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An agency of the European Union

10 June 2025
EMA/23830/2025

Overview of comments received on "Guideline on allergen products development for immunotherapy and allergy diagnosis in moderate to low-sized study populations"

(EMA/CHMP/72790/2024)

Name of organisation or individual	General or Specific comment	Line from (line nr. or 0 for general comment)	Line to (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
SmartPractice	General	0	0	SmartPractice suggests providing more detailed description of the minimum requirements for the quality information for Type IV allergens. This helps prevent resource-intensive deficiencies		Partially accepted. Some specific comments were implemented, however, the guideline is meant to stay high level.
SmartPractice	General	0	0	SmartPractice suggests reiterating that all clinical studies, including epidemiological studies involving the use of unapproved allergens, must comply with EU regulations for clinical trials. This includes obtaining authorization for the studies following a review of a clinical trial application submitted to the CTIS. To make such studies economically feasible, the fees for reviewing clinical trial applications for Type IV allergens need to be reduced.		Partially accepted. In case of clinical studies, Regulation (EU) No. 536/2014 applies. The fees are a national issue and out of scope of the guideline.
ALK	General	0	0	ALK calls for more specific requirements for data on development of AIT in moderate to low sized populations. Please see specific related comments in the guideline for your reference.		Acknowledged. Changes were made in relevant sections.
ALK	General	0	0	ALK suggests to consider alternative study design for clinical development program for products without an MA, but which have been on the market for many years and have an established safety profile (e.g. RWE using patient reported outcome tools incorporated or generating clinical data based on historical or uncontrolled data)		Not accepted. It is acknowledged that the products marketed for many years have an established safety profile, providing that pharmacovigilance surveilance was applied. The proposed alternative evidence (e.g. RWE using patient reported outcome tools incorporated or generating clinical data based on historical or uncontrolled data) would be only supportive as already mentioned in the guideline, but is not considered sufficient as the only proof of evidence for efficacy demonstration.
ALK	General	0	0	ALK would like to raise concern for challenges when conducting clinical trials for patients with multiple allergies. Please see comment for lines 347-352.		Acknowledged. This information is already mentioned in the guideline.
ALK	General	0	0	ALK requests to include a list of abbreviations		Accepted. A list of abbreviations has been added.
ALK	General	0	0	ALK requests to include an annex with a list of examples as to what can be considered a low to medium sized allergen		Not accepted. The scope was rephrased to make it clearer which allergens fall within the scope of this guideline.
ALK	General	0	0	Missing “studies” in the section 10.1 Title		Accepted. "Studies" has been added in the title.
Radoslaw Spiewak	General	0	0	Estimated 120 million EU citizens need diagnosis and care of their contact allergy. According to epidemiological data, contact allergy (type IV hypersensitivity) affects 27% EU citizens, but only 6 (0.1%) of 5200 known haptens sensitize more than 1% of them [Diepgen et al. 2016]. This means that proper allergy care to EU citizens requires the availability of hundreds of diagnostic haptens, each needed by a small groups of patients, which means limited renevals. Creating overly restrictive and costly regulations of diagnostic haptens would lead to a withdrawal of a majority of "niche haptens" from the market and thus jeopardise the citizens' access to EBM-based allergy care. Recent events in Germany and Italy demonstrate that overregulation may cut doctors and patients off the needed diagnostics, creating a real and clearly visible problem to millions. While talking to interested parties (national decision makers, doctors, opinion leaders) I have heard many complaints about the "EU hampering our work" and "having hands bound by the EU". This opinion would ultimately spill down to patients who are also citizens and voters. In case of type I allergens, there are established in vitro diagnostic procedures, wich may be used to "Band Aid" the current limitation in prick testing, however, not so for nasal or bronchial provocation tests which are the mainstay of good allergy practice. For type IV allergy, however, there is no validated in vitro diagnosis - antything that could replace missing patch tests. So called "transformation tests" offered by some labs are not validated and their results are doubfrul in many cases. Therefore, overregulation of patch test haptens will immediately affect milions of Europeans. This might undermine their trust in EU laws and institutions. Boris Johnson invented a fake "EU banana regulations" and effectively managed to get UK out of the EU. We should avoid playing into hands of eurosceptics and their external sponsors.		Acknowledged.

Radoslaw Spiewak	Other	0	0	Estimated 120 million EU citizens need diagnosis and care of their contact allergy. According to epidemiological data, contact allergy (type IV hypersensitivity) affects 27% EU citizens, but only 6 (0.1%) of 5200 known haptens sensitize more than 1% of them [Diepgen et al. 2016]. This means that proper allergy care to EU citizens requires the availability of hundreds of diagnostic haptens, each needed by a small groups of patients, which means limited renevals. Creating overly restrictive and costly regulations of diagnostic haptens would lead to a withdrawal of a majority of "niche haptens" from the market and thus jeopardise the citizens' access to EBM-based allergy care. Recent events in Germany and Italy demonstrate that overregulation may cut doctors and patients off the needed diagnostics, creating a real and clearly visible problem to millions. While talking to interested parties (national decision makers, doctors, opinion leaders) I have heard many complaints about the "EU hampering our work" and "having hands bound by the EU". This opinion would ultimately spill down to patients who are also citizens and voters. In case of type I allergens, there are established in vitro diagnostic procedures, wich may be used to "Band Aid" the current limitation in prick testing, however, not so for nasal or bronchial provocation tests which are the mainstay of good allergy practice. For type IV allergy, however, there is no validated in vitro diagnosis - antything that could replace missing patch tests. So called "transformation tests" offered by some labs are not validated and their results are doubfrul in many cases. Therefore, overregulation of patch test haptens will immediately affect milions of Europeans. This might undermine their trust in EU laws and institutions. Boris Johnson invented a fake "EU banana regulations" and effectively managed to get UK out of the EU. We should avoid playing into hands of eurosceptics and their external sponsors.		Acknowledged.
STALLERGENES GREER	General	0	0	This guideline addresses general guidance on the development of medicinal products where only moderate to low-sized study populations are available. However it could be helpful to get more details on the proposed study designs and recommended end-points		Acknowledged. The guideline was intended to give high level recommendations without going into details.
EFA	General	0	0	EFA praises EMA for addressing allergies of medium- to low prevalence, as this is an area of considerable disease burden and yet huge unmet needs. Allergy is a complex disease with numerous different sub-types, and with multiple implications in the socioeconomic and emotional aspects of patients' lives. We need to ensure that no-one is left without an effective treatment or diagnosis. Therefore, EFA is glad to see a continuous commitment to scientific rigour for the development of AIT and diagnostic allergen products. On the other hand, having participated in the consultation on the concept paper on this issue back in 2019, EFA takes note of a considerable delay in publishing this draft guideline (which was, as per the concept paper of 2019, foreseen to be published in 2020). As representatives of the allergy patient community in Europe, EFA had hoped that this work, which affects thousands of people, would have been finalised in a more effective and timely manner.		Acknowledged.
EFA	General	0	0	EFA strongly supports EMA work on AIT and diagnosis of allergic diseases. On the one hand, AIT and its disease-modifying potential can lead to treatment regiments that are more tailored to an individual's genetics, environment, and lifestyle, consistent to the principles of personalised medicine; on the other hand, any solution that contributes to the identification of a notoriously underdiagnosed disease such as allergy is very much welcome by the EFA Community of allergy patients.		Acknowledged.
EFA	General	0	0	To improve readability of the document, EFA would suggest EMA to emphasise more clearly the differences in the approaches between large and medium/low-sized populations i.e. clarifying the requirements where adequate study populations are available (as per the existing guidelines, guidance and common practices), in juxtaposition with the more flexible requirements or the alternative methods in cases of medium/low-sized populations. This should naturally cover all the product development aspects i.e. quality, non-clinical data, clinical development, safety etc for all types of products. Perhaps the use of visual elements e.g. table would be useful in this regard.		Acknowledged.
EFA	General	0	0	Through guidelines such as this, EMA can contribute to optimising patient access to clinical trials. Very often, patients struggle to take part in clinical trials due to access barriers. Information about the undertaking of clinical trials, how patients can attend, what are the benefits and risks involved, is crucial in this respect. Moreover, patient access to clinical trials can be hampered due to long geographic distances, especially in large cross-border clinical trials (usually at Phase III). In the case of uncommon allergies, where by definition the patient population is scarce, an even greater focus is required to ensure that information arrives in a timely fashion through appropriate channels.		Acknowledged.
EFA	General	0	0	Linked to the comment above, EFA urges EMA to stress that this guideline addresses specifically uncommon allergy types, rather than generally AIT and diagnosis in cases where study populations are limited (limits, as we saw in the previous comment, may arise from various causes). References to uncommon allergies are indeed made in a few occasions in the text (e.g. line 177, 576), yet it would give greater clarity to standardise this reference throughout the document, including in the title. Suggestion for title change: 'Guideline on allergen products development for immunotherapy and allergy diagnosis of uncommon allergies with in moderate to low-sized study populations'		Partially accepted. The reference to "uncommon" allergens has been deleted from the guideline. The guideline is only referring to moderate to low-sized study population and the title change is not accepted.
EFA	General	0	0	The EMA Guideline needs to take into account the fine balance between patient safety and access to medical products. As we have seen in some countries such as Germany, the introduction of specific evaluation criteria for diagnostic products in food allergy has brought a significant downsizing in the product options available in the market (while the prior lack of such criteria allowed for many products, largely uncontrolled and with limited safety requirements). It becomes clear that EMA needs to make optimal assessment of the various implications of a guideline, especially since it is expected to influence also relevant Guidelines of national authorities.		Acknowledged.
EFA	General	0	0	EFA supports the inclusion of paediatric population in clinical studies and trials, especially when linked to a disease for which there is not cure e.g. food allergy. While not necessarily a cure as such, AIT can give patients an opportunity to keep away from exposures to dangerous foods. Of course, safety and efficacy of a treatment are very important, but appropriate information to patients or carers (in case of children population, for example) can lead to better decisions.		Acknowledged.
EFA	General	0	0	Specific comment: EFA stresses that the study of low prevalence diseases could benefit by including less clinical techniques, such as the collection and analysis of Real-World Data (e.g. related to Quality of Life) or even via the development and analysis of specific patient-reported outcomes that could then lead to a more standard clinical trial approach. The latter could be extremely relevant in determining the efficacy aspects of AIT, for example, as it entails patients reporting their symptoms, use of medication etc.		Acknowledged. RWD is already mentioned in the guideline as supportive information.

Diater	General	0	0	The document repeatedly mentions allergen product with moderate to low-sized study populations, but does not define the maximum % prevalence of an allergen to be referred to in this guideline. It is necessary to define the maximum prevalence of an allergen in order to be considered moderate to low-sized study populations. Related to the previous question, if the maximum prevalence % that an allergen must have to adhere to this guideline is not defined, can it be interpreted that any allergen not included in Annex 1 of Recommendations on common regulatory approaches for allergen products (CMDh/399/2019) is within the scope of this guideline?		Partially accepted. The scope has been rephrased to make this clearer.
LETI Pharma S.L.U.	General	0	0	The draft Guideline contains all elements of the GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES (2009) . Phase II and Phase III requirements have only been modified marginally. For rare allergens it remains doubtfully whether the investment into phase II and III even combined in a EEC can ever be efforted taking the low patient numbers into account. Our primary concern is that rare allergens will not be any marketed and patients will not receive the appropriate treatment.		Not accepted. Sponsors are encouraged to suggest alternative study designs considering that efficacy and safety must be demonstrated before a marketing authorisation can be granted.
Chemotechnique MB Diagnostics AB	Specific	58	60	We propose to add reference to the definition of moderate to low-size study population on line 110 and to clarify that all products for epicutaneous diagnosis of contact allergies (type IV) are defined as moderate to low-size study population. We would also appreciate a more specific definition of moderate to low-size study population to avoid the necessity for statistic calculations.	The main aim of the guideline is to address general guidance on the development of medicinal products for the diagnosis and immunotherapy of allergies, where only moderate to low-sized study populations are available in product development (for definition, see section 1). The development of these medicinal products will be facilitated by a risk-based approach.	Not accepted. The definition is mentioned in the guideline after the executive summary.
ALK	Specific	59	60	ALK requests to include specific definition criteria for moderate to low size population		Not accepted. The definition is already included at the end of the introduction section 1.
Task Force (TF) "Legal matters concerning patch test materials" of the European Society of Contact Dermatitis (ESCD), represented by the TF chair Prof. Swen Malte John.	Specific	62	66	We suggest adhering to a very clear differentiation between type I and type IV allergies even in the Executive Summary to avoid confusion. In the Introduction, the difference is clearly stated. Thus, we suggest doing so also in the Executive Summary.	l. 62: The body reacts with signs of inflammation, formation of antibodies in Type I allergy and T-cell activation in Type IV allergy. l. 65: Management for type I allergy may involve avoidance of the allergen, medications to relieve symptoms, or allergen immunotherapy (AIT) to desensitize the immune system to the allergen. Regarding type IV allergy, allergen avoidance is the only measure; there is – to date – no causal therapy available.	Accepted. The text has been amended accordingly.
LETI Pharma S.L.U.	Specific	64	65	Type I IgE mediated reactions can also be delayed reactions, happening up to 24hrs after contact with allergen.	Update the text	Accepted. Amended proposal is inserted to clarify that immediate reactions represent the predominant type of reactions but may not be the only reactions observed.
SmartPractice	Specific	76	77	SmartPractice suggests to separate the 1st general sentence which applies to both Type I and Type IV allergies from the remaining part of the paragraph that only applies to Type I allergens. Furthermore, minor edits are suggested for better clarity and readability.	"Allergy is a common condition with a large variety of different allergen sources causing allergy and the number of sensitized patients varies significantly. The two types of allergies addressed in this guideline are Type I and Type IV allergens." Line break Instead of "Allergy as such is a common condition with a large variety of different allergen sources causing allergy and the number of sensitized patients varying strongly for the respective allergen sources." (no line break).	Accepted. The sentence has been updated as suggested.
Task Force (TF) "Legal matters concerning patch test materials" of the European Society of Contact Dermatitis (ESCD), represented by the TF chair Prof. Swen Malte John.	Specific	85	87	We suggest highlighting that the clinical manifestations of type IV hypersensitivity reactions are not always confined to a small localized skin area; they can involve the skin diffusely and manifest in various clinical forms.	Following "In type IV hypersensitivity, there is activation of T cells and of macrophages that interact and secrete various cytokines ultimately resulting in delayed skin reactions,": "primarily manifesting as allergic contact dermatitis at the site of contact with the allergenic substance. However, if the allergen is not identified, recurrences are inevitable, and the reaction might spread beyond the contact site with the allergen or even become generalized. Type IV hypersensitivity can also manifest as photoallergic contact dermatitis, allergic contact stomatitis, allergic contact conjunctivitis, allergic reactions to implanted medical devices (e.g. endoprostheses, implants, stents), systemic allergic dermatitis, and a range of drug eruptions. For instance, a stent failure due to type IV allergy can lead to life-threatening consequences."	Not accepted. The guideline is intended to remain high level.
Chemotechnique MB Diagnostics AB	Specific	85	87	Add "(hapten)"	In type IV hypersensitivity, there is activation of T cells and of macrophages that interact and secrete various cytokines ultimately resulting in delayed skin reactions almost exclusively at the site of contact with the allergenic substance (hapten).	Not accepted. The allergising agent is considered to be sufficiently defined by the current wording.
EFA	Specific	88	92	Proposal to mention that some current diagnostic tests are unreliable and may fail to detect certain types of allergies that are not IgE-mediated (Type IV), or that may have emerged recently.		Not accepted. While it is agreed that this may be the case for individual products, the scope of the guideline is to provide options for relevant products to be made available to patients.
Chemotechnique MB Diagnostics AB	Specific	89	92	Replace "allergen avoidance" with "hapten avoidance".	Allergen extracts for diagnosis and therapy are needed to manage patients with type I allergies, while for patients with type IV allergies allergen products are currently only used for diagnosis of type IV allergies and treatment of these type IV allergies involve hapten avoidance.	Not accepted.

Task Force (TF) "Legal matters concerning patch test materials" of the European Society of Contact Dermatitis (ESCD), represented by the TF chair Prof. Swen Malte John.	Specific	105	105	The availability of type IV patch test allergens in Europe is currently precarious. This severely compromises adequate diagnosis of contact allergy, leading to extremely serious consequences for affected patients. Whilst we appreciate this guideline initiative, we suggest that the guideline gives explicit guidance to urgent and pragmatic solutions of the unacceptable problem of physicians throughout Europe who are currently unable to correctly diagnose their patients with Type IV allergies due to the current problem of availability of allergens. NPPs are mentioned in this context. Regarding NPPs, we make the following comment: We suggest that for new and rare patch test allergens, an authorization is given for a limited time of at least one year (as a named patient product, NPP). In this timeframe, the allergen would be available to use and the certification process can be started. Reference: John, S. M.; Bonertz, A.; Zimmer, J.; Aerts, O.; Bauer, A.; Bova, M.; Brans, R.; Del Giacco, S.; Dickel, H.; Corazza, M.; Crépy, M.-N.; Gallo, R.; Garcia-Abujeta, J. L.; Giménez-Arnau, A. M.; Klimek, L.; Lepoittevin, J.-P.; Ljubojević Hadžavdić, S.; Matura, M.; Mortz, C. G.; Özkaya, E.; Pesonen, M.; Raison-Peyron, N.; Rustemeyer, T.; Skudlik, C.; Spiewak, R.; Stingeni, L.; Suomela, S.; Symanzik, C.; Taylor, J.; Torres, M.; Uter, W.; White, I.; Wilkinson, M.; Mahler, V.; Johansen, J. D. (2024): 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. Contact Dermatitis. Epub ahead of print: doi.org/10.1111/cod.14580.	Following line 105: "However, considering the current dramatic shortage of diagnostic allergens with a marketing authorization for patch testing and the resulting need to swiftly provide such test preparations in the near future, a temporary exception for new and rare type IV allergens regarding NPPs should immediately be implemented. This exception for new and rare type IV allergens via NPP for a limited time of one year would allow for rapid availability of these allergens and the marketing authorization process could be accomplished in parallel within the year."	Not accepted. The guideline defines adequate expectations on data to be provided. However, a marketing authorisation without a minimal set of data as described in the guideline is not considered acceptable.
SmartPractice	Specific	109	109	Minor editorial change	"Within this guideline, low..." Instead of "Within this GL, low..."	Accepted.
Prof. Dr. med. Oliver PFAAR	Specific	118	118	intradermal/intracutaneous test is missing (although at the moment available for insect venoms only). However, later in the guideline the term occurs (line 292).		Accepted. Intradermal/intracutaneous has been added.
ALK	Specific	121	122 and 132	ALK strongly recommends to specify type I and IV allergens covered by the guideline in the Annex of this guideline		Not accepted. The scope is provided through reference to CMDh/399/2019 guideline.
LETI Pharma S.L.U.	Specific	122	127	Asthma is lower airway (122), which is contradictory with not being included asthma (127)	update the text	Not accepted. The first sentence describes that allergen products and their action are covered generally by the guideline, regardless of the affected organ system. However, specific indications are not covered, as stated in the following sentence. Therefore, this is not considered to be contradictory.
Chemotechnique MB Diagnostics AB	Specific	132	134	Please consider that there are some type IV diagnostic allergens for test in vivo, that have a very low allergy prevalence ("rare allergy") and that, therefore, might have to be excluded from this guideline as discussed in section 7 of Recommendations on common regulatory approaches for allergen products. We propose to add text to open up for the need of NPP for some type IV diagnostic allergens for "rare allergy".	In addition, this guideline does not cover type IV diagnostic allergens for test in vivo, that have a very low allergy prevalence ("rare allergy") according to section 7 of Recommendations on common regulatory approaches for allergen products where NPP should be an alternative.	Not accepted. The guideline specifically also includes such "rare" allergies.
STALLERGENES GREER	Specific	135	135	" For the present guideline to be pertinent, the Applicant should soundly justify that deviation from current guidelines concerning AIT (CHMP/EWP/18504/2006) or diagnostic products (CPMP/EWP/1119/98/Rev. 1) are appropriate due to the reduced population of interest, considering EU epidemiology data (presence of allergen in the environment, rate of sensitization, clinical allergy prevalence) and other relevant factors." In this sentence, it could be useful to better define the meaning of "appropriate" and to give some details on what could be the other relevant factors (co-sensitisation/allergy? penetration?)		Not accepted. Several examples on aspects to be considered are already mentioned in the current text.
EFA	Specific	135	141	Need to acknowledge here that allergic conditions are very often underdiagnosed.		Not accepted. There is already reference on the unmet medical need (see section 1 of the guideline).
EFA	Specific	163	172	EFA applauds EMA for championing high quality standards in the process of manufacturing allergen products for treatment and diagnostic purposes, and for ensuring patient safety. Given that this is about sensitive medicinal products, such a commitment to quality can have a boosting effect in the involvement of patients in clinical development procedures, while also contributing to the overall trust.		Acknowledged. No change required.
SmartPractice	Specific	164	166	The Introduction for Quality Aspects may require clarification regarding the requirement for a 'full set of data and no major differences in quality documentation for allergen products.' This requirement appears inconsistent with the previously issued recommendation of common regulatory approaches, which acknowledge that APIs for Type IV allergens are often atypical and may not meet GMP requirements. Obtaining a full set of data, as expected for the Drug Substance Module, from non-GMP API manufacturers is not feasible.	Suggested lines 164-166 are provided below: 164 In general, for all allergen products and their intermediates manufactured by a method involving an 165 industrial process as defined by Directive 2001/83/EC, as amended, a full set of data on quality is 166 expected unless the API is considered "atypical". The full set of data should include specific manufacturing and quality control aspects on allergen...	Not accepted. Specific expectations for Type IV allergens are listed. Also, the use of "atypical" would require clear definition and may be confusing.

Chemotechnique MB Diagnostics AB	Specific	164	166	The quality requirements for epicutaneous products for the diagnosis of contact allergies (“Patch test haptens”) should be differentiated from other allergen products, as skin prick test and therapy allergens. There are crucial differences between the two types of allergens that warrant separate regulations; first of all, for type IV allergies there are neither in vitro diagnostic tests, nor treatment therapies, in addition patch test haptens are low risk/high-benefit products administered on intact skin and lastly, a much higher number of patch test haptens are needed for the diagnosis of Type IV allergies compared to tests for Type I allergies. Although the prevalence of Type IV Contact Allergy (all types) in the general population is very high, affecting more than 20% (Alinaghi F, Bennike NH, Egeberg A, Thyssen JP, Johansen JD. Prevalence of contact allergy in the general population: A systematic review and meta-analysis. Contact Dermatitis. 2019;80:77–85) the disease is underdiagnosed. To exemplify, a hapten that surpasses a 0,5-1% positivity rate in routine patch testing is considered by the European Society of Contact Dermatitis for inclusion in the standard baseline patch test series. Data from pooled baseline patch test results in Europe (Uter et al. Patch test results with the European baseline series, 2019/20—Joint European results of the ESSCA and the EBS working groups of the ESCD, and the GEIDAC. Contact Dermatitis. 2022) gives us reason to believe that only 0,003% of the general population in Europe is patch tested annually. Consequently, a 0,5-1% positivity rate in routine patch testing might account for as few as 2-3 persons out of 10,000,000 in the general population yearly. In light of the above, haptens not included in the European baseline, should be subject to NPP.	n/a	Not accepted. The guideline specifically also includes "rare" allergies as well as specific considerations on Type IV alleriges.
LETI Pharma S.L.U.	Specific	168	170	Statements in lines 168-170 regarding quality requirements are in part contradictory regarding the necessary exceptions regarding the potency (total allergenic activity) as described in lines 177 – 180		Accepted. "typically" is added to make clear that there may be cases where limited modifications can be acceptable.
ALK	Specific	175	176	ALK would like to ask for clarification in the guideline for “technical possibility” of potency testing with the mentioned assay		Partially accepted. Technical possibility may depend on various factors and may need to be a case-by-case decision. Phrasing amended accordingly.
LETI Pharma S.L.U.	Specific	177	177	In the context of creating sera pools, some guidance regarding the minimum sufficient number of patients for low prevalence allergies would be appreciated.		Partially accepted. Information and expectations on sera pools are provided in the existing guideline EMEA/CHMP/BWP/304831/2007. Reference to this is added.
LETI Pharma S.L.U.	Specific	182	183	Relevant allergens are not clearly defined. Does it mean major allergen? Does it mean commercially available, or Eur Ph approved? Quantification of non previously Eur Ph validated allergens should not be required		Not accepted. Further definition is not considered required as there is no change according to current guideline EMEA/CHMP/BWP/304831/2007, which is also referenced in the following sentence: The allergens relevant for the product have to be defined by the manufacturer.
Chemotechnique MB Diagnostics AB	Specific	216	220	a) Clearly state that the source materials, i.e. active substances, do not have to comply with GMP standards and that technical data sheets are regarded as sufficient documentation. b) Which "respective requirements" are referred to here? Presumably this is referred to Directive 2001/83/EC. Could this be clarified?	The active substances do not have to comply with GMP standards, technical data sheets are regarded as sufficient documentation. Supplier qualifications of active substance suppliers will be risk-based, e.g. by questionnaires. Respective requirements (Directive 2001/83/EC, as amended) apply once the source material is introduced into the manufacturing process for the medicinal product.	Partially accepted and amended accordingly.
SmartPractice	Specific	218	218	Manufacturing sites for finished products may encounter difficulties when sourcing substances labeled 'not for human use.' Suppliers, concerned about liability, might decline to sell these chemicals to manufacturers of human medicines. Incorporating a statement addressing this concern in guidelines would offer a framework for purchasing such substances for manufacturers of patch test allergens.	Suggested additions to lines 218-219: 218 "... settings (e.g. hair dyes, cosmetics). Some of the active ingredients are labeled "Not for human use." The patch test manufacturers are authorized to use non-GMP substances and substances labeled "Not for human use" for patch test formulations manufacturing if they are relevant for the diagnosis of allergic contact dermatitis. Respective requirements apply..." Instead of "218 ... settings (e.g. hair dyes, cosmetics). Respective requirements apply ..."	Not accepted. The guideline already clarifies that such substances may be acceptable for use as API in epicutaneous test allergens.
SmartPractice	Specific	219	220	Manufacturing sites for finished products may encounter difficulties to obtain documentation such as "technical data sheets ", in such cases, developing relevant internal analytical procedures is needed.	Suggested edits are below: "Technical data sheets for such source materials should be provided. If an atypical API manufacturer does not provide technical data sheets, the finished product manufacturer should develop relevant internal analytical procedures to ensure batch to batch consistency. "	Accepted. Phrasing amended accordingly to account for such scenarios.
SmartPractice	Specific	219	220	A harmonized approach at the EU level is needed to waive the GMP requirements for supplier audits for all raw materials and packaging materials, allowing for flexibility in supplier qualification. This necessity arises from the fact that a small facility manages a high number of active substances (over 500 APIs and other materials). Notably, over 80% of raw materials are not conventional pharmaceutical active ingredients and are not produced under GMP conditions, thereby exempting them from GMP audits. For the raw materials produced under GMP conditions, pharmaceutical companies are required to audit these suppliers. However, these suppliers are often reluctant to host audits from multiple customers and offer costly audit reports for purchase, conducted by an accredited third-party auditing organization. This approach is economically unviable. A paragraph detailing this particularity was added after line 219.	Additional paragraph is provided below. This paragraph follows the sentence suggested above and finishing in "...batch to batch consistency" It is regarded acceptable to replace the audit of active ingredient and packaging materials suppliers with an alternative process. This process shall include a supplier qualification questionnaire for the initial qualification and continuous evaluation of the supplier performance. The QP declaration shall clearly state the quality of the allergen and which substances that are not guaranteed to be manufactured according to GMP and how the required quality is ensured. Post-approval changes in suppliers of active substances for Type IV allergens are considered minor (“Do and Tell” procedure) as long as the new API complies with the in-house acceptance criteria for the active ingredient.	Partially accepted. Amended the text with regard to audits. Change not accepted concerning changes in suppliers. Post approval changes in suppliers often result in severe changes in product characteristics. *Do and Tell* procedures are not considered sufficient for such changes.
SmartPractice	Specific	221	221	SmartPractice recommends adding a clarification regarding the grouping of formulations for manufacturing procedures and process validation. This clarification would prevent any confusion with other grouping strategies, such as using the stability of one product to determine the shelf life for a group of products.	Suggested clarification for the Line 221 is provided below: 221 "It is regarded acceptable to group products into suitable manufacturing process categories for the matrix approach of the validation of the manufacturing process. Such..."	Accepted.

Chemotechnique MB Diagnostics AB	Specific	221	221	It should be possible to apply the process categories groupings also for stability studies.	The matrix approach is also applicable in the stability studies of the products.	Not accepted. Stability characteristics are considered highly dependend on the individual API.
Chemotechnique MB Diagnostics AB	Specific	221	221	Please give guidance whether one matrix can be registered as one MA. The possibility of grouping MAs would facilitate life-cycle management (e.g. variations) and cost.	The selection of a representative product for a category will be based on final product characteristics, reflecting the properties of the constituents/substances in the product category. Such a product category will constitute one MA application.	Not accepted. A single product requires a singly MA according to European legislation. See also CMDh guidance on allergen products with regard to this issue (CMDh/399/2019).
Chemotechnique MB Diagnostics AB	Specific	221	224	The categories can be divided depending on the form of the active substance and the matrix, resulting in four category of patch test haptens: For semi-solid dosage form category: - A liquid active substance in a semi-solid vehicle - A solid active substance in a semi-solid vehicle For liquid dosage form category: - A liquid active substance in a liquid vehicle - A solid active substance in a liquid vehicle	Such categories can be based on a combination of main characteristics, such as dosage forms (suspension ointments, emulsion ointments, liquids), batch sizes (or batch size range), drug substance properties/characteristics (e.g. solubility) and drug substance concentrations (e.g. 0.1% to 1%).	Not accepted. See previous comment.
Radoslaw Spiewak	Specific	223	223	The use of the term "drug substance" in this context seems scientifically incorrect as hapten (the scientifically correct term) used for patch testing is not a medicinal product, i.e. it has no therapeutic purpose. A few exceptions among the 5200 haptens are pharmacologically active molecules (e.g. neomycin) which, however, are not used for therapeutical purposes in the in patch test settings. In other words, such haptens are used in patch testing not because of their pharmacological properties, but because they haptenize proteins which potentially may cause allergic response in sensitized subjects. The term "drug substance" in this sentence implies that it applies only to haptens with pharmacologic properties, i.e. neomycin, caines, tixocortol pivalate or budesonide but not to the majority of haptens used for patch testing, like nickel sulfate or methylisothiasolinone, which by no means are drugs. In case this is the real intention of this paragraph (which should be applauded), a more clear statement would be appreciated.	ointments, emulsion ointments, liquids), batch sizes (or batch size range) and hapten	Not accepted. Hapten would be the relevant API in the medicinal product for in vivo diagnosis. For reasons of consistency, the terminology "drug substance" is applied throughout the document.
Chemotechnique MB Diagnostics AB	Specific	224	225	Regarding grouping of products into process categories we note that the manufacturing process of each product in a category has to be identical and it should state that the critical steps of the manufacturing process need to be identical.	Notably, the manufacturing process, i.e. the critical steps, of each product in a category has to be identical.	Not accepted. Criticallity of the process and individual steps are considered to be aspects requiring individual assessment. The limitation to critical steps is not suitable because there is no general definition of the steps which are critical for production of patch tests resulting in heterogenous interpretation.
SmartPractice	Specific	228	228	SmartPractice suggests providing a more detailed description of the minimum requirements for quality information. This helps prevent resource-intensive deficiencies.	A more detailed description of the minimum requirements for quality information is suggested below: 228 " ....process validation. Release testing of the finished product should at least include the assay and identity; stability study shall at least include the assay. Microbiological controls of the finished products produced at the facility shall be performed; nevertheless, reducing the frequency to periodic testing is regarded acceptable based on a risk assessment of the allergen or group of allergens. Analytical methods used for release and stability of the finished product should be validated per Q2(R2). In general, stability studies for epicutaneous patch test preparations should adhere to the guidelines outlined in ICH Q1 A (R2). However, it is acceptable to reduce the testing frequency if adequately justified. For the initial marketing authorization, long-term stability data for the finished product should be provided for at least one batch covering the intended shelf life. Commitment to provide data for two additional batches shall be provided. Waiving or reducing requirements for accelerated condition data, e.g., having only three months of data for one batch, is acceptable if justified through a risk-based approach. For a multi-dose container product available in different packaging sizes made with the same packaging materials, stability data for one batch packaged in one pack size and another batch packaged in another pack size are deemed adequate at the time of the application submission for the long-term stability evaluation, provided the formulations exhibit generally good stability according to risk assessment. Three months of accelerated stability data for one batch in each pack size is deemed sufficient. The batch size of batches evaluated for stability must be at least 1/20 of the commercial batch size. For multi-dose products, in-use stability of one batch should be presented. Photostability data are required for one batch in each pack size unless the allergen is stored in refrigerator or if the applicant can demonstrate that the packaging has light protective properties.	Partially accepted. Additional phrasing is considered to be too detailed in some aspects with regard to the scope of this guideline. Phrasing amended regarding expectations on stability studies.
ALK	Specific	237	238	ALK recommends to be more specific on what is the meaning of “profound” expert statement		Not accepted. The guideline describes the essential topics to be covered by this statement on AIT products. This requirement has already been implemented in procedures for marketing authorisation. No need for revision.
ALK	Specific	252	252	ALK recommends to be more specific on “sufficient data on therapy during pregnancy is available from clinical trials or from the use as NPP”		Not accepted. No specific details can be provided because the guideline is intended to be high level. However, the section has been amended.

EFA	Specific	255	258	EFA would like to have clarifications regarding the expert statement. More information is needed regarding the type of expertise referred to here and what type of expert is considered adequate to provide such a statement.		Not accepted. The guideline describes the essential topics to be covered by this statement. This requirement has already been implemented in procedures for marketing authorisation. No need for revision.
SmartPractice	Specific	262	263	Minor editorial changes	"262 Therefore, normally data is available from technical data sheets and literature, thus for compiling the available 263 non-clinical bibliographic data are sufficient." Instead of "262 Therefore, normally data is available from technical data sheets and literature, thus for compiling the 262 non-clinical data bibliographic data are sufficient. "	Not accepted. The proposed wording is considered as less clear. Therefore, the current wording is kept.
Chemotechnique MB Diagnostics AB	Specific	262	267	Given the extensive previous human experience of patch test haptens, and given the low dose levels, the acute duration of exposure, and the minimal systemic exposure expected in subjects via the dermal route, it may be concluded that the haptens are safe for clinical use. Based on the safety profile and substantial previous use of those products we propose that a summary of literature data published in scientific journals or textbooks/monographs is sufficient for patch test haptens that already are in clinical use. For new emerging haptens module 4 should be provided, based on literature data, expert reports, and statements.	If such data are not available, in vitro data can be sufficient where justified. It may be acceptable to base the in vitro data on e.g. literature data, expert reports, statements, and technical data sheets.	Not accepted. The guideline already mentions the different possibilities. Reference is made to section 5.3 of this guideline and the CMDh guideline on Recommendations on common regulatory approaches for allergen products (CMDh/399/2019).
SmartPractice	Specific	267	267	Minor editorial changes	267 "...tests. If such data are not available, in vitro data can be sufficient where justified. Moreover, available data on 268 the potential to provoke unspecific local (irritative) reactions should be included." Instead of 267 "...tests. If such data are not available, in vitro data can be sufficient where justified. Moreover, data on 268 the potential to provoke unspecific local (irritative) reactions should be included."	Not accepted. The proposed change is not considered as a minor editorial change, as it seems to broaden the criteria, limiting it to a need to provide only the available data rather than defining the requirement.
ALK	Specific	278	297	ALK recommends to address possible indication/treatment goals for food and venom allergies		Partially accepted. A sentence has been added in section 6 under 'Allergy immunotherpay products' to mention that treatment of non-inhalant allergens (i.e. food and venom allergies) may fall under this guideline.
ALK	Specific	278	297	ALK sees the need to address possibility of adding rare food and venom allergens to the guideline		Not accepted. There are specific considerations on insect venom allergens and food allergens in the guideline. According to the present state there is no need for these two sections to go into more detail. Please also see considerations on previous questions on this topic.
ALK	Specific	278	297	ALK suggests to include a section clarifying that data fulfilling the EMA criteria from outside Europe may be sufficient for registration in Europe		Not accepted. Regional aspects of clinical trials conducted are neither part of the GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES (2009) nor this guideline. It is considered self-evident that the region in which the clinical trial is conducted is of relevance for the tested allergy and results may be transfererd to the region the MA is intended.
ALK	Specific	278	297	ALK proposes guidance to include an explanation that efficacy and safety data for an allergen product that has been demonstrated in a smaller development program may be used for registration for cross-reacting allergens that do not belong to the same homologous group		Not accepted. The concept of homologous groups remains unaffected. A marketing authorisation based solely on data outside the homologous groups is not considered adequate. However, alternative strategies can be possible, provided that the proposed approach is scientifically proven and according data has been gained in suitable studies. Bridiging strategies may be a possible approach. Applicants are welcome to present such proposals.
EFA	Specific	281	293	EFA suggests adding in this section indications and treatment goals that are relevant also for food allergy, as another disease where AIT should be an option. There are plenty of uncommon allergies to foods, including products that fall under wider categories of known food allergens. For example, the case of nuts: while it is a broad family of products (regulated as allergens under EU law), the category still includes nut types linked to low prevalent allergies e.g. macadamia nut or pine nut. Moreover, we would suggest addressing also insect venom allergy in this section. Studies show that climate change causes the expansion of stinging and urticating insects towards new geographic areas, increasing the potential for human contact and therefore the frequency of potential allergic reactions.		Accepted. A sentence has been added in section 6 under 'Allergy immunotherapy products' to mention that treatment of non-inhalant allergies may fall under this guideline.
STALLERGENES GREER	Specific	282	282	" Treatment of allergic asthma is considered a different indication and would require a separate clinical trial. " Could this sentence be clarified ? How to deal with the same issue of low patient population (issues that will be amplified considering that asthma is less frequent than AR)? Will other guidelines be proposed or should we consider that the same guideline also apply to asthma BUT separate development will be needed?		Partially accepted. (see also response to LETI Pharma line 286) As already known from EMA GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES (2009), treatment of allergic asthma is considered a different indication and requires a separate clinical trial. Requirements are found in the guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01/Rev.1). The guideline concerned here, however covers generally all indications, but separate clinical trials are required for asthma in comparion to AR/ARC.

LETI Pharma S.L.U.	Specific	286	286	Asthma can be considered “an allergic symptom” better explanation of removal of asthma from this guideline is required.	update the text	Accepted. (see also response to stallergenes line 282) The scope of the guideline (section 2) has been updated to clarify that the guideline does not cover the indication of atopic dermatitis or asthma as these conditions will require separate clinical trials (e.g. different study design, endpoints etc.).
EFA	Specific	298	304	In this section, EFA recommends the inclusion of more criteria for patient selection, such as the root of administration and the age of individuals tested. Selection of patients requires a careful cross-evaluation of these aspects and the consideration of existing conditions e.g. when using patches with adhesive to patients with skin disease such as atopic eczema, or when using injections to children.		Not accepted. It is not possible to address these aspects at that level of detail. The guidance is intended to be kept high level.
STALLERGENES GREER	Specific	313	313	The second part of the sentence "but in a multi-national Phase III study, where large geographical distances to an EEC may need to be covered, this can be challenging." does not guide nor aid the Applicant in making its decision.	Environmental exposure chambers (EECs) with inhalant allergens can be considered to enhance patient selection for Phase II or Phase III studies	Accepted. The sentence has been updated as suggested.
ALK	Specific	326	326	ALK proposes to change “criteria are recommended” to “should be requested”		Partially accepted. The wording has been amended to "… the following is requested:"
STALLERGENES GREER	Specific	327	327	documented clinical history of IgE-mediated (skin prick test and/or provocation test and allergen-specific IgE) seasonal/perennial allergic rhinitis/rhino-conjunctivitis (needing symptom-relieving medication) with controlled bronchial asthma or without asthma, attributable to uncommon seasonal/perennial allergen(s) (see section 2)	documented clinically relevant history of IgE-mediated (skin prick test and/or provocation test and allergen-specific serum IgE) seasonal/perennial allergic rhinitis/rhino-conjunctivitis ….	Partially accepted. The sentence has been updated with 'documented comprehensive clinical history..' (instead of relevant as suggested - this is to be in line with other section of the guideline).
EFA	Specific	327	330	EFA urges EMA to keep in mind that in specific cases patients with rhinitis may test negative in skin prick test and in allergen-specific IgE test, but positive in a nasal provocation test. This is partly due to the fact that the sensitisation is identifiable only at the local level in the nasal system. Therefore, the Guideline needs to make clear that a positive nasal provocation test would be sufficient for a patient to be considered eligible for selection to a clinical trial on an AIT product for rhinitis.		Not accepted. There is no scientific consensus at present.
Prof. Dr. med. Oliver PFAAR	Specific	328	328	The nomenclature regarding allergic rhinitis /rhinoconjunctivitis should be updated: instead of seasonal and perennial the use of intermittent and persistent is preferred		Accepted. The notion of intermittent and persistent has been added in the guideline as suggested.
Prof. Dr. med. Oliver PFAAR	Specific	331	331	“appropriate minimum levels of symptoms” is not further specified. I encourage to be more specific here as this criterion is fundamental for enrolling appropriate patients in trials.		Accepted. The sentence has been updated to reflect that 'appropriate minimum level of symptoms (moderate/severe)' are according to international criteria (e.g ARIA classification).
Prof. Dr. med. Oliver PFAAR	Specific	334	336	contraindications read vague to some extent and should rewritten in line with current guidelines and SMPCs of AIT products.		Not accepted. The guideline is not intended to be so specific.
ALK	Specific	334	334	ALK recommends to remove “severe” asthma patients from exclusion criteria, to allow broader population to be studied		Not accepted. This is out of the scope of this guideline and in line with EAACI Allergen Immunotherapy User's Guide (2020).
ALK	Specific	335	335	ALK recommends to consider shortening the cut-off to 3 years to allow sufficient number of patients to be included in the clinical development program – e.g. If a patient stopped the treatment (due to other reasons than safety) for a cross-reacting allergen, he/she should be considered to be included in the planned trial		Not accepted. The 5-year cut-off is in line with the CHMP guideline. (CHMP/EWP/18504/2006).
ALK	Specific	347	352	ALK proposes to add information on the development of multiple-food allergy products and related requirements (e.g. tree nut or multi-food allergies)		Not accepted. This is out of the scope of this guideline.
ALK	Specific	350	350	ALK requests to rephrase “History of IgE-mediated systemic allergic reactions” to “History of IgE-mediated allergic reactions”		Accepted. The sentence has been updated as suggested.
ALK	Specific	351	351	ALK would like to suggest to consider removing the requirement for DBPCFC that might not be relevant for all trials. A broader definition for the trial population should be based on medical history, IgE and/or SPT to mimic clinical practice.		Not accepted. DBPCFC is considered to be the current gold standard.
ALK	Specific	353	375	ALK asks to mention requirements for oral food challenges		Not accepted. Oral food diagnostic test is a new field of development which limits further detailing in this guideline. Applicants are invited to seek scientific advice as needed.

ALK	Specific	353	375	ALK recommends to specify a comprehensive clinical history		Accepted. "comprehensive" has been added as suggested.
ALK	Specific	361	361	ALK proposes to change “Comprehensive clinical history” to “documented clinical history”		Not accepted. Comprehensive clinical history is kept in the guideline. The proposed change is not sufficient, clinical history has to be comprehensive and not only documented.
Prof. Dr. med. Oliver PFAAR	Specific	400	400	the request for Palcebo-controls in Phase II is much supported. Harmonization of terminology = not “allergen specific immunotherapy”, but “allergen immunotherapy”: change throughout the text		Accepted. The wording has been harmonised as suggested and solely the agreed term 'allergen immunotherapy' is used.
ALK	Specific	408	408	ALK asks to clearly state what “sufficiently justified” means		Not accepted. There is no need to reword the sentence. It means that the applicant can provide a profound justification for the fact that a phase II dose-finding study has not been conducted and the competent authority will check if the justification is suffient for acceptance.
ALK	Specific	424	424	ALK recommends to clearly state what “sufficient amount of safety data must be generated in first human study” means		Not accepted. During the various steps of clinical development available data on safety have to be provided to decide on the next steps in the development. It is self-evident that the data collected in the first-in human-study, in the field of AIT a phase II trial, needs to be sufficient to decide on the possibility to further continue development in a larger group of subjects (phase III). No general rules on number of subjects or kind of examinations can be made.
LETI Pharma S.L.U.	Specific	424	424	Does “Sufficient amounts” mean number of patients defined according to statistical analysis? Clarification is needed.		Not accepted. See response to ALK line 424. Sufficient amounts does not refer necessarily to the statistical analysis. Please also see the answer to ALK line 424.
Prof. Dr. med. Oliver PFAAR	Specific	436	453	First of all, I appreciate that EMA has delivered the guideline on clinical development programs in Allergen Immunotherapy (AIT) with low to moderate sized populations and in particular focussed on the important claim “treatment of allergic symptoms” due to the practible concerns in performing these trials in these populations. Besides, recommending Allergen Exposure Chambers (AEC) as appropriate measures for selecting patients for trials is much acknowledged. Several AEC are in use worldwide and several groups have collaborated in Position Papers of the European Academy of Allergy and Clinical Immunology (EAACI) on their potential role in the clinical development programs in AIT aimed to improve this technology for scientific and regulatory needs. The international Task-Force members have reported a comprehensive overview on the technical standards (and comparability) of different AEC-models worldwide and also underscored the need for a formal clinical validation through a “hybrid”-approach to explore the test-to-test reliability in comparisons of testing AIT efficacy under natural (e.g., seasonal) allergen exposure and under standradized conditions in an AEC. First trials following this recommendations are being currently performed. In conclusion: based on a solid ground of data, AEC may play an important role especially in the evaluation of efficacy of AIT -even in PHASE III-trials- in small to moderate affected populations such as e. g., animal dander or mould allergies (in which practical reasons (power of trial, standardization of allergen exposure) may be a limitation factor for successful field trials. For these conditions, I am convinced that this approach will be able to fill important gaps in detecting clinical efficacy of AIT out of the ‘classical’ (field-based) pattern in the clinical development programs for PHASE III-trials. 1. Pfaar O, Calderon MA, Andrews CP, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future - an EAACI Position Paper. Allergy. Jul 2017;72 (7):1035-1042. doi:10.1111/all.13133 2. Pfaar O, Bergmann KC, Bonini S, et al. Technical standards in allergen exposure chambers worldwide - an EAACI Task Force Report. Allergy. Dec 2021;76 (12):3589-3612. doi:10.1111/all.14957 3. Rosner-Friese K, Kaul S, Vieths S, Pfaar O. Environmental exposure chambers in allergen immunotherapy trials: Current status and clinical validation needs. J Allergy Clin Immunol. Mar 2015; 135(3):636-43. doi:10.1016/j.jaci.2014.10.045 4. Pfaar O, Zieglmayer P. Allergen exposure chambers: implementation in clinical trials in allergen immunotherapy. Clin Transl Allergy. 2020;10:33. doi: 10.1186/s13601-020-00336-9 5. Pfaar O, Agache I, de Blay F, et al. Perspectives in allergen immunotherapy: 2019 and beyond. Allergy. Dec 2019;74 Suppl 108:3-25. doi:10.1111/all.14077		Acknowledged. Considerations on Environmental Exposure Chambers (EEC) are included in the guideline.
STALLERGENES GREER	Specific	447	447	Study subjects will need to fulfil adequate inclusion and exclusion criteria including a documented clinical history of IgE mediated allergic disease and a positive allergy testing via specific serum IgE and/or a positive skin prick test (SPT). For further details see chapter 7.	Study subjects will need to fulfil adequate inclusion and exclusion criteria including a documented clinically relevant history of IgE ….	Accepted. The comment is in generally endorsed. Although 'clinically relevant' is used here in a different way than used for 'study endpoints', the comment is considered reasonable. The sentence has been updated with 'a documented comprehensive clinical history' to be in line with other section of the guideline.
STALLERGENES GREER	Specific	450	450	RWE "robust" trials" could also be considered for low prevalence allergens (ex: Registries, prespecified and published protocols/SAP...) in addition to bibliographical data, especially for allergens that have been used since decades as NPP products		Not accepted. As detailed in other parts of the guideline RWD/RWE are considered supportive only.

STALLERGENES GREER	Specific	458	458	As pollen counts are unpredictable, a tertile analysis may also be proposed in the protocol to overcome this limitation		Not accepted. The competent authorities are available to discuss possible study designs during a scientific advice meeting. However, this point has no relvance for the scope of the guideline.
STALLERGENES GREER	Specific	490	490	If sting provocation is not possible, and if the comparison of the severity of reactions after the most recent sting (pre-VIT) and after field re-stings (during VIT) are used as efficacy end-points, will a conditional MA be granted until these complementary data are available?		Acknowledged. CHMP may grant a conditional marketing authorisation for a medicine if it finds that all of the following criteria are met: * the benefit-risk balance of the medicine is positive; * it is likely that the applicant will be able to provide comprehensive data post-authorisation; * the medicine fulfils an unmet medical need; * the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required. https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation
ALK	Specific	493	503	ALK would like to suggest to expand to other diagnostic products in addition to the skin prick test (e.g. oral food challenge, nasal provocation test)		Not accepted. The recommendations in the Guideline are not restricted to skin prick test allergens, other test allergens are already mentioned in the scope in section 2 of the Guideline: "Diagnostic allergens for test in vivo: type I (prick test, provocation test, intradermal/intracutaneous test) and type IV (epicutaneous patch test)"
LETI Pharma S.L.U.	Specific	497	498	What is the definition of “limited patient population”? What is the definition of medium to low size	update text	Not accepted. There is no concluding definition regarding "limited patient population" or "medium to low sized patient population" because a prevalence cut-off is not considered feasible and other factors are considered relevant (clinical relevance of sensitisation, common clinical co-allergies, etc). Therefore, no cut-off value is mentioned but the applicant should justify, why the allergen product is considered to be within the scope of the guideline. Only those allergens mentioned in Annex 1 of the Recommendations on common regulatory approaches for allergen products (CMDh/399/2019) are generally excluded from this guideline.
STALLERGENES GREER	Specific	510	513	In Europe, other units exist, e.g. IR/ml defined on the basis of a given wheal diameter and not in comparison to skin reactivity to histamine dihydrochloride	A strength according to 10 HEP or 10.000 BU (same wheal size in a median sensitive patient with a wheal provoked by a positive reference solution consisting of histamine 54.3 mmol/l (e.g. histamine dihydrochloride 10 mg/ml)) may be a useful concentration. Alternatively, a strength in IR/mL (Index of Reactivity per milliliter) corresponding to a given significant wheal diameter can also be considered. In Europe, mostly these methods are performed	Not accepted. The comment is acknowlegded, however not the proposed wording. The stated methods and concentrations are only examples which is evident from the wording using "e.g." in front of the methods and "may be a useful concentration". It is not excluded to use another test. However, as the method to determine IR/ml is understood to be only used by a single company, it should not be explicity mentioned in the guideline.
ALK	Specific	512	513	ALK recommends to explain where the mentioned method is performed outside of Europe, “In Europe, mostly this method is performed”		Not accepted. No changes are considered needed. The sentence means that in Europe mostly biological standardisation is done according to the Nordic guidelines in contrast to the ID50EAL method which is mostly performed in the USA and is described in the following lines.
ALK	Specific	523	523	ALK proposes to change “...could be considered” to “can be performed”		Partially accepted. 'could be considered' has been replaced by 'can be conducted'.
SmartPractice	Specific	545	546	SmartPractice believes that conducting clinical trials with a reasonable number of patients to establish an appropriate dose/concentration should be encouraged. This stands in contrast to the widely used approach of relying on the data collected over 10 years on non-approved allergens to support their registration.	545 "...provided. Data from registries could for example be used, nevertheless, using data from controlled clinical trials is strongly encouraged. Moreover, there should always be data on 546 the sensitization potential of the substance."	Partially accepted. The sentence has been clarified as follows: 'While data from controlled clinical trials are recommended, data from registries may also be used.'
Chemotechnique MB Diagnostics AB	Specific	545	546	We note that there should always be data on the sensitization potential of the substance. We suggest clarifying that case reports and/or epidemiological studies should be regarded as sufficient data in terms of sensitization potential. It should also be clarified if the data concerns the substance itself or for the substance in the final preparation.	Moreover, there should always be data on the sensitization potential of the substance if available, otherwise case reports and/or epidemiological studies will suffice.	Not accepted. If there are no data that the substance has a sensitisation potential it is really questionable why there should be a need to have this substance as epicutaneous patch test. In section 10.1 it is specified that epidemiological studies or case reports may be used to verify the sensitisation potential. No change in wording is needed.

SmartPractice	Specific	546	546	The published sources often lack dose-ranging data, and in the absence of dose-response studies, it is impossible to provide a rationale for dose selection and demonstrate that the dose is optimal based on uncontrolled epidemiological studies. Therefore, in the case of emerging allergens with fewer than 10 years of documented use in humans, dose-response data must be provided as a minimum requirement for authorizing their marketing. Performing an additional confirmatory efficacy study should not be required, as it is possible to collect data for PR and RI calculation in a dose-finding study.	Added paragraph is provided below: 546 " ...the sensitization potential of the substance. For the development of new allergens or to update existing formulations with, for example, a more relevant dose or excipient, it is considered acceptable to conduct a single study that combines dose finding and efficacy assessment. "	Partially accepted. A sentence has been added under section 10.1, as suggested. Reference is made to new medicinal products rather then new allergens.
SmartPractice	Specific	546	546	SmartPractice suggests reiterating that all clinical studies, including epidemiological studies involving the use of unapproved allergens, must comply with EU regulations for clinical trials. This includes obtaining authorization for the studies following a review of a clinical trial application submitted to the CTIS. To make such studies economically feasible, the fees for reviewing clinical trial applications for Type IV allergens need to be reduced. To accelerate the process of conducting dose response studies, which are intended to select the most appropriate allergen (salt/oxide/element) and its dose/concentration, we propose to perform these studies in 10-15 patients. Reducing CMC requirements is necessary to optimize the timeline for initiation of the trials considering the time and resources necessary for developing and validating analytical methods, collecting stability data and the CTIS review cycle.	The paragraph below should follow the paragraph suggested above: "548 All clinical studies including epidemiological studies, which involve the use of unapproved allergens must be authorized following a review of a clinical trial application submitted to the CTIS. It is acceptable to provide reduced quality information in a clinical trial application for products for epicutaneous diagnosis of contact allergies. If a stability indicating method is not available, the IMPD must include the following information for the active ingredient, manufacturing process, finished product control, and stability: - technical data sheets for each active ingredient, - analytical standard procedure which shall at least include testing for appearance and identity of each active ingredient. Identity test shall use an analytical method validated for specificity. - description of the manufacturing process which must be controlled by thoroughly documenting each step of weighing, compounding, and packaging of the finished product. - analytical standard procedure for the finished product release which shall at least include testing for appearance, identity of each active ingredient, and particle size and homogeneity for ointments. – commitment to attribute a shelf life of 3 months to the clinical trial material, unless a longer shelf life can be justified. "	Not accepted. It is not the scope of the guideline to reiterate general requirements regarding clinicals trials or epidemiological studies or the differentiation what would be a clinical study and what can be an epidemiological study. Moreover, this section deals only with the clinical documentation, not with CMC issues. These are described in Section 4.2.
Radoslaw Spiewak	Specific	547	547	A typo?	Dose-finding studies	Accepted. The typo has been corrected.
Radoslaw Spiewak	Specific	549	549	The scientifically correct term for molecules causing contact hypersensitivity and used in patch tests are "haptens". Haptens are small-molecular weight molecules with no immunogenic properties. The effective antigens for type IV allergey emerge as products of haptenization of autologous (body's own) proteins. Thus, the antigens here are made in 99% of body's own proteins. This is in contrast to allergens, which are 100% allogenous (foreign) proteins that intrinsically possess antigenic properties.	of medicinal products. However, for epicutaneous test hapten products, classical dose-finding studies	Not accepted. It is correct that molecules causing contact hypersensitivity are "haptens". However, it is uncommon to include "hapten" in the naming of the products. Thus, "epicutaneous test products" is the correct term and means a product which contains the hapten. No change needed.
Chemotechnique MB Diagnostics AB	Specific	551	553	We propose to include information covering the following in the guideline in case studies are to be performed: We propose that a marketing authorization application can be made either on published literature or based on clinical data from a minor dose response study (3 dilutions) in 15-20 patients with suspected or known allergy to the studied hapten. The formulations used in these dose response studies must be controlled and produced according to GMP. The following criteria for defining an appropriate hapten formulation and dose are proposed: • A dilution series eliciting a positive response in at least the majority of subjects with suspected or known allergy. • The optimal hapten dose is defined as the lowest dilution series dose eliciting a positive response in the highest number of subjects who respond positively to the dilution series hapten with the lowest rate of irritant and doubtful reactions. The study site should be a site/clinic approved by an approved competent organization with knowledge of allergic contact dermatitis diagnosis and patch test products. To conduct the studies the patch test hapten must show documented: 1) control of active ingredient identity 2) manufacturing in a GMP approved facility 3) manufacturing process with in-process controls 4) controls of the finished product including verification of identity, particle size and homogeneity by microscopic determination. 5) release to clinical study site by the Qualified Person (QP) taking responsibility for the above The clinical centers would be allowed to conduct the dose response studies without going through a traditional clinical application process, but the study should be approved by an ethics committee if required. Data from these studies along with published clinical data and a non-clinical report would support the registration of the new haptens.	A marketing authorization application can be made either on published literature or based on clinical data from a minor dose response study (3 dilutions) in 15-20 patients with suspected or known allergy to the studied hapten. The clinical centers would be allowed to conduct the dose response studies without going through a traditional clinical application process, but the study should be approved by an ethics committee if required. Data from these studies along with published clinical data and a non-clinical report would support the registration of the new haptens.	Not accepted. It is not acceptable to omit any proof of efficacy (Please see also response to comment below). Thus, to have generally only dose-finding data in a limited number of patients is not acceptable. Moreover, most bullet-points refer to quality requirements which should not be detailed in the section on clincal development. In addition, this guideline cannot supersede the legislation e.g. in which cases approval of an ethic commitee is sufficient (e.g. for epidemiological studies) or when approval of a clinical trial via a CTIS procedure is necessary. Proposed change not accepted.
Radoslaw Spiewak	Specific	554	554	It is unclear, what would a "medical need" be in this context?	e.g., of reactions in certain occupation groups may be another source of data documenting diagnostic	Partilally accepted. Only substances should be used in epicutanous patch test products for which there is a medical need to test. The predominant requirement therefore is that the substance has a sensitisation potential. To make it more clear, the following wording has been included at the end of section 10.2: "Reactions in certain occupation groups may be another source of data documenting sensitisation potential and thereby the medical need to develop a patch test product."
Radoslaw Spiewak	Specific	555	555	Ein Tippfehler?	need and sensitization potential. Regarding dose-finding, concentrations used e.g. in cosmetics may be	Accepted. The typo has been corrected.

Chemotechnique MB Diagnostics AB	Specific	562	563	As concluded in section 10 sensitivity and specificity, can often not be determined, data for the clinical assessment of patch test haptens on the positivity ratio (PR) and the reaction index (RI) we therefore suggest to waive any further requirement of confirmatory studies other than the dose finding data proposed.	As data on sensitivity and specificity, often cannot be determined, waiving any further requirement of confirmatory studies other than the dose finding data would be deemed acceptable.	Not accepted. A general waiver for efficacy data is not acceptable. The proof of efficacy should be due to the best method which is feasible for the individual allergen. Thus, for allergens, where determination of sensitivity and specificity is possible, it should be determined. If this is not possible, PR and RI should be determined. Only if this is also not possible, which has to be justified by the applicant, such data might be omitted. No change necessary.
SmartPractice	Specific	569	569	A clarification is included to prevent confusion during the development of patch test formulations containing substances with intrinsic irritant properties, such as metal salts and other acidic substances. It's common for these substances to yield PR (Primary Irritation) and RI (Relative Irritancy) values outside the ranges considered 'suitable' or 'good' in literature. While reducing the active ingredient concentration can decrease the frequency of irritant reactions, it may also decrease the intensity and number of positive reactions, potentially missing relevant positive reactions in weakly sensitized patients. Therefore, dose-ranging studies, as described in Section 5.2, are necessary. Formulations with PR and RI values outside the typical ranges are acceptable for approval but with caution noted in the Summary of Product Characteristics (SmPC).	569 "...manufacturers should be submitted wherever available in addition to limited data from clinical studies. If the positivity ratio (PR) and reaction index (RI) fall outside the ranges described in the literature for a "suitable" or "good" formulation [2,3,4], indicating that an allergen may produce frequent irritant or doubtful reactions due to its intrinsic chemical and physical properties, the SmPC should include a caution. This caution should advise that such an allergen may require a more careful examination of the patch test site reactions."	Not accepted. This is out of the scope of this guideline.
EFA	Specific	575	586	EFA fully understands the legal and ethical implications of prioritising adults in clinical trials. However, we would like to stress the following considerations: 1. When conducting an extrapolation exercise, both regulatory authorities and applicants need to keep in mind that children are not small adults. This means that data from adult populations cannot be extrapolated easily to children due to the huge differences in the immune system of each age group.		Acknowledged. According to the EU Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use (Paediatric Regulation) any MAA for a new medicinal product should include either the results of studies conducted in compliance with an agreed paediatric investigation plan (PIP), or an EMA decision on a waiver or on a deferral. Please see also below comments (lines 125, 126)
EFA	Specific	575	586	2.It is reasonable to prioritise adults in clinical trials conducted for drug products, where there is an unknown component being tested (as opposed to food products, for example). The findings can then be used as evidence basis to assess the product's use in children population. This consideration needs to lead to a differentiation between drugs and AIT products in the context of this Guideline.		Partially accepted. The first part of this comment is agreed and in line with the paediatric regulation (Paediatric Regulation EC 1901/2006). See also above comment. However, the proposed differentiation between drugs and AIT products is not fully shared. Therefore not accepted.
EFA	Specific	575	586	3. Linked to the previous, in the case of food allergy, the focus group should be the children. There should be an option of separate clinical trials conducted with children, based on the fact that most allergies are growing during childhood. In addition, there are known AIT products for food allergy that are not even effective in adults, so having clinical trials with adults would not lead to marketing authorisation. Besides, according to current knowledge (e.g. Finnish Allergy Programme), the ideal age to determine the tolerance level of the immunity system to a specific food allergy is at the beginning of childhood, which explains why studies on children are proven more effective than those on adults. Of course, clinical trials with children need to be conducted based on the highest ethical and safety standards, and ensure that children are well-informed, asked for their consent, and respected.		Accepted. It could be expected that in case of food allergy, children will benefit more from AIT than adults. In this case it could be relevant to start the studies in paediatric population, based on agreed paediatric investigation plan. A sentence has been included at the end of section 12.
STALLERGENES GREER	Specific	578	579	Mention is made that extrapolation can be done when population is too low. Or to include patients from these low population to trials. RWE is not mentioned as supportive data for products that are already marketed. For low prevalence population, registries could also be considered should data are missing or not robust	RWE data or registries can also be used to demonstrate product's safety and efficacy.	Partially accepted. As detailed in other parts of the guideline RWD/RWE are considered supportive only. See sections 8.2.1. and 10 of the guideline.
Diater	Specific	231	231	Section 5.1 recognises that natural allergens are considered to be basically non-toxic, and therefore the development of a toxicity programme would not apply. However, for chemically modified allergens, repeat-dose toxicity tests including local tolerance, reproductive, developmental toxicity and genotoxicity are defined as mandatory. The following question is proposed: If the allergen has been previously marketed as NPP, and the pharmacovigilance reports are available, could Repeat-dose toxicity including local tolerance tests be waived, it seems reasonable that the accumulated human experience avoids this a posteriori developmental animal toxicity.		Partially accepted The need for performing animals studies will always be evaluated to comply with the 3R principles. Thus, if an allergen product has been previously marketed as NPP, all available safety data should be provided in the dossier, to consider if a repeat-dose study is necessary. A general waiver is not possible. The text in the guideline has been rephrased.
Diater	Specific	238	238	Keeping in mind that risk benefit conclusion is accepted, we consider that it is important to add specifically that pharmacovigilance data and real market NPP experience can be included in this profound expert statement. This is also aligned with the 3R principle "Regulatory acceptance of 3R (replacement, reduction, refinement) testing approach" (EMA/CHMP/CVMP/JEG-3Rs/450091/2012).		Partially accepted. Data from marketing experience as phamacovigilance data have to be submitted within the dossier. Of course, in the expert statement it could and should be referred to these data. To make this more clear, a statement was included in the guideline that the need to perform animal studies should be evaluated based on available data (see comment above).