

Clinical Letter

Limited availability of diagnostic allergens for patch testing compromises patient care

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Apart from a patient's history, patch testing is the gold standard in the diagnosis of delayed-type hypersensitivities (type IV allergies according to Coombs and Gell) [1, 2]. Taking a detailed allergy history – followed by a clinical exam – yields a suspected diagnosis upon which diagnostic tests and the selection of individually required patch test series are based [1–3]. Patch testing is usually diagnostically conclusive and marked by low complication rates [1, 2].

With a one-year prevalence of 7 % (federal health survey in the year 2000), clinically manifest contact allergies are common among the German population, and require adequate diagnostic work-up [4].

For the vast majority of type IV hypersensitivities – unlike immediate-type allergies – there are no equivalent in vitro diagnostic tests and no specific immunotherapies allowing for a causal treatment approach [5–7]. Thus, identification and avoidance of the causative contact allergen is key with regard to successful treatment of contact allergies.

Since the implementation of the 12th amendment of the Medicinal Products Act (AMG) in 2004, allergen-containing preparations have been classified as medicinal products under Section 4, Sub-section 5 of the AMG. This applies to therapeutic as well as diagnostic allergens. Basis for this change in national law was EU Directive 2001/83/EC [8]. As medicinal products, diagnostic test allergens (substances for patch testing, prick testing, intracutaneous tests, and provocation tests) and therapeutic allergens (solutions used in specific immunotherapy for the treatment of immediate-type allergies) are subject to the same complex approval requirements – according to Clinical Trials Directive 2001/20/EC and the Clinical Trials Regulation [9] – as any other pharmaceutical agent.

Ever since the 12th amendment of the AMG went into effect, there have been substantial obstacles to conducting clinical patch test studies. This applies both to clinical approval studies for new patch test substances as well as epidemiological studies with potential allergens to determine the frequency of sensitization to novel allergens, resulting in an ever-increasing diagnostic gap [8].

By voluntarily waiving the marketing authorization for all 267 Almirall-Hermal patch test substances by their present owner, SmartPractice Europe, at the end of September 2015, this situation has been further aggravated (Table 1).

Now and for the foreseeable future, there is no equivalent replacement for 33 diagnostic patch test allergens (Table 1). For various periods of time, test allergens for these 33 contact allergen preparations have no longer been commercially available, and dossiers for monographic approval or renewal of approval have not been submitted to the Paul Ehrlich Institute, the licensing agency for these diagnostic agents.

Currently, only 82 patch test substances are still approved in Germany (test allergens by Brial, which are marketed by SmartPractice Europe following a company merger); other test allergens are also commercially available, as monographic dossiers for their approval under old regulatory requirements (submitted before the end of the transitional period in 2005) are still being processed by the licensing agency. However, given falling sales figures, it is currently unforeseeable whether the company will actually follow through with the approval process.

The waiver of marketing authorization has resulted in a considerable loss of approved patch test substances, which, for other reasons, was already imminent in 2011 (planned amendment to the Regulation on the Manufacture of Medicinal Products and Active Ingredients [AMWHV] Section 1, Sub-section 3, Clause 4, which would have required GMP requirements even in the manufacture of raw materials used in patch test allergens). With the best possible patient care in mind, this amendment was – at the last minute – averted on scientific grounds by the intervention of various allergy societies [7, 10].

The problem arising from the progressive loss of test allergens due to legal requirements affects patch testing, prick testing, intracutaneous tests, and provocation tests.

For manufacturers, the increased expense only pays off if sales figures of test allergens are adequate and prices are sufficiently high, which in turn is an undue financial burden on our colleagues working in an office-based setting. As of January 1, 2016, the price of Vaseline-based and aqueous patch test substances in 5 ml-syringes ranges from € 9 to € 18 per test substance, depending on the contact allergen. The provision of individually required, history-based test series [3] is not covered by statutory health insurance companies.

Moreover, patch testing, which requires considerable resources and personnel (2–3 readings (after 2, 3, and 7 days) following application of the test substances for 48 hours) has – since 2004 – been included in the fixed regular fee physicians are able to charge for patients covered by statutory health insurance; it is not reimbursed on a fee-for-service basis.

Under these conditions, necessary, history-based patch testing – covering the required diagnostic spectrum – can largely only be provided by specialized centers with a large

Table 1 Loss of approved patch test allergens compromises patient care: current ramifications resulting from the waiver of marketing authorization for all Almirall-Hermal patch test allergens (at the end of September 2015).

Number	Lack of availability of patch test allergens	Examples
11	previously approved patch test substances have <i>no longer been available</i> (neither approved nor commercially available) in Germany since December 4, 2015.	▶ Fragrances: majantol (5 % in Vaseline) ▶ Formaldehyde releaser: diazolidinyl urea (2 % Vas.) ▶ Occupational allergen: p-tert. butylphenylglycidyl ether (0.25 % Vas.)
11 other	patch test substances previously approved and available in Germany have <i>no longer been available in the evidence-based test concentration recommended by DKG</i> (neither approved nor commercially available) since Dec 4, 2015.	▶ Rubber accelerator: mercaptobenzothiazole (2 % Vas.) ▶ Preservatives: (MDBGN) dibromodicyanobutane (0.2 % Vas.) ▶ Sodium benzoate (5 % Vas.)
11 other	Patch test substances previously approved and available in Germany are currently still being sold (as long as <i>supplies</i> produced prior to waiving approval <i>last</i>) and <i>will then no longer be available</i> (neither approved nor commercially available)	▶ Fragrances: linalool (stabilized) (10 % Vas.) ▶ Lily aldehyde (10 % Vas.) ▶ Essential oils: ylang-ylang I + II (10 % Vas.) ▶ Jasmin absolute (5 % Vas.) ▶ Sandalwood oil (10 % Vas.) ▶ Occupational substances: trimethylhexane-1,6-diamine (isomer mixture) (0.5 % Vas.) ▶ Abietic acid (10 % Vas.) ▶ Preservatives: methylisothiazolinone (0.05 % in water), which is used both in cosmetics and in the industrial realm. Due to a drastic increase in the frequency of sensitization, methylisothiazolinone (MI) 0.05 % in water has been included in the DKG standard series, in addition to the MCI/MI mixture [7], since Jan 1, 2014: about two-thirds of MI-positive individuals are also positive on patch testing when using the MCI/MI mixture, whereas one-third of individuals sensitized to MI remain unidentified when tested merely using the MCI/MI mixture [7].

percentage of occupational dermatology patients or those with private insurance [11]. Here, patch testing is covered on a fee-for-service basis according to UV-GOÄ (reimbursement schedule for occupational diseases) or GOÄ (reimbursement schedule for patients covered by private (non-statutory) health insurance), thereby subsidizing patch tests not reimbursed by statutory health insurance companies.

The progressive concentration at few specialized centers that conduct such history-based, individual patch testing, including exposure-related allergens beyond the standard series, is reflected in the manufacturers' sales figures for patch test substances, which have been falling for years. This further drives the vicious cycle, and reinforces the lack of willingness on the part of allergen manufacturers

- ▶ to seek marketing authorization for diagnostic patch test agents for novel contact allergens under current AMG requirements and
- ▶ to maintain existing marketing authorizations, accepting the associated obligations regarding pharmacovigilance.

Such limited availability of diagnostic patch test allergens compromises patient care and the successful treatment of manifest contact allergies.

With the best possible patient care in mind, the authors therefore believe that this problem has to be solved. However, this is only possible if statutory health insurance companies are obliged to cover the expenses arising from the provision of test allergens. This would ensure comprehensive, adequate patient care, and avert further restrictions in the availability of diagnostic patch test allergens.

Conflict of interest

Vera Mahler has received lecturing fees from Almirall-Hermal and SmartPractice Germany. Axel Schnuch, Andrea Bauer, Thomas Werfel, Klaus Strömer, Alexander Enk, Thomas Bieber, Ludger Klimek declare no COI.

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On behalf of the German dermatology and allergy societies:

- (1) German Contact Allergy Group (DKG)
- (2) Information Network of Departments of Dermatology (IVDK)
- (3) Work Group Occupational and Environmental Dermatology (ABD)
- (4) German Society of Allergology and Clinical Immunology (DGAKI)
- (5) Professional Association of German Dermatologists (BVDD)
- (6) German Society of Dermatology (DDG)
- (7) Professional Association of German Allergists (AeDA)

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