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Diagnostic gap due to missing patch test allergens—status quo and possible scenarios for mitigation

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Summary According to European Directive 2001/83/EC, test and therapeutic allergens are medicinal products in all Member States of the European Union. This applies equally to prick test and to patch test (PT) allergens (haptens). All test allergens commercially marketed in Germany are finished medicinal products requiring marketing authorization (MA). Currently, 211 PT substances are authorized in Germany, and an additional 59 are in an ongoing MA process and are marketable under a transitional provision until a decision on MA is made. The regulatory guidance (CMDh/399/2019) of the Co-ordination Group for Mutual Recognition and Decentralized Procedures—Human (CMDh), published in July 2020, specifies the regulatory requirements for different allergen products. Due to differences in origin and exposure, use, mode of action, and safety risks, the guideline clearly differentiates between products with active ingredients of biological origin (allergen extracts from natural source materials) and products with active ingredients of non-biological origin (hapten-based PT substances). Currently, guideline-compliant patch testing is hampered by the lack of numerous commercial PT allergens from the standard and special test series. Background and possible scenarios for mitigation are presented here.

Keywords Well-established use · Mixed marketing application · Supply chain · Testing of patient-owned substances · Pharmacy manufacturing · Single drug importation

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Abbreviations

AIT	Allergen immunotherapy
AMG	German Medicinal Products Act (*Arzneimittelgesetz*)
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures—Human
DDG	German Dermatological Society
DGUV	German Social Accident Insurance
DKG	German Contact Dermatitis Research Group
EMA	European Medicines Agency
EU	European Union
GMP	Good manufacturing practice
MRP	Mutual recognition procedure
PEI	Paul-Ehrlich-Institut
PR	Positivity ratio
RI	Reaction index

Background

The epicutaneous patch test is the diagnostic standard for the detection or exclusion of delayed-type sensitization in cases of suspected contact dermatitis. The selection of allergens to be tested is generally based on the patient's medical history and identified exposures [1, 2]. Test recommendations for specific work-related exposures in particular high-risk occupations have been published [2]. Regardless of the selection of test allergens based on the patient's medical history, testing of the "baseline series" is recommended [1]. In addition to the baseline series and special series based on the patient's medical history, it may be necessary to test products or substances that are not commercially available as test preparations, but which the patient has used and brought along for testing (patient's own material; [1]).

The composition of the specified test series (https://dkg.ivdk.org/testreihen.html) is regularly updated by the German Contact Dermatitis Research Group (DKG) on the basis of new findings on exposure and availability of contact allergens [2]. At the present time, however, guideline-compliant patch testing is hampered by the lack of numerous commercial patch test allergens from the baseline series and the special (test) series. Background information and possible scenarios for mitigation are presented here.

Availability of commercial patch test substances

According to the S3 guideline on epicutaneous patch testing with contact allergens and drugs [1], it is recommended—if available—to use **Galenically** tested allergen preparations that have been authorized as medicinal products or are marketable. Currently, 211 commercial patch test substances are authorized in Germany (https://www.pei.de/EN/medicinal-products/allergens/epicutaneous-test/epicutaneous-test-node.html; last accessed on 29.10.2023); a further 59 patch test allergens are currently in an ongoing marketing authorization (MA) procedure and are marketable according to Section 141 (4) of the German Medicinal Products Act (AMG) until the decision on MA is made ([3]; https://www.pei.de/EN/medicinal-products/allergens/test-marketable/marketable-node.html; last accessed on 10.9.2023). However, these current lists, which are available on the website of the Paul-Ehrlich-Institut, do not allow any conclusions to be drawn about the actual availability of the products. To date, there is only one pharmaceutical manufacturer distributing authorized or marketable patch test substances on the German market; which test allergens are currently available from the manufacturer can be found on the website of the allergen manufacturer under "Information from the management on the status of delivery residues. Current availability of test substances Germany" (https://www.smartpracticeeurope.com/spegerman/pdfs/Verf%C3%BCgbarkeit%20Testsubstanzen%20Deutschland-en-us.pdf; last accessed: 29.10.2023). According to the manufacturer, current backlogs of authorized or marketable patch test allergens are due to interrupted supply chains in the procurement of raw materials for the active ingredients.

A second supplier of patch test substances based in Sweden is subject to supervision by the Swedish Medicines Agency. Under the authority's jurisdiction, the company's products can be dispensed to individual pharmacists in Sweden as unauthorized (non-licensed) medicinal products based on individual exceptional permission from the authority for 1 year. This exemption does not include distribution abroad. According to the Swedish company, mail order sales to Germany have been suspended from 18 October 2023 until further notice.

New contact allergens are generally not detected by testing with commercial test series and are initially detected in the testing of patient-owned substances [1]. If the clinical significance and prevalence of a new contact allergen becomes apparent, an MA application for a novel commercial patch test substance may be of interest in order to close the diagnostic gap (see below).

Legal basis of patch test allergens

According to the valid definition of the European Directive 2001/83/EC [4], both test and therapy allergens are medicinal products in all member states of the European Union (EU). This applies equally to prick test allergens and patch test allergens (haptens). All test allergens sold commercially in Germany are finished medicinal products requiring MA. According to Article 6 of the aforementioned Directive, a medicinal product may only be placed on the market in an EU Member State if the competent authority of that Member State has granted MA or if MA has been granted by the European Commission for all EU Member States in accordance with Regulation (EC) No. 726/2004 [5, 6]. In Germany, the requirements of Directive 2001/83/EC have been fully implemented in the AMG. Test allergens that are commercially available abroad—with or without national authorization—are generally not marketable in Germany unless they are authorized in Germany. Importing such test substances from third countries without an import permit or placing them on the market in Germany without MA is a criminal offence under the German Medicines Act; reference is made to potential exceptions under Section 73 (3) (see below; [6]). In Germany, the approval and monitoring of the import and placing on the market of medicinal products are within the responsibility of the federal state authorities (*Länderbehörden*).

The regulatory guideline (CMDh/399/2019) published by the CMDh in July 2020 sets out the regulatory requirements for different test and therapy allergens [7]. Due to their different origin and exposure, application, mode of action, and safety risks, the guideline makes a clear distinction between products with active substances of biological origin (allergen extracts from natural starting materials) that are used for allergen immunotherapy (AIT) or for the in vivo diagnosis of type I (IgE)-mediated allergic diseases (e.g., in prick tests or nasal provocation tests) and products intended for the diagnosis of cell-mediated type IV allergies (hapten-based epicutaneous patch test substances; [7, 8]). For the latter, legal bases may be used applying simplified MA application routes without provision of manufacturer's own clinical studies or with manufacturer's limited studies [7].

Simplified marketing authorization routes for new patch test allergens

The requirements for an MA dossier can be found in Annex I of Directive 2001/83/EC as amended [4]: While for commonly used allergen products with active substances of biological origin, a full MA application (with the complete modules 1–5, including manufacturers' own clinical studies) according to Article 8 (3) of Directive 2001/83/EC is usually required, for patch test substances, authorization routes based on other legal bases (Article 10a ["well-established use"] or Article 8 (3) in conjunction with Annex I Part II Section 7 ["mixed marketing application"] of Directive 2001/83/EC) can be used [7, 8]. Each respective legal basis is associated with specific data requirements. It is up to the applicant to decide which legal basis is chosen for the MA application. It is recommended to seek scientific advice from the competent authority (in Germany: Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines) prior to submitting a MA application.

"Well-established use" application (Article 10a of Directive 2001/83/EC)

As patch test allergens are non-biological medicinal products, the application for authorization according to Article 10a can be applied under the following conditions: Provided that the applicant can demonstrate that the active substance has already been in medicinal use in the EU for at least 10 years without a regular MA having been granted and that it has a recognized efficacy and an acceptable level of safety, the applicant is not required to submit preclinical and clinical trial results. The results of these trials are replaced by relevant scientific documentation, i.e., preclinical and clinical information contained in the application may consist solely of bibliographic data. In these cases, the MA is based on the well-established general medicinal use in the EU (according to the requirements in Annex I Part II Section 1 of Directive 2001/83/EC). This requires evidence that the active substance(s) of a medicinal product for the claimed therapeutic indication(s) has/have been in well-established medicinal use in the EU for at least 10 years and has/have a recognized efficacy and an acceptable level of safety. Data should be provided to demonstrate that the cited literature submitted to prove the safety and efficacy of the active substance(s) is relevant to the allergen product in the marketing application [7, 8]. All patch test allergens authorized in Germany have been authorized under the conditions of "well-established use" according to Article 10a of Directive 2001/83/EC. If the bibliographic data are not sufficient or the duration of use of the active substance of 10 years is not completed to support an application for authorization and additional (non-) clinical data are required, the application should follow a "mixed marketing application" according to Article 8 (3) in conjunction with Annex I Part II Section 7 of Directive 2001/83/EC [7].

"Mixed marketing application" (Article 8 (3) in conjunction with Section 7 of Part II of Annex I to Directive 2001/83/EC)

For the authorization of patch test allergens, it may be difficult to recruit a sufficient number of relevantly diseased study participants to obtain clinical data that meet the requirements of the current guideline on clinical evaluation of diagnostic products (CPMP/EWP/1119/98/Rev. 1; [9]). According to Annex I, Part II, Section 7 of Directive 2001/83/EC, it may be acceptable in such cases for Modules 4 and/or 5 in the MA application to consist of a combination of reports on a limited number of non-clinical and/or clinical studies conducted by the applicant and bibliographical references. It is necessary to justify in a comprehensible manner that the submitted bibliographic data are relevant to the patch test substance in the MA application [7, 8].

A specific scientific guideline for rare or less common allergies (where only a few patients with the allergy in question are available for clinical trials) is currently being developed by the Committee for Medicinal Products for Human Use (CHMP), the committee of the European Medicines Agency responsible for preparing the Agency's opinions on all issues relating to medicinal products for human use (based on the corresponding concept paper [10]).

This new guideline will be applicable to all allergens/haptens not listed in Annex I of the CMDh guideline (CMDh/399/2019; [7] for which a full application for authorization is required under Article 8(3) of Directive 2001/83/EC (Table 1)).

This second guideline, which is currently (as of 11.09.2023) in the consensus process in the various Working Parties of the European Medicines Agency (EMA), reflects in particular the existing regulatory consensus within the EU Member States on specific quality and clinical requirements for patch test allergens. This concerns, for example, criteria for patient selection and the clinical development of epicutaneous test substances. Due to the lack of an objective external criterion or comparator, which prevents the determination of sensitivity and specificity, the guideline on clinical evaluation of diagnostics (CPMP/EWP/1119/98/Rev. 1; [9]) is often not applicable for the investigation of new patch test substances regardless of the size of the patient population. Therefore, other parameters such as the positivity ratio (PR; [11]) and the reaction index (RI; [12]) of the patch test preparations should be reported as alternative endpoints. High-quality registry data can be used. Data on the frequency of sensitization to the substance should always be provided. It should be acknowledged that starting materials of the active substance do not meet the standards of good manufacturing

Table 1 Allergen sources for allergens subject to authorization

An application for marketing authorization and the provision of complete documentation (with the complete modules 1–5, including the applicant's own clinical studies) in accordance with Article 8 (3) of Directive 2001/83/EC is considered mandatory for products containing allergens from the following allergen sources and intended for allergen immunotherapy or in vivo allergen diagnosis:
Pollen of the group of sweet grasses from the family Poaceae (Gramineae), subfamily Pooideae
Pollen of the birch group
Pollen of the Oleaceae group
Pollen of the Cupressaceae group
Pollen from *Ambrosia artemisiifolia* and *Ambrosia trifida*
Pollen of *Parietaria judaica* and *Parietaria officinalis*
The group of house dust mites of the genus Dermatophagoides
Bee and wasp venom
Felis domesticus (cat)
Arachis hypogaea (peanut)
Prunus persica (peach)
According to Annex I to the CMDh guideline "Recommendations on common regulatory approaches for allergen products" (CMDh/399/2019; [7]), authorization according to Article 8 (3) of Directive 2001/83/EC is considered mandatory for diagnostic and therapeutic allergen products containing the common allergen sources listed in Table 1. This is not the case for epicutaneous test allergens.

practice (GMP), as they are usually manufactured for use in other areas (e.g., hair dyes, cosmetics; i.e., they are "atypical active substances" that originate from the chemical industry outside the pharmaceutical legislation). Therefore, the corresponding GMP requirements only apply as soon as the starting material is introduced into the manufacturing process of the medicinal product. If the new guideline is intended to be used for the authorization of a patch test substance, the applicant should provide sound justification that a deviation from the current guidelines for diagnostic products (CPMP/EWP/1119/98/Rev. 1; [9]) is appropriate due to the smaller target population based on epidemiological data from the EU (e.g., presence of the contact allergen in the environment, frequency of sensitization, prevalence of clinical disease). By justified omission of Phase II and III studies, and taking into account the MA requirements outlined in the respective guideline, market access for new commercial patch test substances in the Member States and also the application for mutual recognition procedures (MRP) will be facilitated.

The availability of test allergens, even from less common allergen sources, is of public interest from the point of view of the Paul-Ehrlich-Institut. High quality and standardization of test allergens are essential for the diagnostic performance of test allergens [13–15]. Both the maintenance of existing MAs as well as novel MAs for in vivo diagnostics for type I and type IV allergies are necessary [15]. With regard to the preservation or withdrawal of MA of test allergens for the detection of less common allergen sources, allergen manufacturers mainly state economic aspects (low demand, manufacturing costs, fees charged by national authorities and the EMA). In order to keep rare test allergens available on the German market, since 2018 the Paul-Ehrlich-Institut, with the approval of the Federal Ministry of Health, grants a fee reduction to one quarter for all official acts (e.g., scientific advice, new MA, official batch release testing, and the processing of variations) for rare test allergens upon application by the manufacturer [6].

Potential measures to mitigate the diagnostic gap for existing supply backlogs of commercial patch test substances

Accelerating the re-availability of authorized patch test substances in the event of interrupted supply chains

With regard to temporary supply backlogs of patch test substances authorized or marketable in Germany as a result of interrupted supply chains for the provision of starting materials for the active substance, it may be necessary to change the supplier. This is a type II variation[1] requiring approval, which must be communicated to and approved by the regulatory authority; for this purpose, the manufacturer must prove that the new starting material used is comparable to the starting material used within the scope of the approval. This is necessary as the diagnostic performance of the patch test substance may be completely different if the new starting material is not comparable. The Paul-Ehrlich-Institut has prioritized personnel resources for the rapid processing of incoming variations in connection with patch test substances. On the manufacturer side, consideration is being given to qualifying several suppliers of raw materials in parallel in order to be prepared for future supply chain disruptions.

Testing of the patient's own material

The testing of the patient's own material in a suitable test concentration contributes significantly to reducing the existing diagnostic gap in the case of temporarily unavailable commercial patch test substances and in the case of special exposures—especially in the investigation of workplace-related contact allergies. According to the exemption provision in Section 13 (2b) AMG, treating physicians are authorized to manufacture a medicinal product "for the purpose of personal use in a specific patient" without an MA under pharmaceutical law [16]. For patch testing of patient-owned substances, it is necessary to gain an overview of the product composition by reviewing safety data

[1] Variations that may have a significant impact on the quality, safety or efficacy of the medicinal product must be classified as a type II variation and must be submitted to the competent authority for approval.

sheets, master formulations, and other available information [17, 18]. Consultation of reference works is usually necessary to determine the appropriate test concentration of patient-owned substances (e.g., [17–19]). If possible, individual components of the patient's own products should be tested separately and the pH value (suitable for testing: pH 4–9) should be checked and adjusted [17]. The test concentration of an individual contact allergen in a finished product should not exceed the recommended test concentration for this allergen. However, a negative test result does not reliably rule out a contact allergy to the components contained therein [17]. The use of patch test substances produced from the patient's own material requires—as with the testing of commercial test substances—informed consent from the patient. Additionally, it is subject to Section 67 AMG (general obligation to notify), i.e., the one-time obligation *to notify* the responsible good clinical practice (GCP) inspectorates of the federal states of testing patients' own materials; there is *no obligation to obtain approval* [16]; https://dkg.ivdk.org/dok/InformationenParagraph_67_AMG.doc; last accessed 11.09.2023).

Preparation of epicutaneous test substances by public pharmacies

The manufacture of test substances as prescription medicinal products by a public pharmacy without authorization is permitted without MA pursuant to Section 13 (2) no. 1 in conjunction with Section 13 (2a), Sentence 2 no. 3 AMG within the scope of normal pharmacy operations [6]. However, it should be noted in this regard that, according to the experience gained from the research project 317a ("Quality control of the diagnostics for occupational type I allergies") funded by the German Social Accident Insurance (DGUV), the production of test allergens for the detection of type I and type IV allergies is not established in everyday pharmacy practice, the procurement of starting materials can be a challenge, and only a small number of pharmacies will potentially be available for this purpose. An "ad hoc working group on patch testing" of the German Dermatological Society (DDG), which was set up by the DDG Presidium in June 2023 in view of the reduced availability of commercial contact allergens for patch testing, is currently exploring these and other options to improve the supply situation.

Single import in derogation from the prohibition of introduction

In order to temporarily avoid supply bottlenecks, Section 73 (3) AMG[2] could be applied as an option for individual imports for the treatment of individual patients.

The exception (regulated in Section 73 (3) AMG) to the prohibition of the introduction of medicinal products set out in Section 73 (1) Sentence 1 AMG presupposes that the finished medicinal products may be lawfully marketed in the country from which they are brought to Germany. In the case of doubt, the importing pharmacists must ensure that the individually imported medicinal product that they are placing on the market is also marketable as a medicinal product in the exporting country (see [20]).

As the questions regarding the potential applicability and possible implementation practice of this exemption do not fall within the area of responsibility of the Paul-Ehrlich-Institut, but are in the responsibility of the federal states, a clinic interested in this should contact the responsible federal state authority (*Länderbehörde*; https://www.zlg.de/arzneimittel/deutschland/laenderbehoerden).

[2] (3) By way of derogation from subsection (1) sentence 1, finished medicinal products are not authorised for marketing or registered for trade within the purview of this Act or that are not exempted from the obligation to obtain a marketing authorisation or registration, may be introduced into the purview of this Act:.

1. if they are ordered by pharmacies on the basis of an order received from individual persons in a small quantity and are dispensed by these pharmacies within the framework of the existing pharmacy operating licence,.

2. if they may be legally placed on the market in the State from which they are introduced into the purview of this Act, **and**

3. if no medicinal product for the therapeutic indication in question, which is identical in terms of the active substance and comparable in terms of the strength, is available within the purview of the Act,.

or if they are ordered in the appropriate quantity needed to ensure the proper treatment of the hospital's patients, for the purpose of temporarily stocking a hospital pharmacy or a hospital supply pharmacy, under the prerequisites contained in no. 2, and dispensed by this hospital pharmacy or hospital supply pharmacy under the prerequisites contained in no. 3 within the framework of the existing pharmacy operating licence, for the purpose of administration to a patient of said hospital, under the direct personal responsibility of a physician, or if they are to be held in stock for emergencies pursuant to the provisions of the legislation on pharmacies or the requirements of occupational accident insurance, or within the sphere of responsibility of the Federal Ministry of Defence, or must be procured at short notice if, within the purview of this Act, medicinal products for the therapeutic indication are not available. Ordering pursuant to sentence 1 no. 1 and dispensing pursuant to sentence 1 of medicinal products introduced into the territory governed by this Act from a country that is not a Member State of the European Union or other States Parties to the Agreement on the European Economic Area require a prescription from a physician or dentist. Further details are settled by the Ordinance on the Operation of Pharmacies.

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Declarations

Conflict of interest V. Mahler declares that she has no competing interests.

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