Authorised allergen products for intracutaneous testing may no longer be available in Germany

Allergy textbooks have to be re-written

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Key words
intracutaneous testing – allergic rhinitis – diagnostic test allergens – allergen products – marketing authorisation

Submitted
February 13, 2015

Accepted
February 23, 2015

German version
www.springer-medizin.de/allergo-journal

Abstract

Background: Beside the skin prick test, the intracutaneous test represents the most important skin test method for detecting type-1 allergies. With the incorporation of European directives into national law, test allergens used for allergy diagnosis are deemed medicinal products within the meaning of the German Medicinal Products Act (Arzneimittelgesetz) and therefore require marketing authorisation for distribution in Germany. The high costs of acquiring and maintaining these authorisations have lead to no new finished intracutaneous test products being authorized in Germany for more than 20 years. Instead, most manufacturers have voluntarily withdrawn their existing marketing authorisations for intracutaneous test extracts. The last manufacturer to offer approved finished allergen products for intracutaneous tests recently announced that it would now cease production and distribution of these solutions.

Methods: Research on the current European and German legislation; selective literature search in Medline, including national and international guidelines and Cochrane meta-analyses; licensing information on the Paul-Ehrlich-Institute homepage (www.pei.de) as well as in the Bundesanzeiger (Federal Gazette).

Results: According to information on www.pei.de, marketing authorisations still existed as of 31.01.2015 for intracutaneous test solutions of six grass/cereal/herbal pollens, seven tree pollens, ten food allergens, twelve moulds and yeasts as well as two fungal mixtures, five house dust and storage mites and five animal epithelia/danders, all held by

Abbreviations

AIT	Allergen-specific immunotherapy
AMG	German Medicinal Products Act (Arzneimittelgesetz)
AR	Allergic rhinoconjunctivitis
EAACI	European Academy of Allergology and Clinical Immunology
IgE	Immunoglobulin E
IHRP	In-house reference preparation
SIT	Specific immunotherapy
WHO	World Health Organization

only one company in Germany. These marketing authorisations were granted between 16th March 1987 and 17th January 1992; more recent marketing authorisations do not exist.

Conclusions: European legislation and the associated increase in production and licensing costs have already lead to numerous suppliers withdrawing their marketing authorisation for diagnostic test allergens – marketing authorisations for 443 diagnostic allergens were voluntarily withdrawn by manufacturers in 2013 alone. If the announced restrictions on the allergen portfolio go ahead, considerable problems in the management of allergy patients in Germany due to the discontinuation of the intracutaneous test are likely to be encountered. Moreover, the fact that a diagnostic procedure that has been established for decades seems set to disappear quite simply because all the requisite substances vanish from the market in one fell swoop may well be without parallel in modern medicine.

The situation for skin prick test allergens is less dramatic, although, here again, the available range is becoming increasingly limited.

Cite this as: Klimek L, Werfel T, Vogelberg C, Jung K. Authorised allergen products for intracutaneous testing may no longer be available in Germany. Allergy textbooks have to be re-written. Allergo J Int 2015;24:84–93
DOI: 10.1007/s40629-015-0051-7

Introduction

The most frequent immunoglobulin E (IgE)-mediated type-1 (immediate-type allergies) allergic diseases include allergic rhinoconjunctivitis, allergic bronchial asthma, food allergies, insect venom allergies and anaphylactic reactions. They are often caused by allergies to pollen, mites, animal dander, foods, natural rubber latex, insect venoms and drugs. Diagnosis is based on patient history, clinical examination, skin tests, detection of specific IgE antibodies in serum, and provocation tests [1].

In recent decades, an increase particularly in the number of allergies to ubiquitous airborne allergens has been well documented in most industrialized countries [2, 3, 4, 5, 6]. The allergy sufferer's career often begins in childhood with atopic dermatitis and food allergy, followed later by allergic asthma and allergic rhinoconjunctivitis (AR) [7].

Of these, AR represents the most widespread allergic disease [7, 8]. The worldwide prevalence of self-reported rhinitis symptoms in adolescents has been published to be 3.2 %–66 %, with the median at approximately 25 % [5, 6, 8].

„Hayfever" (pollen-related seasonal or intermittent AR) has already been diagnosed at least once in 13 %–24 % of adults in Germany, whilst 16 %–36 % of German adults show sensitization to inhalant allergens [9].

A distinction is made between intermittent (< 4 weeks/year) and persistent (> 4 weeks/year) symptoms of AR. Symptoms are classified as moderate to severe when rhinorrhea, impaired nasal breathing, and eye symptoms adversely affect untreated patients in their daily activities and/or sleep.

The aim of the therapy of allergic diseases is to treat symptoms and prevent disease progression. At present, this goal can only be achieved with allergen-specific immunotherapy (AIT, SIT), a method oriented to treating the immunological cause of allergic disease. Thus, this approach is able to reduce symptoms and drug use, has a disease-modifying effect and counteracts the naturally often seen disease progression and broadening of the allergy spectrum [10–13].

However, allergies are often treated too late and inadequately, thereby causing largely avoidable sequelae with considerable secondary costs [14, 15, 16]. These are estimated to be between 36.7 and 385.1 billions Euro/year, depending on the basis of calculation used [15]. Advanced disease is associated with higher treatment costs [17].

In a treatment study commissioned by the Medical Association of German Allergologists (Ärzteverband Deutscher Allergologen, AeDA) and headed by Professor Dr. Jürgen Wasem from the chair of Medical Management at the University of Duisburg-Essen, a team of authors systematically analyzed over 40 million records of members of the German statutory health insurance with regard to the occurrence of allergic disease and the prescription of SIT [18]. Only 7 % of patients with AR and only 5 % of patients with allergic bronchial asthma received SIT [18]. The number of medical practices offering any form of allergy diagnosis or treatment at all has gone down by 31 % for AR and 27 % for allergic asthma over the last 4 years. According to the data, the strongest withdrawal from allergology was observed among general practitioners (–50 %) and specialists in internal medicine (–43 %).

Three German allergy associations, the AeDA, the German Society for Pediatric Allergology and Environmental Medicine (Gesellschaft für Pädiatrische Allergologie und Umweltmedizin, GPA) and the German Society for Allergology and Clinical

Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI), interpret these results as a dramatic under-treatment of allergy sufferers in Germany. Against this backdrop, the developments seen in allergology as a consequence of European legislation as discussed below can be considered alarming. As a result, allergy diagnosis – and thus also the treatment of patients – now faces a new and formidable hurdle.

In vivo allergy diagnosis: difficult times for the intracutaneous test

Besides the skin prick test, the intracutaneous test represents the most important skin test method for detecting type-1 allergies. The fact that legislation (see below) has made it considerably more complex to maintain marketing authorisation for diagnostic skin test allergens has lead to the loss of approximately 50 % of all approved test allergens in recent years. There are fears across Europe that in vivo allergy diagnosis may be lost as a result of changes in legal requirements [19].

Extracts with marketing authorisation for intracutaneous testing are particularly affected.

The last remaining company to offer approved finished allergen products for intracutaneous testing (according to www.pei.de) recently announced that production and delivery would soon be halted.

Thus, intracutaneous testing is in danger of disappearing from the clinical allergist's routine diagnostic arsenal. As a consequence, the long-standing consensus on the importance of this test in the diagnosis of allergy patients would be worthless. If this is the case, textbooks on allergic diseases will have to be re-written.

Skin testing

After haven taken the patient´s history, skin tests are the next steps in the diagnosis of allergies. Skin tests are fast and relatively cost-effective to perform. They are generally also sufficiently reliable and have a low complication rate [20, 21]. Taking a thorough patient history and performing a clinical examination produces a suspected diagnosis, which forms the basis for skin testing [1].

Skin testing involves diagnostic allergen exposure, i. e., a dermal provocation test. Allergic or non-allergic (e. g. toxic or pseudo allergic) mechanisms can underlie reactions involving the clinical symptoms of an immediate-type allergy. Predominantly immediate-type allergic reactions are elicited by an IgE-mediated mechanism [1].

The principle of skin testing in IgE-mediated immediate-type allergy consists of applying the allergen to perivascular mast cells in the dermis [1]. Mediators released by mast cells trigger a test reaction within minutes, a reaction clinically equivalent to the triple response of Lewis caused by the injection of histamine [1]:

- Local redness due to vasodilation
- Dermal edema caused by increased capillary permeability
- Erythema in the surrounding area due to axon reflex

Redness (erythema) and wheal (urtica) are clinically visible, peaking within 15 min following histamine injection [22]. Allergen-induced reactions peak after 15–20 min. Delayed immediate-type reactions may appear some hours later in the form of wheals or erythema. Late-phase reactions that appear within hours to several days after the test, e. g., as red papules or dermatitis, are also possible [1]. Skin tests are normally performed on the volar side of the forearm or on the back. It should be noted that the diameter of skin test reactions on the back is greater than those on the forearm [23, 24]. In addition, reactions on the back are smaller in the upper compared with the lower third [25]. The test site is marked with pen in such a way that the individual reactions can be readily attributed to test preparations. Sufficient distance should be left between test sites [26, 27, 28].

A number of manufacturers offer commercial allergen test extracts for skin testing. The composition and standardization of test solutions is crucial to the sensitivity, specificity and reproducibility of test results [1]. The approval of diagnostic test allergens enables the use of controlled, as well as qualitatively and quantitatively standardized extracts [26, 29].

The skin prick test

Since it is relatively simple and fast to perform, the skin prick test is the most frequently used test in clinical routine. Its sensitivity and specificity are adequate and the complication rate low [30, 31, 32]. Due to the good reproducibility of test results, low risk of systemic reactions and good correlation with clinical responsiveness, the skin prick test is considered the skin testing method of choice [26, 29, 33].

The intracutaneous test (intradermal test)

The test solution is drawn into a tuberculin syringe and 0.02–0.05 ml is injected strictly intracutaneously using a 21-gauge needle [1]. The injected volume should form a wheal approximately 3 mm in diameter on the surface of the skin. The test solution must be sterile and both approved and suitable for intracutaneous use [1]. Although intracutaneous tests have better sensitivity compared with skin prick tests, they require different allergen test solution concentrations [34, 35, 36, 37]. Thus, an intracutaneous test may be indicated even in the presence of a negative prick test [1]. It is also recommended as an initial skin testing method in the case

of weakly reactive allergens [29, 33, 34, 35, 36, 37]. In addition, intracutaneous tests are used to detect delayed reactions or late-phase reactions in both negative and positive immediate reactions [1].

In addition to their use in the diagnosis of individual patients, intracutaneous tests are also used for the biological standardization of therapeutic allergenic extracts.

There are currently two fundamentally different approaches to this [38]; for biological standardization, skin test methods are based on either:

a) The US approach [39], involving the use of intracutaneous tests in 15 highly sensitive patients, or

b) The Scandinavian approach, based on the Danish standardization program from 1976 [40]. This involves performing skin prick tests on 20 moderately to highly sensitized patients.

Both procedures are also widely used in Europe to quantify the biological activity of allergen extracts and are expressed in various biological units.

Allergen manufacturers generally characterize their therapeutic and diagnostic allergen extracts according to the in-house reference preparation (IHRP) principle, whereby each batch of an allergen product is compared with an internal reference standard. IHRPs are determined using one of the above-mentioned principles and company-specific biological units are defined. This makes it possible to compare individual batches of a manufacturer with one another – not, however, to compare the biological activity of products of different manufacturers [41]. IgE inhibition tests are often used as in vitro standardization methods and are stipulated as controls for consistency between different batches ("batch-to-batch consistency") [38] in accordance with the European Pharmacopoeia monograph on allergen products. The IgE inhibition test measures to what extent the administration of soluble allergen is able to inhibit binding between specific IgE from patient serum and the solid phase-bound allergen [38]. Differences in therapeutic and diagnostik allergens are existing in the monograph with regard to validated efficiency measures.

Reading and documenting test reactions

The reading of immediate reactions is carried out after 15–20 min [27, 42], once all test material remaining on the skin has been removed with a swab [43].

Readings include measuring erythema and wheals; the latter can be made more readily visible by gently stretching the skin. There are various methods for documenting the test reaction. With the skin prick test, a mean wheal diameter of > 3 mm or a wheal surface area of > 9 mm^2 is considered positive; with the intracutaneous test, a wheal diameter of > 5 mm is considered positive [44, 45]. This is calculated as the sum of the largest diameter and its largest perpendicular diameter (in millimetres) divided by two. Planimetric techniques are indicated when readings are made for scientific purposes.

Generally, only one reading is made after 15–20 min (immediate reading). In order to measure delayed reactions or late-phase reactions when indicated, additional readings are made after approximately 6–8, 24, and 48 h, possibly even later. Patients should also be instructed to report delayed reactions at their follow-up visit. Where necessary, the test is then repeated with appropriate reading times. Delayed reactions are documented by recording the two largest perpendicular diameters of erythema and induration, (in millimetres), as well as providing a morphological description (e. g., papules, blisters or desquamation).

Methods

The present publication uses the latest analyses from the German and international guidelines, the Cochrane Database, the position papers of the EAACI and the WHO, the European and German legislation, the results of selective Medline searches, and the marketing authorisation information on the homepage of the Paul-Ehrlich Institute (PEI; www.pei.de) and in the Bundesanzeiger (Federal Gazette). The following search terms were used: intracutaneous test; intradermal test; allergen skin tests; allergic rhinitis; diagnostic test allergens; allergen products; marketing authorisation; EU Directive 89/342/EEC, EU Directive 2001/83/EC; Guideline on Allergen Products; Monograph on Allergen Products; „Producta Allergenica".

European legislation on allergy diagnostic products

With the incorporation of European laws (e. g. EU Directive 89/342/EEC, EU Directive 2001/83/EC Article 1) [46, 47] into national law, test solutions for allergy diagnosis are deemed to be medicinal products within the meaning of the German Medicinal Products Act and therefore require marketing authorisation for distribution in Germany. For each individual allergen and each route of administration of a test solution, dossiers documenting the preparation in terms of quality, efficacy and tolerability need to be created.

Thus, the „Guideline on Allergen-Products: Production and Quality lssues (EMEACHMP/BWP/30483/2007)", which redefined the standardization and characterization of allergen products, was published in May 2009 [48]. Furthermore, the chapter „Monograph on Allergen Products (01/2010: 1063 Producta Allergenica)" was published in the European Pharmacopoeia in 2010 and made compulsory

as the basis for regulatory documentation for all European allergen product manufacturers [49].

Diagnostic products are medicinal products (Paragraph 4, Section 5 of the German Medicinal Products Act; Arzneimittelgesetz, AMG) [50]

Paragraph 2 – the term „medicinal product" [50]: Medicinal products are substances or preparations made from substances which:

1. Are intended for use on or in the human or animal body and are intended for use as substances with properties for the curing, alleviating or preventing of human or animal diseases or disease symptoms, or
2. Can be used in or on the human or animal body or can be administered to a human being or an animal, either:
   - a) to restore, correct or to influence the physiological functions through a pharmacological, immunological or metabolic effect, or
   - b) to make a medical diagnosis.

Paragraph 4, section 5 AMG [50]: Allergens are medicinal products within the meaning of paragraph 2, section 1, containing antigens or haptens and intended for use on human beings or animals for the detection of specific defense or protective agents (test allergens) or containing substances which are used to achieve an antigen-specific reduction of a specific immunological hypersensitivity (therapeutic allergens).

Marketing authorisation is mandatory for diagnostic products/medicinal products (paragraph 21 AMG) [50]: Obligation to obtain marketing authorisation [50]: Finished medicinal products which are medicinal products as defined in paragraph 2 section 1 or section 2 number 1, may only be placed on the market within the scope of the present Act, if they have been authorised by the appropriate higher federal authority or if the European Community or the European Union has granted an authorisation for them to be placed on the market in accordance with article 3 paragraph 1 or 2 of Regulation (EC) No. 726/2004 also in conjunction with Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12th December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004 (OJ L 378 of 27.12.2006, p. 1) or Regulation (EC) No. 1394/2007. The same shall apply to medicinal products which are not finished medicinal products and which are intended for administration to animals, provided they are not intended for distribution to pharmaceutical entrepreneurs holding an authorisation for the manufacture of medicinal products.

From a legal point of view, diagnostic products were already seen as medicinal products as of 1st January 2009 (paragraph 141, section 4 AMG); however, the practical implementation of the process has been subject to delay.

Paragraph 141, section 1 AMG [AMG 2014]: Medicinal products that are on the market on 5th September 2005 and are subject to paragraphs 10 and 11, must be placed on the market by the pharmaceutical entrepreneur two years after the first prolongation of the marketing authorisation or registration following 6th September 2005 or, if they are exempted from the need for a marketing authorisation or registration at the time referred to in the ordinance pursuant to paragraph 36 or Section 39, or if they do not require a prolongation, on 1st January 2009 pursuant to paragraphs 10 and 11. Up to the relevant dates referred to in sentence 1, medicinal products may be placed on the market by pharmaceutical entrepreneurs and, after these dates, also by wholesale and retail distributors with labelling and a package leaflet complying with the provisions applicable up to 5th September 2005. This shall be without prejudice to Section 109.

As a result of these more stringent requirements, companies are obliged to conduct extensive new quality control investigations on their products.

Results

According to information on www.pei.de, marketing authorisations still existed for intracutaneous test solutions of six grass/cereal/herbal pollens, seven tree pollens, 10 food allergens, 12 moulds and yeasts as well as two fungal mixtures, five house dust and storage mites and five animal epithelia/danders from only one company in Germany (Allergopharma GmbH & Co. KG) as of 22.01.2015. These marketing authorisations were granted between 16th March 1987 and 17th January 1992; more recent marketing authorisations do not exist.

According to information of the PEI the authorisation holder has given up these authorisations in Septemper 2014. The Federal Gazette is the official publication organ of the PEI. According to information from Allergopharma GmbH & Co. KG, the above-mentioned allergenic extracts for intracutaneous testing will no longer be produced and distributed. The time and effort of maintaining marketing authorisation was given as the reason for this.

At the time this publication went to print, the authors had been unable to find information published in the Federal Gazette relating to the surren-

Tab. 1: Intracutaneous test allergens approved in Germany*

Extinct approvals					
	2015	2014	2013	2012	2011
Intracutaneous test allergens		47	159	2	
Present approvals					
	2015	2014	2013	2012	2011
Intracutaneous test allergens	0	47	206	208	208

**Tab. 2 demonstrates the numbers of authorized intracutaneous test allergens over the last 5 years according to information by the Paul-Ehrlich-Institute (personal communication by S. Vieths, S. Kaul, A. Bonertz). The table does not provide information as to whether the products were also commercially available. The information provided on the relevant product licence is legally binding. This does include all extinct approvals independent on the reason that have been announced to the PEI before January 1st of the respective year. Extinctions from 2014 still have not been published in the Bundesanzeiger (Federal Gazette). According to recent personal information from another company, marketing authorizations for their intracutaneous test allergens are already existing and will be published at www.pei.de after the print of this article.*

der of the marketing authorisations for the above-mentioned intracutaneous test allergens. However, the publication in the Federal Gazette, thus the extinction of authorisations and the fellowing actualisation at www.pei.de is awaited soon.

Discussion

Impact on patients and allergists

The changes in European legislation and their implementation in national law have caused a sharp rise in the cost of diagnostic solutions for both skin and provocation testing [46].

As a result, ever fewer physicians are performing allergy testing, as effectively demonstrated by the „Wasem study" [18]. Thus, undiagnosed patients will also not receive allergen-specific therapy (i. e. allergen-specific immunotherapy). The process appears to continue – with more negative consequences in the future.

Furthermore, high production/marketing authorisation costs alongside shrinking sales figures have forced manufacturers to cut approved diagnostic allergens available en masse. According to information from the PEI, the marketing authorisations for 443 diagnostic allergens were voluntarily withdrawn by their manufacturers in 2013 alone (**Tab. 1**).

Thus the possibilities of allergy diagnosis using skin and provocation tests are inevitably becoming ever more restricted. Already today, numerous rare allergies cannot be diagnosed in a guideline-compliant manner – simply because the relevant approved test allergens are not available.

Tab. 2 lists the preparations for intracutaneous testing for which valid marketing authorisations were held as of 31.01.2015, according to the PEI (www.pei.de). The information provided in the relevant marketing authorisation certificate is legally binding. However, the table does not provide information as to whether the preparations were commercially available. Official publications of the PEI appear in the Bundesanzeiger (Federal Gazette); the most recent publication is Bundesanzeiger publication No. 402 of 08.10.2014 (source, BAnz AT 21.01.2015 B5). The authors have not as yet found information published in the Bundesanzeiger relating to the surrender of marketing authorisation for these intracutaneous test allergens.

However, according to PEI information (at www.pei.de), the last manufacturer to offer approved finished allergen products for intracutaneous testing in Germany recently announced that it would cease production and distribution of test allergens for intracutaneous testing.

Such a development is unique in modern medicine: a diagnostic procedure that has been established for decades seems to disappear from the healthcare system, quite simply because all the requisite substances will vanish from the market in one swoop. A scenario of this kind is comparable with a withdrawal of all radiocontrast media from the market, a move that, overnight, would make it impossible to perform contrast-enhanced radiological diagnosis.

This step has significant repercussions for the German field of allergology, as well as for the treatment of allergicpatients in Germany.

All current guidelines and textbooks recommend the intracutaneous test for specific indications on the basis of its greater sensitivity compared with the skin prick test, as well as for use in the case of weakly reactive allergens, or to detect delayed or late-phase reactions.

The availability of intracutaneous test allergens for routine diagnosis depends on a sufficiently

Tab. 2: Intracutaneous test allergens approved in Germany*

Intrakutantest: Gräser-/Getreide-/Kräuterpollen			
Description	**Marketing authorisation holder**	**License number**	**License date**
Mugwort, common	Allergopharma GmbH & Co. KG	75a/87	31.03.1987
Grasses	Allergopharma GmbH & Co. KG	387a/86	16.03.1987
Dandelion	Allergopharma GmbH & Co. KG	83a/87	31.03.1987
Ragweed	Allergopharma GmbH & Co. KG	86a/87	31.03.1987
Rye	Allergopharma GmbH & Co. KG	427a/86	17.03.1987
Plantain	Allergopharma GmbH & Co. KG	88a/87	31.03.1987
Intracutaneous tests: Tree pollen			
Description	**Marketing authorisation holder**	**License number**	**License date**
Acacia, false (Robinia)	Allergopharma GmbH & Co. KG	398a/86	17.03.1987
Birch	Allergopharma GmbH & Co. KG	388a/86	17.03.1987
Beech (common beech)	Allergopharma GmbH & Co. KG	399a/86	17.03.1987
Alder	Allergopharma GmbH & Co. KG	402a/86	17.03.1987
Hazel	Allergopharma GmbH & Co. KG	406a/86	17.03.1987
Plane	Allergopharma GmbH & Co. KG	413a/86	17.03.1987
Elm	Allergopharma GmbH & Co. KG	414a/86	17.03.1987
Intracutaneous tests: Foods			
Description	**Marketing authorisation holder**	**License number**	**License date**
Oatmeal	Allergopharma GmbH & Co. KG	279a/87	03.08.1987
Chicken egg (yolk)	Allergopharma GmbH & Co. KG	288a/87	03.08.1987
Chicken egg (white)	Allergopharma GmbH & Co. KG	287a/87	03.08.1987
Potato	Allergopharma GmbH & Co. KG	272a/87	03.08.1987
Cow's milk	Allergopharma GmbH & Co. KG	290a/87	03.08.1987
Corn flour	Allergopharma GmbH & Co. KG	281a/87	03.08.1987
Brazil nut	Allergopharma GmbH & Co. KG	264a/87	03.08.1987
Rye flour	Allergopharma GmbH & Co. KG	284a/87	03.08.1987
Tomato	Allergopharma GmbH & Co. KG	266a/87	03.08.1987
Wheat flour	Allergopharma GmbH & Co. KG	285a/87	03.08.1987
Intracutaneous tests: Moulds and yeast			
Description	**Marketing authorisation holder**	**License number**	**License date**
Alternaria tenuis (A. alternata)	Allergopharma GmbH & Co. KG	328a/87	03.08.1987
Aspergillus fumigatus	Allergopharma GmbH & Co. KG	351a/87	10.08.1987
Botrytis cinerea	Allergopharma GmbH & Co. KG	352a/87	10.08.1987
Cladosporium herbarum	Allergopharma GmbH & Co. KG	355a/87	10.08.1987
Curvularia lunata	Allergopharma GmbH & Co. KG	356a/87	10.08.1987
Fusarium moniliforme	Allergopharma GmbH & Co. KG	357a/87	10.08.1987
Helminthosporium halodes	Allergopharma GmbH & Co. KG	358a/87	10.08.1987
Mucor mucedo	Allergopharma GmbH & Co. KG	360a/87	10.08.1987

Tab. 2: Intracutaneous test allergens approved in Germany*

Intracutaneous tests: Moulds and yeast			
Penicillium notatum	Allergopharma GmbH & Co. KG	362a/87	10.08.1987
Fungi I	Allergopharma GmbH & Co. KG	371a/87	10.08.1987
Fungi II	Allergopharma GmbH & Co. KG	372a/87	10.08.1987
Pullularia pullulans	Allergopharma GmbH & Co. KG	364a/87	10.08.1987
Rhizopus nigricans	Allergopharma GmbH & Co. KG	365a/87	10.08.1987
Serpula lacrymans (Merulius lacrymans)	Allergopharma GmbH & Co. KG	367a/87	10.08.1987
Intracutaneous tests: House dust mites and storage mites			
Description	**Marketing authorisation holder**	**License number**	**License date**
Acarus siro	Allergopharma GmbH & Co. KG	66a/91a	17.01.1992
Dermatophagoides farinae	Allergopharma GmbH & Co. KG	467a/87	15.02.1988
Dermatophagoides pteronyssinus	Allergopharma GmbH & Co. KG	466a/87	20.01.1988
Lepidoglyphus destructor	Allergopharma GmbH & Co. KG	67a/91a	17.01.1992
Tyrophagus putrescentiae	Allergopharma GmbH & Co. KG	68a/91a	17.01.1992
Intracutaneous tests: Animal epithelia/dander			
Description	**Marketing authorisation holder**	**License number**	**License date**
Hamster epithelium	Allergopharma GmbH & Co. KG	25a/87	19.03.1987
Dog epithelium	Allergopharma GmbH & Co. KG	27a/87	19.03.1987
Cat epithelium	Allergopharma GmbH & Co. KG	389a/86	17.03.1987
Horse epithelium	Allergopharma GmbH & Co. KG	32a/87	19.03.1987
Cow epithelium	Allergopharma GmbH & Co. KG	34a/87	19.03.1987

**Products for intracutaneous testing, with valid marketing authorisation in Germany as of 31st January 2015 according to the Paul-Ehrlich Institute (PEI; www.PEI.de). The table does not provide information as to whether the products were also commercially available. The information provided in the relevant product license is legally binding. Official publications of the PEI appear in the Bundesanzeiger (Federal Gazette); the most recent publication is Federal Gazette publication No. 402 of 08.10.2014 (source, BAnz AT 21.01.2015 B5). According to recent personal information from another company, marketing authorizations for their intracutaneous test allergens are already existing and will be published at www.pei.de after the print of this article.*

high turnover of test allergens at a reasonable price.

The authors believe that the current problem can only be addressed by including diagnostic allergens (test solutions for skin prick, intracutaneous and provocation testing, as well as patch test materials) in regional medical supplies agreements in Germany. Medical supplies refer to the basic supplies of a medical practice in terms of medicinal products and surgical dressings, as well as medical devices and other items. The prerequisite for medical supplies is that they are required not for only one patient, but for several patients. Test allergens fulfill this prerequisite.

In this way, the funding of diagnostic allergens would be guaranteed. This decoupling of costs from the physician's fee (from the physician fee schedule) would permit the physician to perform a thorough diagnosis based purely on a consideration of the patient's well-being and without economic constraints.

The situation for skin prick test allergens is less dramatic: all large allergen manufacturers will continue to offer skin prick test allergens, although here again, the available range is becoming increasingly limited.

Objectives

The goal of this work is to disseminate current knowledge on the possible changes to in vivo diagnosis as a result of developments in European legislation on diagnostic allergens, including:

- The indications for and performance of diagnostic allergen applications to skin and mucosa
- Information on the current legal requirements for diagnostic allergens

- The impact on patients and allergists of the current European legislation on skin test allergens
- Potential solutions for keeping intracutaneous test allergens available for routine diagnosis in the context of German healthcare.

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Comment

In consultation with the authors, this article will be published simultaneously in the Allergo Journal International and in the journal Allergologie.

Acknowledgement

The authors thank S. Vieths, S. Kaul und A. Bonertz, Paul-Ehrlich-Institut, Langen for valuable information and committed and straight forward discussions.

Conflict of interest

The authors state that there are no conflicts of interest.

Cite this as

Klimek L, Werfel T, Vogelberg C, Jung K. Authorised allergen products for intracutaneous testing may no longer be available in Germany. Allergy textbooks have to be re-written. Allergo J Int 2015;24:84–93
DOI: 10.1007/s40629-015-0051-7

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