	—	One product from 1 pharmaceutical company (A)	One product from 1 pharmaceutical company (A)	—	—	—	—	—	—	—	—	—	4		
Commercial treatment allergen products developed and marketed under the TAO	Native allergens								Modified allergens (allergoids)								No. of products
	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)	Bee, wasp venom	Other	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)	Bee, wasp venom	Other			
SCIT																	
Aqueous extracts	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	
Lyophilized	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	
Alum adsorbed	—	—	—	—	—	—	—	Eight products from 2 pharmaceutical companies (E, G)	Sixteen products from 2 pharmaceutical companies (E, G)	Three products from 2 pharmaceutical companies (E, G)	Ten products from 3 pharmaceutical companies (B, D, G)	—	—	—	37		

(Continued)

TABLE III. (Continued)

Commercial treatment allergen products developed and marketed under the TAO	Native allergens								Modified allergens (allergoids)								No. of products
	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)		Bee, wasp venom	Other	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)		Bee, wasp venom	Other	
Tyrosine adsorbed	—	—	—	One product from 1 pharmaceutical company (C)	—	—	—	—	—	—	—	—	—	—	—	—	1
Tyrosine adsorbed and MPL adjuvanted	—	—	—	—	—	—	—	—	One product from 1 pharmaceutical company (C)	One product from 1 pharmaceutical company (C)	Two products from 1 pharmaceutical company (C)	—	—	One product from 1 pharmaceutical company (C)	—	—	5
SLIT																	
Drops, liquid	Five products from 3 pharmaceutical companies (A, C, G)	Nine products from 4 pharmaceutical companies (A, C, D, G)	One product from 1 pharmaceutical company (G)	Five products from 4 pharmaceutical companies (A, C, D, G)	—	—	—	—	One product from 1 pharmaceutical company (F)	One product from 1 pharmaceutical company (F)	—	—	—	—	—	—	22
Tablets	—	—	—	—	—	—	—	—	One product from 1 pharmaceutical company (F)	One product from 1 pharmaceutical company (F)	—	—	One product from 1 pharmaceutical company (F)	—	—	—	3

Commercial allergen products (NPPs)	Native allergens								Modified allergens (allergoids)								No. of products
	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)	Bee, wasp venom	Other	Birch, hazel, alder pollen	Grass pollen and grass/crop mixes	Birch, hazel, alder/grass pollen mix	HDM	Weed pollen and weed pollen mixes (including grass and birch)	Bee, wasp venom	Other			
SCIT																	
Aqueous extracts	NA*	NA*	NA*	NA*	—	NA*	—	NA*	NA*	NA*	NA*	—	NA*	—			
Lyophilized	NA*	NA*	NA*	NA*	—	NA*	—	NA*	NA*	NA*	NA*	—	NA*	—			
Alum adsorbed	NA*	NA*	NA*	NA*	Provision of individual products of this composition by 3 pharmaceutical companies on individual prescription (A, E, G)	NA*	Tree pollen (other than birch, alder, hazel; mites (other than <i>D pteronyssinus</i> and <i>D farinae</i>), molds, animal epithelia, and insect allergens (other than bee and wasp venom)	NA*	NA*	NA*	NA*	Provision of individual products of this composition by 3 pharmaceutical companies on individual prescription (D, E, G)	NA*	Tree pollen (other than birch, alder, hazel); mites (other than <i>D pteronyssinus</i> and <i>D farinae</i>), molds, animal epithelia	Not specified		
							Provision of individual products of this composition by 3 pharmaceutical companies on individual prescription (A, E, G)							Provision of individual products of this composition by 2 pharmaceutical companies on individual prescription (E, G)	Provision of individual allergen-specific alum-adsorbed products by 4 pharmaceutical companies on individual prescription (A, D, E, G)		

Tyrosine adsorbed	NA*	NA*	NA*	NA*	Provision of individual products of this composition by 1 pharmaceutical company on individual prescription (C)	NA*	Tree pollen (other than birch, alder, hazel; mites (other than <i>D pteromyssinus</i> , <i>D farinae</i>), molds, animal epithelia	NA*	NA*	NA*	NA*	Provision of individual products of this composition by 1 pharmaceutical company on individual prescription (C)	NA*	—	Not specified
Tyrosine adsorbed and MPL adjuvanted	NA*	NA*	NA*	NA*	—	NA*	—	NA*	NA*	NA*	NA*	Provision of individual products of this composition by 1 pharmaceutical company on individual prescription (C)	NA*	Olive tree	Provision of individual allergen-specific tyrosine-adsorbed MPL adjuvanted products by 1 pharmaceutical company on individual prescription (C)
SLIT															
Drops, liquid	NA*	NA*	NA*	NA*	Provision of individual products of this composition by 3 pharmaceutical companies on individual prescription (A, D, G)	NA*	Tree pollen (other than birch, alder, hazel; mites (other than <i>D pteromyssinus</i> , <i>D farinae</i>), molds, animal epithelia	NA*	NA*	NA*	NA*	—	NA*	—	Not specified
Tablets	NA*	NA*	NA*	NA*	—	NA*	—	NA*	NA*	NA*	NA*	Provision of individual products of this composition by 1 pharmaceutical company on individual prescription (F)	NA*	Tree pollen (other than birch, alder, hazel; animal epithelia	Provision of individual SLIT products (tablets) by 1 pharmaceutical company on individual prescription (F)

As of November 2018, no responsibility is accepted for the availability of products and completeness of this information.

Risk of systemic Reactions and anaphylaxis of AIT products used in Germany is low according to pharmacovigilance data. From November 1, 2016, to October 31, 2017, in the Pharmacovigilance database of the Paul-Ehrlich-Institut, 301 suspected spontaneous cases of adverse reactions under AIT treatment were reported from Germany (for comparison, all cases with reported adverse reactions to biomedicines and vaccines = 14,932). In 103 of 301 cases, the reaction had been reported as an anaphylactic reaction or anaphylactic shock. In 74 of 301 cases, SLIT had been used; in 226 cases SCIT and in 1 case both a sublingual and a subcutaneous AIT product had been applied. In 1 case the outcome had been reported as fatal because of a yellow jacket sting despite 4 years of venom immunotherapy.

All allergen preparations (except for lyophilized), compounding, and dilutions (for build-up and for maintenance) are industrially produced and distributed in vials (labeled with the patient name) by the respective pharmaceutical company. Products from 7 pharmaceutical companies (A-G) are marketed in Germany.

Because of their heterogeneous composition and administration, products are not directly comparable. Administration follows individual instructions, as outlined in the summary of product characteristics.

HDM, House dust mite; MPL, monophosphoryl lipid A; NA, not applicable in Germany; TAO, therapy allergen ordinance (applicable to all NPPs for birch, sweet grasses [except for maïs], house dust mites, and bee and wasp venom, which all need to provide quality and clinical data for MAs within a maximal period of 8 years).

*Mandatory in development process under TAO.

point. Once the corresponding candidate reference methods have been successfully validated in international ring trials and accepted by the European Pharmacopeia Commission, use of reference allergens and standards methods will become mandatory through implementation in the European Pharmacopeia Monograph on Allergen Products. A current BSP090 program by the European Directorate for the Quality of Medicines and Health Care intends to qualify recombinant allergen preparations as references, as well as immunoassays for quantification of individual major allergens. The first successful results of this activity have been submitted and reported.¹¹

REGULATION AND CLINICAL DEVELOPMENT OF NEW PRODUCTS

US regulatory standards

When the FDA began to regulate allergen extracts as pharmaceuticals, 3 advisory panels were convened to review the portfolios of manufacturers granted licenses. Extracts of more than 1200 species were reviewed for efficacy and safety. In the early 1970s, the FDA requested expert panels to classify commercial allergenic extracts as follows: *Category I*, approved (safe, effective, and not misbranded); *Category II*, not approved (unsafe, ineffective, or misbranded); or *Category III*, data insufficient for classification and pending approval. A Category I FDA designation required that (1) accumulated evidence indicates the extract is safe; (2) the extract is derived from a well-defined source material; (3) the extract has definable or measurable constituents and is capable of being standardized; (4) the extract has been demonstrated to be effective through skin testing in defined allergic and nonallergic subjects and/or through serum specific IgE testing with appropriate sera; (5) in lieu of item 4, it is acceptable if the extract is closely analogous to products shown to be effective; and (6) the product is properly labeled.¹² Nonstandardized products (no standard of potency) were placed in Category III (Table IV) pending approval. These were subclassified as follows: *IIIA*, a product that could remain on the market with a favorable risk/benefit ratio, pending completion of testing, or *IIIB*, removed from the market because of unfavorable risk/benefit pending completion of testing.

There was an initiative in the early 1980s to reclassify all Category III products as either Category I or Category II. Although an expert panel made recommendations at that time, this task has not been completely accomplished. The manufacturers were granted licenses to sell the nonstandardized products, until which time the FDA reclassified them as Category I or II. The strength of nonstandardized extracts was determined by weight per volume extraction (Table I). During this time, licenses have been issued based on safety and effectiveness data for standardized extracts, including short ragweed, Hymenoptera venom, cat hair or pelt, house dust mite, and some grasses (Table IV), removing their nonstandardized counterparts. The FDA in 2011 proposed classification of all 1200 species based on literature reviews up to 2011.^{12,13} Currently, there are no products pending approval for reclassification.

There is no formal FDA guidance issued through the Center for Biologics Evaluation and Research (CBER) for clinical development of novel AIT products, including parameters for performing phase I, II, and III clinical studies. Each product under development in the United States is considered separately by the CBER. Recent development and FDA approval of SLIT represents the

only precedent for new product development in the United States, and much has been borrowed from EU precedents (Fig 1).

EU regulatory background

EU legislation provides a common regulatory framework within the 28 EU MSs but also enables MSs to regulate specific aspects at the national level. The regulatory situation is complex and has been addressed in 2 recent task force publications of the European Academy of Allergy and Clinical Immunology.^{14,15} Allergens for allergen immunotherapy (AIT) and *in vivo* testing have been generally considered medicinal products (drugs) by European legislation since 1989 and are now included in the community code of human medicines (Directive EC 2001/83 EC). In general, a marketing authorization (MA) is required for allergens. Within the MA procedure, the pharmaceutical company has to provide evidence for impeccable quality, efficacy, and safety (Fig 1, B). Only products with a positive benefit/risk ratio can be granted an MA. A selection of legal and guidance documents relevant for regulation of AIT products in the EU are summarized in Table E2 in this article's Online Repository at www.jacionline.org.

However, MSs can exempt products from MA that (1) are manufactured based on a prescription for an individual patient (named patient products [NPPs]) or (2) under certain preconditions if manufactured in pharmacies. These regulatory tools are heterogeneously used by EU MSs, creating a highly complex situation. For example, in Scandinavian countries, such as Denmark and Sweden, an exemption for marketing NPPs without authorization does not exist. In contrast, in Germany, The Netherlands, and several other EU MSs, both authorized allergens and NPPs are on the market. In Spain, Portugal, and France NPPs have the largest market share. In Germany there are currently 65 AIT products (for the treatment of allergies against pollen from birch, alder, hazel, grasses, rye, *Parietaria* species, plantain or ragweed, house dust mite, and bee or yellow jacket venom) manufactured by 6 manufacturers holding MAs, as well as many more less frequently used NPP products. Since 2008, when the therapy allergen ordinance (Therapieallergene-Verordnung) came into effect, an MA procedure has been mandatory in Germany for specific frequent allergen sources (pollens of birch, alder, hazel and sweet grasses, house dust mites, bee venom, and yellow jacket venom).¹⁶ NPPs are normally nonstandardized, whereas the vast majority of authorized AIT products in the EU are biologically standardized.¹⁷ Results of several phase II trials conducted with therapy allergen ordinance products indicated that the marketed dose of many NPPs was suboptimal and underlined the necessity of a product-specific assessment of AIT products.

Different regulatory procedures exist for authorization of medicinal products in the EU (for details, see Bonertz et al¹⁴):

- The centralized procedure is coordinated by the European Medicines Agency (EMA) and would lead to authorization of a medicinal product in all EU MSs. The centralized procedure is mandatory for medicines derived from biotechnological processes (eg, AIT products based on recombinant allergens or peptides) but not for allergen extracts. To this point, only extract-based AIT products have been licensed within the EU.
- Both the mutual recognition procedure and the decentralized procedure facilitate coordinated national MAs of medicinal products in select MSs.

TABLE IV. Descriptions of nonstandardized and standardized commercial aqueous products available in the United States approved for diagnostic testing and SCIT

Nonstandardized aqueous treatment and diagnostic products*		
Weight/volume and PNU†	Strength	Formulation
Pollens	1:10 wt/vol	Coca solution‡
	1:20 wt/vol	Coca solution, 50% glycerin§
	10,000-40,000 PNU	Coca solution
Diagnostics: dropper vials	1:20 wt/vol	Coca solution, 50% glycerin
Epithelia	1:10 wt/vol	Coca solution
	1:20 wt/vol	Coca solution, 50% glycerin
	10,000-40,000	Coca solution
Acetone precipitation	1:50-1:100 wt/vol	Coca solution
Diagnostics: dropper vials	1:10 wt/vol	Coca solution, 50% glycerin
	1:20 wt/vol	Coca solution, 50% glycerin
Fungal/mold	1:10 wt/vol	Coca solution
	1:10 wt/vol	Coca solution, 50% glycerin
	1:20 wt/vol	Coca solution, 50% glycerin
Dialyzed	10,000-40,000 PNU	Coca solution
Dialyzed	10,000-20,000 PNU	Coca solution, 50% glycerin
Diagnostics: dropper vials	1:10 wt/vol	Coca solution, 50% glycerin
	1:20 wt/vol	Coca solution, 50% glycerin
Dialyzed	10,000-20,000 PNU	Coca solution, 50% glycerin
Foods: diagnostics only	1:10 wt/vol	Coca solution, 50% glycerin
	1:20 wt/vol	Coca solution, 50% glycerin
Standardized aqueous treatment and diagnostic products¶		
Allergy units and strengths from FDA#	Strength	Formulation
Standardized grasses**	10,000 BAU/mL	Coca solution, 50% glycerin
	100,000 BAU/mL	Coca solution, 50% glycerin
Diagnostics: same vials as treatment vials		
House dust mite: <i>D farinae</i> and <i>D pteronyssinus</i>	10,000 AU/mL	Coca solution, 50% glycerin
Diagnostics: same vials as treatment vials		
Cat hair/pelt	10,000 BAU/mL (equal to 10-19.9 FDA Fel d 1 units/mL)	Coca solution, 50% glycerin
Diagnostics: same vials as treatment vials		
Short ragweed Amb a 1 in FDA units/mL on label††	1:10 wt/vol	Coca solution
	1:20 wt/vol	Coca solution, 50% glycerin
Diagnostics: dropper vials	1:20 wt/vol	Coca solution, 50% glycerin
Stinging insect Hymenoptera venoms‡‡		
Discontinued in 2018	100 µg/mL	Lyophilized with 300 µg HSA
	100 µg/mL	Lyophilized HSA free
Diagnostics: same vials as treatment vials		

HSA, Human serum albumin.

*No standard of potency: most commercial allergens are 1:10 or 1:20 wt/vol, with some exceptions because of safety or precipitation concerns.

†Protein nitrogen unit, Kjeldahl method, 17,000 PNU per milligram of protein.

‡Coca solution: 0.5% sodium chloride, 0.28% sodium bicarbonate, phenol, 0.4%, pH 7 to 8.5.

§Some 50% Coca solutions do not contain phenol if source material was extracted directly with 50% glycerin.

||Acetone precipitation produces a concentrated protein precipitate that is reconstituted.

¶Standardized allergens were mandated by the FDA by using FDA references and standards only.

#Allergy or arbitrary units were used only for house dust mites, and bioequivalent allergy units were used for cat and grass, both of which were based on ID50 EAL skin test titration.

**Standardized grasses, Bermuda, Timothy, orchard, meadow fescue, Kentucky bluegrass, redtop, perennial ryegrass, and sweet vernal.

††Short ragweed is the first FDA-standardized product and is not adjusted for potency but must meet Amb a 1 specifications, and value is shown on the label.

‡‡Stinging insect *Hymenoptera* venoms: honey bee, yellow jacket, yellow hornet, bald-faced hornet, and paper wasp.

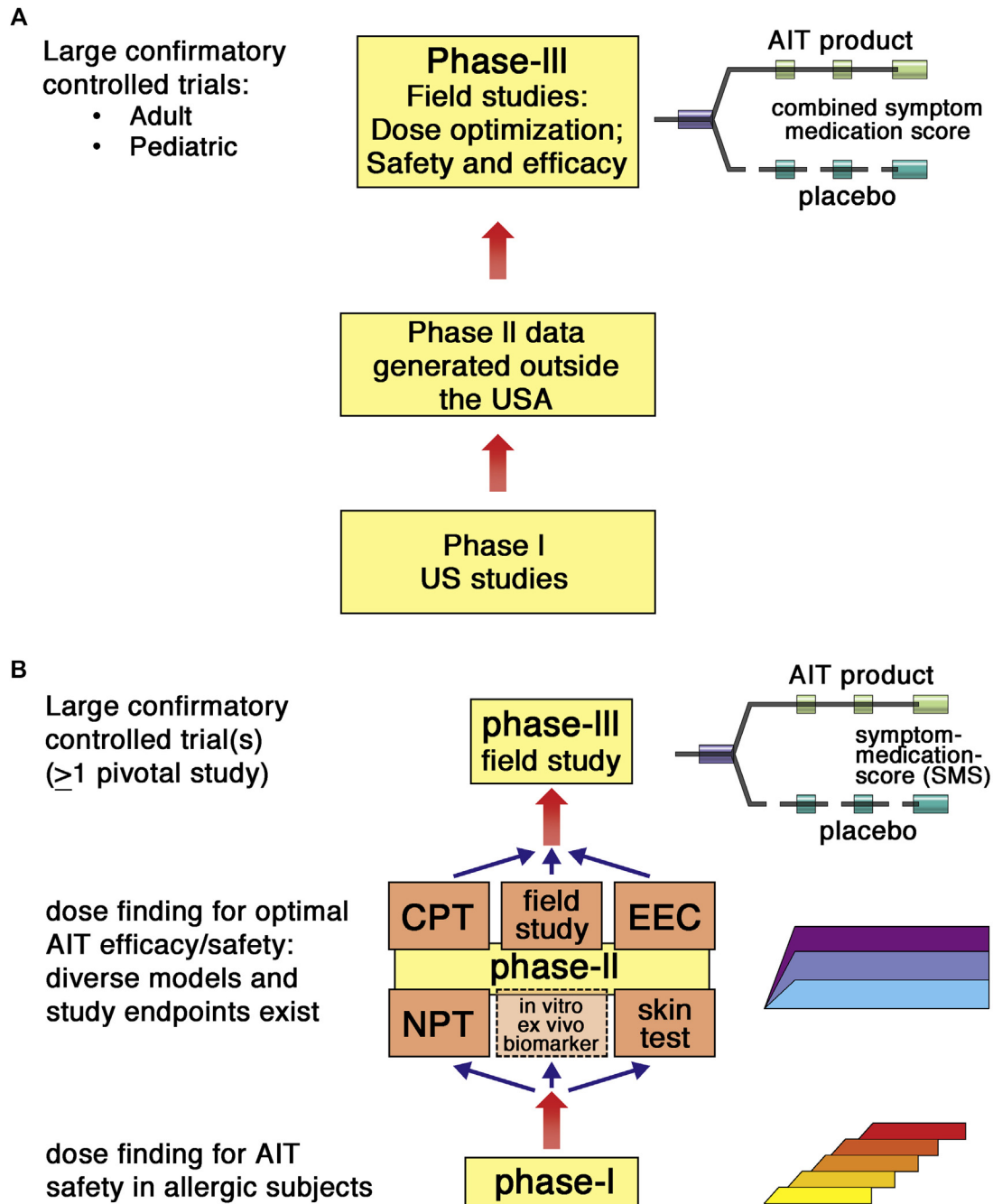


FIG 1. **A**, The clinical development framework for AIT products in the United States is based exclusively on the model shown here for developing SLIT tablets. No common FDA/CBER guidance has been issued. **B**, Clinical development framework for AIT products (EU, according to EMA guidelines). The center figure shows optional models and methods for phase II dose-finding studies for establishing optimal balance between product efficacy and safety. Additional laboratory-based methods and biomarkers (dotted line) are optional but not sufficient as study end points. CPT, Conjunctival provocation test; EEC, environmental exposure chamber; NPT, nasal provocation test.

- Finally, an MA in only one country can be achieved by using a purely national MA procedure.

Regardless, whether a purely national or an EMA procedure is pursued for obtaining an MA for an AIT product, the quality of the

investigational product is assessed in compliance with the “Guideline on allergen products: production and quality issues” (EMA/CHMP/BWP/304831/2007), and the clinical development plan has to comply with the “Guideline on the clinical development

of products for specific immunotherapy for the treatment of allergic diseases” (CHMP/EWP/18504/2006). This includes successful performance by the investigational product in phase I, II, and III studies (Fig 1, B).

Phase I studies of investigational products for AIT are tested in patients with known allergy at different doses to provide preliminary data on safety and tolerability, the maximum tolerated dose, and a suitable dose escalation scheme. After establishing a tolerable dose range, phase II studies are performed to establish a dose-response relationship with clinical efficacy. Such dose-finding studies (phase II) might comprise a short-term treatment (eg, 2-4 months) with different doses in several study arms. Provocation tests (eg, conjunctival, nasal, or bronchial provocation) or allergen challenges conducted in environmental exposure chambers using nasal or ocular symptoms scores as primary or secondary clinical end points can be used to determine optimal doses for phase III studies. Confirmatory phase III studies of AIT investigational products are required for registration and should be performed by using a randomized placebo-controlled double-blinded design. The primary end point must reflect both symptom severity and the required intake of rescue medication. In general, clinically important improvement in these outcomes relative to placebo must be demonstrated for authorization.

DIAGNOSTIC EVALUATION TO IDENTIFY RELEVANT ALLERGENS FOR AIT

US diagnostic approach

AIT is recommended for patients with (1) a clinical history of symptoms associated with specific aeroallergen exposures (eg, seasonal allergic rhinitis or allergic asthma) or systemic reactions to Hymenoptera venom stings (ie, anaphylaxis) and (2) skin test evidence of IgE-mediated sensitization to clinically relevant allergens.⁴ As shown in Table IV, skin prick tests with standardized and/or nonstandardized crude commercial pollen, mold, house dust mite, and mammalian extracts (also used in treatment) are the primary tools used to confirm IgE-dependent aeroallergen sensitization. These data guide selections of AIT allergens. Although there is variation between clinical practices, aeroallergen skin prick test panels are tailored to include at least the minimal number of clinically relevant indoor and outdoor aeroallergens in each geographic area.⁴ Test panels of outdoor aeroallergens are based on local aerobiology studies characterizing diverse wind-borne pollens and mold species during specific allergy seasons. In clinical practice a positive test response is defined as a wheal at least 3 mm larger than that elicited by the diluent control with a flare response.

In the United States intradermal titration testing is used to confirm sensitization to Hymenoptera venoms and to identify aeroallergen sensitization in patients with negative skin prick test responses.¹⁸ Although the specificity of intradermal testing with diluted aeroallergens is uncertain, this method is widely used to further evaluate patients with negative skin prick test responses and a convincing history of clinical sensitivity.¹⁹ Commercial serum specific IgE tests (eg, fluorescent enzyme-linked immunoassays) are not routinely used to diagnose allergy or select appropriate aeroallergens for AIT unless antihistamines cannot be withdrawn or coexisting skin disorders (eg, dermatographia) preclude skin testing. In the United States direct nasal or conjunctival challenge testing is not routinely used in clinical practice for confirming or excluding clinical sensitization to specific aeroallergens.

European diagnostic approach

In general, a clinical history of intermittent or persistent allergic symptoms leads to an allergy work-up, including skin testing (mostly skin prick tests for inhalant allergens and sometimes intradermal test for Hymenoptera venoms), allergen-specific IgE detection *in vitro*, or both. Demonstration of IgE-mediated sensitization to the suspected allergen source with a clear relationship to clinical symptoms on allergen exposure is a prerequisite for AIT.

In case of contradicting results or polysensitization, additionally, nasal or conjunctival challenge tests can be performed to identify the most clinically relevant allergen source or sources.²⁰ *In vitro* component-resolved diagnostics detecting specific IgE to source-specific marker allergens can uncover primary sensitizations and increase test accuracy, particularly if cross-reactivity to pollen pan-allergens (profilins and polcalcins) leads to broad positive skin test responses to pollen-derived extracts with questionable clinical relevance.²⁰⁻²² Availability of standardized or high-quality allergen extracts, as well as proof of efficacy of the planned AIT for the respective indication and age group, are further prerequisites for AIT in case allergen avoidance is not possible or inadequate.²³ The Allergic Rhinitis and its Impact on Asthma guidelines (2016 revision) and current recommendations for AIT apply directly to moderate-to-severe allergic rhinitis. They might be less applicable to treatment of patients with mild allergic rhinitis who frequently do not seek medical help and self-manage their symptoms with medications available over the counter.²⁴

CLINICAL ADMINISTRATION OF AIT, INCLUDING BUILD-UP SCHEDULES AND MANAGING RISK

Further information can be found in Table V.^{4,18,20,23-29}

SCIT practices in the United States

AIT with SCIT is recommended for patients with clinically relevant sensitization to multiple aeroallergens determined by using skin prick or intradermal skin tests. Clinicians determine the clinical relevance of aeroallergen sensitizers based on a history of rhinitis or asthma symptoms temporally associated with environmental aeroallergen exposure. Except for monosensitized patients, patient-specific vials are prepared with mixtures of multiple aeroallergens. Multiple specific vials are prepared for each patient to achieve adequate therapeutic maintenance doses of each treatment allergen. Knowledge of cross-reactivity between certain pollen species groups, such as northern pasture grasses (>95% allergenic cross-reactivity), might allow selection of a single representative species (eg, Timothy grass). For other clinically relevant seasonal pollens in which cross-allergenicity between species is less well defined (ie, tree and weed pollen and mold spores), multiple species that elicit positive skin test results are selected for patient-specific vials. For example, a study in the Midwestern United States found that extracts of 8 of 15 local tree species (American sycamore, American elm, box elder, red maple, red oak, white ash, cottonwood, and black walnut) elicited positive skin prick test responses in more than 50% of patients with seasonal allergic rhinitis (ie, a major *in vivo* allergen source).³⁰ Seven of the most predominant allergen sources eliciting positive skin test responses in the majority of clinically allergic patients were selected for diagnosis and SCIT treatment in that clinic.

TABLE V. Selection of clinical guidelines relevant for administration of AIT in the United States and Europe

	Links
Clinical AIT guidelines in North America	
Cox et al ⁴	https://www.ncbi.nlm.nih.gov/pubmed/21122901
USP Chapter 797 Compounding Guidelines with proposed revisions for mixing allergen extracts ²⁹	https://www.usp.org/compounding/797-download
Greenhawt et al ²⁵	https://www.ncbi.nlm.nih.gov/pubmed/28284533
Golden et al ¹⁸	https://www.ncbi.nlm.nih.gov/pubmed/28007086
Selected clinical AIT guidelines in Europe	
Roberts et al ²⁰	https://www.ncbi.nlm.nih.gov/pubmed/28940458
Halken et al ²⁶	https://www.ncbi.nlm.nih.gov/pubmed/28902467
Sturm et al ²⁷	https://www.ncbi.nlm.nih.gov/pubmed/28748641
Pajno et al ²⁸	https://www.ncbi.nlm.nih.gov/pubmed/29205393
Brożek et al ²⁴	https://www.ncbi.nlm.nih.gov/pubmed/20816182
Pfaar et al ²³	https://www.ncbi.nlm.nih.gov/pubmed/26120539

Mixing of aqueous allergen extracts is performed by nurses or allied health personnel in allergy practices or clinics under the supervision of practicing allergists.⁴ Each allergen is transferred under aseptic conditions from concentrated commercial stock bottles and mixed with other allergens in patient-specific maintenance vials. Single-allergen vials are prepared for monosensitized patients. Some practicing allergists compound with commercially produced mixes (eg, mixtures of tree or mold species). The prescribing allergist must consider cross-dilution and precalculate the quantity of each allergen extract added to mixed maintenance vials to ensure that the final injection dose of each allergen administered from a mixed vial is within the known range of therapeutic efficacy, as shown in Table IX in the AIT Practice Parameter 3rd Update.⁴ Allergen manufacturers provide stock tree, grass, and weed mixes. A common tree mix contains ash, birch, box elder, cottonwood, elm, hickory, oak, sycamore, black walnut, and willow. A common weed mix might contain cocklebur, pigweed, English plantain, and lamb's quarter. Mixes of mold extracts containing up to 6 different genera (*Alternaria*, *Aureobasidium*, *Bipolaris*, *Cladosporium*, *Drechslera*, and *Helminthosporium* species) are also available.

Personnel who compound or prepare mixed extract vials in an outpatient clinic setting are required to follow guidelines issued by the USP (USP 797–Pharmaceutical Compounding) to ensure sterility and prevent bacterial contamination. Currently, the USP guideline allows for exceptions for allergen patient vials, extending beyond use dates and less stringent sterile environment requirements.²⁹ These allergen compounding rules are also extended to federal law (see Table E2). For those patients initiating build-up of SCIT, serial 10-fold dilutions of maintenance vials (designated 1:1 concentration) are prepared by using methods in compliance with USP 797 guidelines.²⁹ Build-up is initiated with a higher dilution (eg, 1:100,000 or 1:10,000 concentrations), and aeroallergen doses are progressively increased until maintenance is achieved (Fig 2, A). Traditionally, practicing allergists have used slow build-up protocols requiring 1 to 2 weekly

injections over many months, but recently, accelerated build-up schedules, including cluster regimens, can reduce build-up time to maintenance to 1 to 3 months. Once maintenance doses have been achieved, injections are continued every 2 to 4 weeks for 3 to 5 years to achieve sustained benefit after discontinuation.^{4,31}

Local reactions to aqueous aeroallergen injections are common, and systemic reactions occur in approximately 1:1000 injection visits.³² Rare fatal anaphylactic reactions after SCIT injections have been estimated in 1 in 2.5 million injection visits.³³ Because most fatal events have been identified among asthmatic patients, injections are withheld or not recommended for patients with severe or uncontrolled asthma, previous severe systemic reactions, or severe concomitant medical conditions that could reduce the likelihood of surviving anaphylaxis.⁴ Before each injection, asthmatic patients are screened in most allergy clinics for recent reduction or loss in asthma control. Injections are withheld in such patients until asthma control is restored. Surveillance of severe and fatal systemic reactions, co-sponsored by the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology, is conducted annually among practicing allergists in the United States.³²

SLIT practices in the United States

Recently, FDA-approved SLIT tablets have been introduced to US allergists. These products are administered as recommended by the product information and identical to other countries, with the exception that an epinephrine autoinjector that must be prescribed before initiating treatment.³⁴ Four FDA-approved SLIT products are commercially available, including 2 grass tablets and 1 ragweed tablet, for treating seasonal allergic rhinitis, as well as a house dust mite product (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* combined tablet) for perennial allergic rhinitis. Allergists in the United States might consider SLIT tablet therapy in patients with allergic rhinitis with 1 or 2 clinically relevant pollen seasons, but often recommend SCIT to polysensitized patients with clinical sensitivity to multiple aeroallergens.²⁵ Based on placebo-controlled trials, HDM SLIT tablets are recommended in Europe (ie, Global Initiative for Asthma guidelines) for treating allergic asthma triggered by HDM, but no approval exists for HDM-related asthma in the United States.³⁵ Although severe systemic reactions to SLIT are rare, FDA-approved SLIT tablets are contraindicated in patients with severe or uncontrolled asthma, eosinophilic esophagitis, or history of severe systemic allergic reactions.^{25,34}

Off-label use of sublingual drops prepared from commercial allergen extracts is widely practiced in the United States. Commercial aqueous extract products are not FDA approved for sublingual administration, and these have not been rigorously studied in double-blind placebo-controlled studies. Thus effective and safe dose ranges have not been characterized for commercial aqueous allergen extracts (marketed for SCIT) used in the preparation of nonapproved SLIT drops. Because of insufficient clinical data, use of aqueous SLIT formulations have not been endorsed by the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Joint Task Force.

AIT practices in the EU

Currently, in EU MSs, both NPPs and licensed AIT products are being used, with NPPs prescribed mainly for rare allergens.

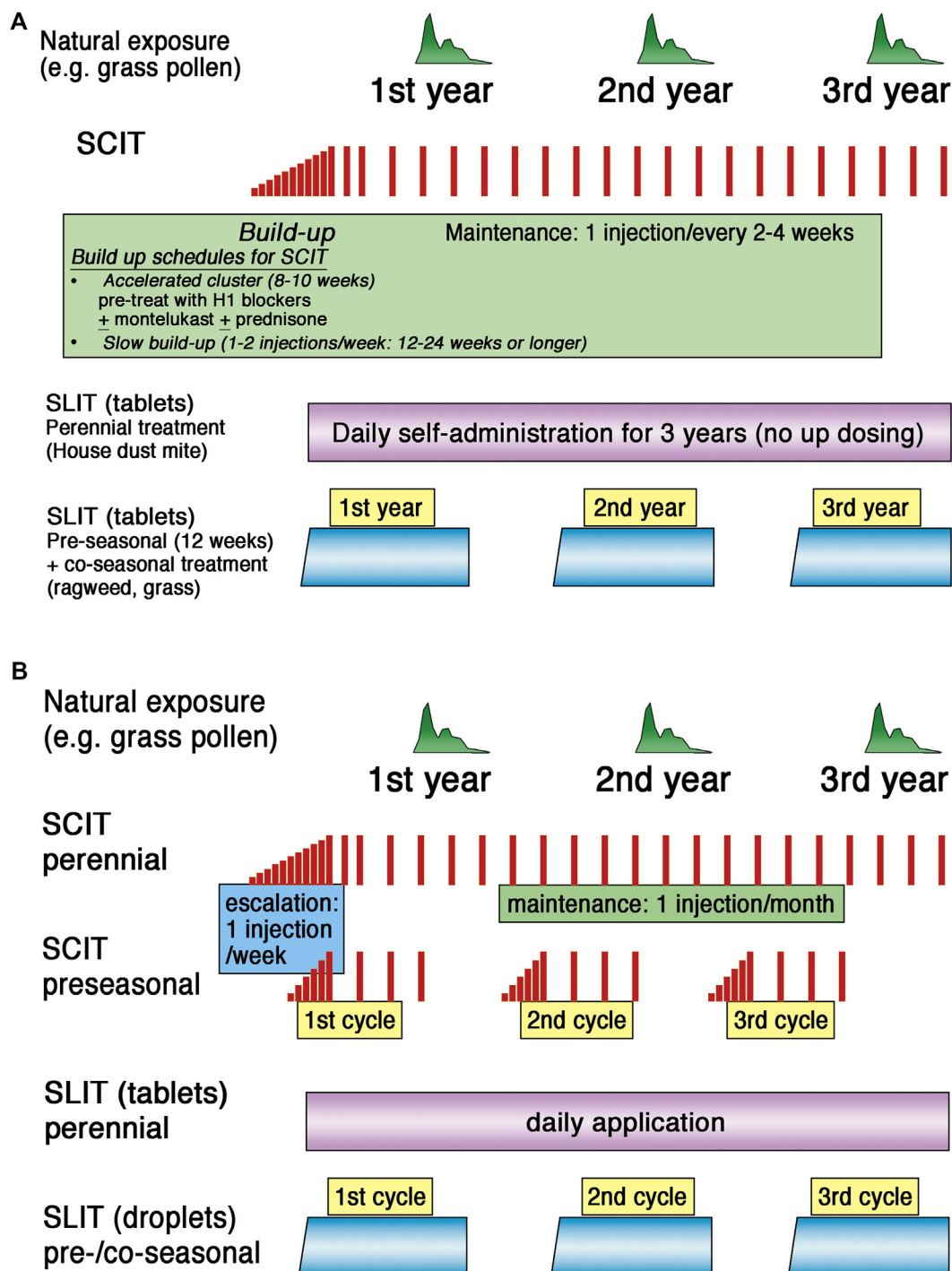


FIG 2. A, Common schedules in the United States for administering SCIT and SLIT. B, Common AIT application schedules in Europe: AIT for seasonal allergies (eg, grass pollen). For SCIT, *single lines* indicate subcutaneous injections. For SLIT, *solid bars* indicate daily sublingual application.

Licensed AIT products (SLIT and SCIT products) are available for the treatment of allergic rhinoconjunctivitis with or without asthma, as well as for Hymenoptera venom allergy. Both NPPs and licensed AIT products are provided by the manufacturer as a single-allergen preparation or as compounded mixtures (Table III). Build-up and maintenance treatment vials are delivered preformulated in different vials of different allergen content.

Licensed AIT products have been granted an MA based on a product-specific positive benefit/risk ratio, which included assessment of impeccable quality, efficacy, and safety. Also, after granting an MA, an acceptable safety profile is followed up through pharmacovigilance systems implemented on a national and European level. The risk of systemic reactions and anaphylaxis of AIT products (eg, used in Germany) is low according to

pharmacovigilance data: from November 1, 2016, to October 31, 2017, in the Pharmacovigilance database of Paul-Ehrlich-Institut, 301 suspected spontaneous cases of adverse reactions under AIT treatment were reported from Germany (for comparison, all cases with reported adverse reactions to biomedicines and vaccines = 14,932). In 103 of 301 cases, the reaction was reported as an anaphylactic reaction or anaphylactic shock. In 74 of the 301 cases, SLIT had been used, in 226 cases SCIT and in 1 case both a sublingual and a subcutaneous AIT product had been applied. In 1 case the outcome was reported as fatal because of a yellow jacket sting despite 4 years of venom immunotherapy. In Germany, there is a legal obligation for pharmaceutical companies to report cases of suspected adverse drug reactions as laid down in the German Medicinal Products Act (AMG) and a professional obligation for physicians and pharmacists to report such cases in accordance with the Professional Code of Conduct. In the post-marketing setting the marketing authorization holder is obliged to electronically transmit all information on all suspected cases of serious adverse drug reactions occurring in Germany or abroad within 15 days, of nonsevere adverse drug reactions occurring in Germany or in a member state of the European Union within 90 days of becoming known, to the European database for the collection of suspected adverse drug reactions (EudraVigilance database). Reports of suspected adverse reactions received by the Paul-Ehrlich-Institute directly are also reported to the EudraVigilance database. Despite these obligatory reporting requirements, not all cases will be reported and a relevant amount of underreporting has to be considered. Therefore, from the spontaneous reporting system no incidences could be calculated.

Traditionally, AIT was conducted as SCIT in Europe. In the 1980s, SLIT became more popular and gained acceptance in position papers and guidelines in the 1990s.

There are large national differences in the preference for different types of products and therapeutic options. For example, allergoids have a considerable market share in Germany but not in Scandinavia. SLIT is prescribed very commonly in France and Italy but much less so in Germany and Spain, where SCIT is traditionally preferred. Because considerable heterogeneity in composition and effectiveness between products exists, product-specific evaluations^{20,36} have been recommended for future clinical guidelines, initially being adopted by recent German AIT guidelines.²³ In addition to considering product-specific quality of evidence of efficacy, the choice of an AIT product for each case (ie, SLIT vs SCIT and preseasonal vs perennial treatment protocols; Fig 2, B) is guided by licensed indications, availability, disease severity (eg, concomitant asthma), age, patient preferences, and the physician's preference and experience. Furthermore, payer authorization for payment of AIT products varies between different EU MSs and might affect the use of an AIT product.³⁷

Despite long experience with AIT products in Europe, many challenges remain. With the diversity of definitions, methods of administration, and different allergen products used, research studies have produced conflicting outcomes. This has resulted in confusion about the benefits and risks of AIT among policymakers and professionals, as well as in the variable availability of AIT products, regulation, and reimbursement policies globally.³⁸ To settle existing controversies, the European Academy of Allergy and Clinical Immunology has recently completed an AIT Guidelines Project to document and facilitate high-quality

clinical practice for AIT.³⁸ The resulting guidelines are based on scientific evidence (including published studies up to 2015). These documents received contributions from multidisciplinary and multiple professional groups. The guideline recommendations, centered on the allergic patient, highlight the benefits and harms of AIT and are intended to serve as guidance for a homogeneous approach for clinical AIT practices in the EU.^{14,15,20,26-28,39}

UNMET NEEDS AND CONTROVERSIES

As described in this article, there are benefits and limitations for AIT, as practiced in Europe and the United States. To address important and clinically relevant questions that cannot be addressed because of the absence or low quality of current medical evidence, we have listed below important issues that remain unanswered.

Unmet needs in the United States

1. Nearly all placebo-controlled studies of SCIT have evaluated the efficacy of treatment with single aeroallergens. Few studies have examined the relative efficacy of SCIT injections administered to polysensitized patients from vials containing mixes of multiple aeroallergens.
2. Nearly all products approved for SCIT in the United States are aqueous extracts. Compared with aqueous products in the United States, alum-absorbed suspensions used in Europe could delay systemic absorption and reduce risk of severe anaphylactic reactions. Allergoid products with reduced allergenicity could also reduce severe systemic reactions. Head-to-head studies of aqueous versus nonaqueous formulations could address the relative safety profiles of these products.
3. No official guidance exists in the United States for clinical development and approval of new therapeutic allergen products.
4. Multiple tree pollen extracts are routinely used in the United States, yet it is unknown whether treatment with 1 or 2 tree pollens is equal to or less effective than multiple tree pollens. Such studies might be more feasible when standardized SLIT or SCIT tree products become available.
5. Practicing allergists in the United States generally support the notion that SCIT is more effective than SLIT. Indirect comparisons of these 2 modalities are not conclusive.² Adequately powered head-to-head phase III studies using products for which dosing has been optimized within a clinical development program might be needed to resolve this issue.
6. Although placebo-controlled studies in Europe have demonstrated the efficacy and safety of house dust mite tablet SLIT in treating mild and moderate allergic asthma triggered by HDM,³⁵ such studies would be needed to obtain an asthma indication in the United States.

Unmet needs pertinent to the EU

1. In addition to the well-established indication of AIT for allergic rhinitis, there is a need for more high-quality clinical trials on further indications, including treatment of

food allergies and prevention of specific allergic manifestations (eg, asthma).

2. Despite commercial AIT products for food allergies being under clinical investigation, at this point, it is not established clinical practice. Longitudinal, prospective, well-designed studies are needed to fill the many gaps yet to be addressed, with the final goal of extending food allergen-based AIT protocols in clinical practice as standard medical therapy.³⁸
3. Considerable gaps were identified concerning a long-term disease-modifying effect of AIT, particularly in the pediatric population, calling for well-designed studies in this population.³⁸
4. At this point, in various EU MSs, allergens are mostly available as NPPs. Most MSs do not have comprehensive information for these products. Accordingly, documentation or independent evaluation on quality, safety, and efficacy are typically not available.
5. For rare allergen sources, where the number of affected patients is scarce, robust data from randomized controlled trials might not be possible to obtain.²⁰ However, specific quality requirements (eg, protein content and qualitative and quantitative allergen content), as well as clinical data from smaller populations, appear to be feasible.
6. An EU-wide harmonization of regulatory requirements differentiating between rare and frequent allergens for *in vivo* diagnostics, as well as for AIT, seems to be feasible. For this purpose, novel regulatory and scientific guidelines, respectively, are being prepared by the Coordination Group for Mutual Recognition and Decentralized Procedures–Human and by the RIWP Rheumatology/Immunology Working Party of the Committee for Medicinal Products for Human Use within the EMA.

We thank Gabriele Weber, Deputy Head of the Section of Pharmacovigilance I at PEI, for data review and analysis of adverse events linked to AIT.

What is known?

- Multifaceted differences between AIT products, regulation, and best practice exist between the United States and Europe.

What is still unknown?

- Efficacy in clinical studies and effectiveness of the different AIT approaches in Europe and the United States under real-life conditions remain subjects for further research.

REFERENCES

1. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998;102:558-62.
2. Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? *J Allergy Clin Immunol* 2016;137:339-49.
3. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010;8:CD001186.
4. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(suppl):S1-55.
5. Slater JE, Esch RE. Preparation and standardization of allergen extracts. In: Adkinson NF, Bochner BS, Burks W, Busse WW, Holgate ST, Lemanske RF Jr, editors. *Allergy: principles and practice*. 8th ed. Philadelphia: Mosby; 2014. pp. 470-81.
6. Codina R, Lockey RF. Pollen used to produce allergen extracts. *Ann Allergy Asthma Immunol* 2017;118:148-53.
7. Zimmer J, Bonertz A, Vieths S. Quality requirements for allergen extracts and allergoids for allergen immunotherapy. *Allergol Immunopathol (Madr)* 2017;45(suppl 1):4-11.
8. Calderón M, Cardona V, Demoly P. EAACI 100 Years of Immunotherapy Experts Panel. One hundred years of allergen immunotherapy European Academy of Allergy and Clinical Immunology celebration: review of unanswered questions. *Allergy* 2012;67:462-76.
9. Nordic Council of Medicines. 2nd ed. Registration of allergenic preparations. Nordic guidelines. Vol 23. Uppsala, Sweden: NLN Publications 1988.p.1-34.
10. Turkeltaub PC, Rastogi SC, Baer H, Anderson MC, Norman PS. A standardized quantitative skin-test assay of allergen potency and stability: studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. *J Allergy Clin Immunol* 1982;70:343-52.
11. Kaul S, Zimmer J, Dehus O, Constanzo A, Daas A, Buchheit KH, et al. Validation of ELISA methods for quantification of the major birch allergen Bet v 1 (BSP090). *Pharmeur Bio Sci Notes* 2017;2017:69-87.
12. Slater JE, Menzies SL, Bridgewater J, Mosquera A, Zinderman CE, Ou AC, et al. The US Food and Drug Administration review of the safety and effectiveness of nonstandardized allergen extracts. *J Allergy Clin Immunol* 2012;129:1014-9.
13. Center for Biologics Evaluation and Research report of scientific and medical literature and information on non-standardized allergenic extracts in the diagnosis and treatment of allergic disease; availability. *Federal Regist* 2011;76:59407-8.
14. Bonertz A, Roberts G, Hoefnagel M, Timon M, Slater J, Rabin R, et al. Challenges in the implementation of EAACI guidelines on allergen immunotherapy. A global perspective on the regulation of allergen products. *Allergy* 2018;73:64-76.
15. Bonertz A, Roberts G, Slater JE, Bridgewater J, Rabin RL, Hoefnagel M, et al. Allergen manufacturing and quality aspects for allergen immunotherapy in Europe and the United States. An analysis from the EAACI AIT Guidelines Project. *Allergy* 2018;73:816-26.
16. Englert L, May S, Kaul S, Vieths S. [The therapy allergens ordinance ("Therapieallergene-Verordnung"). Background and effects]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2012;55:351-7.
17. Zimmer J, Vieths S, Kaul S. Standardization and Regulation of Allergen Products in the European Union. *Curr Allergy Asthma Rep* 2016;16:21.
18. Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol* 2017;118:28-54.
19. Nelson HS, Oppenheimer J, Buchmeier A, Kordash TR, Freshwater LL. An assessment of the role of intradermal skin testing in the diagnosis of clinically relevant allergy to timothy grass. *J Allergy Clin Immunol* 1996;97:1193-201.
20. Roberts G, Pfaar O, Akdis CA, Ansoategui JJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018;73:765-98.
21. Matricardi P, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol* 2016;27(suppl 23):1-250.
22. Kleine-Tebbe J, Matricardi PM, Hamilton RG. Allergy work-up including component-resolved diagnosis: how to make allergen-specific immunotherapy more specific. *Immunol Allergy Clin North Am* 2016;36:191-203.
23. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHN-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of

- Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int* 2014;23:282-319.
24. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. *J Allergy Clin Immunol* 2017;140:950-8.
 25. Greenhawt M, Oppenheimer J, Nelson M, Nelson H, Lockey R, Lieberman P, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. *Ann Allergy Asthma Immunol* 2017;118:276-82.e2.
 26. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: prevention of allergy. *Pediatr Allergy Immunol* 2017;28:728-45.
 27. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy* 2018;73:744-64.
 28. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy* 2018;73:799-815.
 29. USP-NF General Chapter 797: Pharmaceutical compounding—sterile preparation. North Bethesda (MD): The United States Pharmacopeia Convention; 2011.
 30. White JF, Levin L, Villareal M, Murphy K, Biagini R, Wellinghoff L, et al. Lack of correlation between regional pollen counts and percutaneous reactivity to tree pollen extracts in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2005;94:240-6.
 31. James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol* 2011;127:509-16, e1-5.
 32. Epstein TG, Liss GM, Murphy-Berendts M, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013;110:274-8.e7.
 33. Bernstein DI, Wanner M, Borish L, Liss GM. Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36.
 34. Li JT, Bernstein DI, Calderon MA, Casale TB, Cox L, Passalacqua G, et al. Sublingual grass and ragweed immunotherapy: clinical considerations—a PRACTALL consensus report. *J Allergy Clin Immunol* 2016;137:369-76.
 35. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA* 2016;315:1715-25.
 36. Bachert C, Larché M, Bonini S, Canonica GW, Kündig T, Larenas-Linnemann D, et al. Allergen immunotherapy on the way to product-based evaluation—a WAO statement. *World Allergy Organ J* 2015;8:29.
 37. Massaro I, Rossi O, Incorvaia C, Lombardi C. A survey on the perception of allergy specialists about the reimbursed grass pollen tablets for seasonal allergic rhinitis in Italy. *Clin Mol Allergy* 2017;15:15.
 38. Muraro A, Roberts G, Halken S, Agache I, Angier E, Fernandez-Rivas M, et al. EAACI guidelines on allergen immunotherapy: executive statement. *Allergy* 2018;73:739-43.
 39. Ryan D, Gerth van Wijk R, Angier E, Kristiansen M, Zaman H, Sheikh A, et al. Challenges in the implementation of the EAACI AIT guidelines: a situational analysis of current provision of allergen immunotherapy. *Allergy* 2018;73:827-36.

Supplemental Table 1 (Online Repository): Definitions of Allergy Preparation Units used for AIT products by selected European Allergen Manufacturers
modified from: Calderón M, Cardona V, Demoly P; EAACI 100 Years of Immunotherapy Experts Panel. One hundred years of allergen immunotherapy
European Academy of Allergy and Clinical Immunology celebration: review of unanswered questions. Allergy 2012;67(4):462-7

Allergen Manufacturer	website	Units	Definitions (given by allergen manufacturers)
ALK-Abelló, DK	https://www.alk.net/	SQ-U SQ-T	100,000 Standardised Quality - Units (SQ-U) is the optimal maintenance dose of allergen extract administered during subcutaneous immunotherapy. 75,000 Standardised Quality - Tablet units (SQ-T) is the optimal maintenance dose of grass allergen extract administered during sublingual immunotherapy using timothy allergen immunotherapy tablets.
Allergopharma, DE	http://www.allergopharma.com/	TU	Therapeutic units: demonstration of clinical efficacy and safety in clinical studies determines an appropriate dose of the product, and TU are assigned accordingly. TU reflect the quality and consistency of the product on the basis of a comparison with the IHRP as well as the clinical efficacy and safety.
Allergy Therapeutics, UK; Bencard, DE	http://www.allergytherapeutics.com/	TU SU	TU is derived from the corresponding ODC prick test strength. ODC= concentration with the lowest rate of false positive and false negative results at a specified cut-off. SU is the specified reactivity of specific IgG (not IgE) with the allergoid; in the case of grasses, Phl p 1, and in case of birch, Bet v 1.
HAL Allergy, NL	http://www.hal-allergy.com/	AU AUM	Erythema size total of 2 diameters, arithmetical mean of 50 mm = D50. Intradermal test in 15 highly allergic patients, chosen from a pool of patients with no controls.
Laboratorios LETI, ES	https://www.leti.com/en/	HEP	"An allergen extract is defined as having 10 HEP when it causes a specific reaction on the skin consisting of a wheal of the same average size as a positive reference consisting in histamine 54.3 mmol/l (histamine HCl at a concentration of 10 mg/ml), when both solutions are used with the same technique (SPT) in a minimum of 20 individuals who are sensitised and who have a skin reaction to the allergen in question."
Lofarma, IT	http://www.lofarma.it/en/index.html	AU BU/ml 10,000 U/ml	Biological unit that is equivalent to 1/40 of the corresponding unmodified allergen challenge dose assessed by nasal challenge test in volunteers suffering from allergic rhinitis. BU is equivalent to 1/100 of the concentration of extract, which, before being chemically modified, induces at SPT a mean wheal equivalent to histamine 10 mg/ml. Corresponds to 4 µg equivalent/ml of Group 1 major allergens (Der p 1 and Der f 1)
Roxall, ES	https://www.roxall.com/	TU (therapeutic units): 1 TU = 1 BU (same protein	HEP-BU are calculated according to the Nordic Guidelines: 'the activity of an allergen extract is 10 000 BU or 10 HEP per ml when the extract provokes a specific skin reaction in the median sensitive patient with a wheal of the same size as a wheal provoked by a positive reference solution consisting of histamine 54.3 mM (histamine dihydrochloride 10 mg/ml), when both solutions are administered using the same technique (SPT) on at least 20 individuals who are clinically allergic

		content)	and cutaneously reactive to the allergen concerned'
Stallergenes Greer, FR	http://www.stallergenesgreer.com/	IR	The unit IR has been defined to measure the allergenicity of an allergen extract. The allergen extract contains 100 IR/ml when, on a SPT using a Stallerpoint [®] , it induces a wheal diameter of 7 mm in 30 patients sensitised to this allergen (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive SPT to either 9% codeine phosphate or 10 mg/ml histamine.

Abbreviations: EU countries (left column): DE Germany, DK Denmark, ES Spain, FR France, IT Italy, NL The Netherlands, SP Spain, UK United Kingdom.

Terms and units (right columns): BU biological units, HEP histamine equivalent in prick testing, IHRP in-house reference preparation, SPT skin prick test, SQ standardised quality, TU therapeutic units,

Supplemental Table 2 (Online Repository): Manufacturing and Clinical Development Guidelines in the United States and European Union.

Selected legal documents and regulatory guidance documents relevant for AIT products in the USA	Links	Description
Title 21 Chapter I Part 680 - Additional standards for miscellaneous products 680.1 -3 Manufacture of Allergenic Products and testing	https://www.govregs.com/regulations/expand/title21_chapterI_part680_section680.2	Original FDA regulation that specifies source material guidelines including pollens, molds, epithelials , extraction under Current Good Manufacturing Practice (CGMP), and testing requirements
FDA Allergenic Advisory Panel report. Review of IIIA extracts, final review 1983.	https://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenic/UCM271333.pdf	The task of the panel was to reclassify extracts into Category 1 or 2 following safety and immunotherapy efficacy review of literature and information from manufacturers.
21CFR PART 210 -- Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general.	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=210.1	This section of FDA regulation specifies the minimum requirements for manufacture of drugs including biologicals. Allergen manufacturers obtain licenses and undergo regular audits to assure compliance.
FDA Guidance: On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test	https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Allergenic/UCM078638.pdf	Detailed FDA guidance on manufacture of allergenic extracts including source material specifications, building and clean room requirements, organization structure, and testing.
FDA Guidance Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol Nov 2000	https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Allergenic/UCM078624.pdf	FDA guidance on standardized grass and mite potency ELISA IgE competition testing. This document established wider release limits of relative potency of 0.5 to 2.0 for FDA lot release (N=3 plates). Also applied to stability studies of these standardized extracts.
Allergen literature for classification of extracts	https://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenic/UCM272393.pdf http://www.fda.gov/BiologicsBloodVaccines/Allergenic/ucm272115.htm	Literature review for diagnostics and immunotherapy efficacy of all extracts licensed by the FDA. This information is available through these links.
Methods of the allergenic products testing laboratory - October 1993	https://www.scribd.com/document/1425797/US-Food-and-Drug-Administration-94n-0012-bkg0001-01-vol1	This document describes the methods of the Laboratory of Immunobiology of CBER. All USA manufacturers perform allergen testing with these methods, such as ELISA competition, radial immunodiffusion and ninhydrin assay.
Pharmaceutical Compounding – Sterile	http://www.uspnf.com/notices/ge	USP chapter on sterile compounding

Process USP 41 Chapter <797> page 6554 Nov 2015	neral-chapter-797-proposed-revisions	- updated in 2018 - that has recommendations for allergen treatment set compounding and applies to vials with patient names. Sterile technique and location for mixing is specified.
Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application: Guidance for Industry	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm	FDA guideline for sterile compounding biologicals contains an allergen section that follows the USP<797> guidelines for formulation in physician offices.
Compliance Program Guidance Manual Chapter – 45 Biological Drug Products Inspection of Biological Drug Products (CBER) 7345.848	https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/UCM095419.pdf	FDA guidance document for inspection compliance of biological establishments including allergenics. Applies to audits of facilities producing allergen extracts.
Standards and Certification: Laboratory Requirements (42 CFR 493) Clinical Laboratory Improvement Amendments (42 USC 263a) Clinical Laboratory Improvement Amendments (42 USC 263a)	https://www.ecfr.gov/cgi-bin/text-idx?SID=1248e3189da5e5f936e55315402bc38b&node=pt42.5.493&rgn=div5 https://www.gpo.gov/fdsys/pkg/USCODE-2011-title42-chap6A-subchapII-partF-subpart2-sec263a.pdf	FDA regulations issued by the Centers for Medicare & Medicaid Services (CMS) to enact the Clinical Laboratory Improvement Act (CLIA) law. In general terms, the CLIA regulations establish quality standards for laboratory testing performed on specimens from humans for the purpose of diagnosis, prevention, or treatment of disease, or assessment of health. The final CLIA regulations were published in 1992 and amended in 1993, 1995, and 2003. Applies to IgE testing in the USA.
FDA guidance documents applicable to clinical development of allergenic products	Links	Description
Title 21 Part 312 – Investigational New Drug Application	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312	FDA regulations with procedures and requirements governing the use of investigational new drugs in clinical investigations.
Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf	Guidance to applicants to file NDAs, BLAs, or supplemental indications on the evidence demonstrating effectiveness.
Guidance for Industry – Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf	Guidance to applicants on the content and format for the CLINICAL STUDIES section of prescription drug labeling with the objective to provide information most useful to prescribers in treating their patients.
Guidance in manufacturing of most investigational new drugs (IND) including allergenic products used in phase 1 clinical trials.	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.pdf	Guidance to assist in applying CGMP required under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
Title 21 Part 50 – Protection of human	https://www.accessdata.fda.gov/s	FDA regulations intended to protect

subjects	cripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1	the rights and safety of subjects involved in all clinical investigations supporting applications for research or marketing permits.
Title 21 Part 56 – Institutional Review Boards	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1	FDA regulations with general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations supporting applications for research or marketing permits.
Guidance for Clinical Investigators, Sponsors, and IRBs – Adverse Event Reporting to IRBs – Improving Human Subject Protection	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079753.pdf	Guidance to assist the research community in interpreting the requirements for submitting adverse event reports to the IRB.
Selected legal documents/regulatory guidance documents relevant for AIT products in the EU	Links	Description
The European Parliament and Council. Directive 2001/83/EC. The community code relating to medicinal products for human use. Official Journal of the European Union, L 311, 28.11.2001, p. 67ff	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf	This European Directive, which needs to be transferred into national law in all member states (MS), lays down all regulatory aspects for medicinal products for human use. In Article 1, the definition of medicinal products is given, including test and therapy allergens. Article 6 requires a marketing authorization issued by a competent authority for all medicinal products, however, Article 5 defines exemptions from the requirement of a marketing authorization (which has been inconsistently applied to test and therapy allergen in different MS).
The European Parliament and Council. Directive 2001/20/EC. The approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Union, L 121, 1.5.2001, p. 34ff	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf	This European Directive, which needs to be transferred into national law in all member states, regulates GCP conditions in the conduct of clinical trials with investigational medicinal products for human use (to be applied to clinical studies with test and therapy allergens).
The European Parliament and Council. Directive 2003/94/EC. The principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Official Journal of the European Union, L 262, 14.10.2003, p. 22ff	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf	This European Directive, which needs to be transferred into national law in all member states, regulates CGMP conditions in the manufacturing of investigational medicinal products for human use (to be applied to the manufacturing process of test and therapy allergens).
The European Parliament and Council. Directive 2010/84/EC amending, as regards pharmacovigilance, Directive 2001/83/EC. Official Journal of the European Union, L	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf	This European Directive, which needs to be transferred into national law in all member states, regulates the implementation and maintenance of

348, 31.12.2010, p. 74ff	df	a pharmacovigilance system for licensed medicinal products.
Guideline on Allergen Products: Production and Quality issues (EMA/CHMP/BWP/304831/2007)	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003333.pdf	This guidance document defines the state-of-the art requirements concerning the quality and production process of test and therapy allergen products on which the assessment of competent authorities is based during the marketing authorization process. It contains the concept of homologous groups.
Guideline on the Clinical Development of Products for Specific immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006).	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf	This guidance document defines the state-of-the art requirements concerning the clinical development process of allergen products for AIT (including requirements and feasible endpoint for phase I, phase II and phase III studies) on which the assessment of competent authorities is based during the marketing authorization process.
Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1)	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162136.pdf	This guidance document defines the state-of-the art requirements concerning process validation, information and data to be provided in regulatory submissions for the finished dosage forms of chemical medicinal products for human and veterinary use. It incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.
Eur. Ph. Monograph (No. 1063) on Allergen Products. European Pharmacopoeia 9.0	http://online6.edqm.eu/ep900/ (for access registration and login required)	This legally binding monograph applies to the source materials, manufacturing process and identification of natural protein extract-based test and therapy allergens, including preparation of in-house reference standards and tests to be applied.
European Pharmacopoeia. Monograph (No. 2621) on Animal epithelia and outgrowths for allergen Products. European Pharmacopoeia 9.0	http://online6.edqm.eu/ep900/ (for access registration and login required)	This legally binding monograph applies to the source materials, manufacturing process and identification of natural protein extract-based test and therapy allergens derived from animal epithelia.
European Pharmacopoeia. Monograph (No. 2623) on Hymenoptera venoms for allergen products. European Pharmacopoeia 9.0	http://online6.edqm.eu/ep900/ (for access registration and login required)	This legally binding monograph applies to the source materials, manufacturing process and identification of natural protein extract-based test and therapy allergens derived from Hymenoptera venoms.

European Pharmacopoeia. Monograph (No. 2625) on Mites for allergen products. European Pharmacopoeia 9.0	http://online6.edqm.eu/ep900/ (for access registration and login required)	This legally binding monograph applies to the source materials, manufacturing process and identification of natural protein extract-based test and therapy allergens derived from mites.
European Pharmacopoeia. Monograph (No. 2626) on Molds for allergen products. European Pharmacopoeia 9.0	http://online6.edqm.eu/ep900/ (for access registration and login required)	This legally binding monograph applies to the source materials, manufacturing process and identification of natural protein extract-based test and therapy allergens derived from molds.
European Pharmacopoeia. Monograph (No. 2627) on Pollens for allergen products. European Pharmacopoeia 9.0	http://online6.edqm.eu/ep900/ (for access registration and login required)	This legally binding monograph applies to the source materials, manufacturing process and identification of natural protein extract-based test and therapy allergens derived from pollen.
International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use. Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, 1999.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf	This guidance document defines specifications of Test Procedures and Acceptance Criteria for Biotechnological and Biological Products. The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures. The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids.
International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Q1A(R2) Stability Testing of New Drug Substances and Products, 2003.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf	This guidance document defines requirements for Stability Testing of New Drug Substances and Products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a shelf life for the allergen product and recommended storage conditions.
International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process, 2004.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf	This guidance document defines requirements for Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process. Its objective is to provide principles for assessing the comparability of biotechnological/biological products

Codice campo modificato

		before and after changes are made in the manufacturing process for the drug substance or drug product. It applies to proteins and polypeptides, their derivatives, and products of which they are components, e.g., conjugates. These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures. It also states "The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids." The general principles provided in this guideline also to non-biotechnological allergen products derived from natural sources.
International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Q2(R1) Validation of Analytical Procedures: Text and Methodology, 2005.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1_Guideline.pdf	This guidance document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the EC, Japan and USA.
International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Q9 Quality Risk Management, 2005.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf	This guidance document provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).
International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Q10 Pharmaceutical Quality System, 2008.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf	This guidance document applies to the systems supporting the development and manufacture of pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle.
International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Q8(R2) Pharmaceutical Development, 2009.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf	This guidance document covers the process design for pharmaceutical development. It is intended to provide further guidance on the contents of Section 3.2.P.2

		(Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH guideline M4).
International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities), 2012.	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf	This guidance document defines the expectations for active substances. It is applicable to drug substances as defined in the Scope sections of ICH Guidelines Q6A and Q6B, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. It is particularly relevant to the preparation and organization of the contents of Sections 3.2.S.2.2 – 3.2.S.2.6 of Module 3 of the Common Technical Document (ICH M4Q).