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GUIDELINES

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Severely compromised supply of patch test allergens in Europe hampers adequate diagnosis of occupational and non-occupational contact allergy. A European Society of Contact Dermatitis (ESCD), European Academy of Allergy and Clinical Immunology (EAACI), European Academy of Dermatology and Venereology (EADV) task forces 'Contact Dermatitis' and 'Occupational Skin Disease' position paper

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Abstract

Patch testing is the only clinically applicable diagnostic method for Type IV allergy. The availability of Type IV patch test (PT) allergens in Europe, however, is currently scarce. This severely compromises adequate diagnostics of contact allergy, leading to serious consequences for the affected patients. Against this background, the European Society of Contact Dermatitis (ESCD) has created a task force (TF) (i) to explore the current availability of PT substances in different member states, (ii) to highlight some of the unique characteristics of Type IV vs. other allergens and (iii) to

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suggest ways forward to promote and ensure availability of high-quality patch testing substances for the diagnosis of Type IV allergies throughout Europe. The suggestions of the TF on how to improve the availability of PT allergens are supported by the ESCD, the European Academy of Allergy and Clinical Immunology, and the European Academy of Dermatology and Venereology and intend to provide potential means to resolve the present medical crisis.

KEYWORDS
allergen provocation test, European Pharmacopoeia, marketing authorisation, patch test, regulatory framework, skin test allergens, Type IV allergy

1 | INTRODUCTION

Contact allergies (Syn.: Type IV allergies) based on Type IV hypersensitivity reactions according to the definition by Coombs and Gell[1] are caused by haptens (e.g., metals, fragrances, preservatives, constituents of resins or rubber). Other than complete allergens, that is, antigens capable of evoking immunological reactions (e.g., Type I allergens), haptens are small exogenous molecules capable of bonding chemically to autologous proteins. Such protein binding changes the spatial conformation to such an extent that the hapten-protein conjugates can cause contact allergies. Because of the common usage of the term 'allergen' for both full allergens and haptens, the terms 'haptens', 'Type IV allergens' and 'contact allergens' will be used interchangeably in this article. Contact allergies are very frequent, with an estimated 27% of the adult European population being sensitised to one or several of the most common Type IV allergens.[2] They are the underlying cause of common allergic diseases, comprising mainly allergic contact dermatitis, but also photoallergic contact dermatitis, allergic contact stomatitis, allergic contact conjunctivitis, and certain types of immune reactions to implanted medical devices (e.g., endoprostheses, implants, stents), systemic allergic dermatitis,[3,4] and a range of drug eruptions such as maculopapular, eczematous, lichenoid, pustular or fixed drug eruption. Identification of the causative agent is crucial to enable its avoidance and is thus the key to full recovery and prevention of recurrences of the disease. Furthermore, for example, stent failure due to Type IV allergy can lead to life-threatening consequences. Moreover, the collected epidemiological knowledge derived from pooled individual patch test (PT) results of patients is the key instrument for the identification of necessary measures for primary prevention. The PT with diagnostic Type IV allergens is a non-invasive, well-established in vivo method that is the gold standard for diagnosis of contact allergies as no equivalent alternative diagnostic method exists.[5] Its diagnostic value greatly depends on the availability of a broad spectrum of diagnostic Type IV allergens to cover individually relevant haptens from a broad range of occupational and non-occupational exposures. Therefore, the European Society for Contact Dermatitis (ESCD), the European Academy of Allergy and Clinical Immunology (EAACI) and the European Academy of Dermatology and Venereology (EADV) are very concerned about current supply shortages and limitations in the availability of PT substances and is very strongly advocating a pragmatic and expedient regulation of PT diagnostics of Type IV allergens in Europe to allow adequate diagnosis of contact allergies.

In the European Union (EU), allergens for in vivo diagnostics are medicinal products (as first outlined by Council Directive 89/342/EEC[6] and currently by Directive 2001/83/EC[7]). According to Article 1 (2), the second sentence of this Directive, any substance or combination of substances that may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis is defined a medicinal product.

Further, according to Article 1(4)(b) Directive 2001/83/EC,[7] an 'allergen product' is defined as 'any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent'. As Type IV allergens (haptens) are included in this legislation, according to Article 6(1), a marketing authorisation (MA) by the competent authority of that Member State (MS) or in accordance with Regulation (EEC) No 2309/93 is required for placing PT substances for diagnostic testing of Type IV allergy on the market. Facing recently compromised supply chains of raw materials during the pandemic and limited earning opportunities, especially with PT substances containing rarer haptens on the one hand, and simultaneous manufacturing requirements of a drug product and fees of regulatory authorities on the other, manufacturers of diagnostic Type IV allergens have reduced their portfolio of PT preparations and are reluctant to expand it to new emerging or rare contact allergens.

Based on their non-biological atypical drug substances (mostly chemicals that are common and widespread in the industrialised environment, like nickel, natural and synthetic fragrances, resins or textile dyes), specific (simplified) regulatory pathways for MA have already been outlined for PT substances.[8,9] However, these seem to not sufficiently stimulate MA applications (MAA) for PT preparations based on new or less frequent haptens. The shortcomings regarding the availability of PT substances for the diagnosis of Type IV allergens in Europe, if not solved, will lead to a major diagnostic gap for many occupational and non-occupational Type IV allergies. As a consequence, many patients will remain undiagnosed and will be impaired

in their well-being, health, and, in many cases, even in their ability to work.

2 | OBJECTIVES

The ESCD has created a task force (TF)

- to explore the current availability of PT substances in different MS (Table 1);
- to highlight some of the unique characteristics of Type IV allergens compared to other allergens;
- to suggest ways forward to promote and ensure the availability of high-quality PT substances for the diagnosis of Type IV allergies throughout Europe.

3 | BACKGROUND

3.1 | Impact of Type IV allergy and the importance of obtaining a diagnosis

It should be noted that the clinical manifestations of contact allergies normally do not present just as 'small pruritic red skin lesions' (as PT reactions do), but involve the entire anatomic region in contact with the culprit contact allergen(s) (Figure 1). Depending on the individual scope and severity of contact allergies, the patients' quality of life is severely affected, along with impairment of both, social relations and work activities, and consequently, considerable direct and indirect costs of illness arise.[10] Occupational allergic contact dermatitis may result in recurrent sick leave, job loss and, in the worst case, unemployment. In contrast to Type I allergens, experimental approaches of desensitisation with haptens proved not efficient.[11] Therefore, proper diagnosis with identification and subsequent avoidance of the culprit allergen is crucial for successful management and secondary prevention of allergic contact dermatitis.

About 5200 Type IV allergens have already been described.[12] However, new contact allergens and new exposures to known contact allergens are continuously identified due to ever-changing products and product compositions; it is expected that every year, another 5–10 new allergens are detected.[13,14] Our skin is exposed daily to a large amount of common Type IV allergens due to contact with numerous consumer and occupational products. Both adults and children develop contact allergy and allergic contact dermatitis from exposure to chemical substances in their environment, for example, medical devices, consumer products and occupational (chemical) products—some of which are unknown, unexpected and unlabeled.[15] Thus, patch testing leads to the identification of hitherto unidentified contact allergens, not only in adults but also in children (e.g., isobornyl acrylate/IBOA[16,17] and further adhesives in medical devices). Such 'index cases' can provide valuable information on epidemic outbreaks of contact allergy, which, if not contained in a timely manner, would have detrimental health and socioeconomic effects. Patch testing is thus the fundamental basis for the identification of contact allergens not only in individual cases, but also the only means to detect emerging new contact allergy problems. Epidemiological surveillance of contact allergy trends is a proven, valuable basis guiding consumer safety regulation and industry stewardship with regard to manufacturing consumer products which are less sensitizing.

In conclusion, a comprehensive diagnostic work-up based on a broad range of both frequent and rare diagnostic Type IV allergens is essential. Thus, the lack of commercially available PT allergens will make an adequate diagnosis of Type IV allergy almost impossible, with unfavourable consequences for patients, consumers, occupationally exposed individuals, physicians and researchers of EU MS and their entire societies.[15] Undiagnosed contact allergy impacts patients' health and well-being as it might lead to

- recurrent allergic disease manifestation by exposure to one or more unidentified contact allergens;
- potential long-term use of immunosuppressive drugs (with potential adverse side effects);
- disease chronicity;
- lack of fitness for work and substantial socioeconomic implications (considering €5–€8 billion of annual costs due to loss of productivity in industry by occupational contact dermatitis in EU).[18]

Relevant for work-related contact allergies and allergic contact dermatitis, the current EU Strategic Framework on Safety and Health at Work 2021 to 2027[19] defines the key priorities and actions for improving workers' health and safety. The framework addresses rapid

TABLE 1 Regulatory situation of haptens in four exemplary countries (as of 23th of February 2024).

Country	No. of marketing authorisations (MA)	No. of marketable hapten preparations (without MA) under transitional provisions)	No. of hapten preparations as NPPs	No. of haptens on exceptional rule
Germany	205[a]	41	0	0
Italy	6[a]	193	0	234
Poland	2[a]	389	0	0
Sweden	2[a]	0	0	550

Note: All other MAs concern multi-dose containers each of a PT product based on a single hapten or a hapten Mix.
Abbreviation: NPP, named patient product.
[a]Including one MA of a combination product (i.e., a ready to use patch test unit that includes 35 common PT allergens and a negative control).

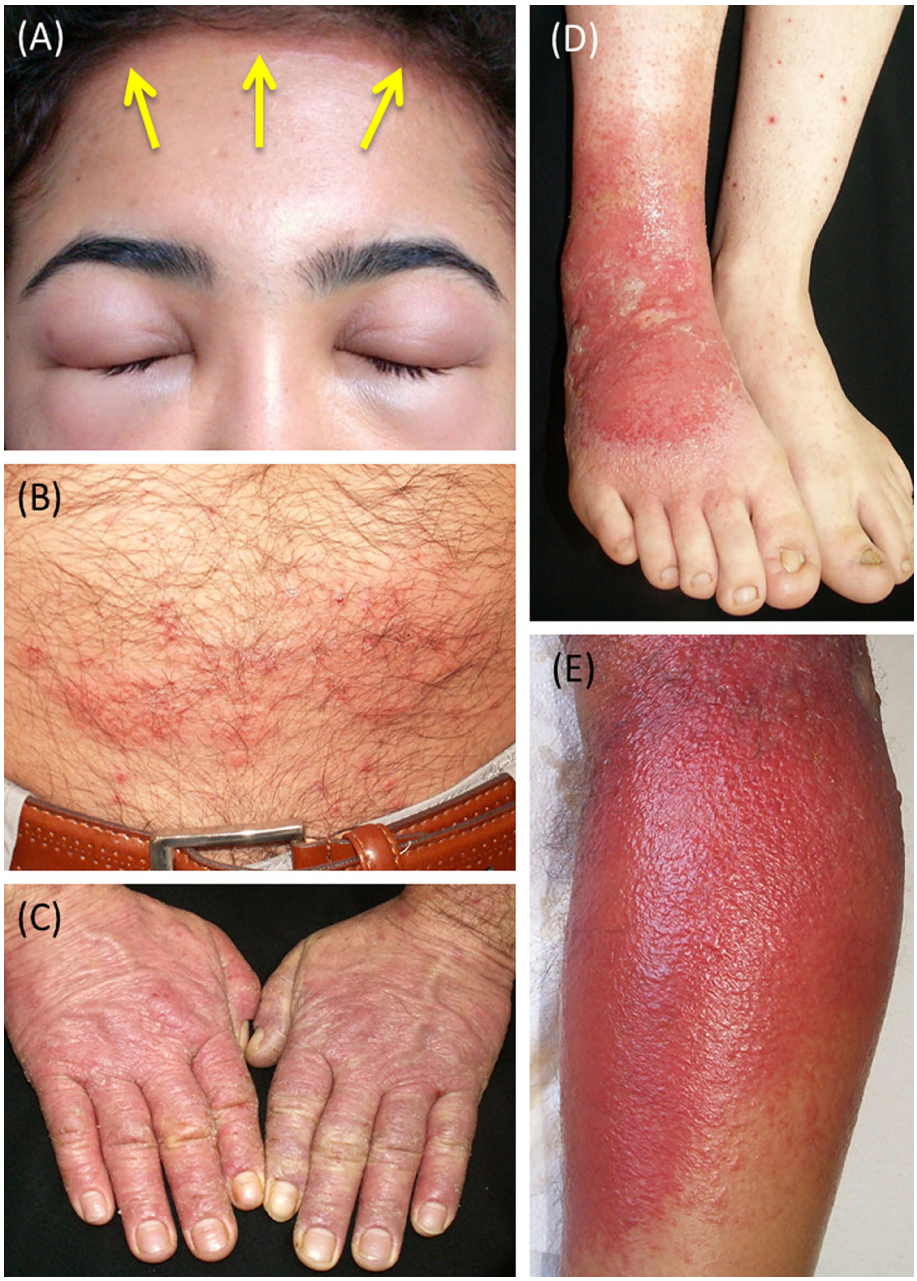

FIGURE 1 Examples of allergic contact dermatitis on (A) the scalp extending beyond the hairline and severe periorbital edema from hair dye. (B) On the abdomen from a metal belt buckle. (C) On the back of the hands of a construction worker due to cement allergens, that is, occupational contact allergens. (D, E) On the foot and leg from topical medicaments.

changes in the economy, demography and work patterns; a conclusive allergological work-up will thus be ever more indispensable to identify allergenic culprits of occupational skin disease. This, in turn, is a prerequisite to reduce health risks at work to protect workers' health and safety. Prevention and treatment of occupational contact dermatitis will fail without the availability of PT allergens characteristic for workplace exposure.

3.2 | The use of test allergens for the diagnosis of Type IV allergy

Test allergens (i.e., PT substances) for the diagnostic of Type IV allergies are standardised chemicals of a defined concentration incorporated in a suitable test vehicle (usually petrolatum or water). During patch testing (Figure 2), the allergen products are placed in small chambers of around 0.5 cm^2 in a standardised dose of ca. 20 mg of the test material and left in place for 2 days.[5] After removal of the applied patches, readings of the PT areas and potentially induced positive test reactions are made according to morphological criteria on Day 3 or Day 4 and preferably Day 7 by visual inspection and palpation. Patch testing is a well-established method in use for 130 years with widely accepted principles of good clinical practice as outlined by the ESCD guidelines.[5]

As Type I and Type IV allergens differ substantially in nature, induced pathomechanism of allergic reactions and medicinal use and risks (Table S1), these differences should be considered in regulation. Key differences to be considered are:

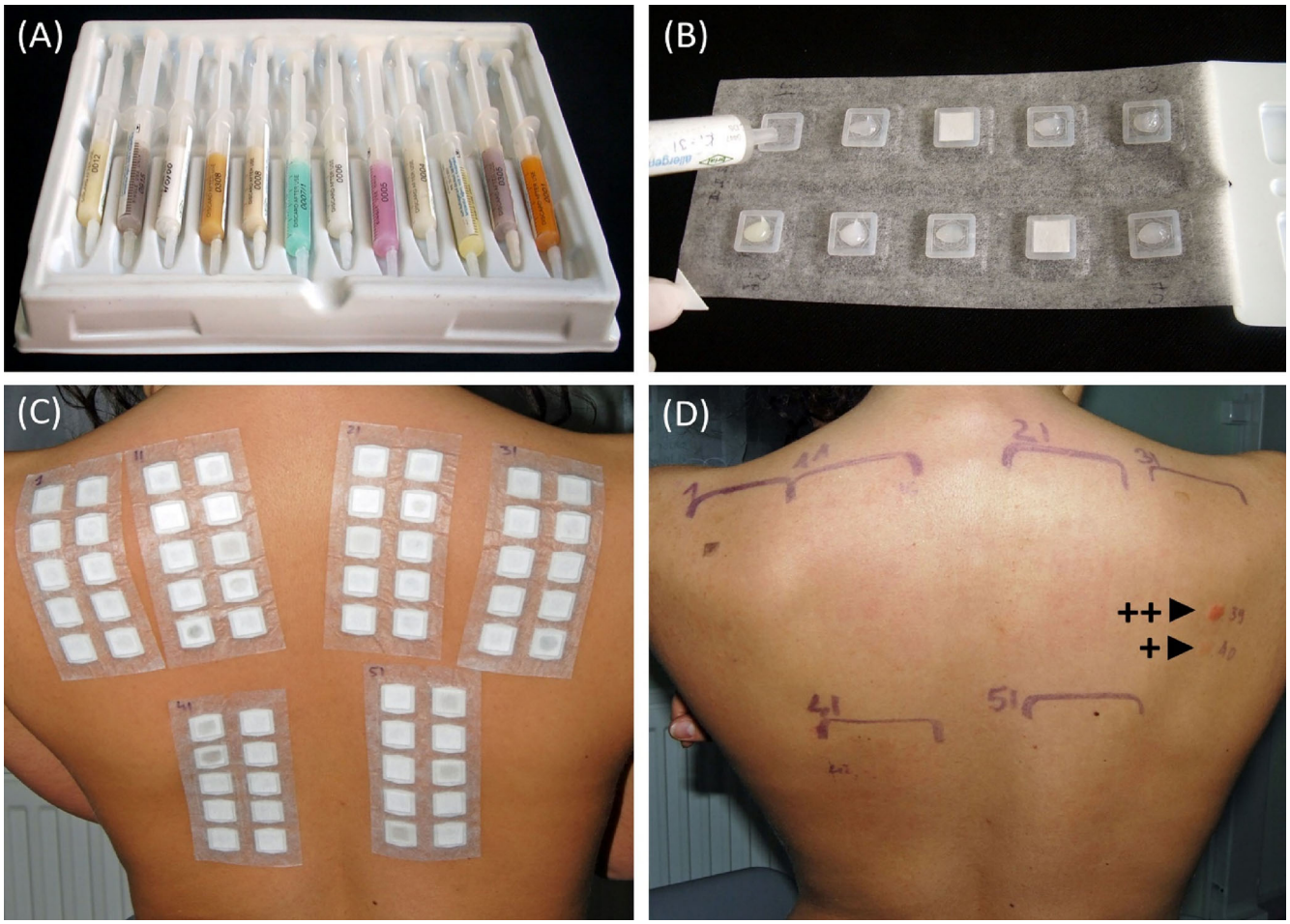

FIGURE 2 The procedure of patch testing. (A) Patch test substances (haptens dispersed in appropriate vehicles) in a tray. (B) Loading patch test chambers with patch test substances of choice. (C) Patch tests mounted on a patient's upper back (the principal patch test area) for 2 days. (D) Patient's back 4 days later with a weak (+) and strong (++) positive patch test reaction to two of the haptens tested. Readings of patch test reactions are performed on Days 2, 3, 4, and 7 according to the European Society of Contact Dermatitis (ESCD) patch test guideline.

TABLE 2 Facts about Type IV allergens and their application in form of patch test preparations.

- Small area of application
- Small total dose
- Topically applied on intact skin
- No risk of general toxicity
- No risk of anaphylaxis for the vast majority of haptens
- Widespread exposure in the environment and everyday life
- Patch testing is the only diagnostic test available for the diagnosis of Type IV allergies
- No validated in vitro tests for routine clinical use exist
- Type IV allergens (haptens) cannot be used for (immuno)therapy

- Type IV allergens are haptens which induce allergic reactions only after interaction with the body's own proteins, whereas Type I allergens (e.g., of pollens, dust mites) are full allergens;
- Type IV allergens in medical use are intended only for diagnosis, whereas Type I allergens are intended for both diagnostic and therapeutic purposes (allergen immunotherapy [AIT]);
- Risks/adverse events related to the medical use of Type I and Type IV allergens differ substantially because of the differences in their biological/chemical nature, their route of administration and exposure, and also because of the nature of the physiological mechanisms involved.
- Type I allergens used as therapy allergens for immunotherapy are applied repetitively (over a period of 3–5 years) and are often administered subcutaneously, whereas Type IV diagnostic allergens are applied on small areas of intact skin, often only once in a lifetime (Table 2). For that reason, the exposure via patch testing is lower in terms of duration, dose and recurrence of use compared to AIT.
- In patch testing, the absorption and systemic effects of the applied haptens are insignificant in most cases. Exposure to Type IV allergens from numerous consumer products in real life usually represents a more significant exposure and may cumulatively entail a much greater risk than their application for 2 days in small amounts during patch testing.

- Furthermore, Type IV allergens (with very few exceptions) do not cause anaphylaxis, and systemic adverse events during patch testing procedures are extremely rare and almost never serious. The safety of the procedure is backed by many scientific papers, which, for example, focus on patch testing in (very young) children[20] or patch testing in severe cutaneous drug eruption.[21]

The experience with patch testing is large enough to affirm that with the current practical guidelines and recommendations of scientific societies safety of patients is ensured. According to good clinical practice, informed consent is always obtained before any patch testing is done.

4 | REGULATORY FRAMEWORK CONDITIONS FOR THE DEVELOPMENT OF ALLERGEN PRODUCTS IN THE EU

In the EU, as defined by Directive 2001/83/EC, both test and therapy allergens are medicinal products (Article 1). Directives must be transferred into national law by all MS. Besides proteinaceous Type I allergens for the treatment and diagnosis of Type I allergies, the definition of medicinal products (according to Article 1) also includes haptens for in vivo diagnostics (PT substances) for diagnosing Type IV allergies. According to Article 6 of this Directive, a medicinal product may not be placed on the market of a MS until a MA has been granted by the competent authority of that MS. For an MA, it must be proven according to the current state of knowledge that the medicinal products are of adequate quality, are effective and safe and there is a positive benefit–risk balance. Exceptions to the above-mentioned MA requirement are possible according to Article 5 of Directive 2001/83/EC: a MS may […] to fulfil special needs, excluded from the provisions of this Directive medicinal products […] formulated in accordance with the specifications of an authorised health-care professional and for use by his individual patients on his direct personal responsibility. This exemption has been applied differently in different MS and led to a heterogenous authorisation status of allergen products (Table 1).

In some MS, the majority of allergen products have historically been distributed according to Article 5 of the Directive 2001/83/EC without a MA as a medicinal product for use by an individual patient (named patient product [NPP]).[9] This in some countries included PT substances, although according to Article 5 of the Directive 2001/83/EC, by definition, the directive is not applicable to multidose diagnostics (e.g., a test allergen preparation in a container used for more than one diagnostic test). The use of non-licensed NPP hampers mutual recognition procedures (MRP), a procedure through which the authorisation of a medicine in one EU MS is recognised by another MS.

Against this background, regulatory and scientific deliberations have aimed to harmonise the regulation of allergen products in Europe,[8,9] briefly summarised here with regard to PT substances. In 2020, in overarching regulatory guideline by the Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh) (CMDh/399/2019, Rev.0) recommendations on common regulatory approaches for allergen products were published that aim to harmonise regulatory approaches within the EU[9] and consequently to simplify mutual recognition of national MA and to increase the availability of allergen products. Only medicinal products for human use intended to be placed on the market in MS that are either prepared industrially or manufactured by a method involving an industrial process are concerned. Based on their different nature of origin and exposure, application, mode of action and safety risks, the CMDh guideline clearly differentiates between products of biological origin (allergen extracts derived from natural source materials) used for AIT, or for in vivo diagnosis of Type I (IgE)-mediated allergic diseases (e.g., skin prick test and nasal provocation test) on the one hand, and products intended for the diagnosis of Type IV cell-mediated allergies (PT substances based on haptens) on the other.[9] The requirements for a MAA dossier can be found in Annex I of Directive 2001/83/EC, as amended. There are different types of applications for MA, each with a specific legal basis (Table 3) which is associated with specific data requirements. The legal basis for the individual MAA is the choice of the applicant. Before submission of a MAA, scientific advice from the competent authority in charge may be requested.

The structure of marketing application dossiers used across Europe, Japan and the United States and beyond follows the Common Technical Document (CTD) standard.[22] The CTD contains five main modules:[23]

TABLE 3 Application types for marketing authorisation, modified from Bonertz et al.[24]

Application type	Legal basis	Characteristics
Full marketing authorisation	Article 8(3) of Directive 2001/83/EC	Full data need to be provided including product-specific data from clinical studies.
Mixed marketing authorisation	Article 8(3) in combination with Annex I Part II Section 7 of Directive 2001/83/EC	Documentation on pre-clinic and clinic consist of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references.
Well-established use	Article 10a of Directive 2001/83/EC	Results of preclinical tests or clinical trials do not need to be provided if the active substance(s) of the medicinal product have been in well-established medicinal use within the EU for at least 10 years. Efficacy and acceptable safety must be evident from appropriate scientific literature.

Abbreviation: EU, European Union.

- Module 1: region-specific administrative information;
- Module 2: overviews and summaries of Modules 3–5;
- Module 3: quality (pharmaceutical information);
- Module 4: non-clinical data (pharmacology/toxicology data);
- Module 5: efficacy data (clinical trials).

For frequent allergen products, as defined in the Annex of CMDh,[9] a full MAA (containing complete Modules 1–5), according to Article 8(3) of Directive 2001/83/EC, is applicable. In contrast, for all other allergen products (e.g., PT substances), alternative MAA approaches can be applied (Table 3)[9,24]:

- Well-established use application according to Article 10a of Directive 2001/83/EC:

This legal basis should typically *not* be applied to therapy allergen products. However, where non-biological drug substances are concerned, as in allergen products for the diagnosis of Type IV allergies, well-established use application under Article 10a can be applied. Where a product has already been in medicinal use in the EU, for at least 10 years without a regular MA, it could be acceptable, in agreement with the National Competent Authority (NCA), that the (non) clinical information present in the MAA only consists of bibliographical data (summarised in Module 2, whereas Modules 4 and 5 remain empty except for the respective list of references). In those cases, the authorisation will be based on well-established medicinal use within the EU (in accordance with the requirements set out in Annex I Part II Section 1 of Directive 2001/83/EC). For this, it needs to be demonstrated that the active substance(s) of a medicinal product in the claimed therapeutic indication(s) has/have been in well-established medicinal use within the Union for at least 10 years, with a recognised efficacy and an acceptable level of safety. Bridging data should be provided to justify that the bibliographical data, presented to support the safety and efficacy of the active substance(s), are relevant for the allergen product in the application. In case the bibliographical data are considered not sufficient to support a MAA and additional (non)clinical data are needed, the application should follow the mixed application according to Article 8(3).

- 'Mixed marketing application' according to Article 8(3) in combination with Annex I Part II Section 7 of Directive 2001/83/EC:

Some medicinal products have specific features, so certain requirements of the MAA dossier (as laid down in Part I of Annex I of Directive 2001/83/EC) need to be adapted. This situation may apply in particular to allergen products used for in vivo diagnosis where a severely limited number of patients restrict the feasibility of obtaining complete clinical data. For authorisation of such allergen products, recruiting an adequate number of subjects to obtain clinical data meeting the requirements as requested by guideline CPMP/EWP/1119/98/Rev. 1) may be a challenge.[8] In line with Annex I, Part II, Section 7 of Directive 2001/83/EC, it can be acceptable in such cases that Modules 4 and/or 5 consisting of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references are provided. For the bibliographical data to be provided as part of the mixed MA, bridging data should be presented to justify that these data are relevant for the allergen product in the application.

Specific guidance for rare or infrequent allergens (where there may be only a few patients with the respective allergy available for clinical studies) is currently in development (building on the Concept Paper on a Guideline for allergen products development in moderate to low-sized study populations EMA/CHMP/251023/2018).[8] This novel guideline considers specific features of PT substances (Table 4). In cases of deviation from the current guideline on the clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1),[25] the applicant should soundly justify that deviation is appropriate due to the reduced population of interest, considering EU epidemiology data (e.g. presence of allergen in the environment, rate of sensitisation, clinical disease prevalence).

5 | CONSIDERATIONS OF TF EXPERTS CONCERNING THE EXISTING REGULATORY FRAMEWORK CONDITIONS FOR THE DEVELOPMENT OF PT SUBSTANCES IN THE EU AND RECOMMENDATIONS FOR THE NEW EUROPEAN MEDICINES AGENCY (EMA) GUIDANCE FOR RARE OR INFREQUENT ALLERGENS

- The existing Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1)[25] which outlines the principles for the clinical evaluation of diagnostic agents intended for in vivo administration in conjunction with the Clinical Trials Regulation EU No 536/2014[26] (https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en) has led to diverse expectations and uncertainties concerning their applicability in the development of new PT preparations. Generally, devising and evaluating new PT diagnostic Type IV allergens differs considerably from the stepwise development and evaluation of new therapies which are classically divided in the pre-licensing Phase I–III trials. Recent regulatory guidance documents[8,9] have addressed and clarified the regulatory framework (see below) for the development of PT allergens. Further scientific guideline development (based on EMA[8]) intended to clarify EU regulatory expectations on the data for PT allergen products being developed with the goal of obtaining MA in case of small patient populations has been announced. The draft of this scientific guideline was published by the EMA in February 2024 and can be commented on until 31 May 2024 (https://www.ema.europa.eu/en/allergen-products-development-immunotherapy-allergy-diagnosis-moderate-low-sized-study-populations-scientific-guideline).
- With this position paper, the TF experts would like to contribute their expertise to clarify and improve the complex situation that

TABLE 4 Specific features of patch test (PT) substances, which will be addressed in more detail in a novel European Medicines Agency (EMA) guideline for allergen products development in moderate to low-sized study populations.

	Aspect of PT development	Amendments to special conditions
Quality	Raw materials	Raw materials for PT substances are typically manufactured for use in other settings (i.e., 'atypical active substance'): *GMP requirements* only apply once the source material is introduced into the manufacturing process for the medicinal product.
	Finished product	Since quality requirements (e.g., identity of the active ingredient, homogeneity, stability and microbiological quality) are mainly independent of the prevalence of the respective allergy, a *full set of data on quality* is expected. These data should include specific manufacturing and quality control aspects on product and intermediates as requested by current pharmaceutical legislation and according to guidelines and the European Pharmacopoeia
	Manufacturing process validation	It is regarded *acceptable to group products* into suitable process categories.
Non-clinic	Non-clinical data set	Since PTs contain predominantly chemical substances, pre-clinical data are normally available from technical data sheets and literature. Thus, for compiling non-clinical data for MAA, *bibliographic data are sufficient*.
Clinic	Criteria of patient selection and clinical development	Due to a lack of a standard of truth or even a surrogate standard of truth or comparator preventing the determination of sensitivity and specificity, the Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1) is often not applicable for the investigation of new PT substances independently of the size of the patient population. In any case it is necessary to describe the full spectrum of PT reactions; from these data the positivity ratio (PR)[29] and reaction index (RI)[30] can be assessed as indicators of performance as alternative endpoints. Wherever possible, these data should be provided; for example, data from registries could be used.
	Phase II dose finding studies	A dose-finding is generally considered necessary as a starting point for successful clinical development of medicinal products. However, for PT allergen products, *classical dose-finding studies* regarding tolerability and efficacy *may not be feasible*. Epidemiological studies may be useful to determine the need for a substance to be provided as PT product. Case Reports, e.g., of reactions in certain occupation groups may be another source of data documenting medical need und sensitisation potential. Regarding dose-finding, doses used, e.g., in cosmetics may be helpful to estimate a suitable dose. In some cases, published threshold values which should not be exceeded may be available and could support the choice of dosage. Wherever available, data from expert associations regarding suitable concentrations for patch testing can be used. Alternatively, any literature data which is suitable for choosing an appropriate concentration should be submitted, incl. case reports.
	Phase III confirmatory efficacy trial (if required by type of intended MAA)	Wherever possible clinical studies should be performed in a sufficient number of patients allowing precise description of the full spectrum of PT reactions, and determination of the positivity ratio (PR) and reaction index (RI). For this purpose, *clinical trials combining several allergens* could be considered. For example, 10 different PT substances can be investigated in one study. Patients allergic to at least one of the investigational allergens should be included based on their history. Patients allergic to another Type IV allergen in the study panel can serve vice versa as negative controls with regard to non-specific local (irritant) reactions for other PT substances included in the study panel.

Abbreviations: GMP, good manufacturing practice; MAA, marketing authorisation application; PT, patch test.

has led to a currently severely restricted availability of PT substances in the MS.

- Pre-licensing trials of the applicant are generally a prerequisite for MAA for pharmaceutical products, however, their applicability to PT products is low. Alternatively, applicable documents for submission in MA dossiers of the PT products are suggested.
- Bibliographic MA[24] (*Well-established use application according to Article 10a of Directive 2001/83/EC*) is pragmatic and helpful for waiving the provision of a dedicated clinical study program. This type of application can be used for medicinal products containing an active substance that has been in *well-established medicinal use* for 10 years or longer and that has a recognised safety and efficacy profile in the literature.
- For *new*/emerging Type IV allergens, the mixed licensing procedure should be used ('*Mixed marketing application*' *according to Article 8 (3) in combination with Annex I Part II Section 7 of Directive 2001/83/EC*), yet kept as simple and low cost as possible. Besides bibliographic data from (inter)national patch testing networks, a small phase III confirmatory efficacy study should suffice, including 10 well-characterised patients with known contact allergy to the hapten (e.g., identified by previous patch testing with patient's own products) and approximately 100 individuals without a history of contact allergy to the hapten.

- For 'new' allergens/haptens, authorised personnel (e.g., certified pharmacist) could prepare PT diagnostic Type IV allergens for individual use (as is done already at a local level in some MS) in concordance with legal requirements, and as such (through publications) provide a bibliography, ultimately also useful for PT suppliers to consider MAA and commercialisation and thus future application of market access for such haptens. However, depending on the hapten it might be difficult for a pharmacist to acquire suitable raw materials.
- Clinicians should be aware of this option and thus be encouraged to publish the individual PT results obtained in their 'index patient(s)'—their input will raise awareness for new haptens and the potential for commercialisation by a manufacturer.
- To this end, licensed PT allergens are currently available only from one manufacturer in the EU. In times of supply chain breakdowns of raw material (as has occurred during the pandemic), this can easily lead to supply shortages, supply delays or supply interruptions of PT substances. For scenarios where there is a supply interruption of licensed PT substances of more than 6 months in a MS, *for a limited time* (not longer than 12 months), extraordinary regulatory measures may be feasible to accelerate provision. For example, (a) priority assessment of variations of the original MA for qualification of a new source of raw material; (b) exceptional provision of PT substances as NPP (under Article 5 Directive 2001/83/EC; this could require an exemption at the national legislative level of a MS and would then probably have to be supplemented by the stipulation that this may only be done after approval by the NCA); and/or (c) importation of authorised or marketable allergen products from another MS for the personal use of a health-care professional could be a way forward in these exceptional circumstances (ideally these options should be reviewed by the CMDh allergen drafting group).[9]
- In the CMDh recommendations on common regulatory approaches for allergen products (CMDh/399/2019), it is pointed out that if no MA is available in a country and an MRP is not possible or not sought by a company, an authorised health-care professional could require the importation of authorised allergen products for personal use, according to the national legislation. However, requirements and distribution paths might be rather complicated and should be elucidated and, if possible, simplified.
- At this point, most licensed PT allergens obtained their MA in a national MA procedure. MRP should be encouraged to expand authorised products to further MS, to allow for market accessibility throughout the EU. Unequal availability in the MS is regarded as unacceptable and should be avoided. However, at the given time, high fees raised by NCAs for multinational procedures and EMA Annual Fees seem to impair such an approach.
- Regarding the high number of PT haptens (>500) that still require a MA in the EU, the procedure is enormously time- and money-consuming. It is noteworthy to bear in mind that licensed diagnostic PT preparations are not associated with a large earning opportunity for the MA holder. Medicines with low earning potential should be subject to different fees than high-priced medicines such as biologics. Fees that are applied by individual countries/agencies and EMA should be reduced for Type IV allergens. For example, by the Decree of 10/7/2018 by the German Ministry of Health, the German NCA has been enabled to grant a fee reduction of 75% for all official regulatory procedures in the context of infrequent test allergens. Such amendment of fees in the context of regulatory procedures dealing with test allergens will probably require political support on the national and European levels.
- It has become apparent that haptens which are only relevant for small patient groups (e.g., exposed in specific occupational settings) are entirely unattractive for manufacturers regarding MA requirements owing to the low earning potential. In this context, a priority list for market access (containing 100–300 PT allergens of moderate use) has been prepared by a pharmaceutical company and MA holder and has been presented to national contact dermatitis societies for notice. Haptens beyond these lists of low demand for small patient groups are not likely to be available as authorised test substances in the foreseeable future. This concerns both emerging new contact allergens as well as (previously) existing MAs for PT preparations only relevant in small patient groups which have often already been withdrawn by the MA holder or are currently not being produced. This will greatly affect public health (decrease in quality of life) and the EU economy (absenteeism, lost productivity, treatment cost).
- One of the PT allergen suppliers with MAs recently shared a company analysis[27] which shows that the cost for producing PT allergens which sell less than 200 units/year is approximately twice their current catalogue price and for the products with sales volumes below 50 units/year, the ratio is eightfold.
- For these very rare haptens, it might be feasible to rethink the applicability of Article 5 Directive 2001/83/EC in general and distribution as NPP. This might require adaptions on a national legislative level; however, this would generally be in line with the CMDh guideline (CMDh/399/2019) and the outlined acceptability of NPP ('The preparation and use of NPPs should be considered only in exceptional cases when no alternative authorised allergen products […] are available'). As soon as there is an authorised test allergen product for this hapten available, which is of proven quality, safety, and efficacy, an NPP should not be marketable any longer.
- For one particular PT diagnostic Type IV allergen, different concentrations and vehicles are separate diagnostic preparations in terms of stability, efficacy and safety. For different vehicles, this is likely important (e.g., stability of a hapten dissolved or dispersed in a given vehicle is something that indeed needs to be verified), and the same is true for higher concentrations in the same vehicle, but it is, for example, far less likely that lower concentrations of the same hapten, in the same vehicle, would pose a significant problem regarding safety (stability and efficacy, of course, might be reduced, or the same). The extent of clinical data required for MA of a modified drug substance concentration should be very limited, as displayed above, for new/emerging Type IV allergens (according to mixed marketing application).
- Different national implementations of Article 5 of Directive 2001/83/EC as national law for the longest time have not

BOX 1 Call to Action

Suggestions to improve the availability of patch test allergens based on the above considerations and findings:

- The main objective is to safeguard actual and potential patients, in fact, all citizens of the EU. Therefore, it is necessary to ensure the availability of adequate and timely medical examinations required for correct diagnosis and efficient management of Type IV allergy which everyone in the EU should be entitled to.
- As Type I and Type IV allergens differ substantially in nature and induce pathomechanism of allergic reaction (Table S1), the TF strongly advises that Type I and Type IV allergens should be regulated separately to address these differences. It is acknowledged that the recent regulatory guidance documents substantially address these differences.
- A simplified MA approach should be used wherever possible (e.g., bibliographic MA or mixed marketing application where applicable), including existing documentation: (1) technical data sheets analysis certificates, toxicology reports, material safety data sheets of the chemicals (2), plausible published data on the clinical use and efficacy of existing PT allergens for the diagnosis of allergic contact dermatitis or related conditions (3) data from validated European network of Registers. For clinical studies in mixed marketing applications, a limited number of well-defined patients should suffice (depending on the allergen, e.g., 10 well-characterised patients with known contact allergy to the hapten [e.g., identified by previous patch testing with patient's own products] and approximately 100 individuals without history of contact allergy to the hapten).
- For mixed marketing authorisation, an appropriate minimum number of patch-tested patients could be justified in the assessment of PT preparations to support marketing authorisation. In addition to the evidence on diagnostic efficacy and safety addressed above, pharmaceutical GMP standards and proof of sustained quality/stability of PT preparations need to be provided by manufacturers.
- For very rare allergens (as described above), distribution as NPP under Article 5 Directive 2001/83/EC should be made possible. Good manufacturing practice is a prerequisite. As soon as an authorised test allergen product for this hapten is available, which is of proven quality, safety, and efficacy, it should no longer be marketable as NPP.
- Distribution as NPP should also be possible for emerging new contact allergens of unclear prevalence (for a limited amount of time, e.g. 12 months) on the order of an authorised health-care professional; for this period, technical data from the manufacturer should suffice.
- If no MA is available in a country and a mutual recognition procedure (MRP) is not possible or not sought by a company, an authorised health-care professional could require the importation of authorised (or marketable) allergen products for personal use, according to the national legislation. Proceedings for this should kept as simple as possible.
- MRPs should be encouraged to expand authorised products to further member states to allow for market accessibility throughout the EU. High fees for multinational procedures should be reduced for PT allergens in view of their low return on interest. High costs should not be shifted to the patient.
- To maintain a high professional level for dermatologists/allergologists, including performing and assessing patch testing, access to diagnostic Type IV PT preparations in all EU countries is also important.
- Accessibility of PT substances should be maintained during recommended transitional periods of up to 8 years for implementation of the CMDh-Guideline (CMDh/399/2019).

allowed for harmonisation among the MS of the EU. Despite the CMDh *Recommendations on Common Regulatory Approaches for Allergen Products* (CMDh/399/2019),[9] published in 2020, at the given time harmonisation has not yet advanced to a level of cross-national facilitation and improved availability of diagnostic allergens. In contrast, during its implementation, a rapid restriction of NPP in the absence of approved PT allergens has complicated patient care in some MS. It is noteworthy to mention that the CMDh-Guideline (CMDh/399/2019) foresees rather long transitional periods (of up to 8 years) for implementation, so it should be possible to maintain the accessibility of PTs in this guided transition.

6 | DISCUSSION AND CONCLUSION

A broad consensus exists among the multi-national and multi-professional representatives of the ESCD, EAACI, and EADV that for both patient care and contact dermatitis research, the availability of safe and reliable PT substances is a prerequisite.[28] PT is the main tool to identify Type IV sensitisations and constitutes a unique method for the identification of new and emerging contact allergies. The availability of a broad, updated, and relevant range of standardised PT allergens is a prerequisite for the epidemiological surveillance of contact allergies to identify contact allergy trends of concern needing further public health attention. It consequently allows for the implementation

of safety limits and the substitution of culprit allergen sources as part of risk management.

The TF identified several main problems that contribute to the current alarming shortage of PT allergens:

1. development and maintenance costs: developing and maintaining existing products in compliance with the current regulation for medicinal products appears for a broad spectrum of PT allergens—including very rare allergens with low sales—not financially sustainable for a manufacturer.
2. very high regulatory fees, especially on the European level, hamper multinational MA procedures and the roll-out of existing national MAs to further MS via MRP.
3. in contrast to development and maintenance costs, the reimbursement of patch testing by health insurance is low in many MS. This contributes to reduced demand for PT substances and a downward spiral in supply and demand.
4. lastly, during the pandemic, supply chains of raw materials supplying the manufacturer and MA holder were interrupted and required time to be re-established.

In order to address these major factors effectively, a multi-stakeholder dialogue between European Scientific Societies (e.g., the ESCD), patient representatives, manufacturers of diagnostic Type IV allergens, NCAs, Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh) and the EMA's, potentially also including the European Commission (EC) is suggested (Box 1).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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