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Pre-Authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE DEVELOPMENT OF PRODUCTS FOR SPECIFC IMMUNOTHERAY FOR THE TREATMENT OF ALLERGIC DISEASE

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	ALK-Abello A/S	Denmark
2	Luis Delgado	Portugal
3	GA2LEN	
4	Laboratorios LETI	Spain
5	Stallergenes S.A.	France
6	Allergy Therapeutics & Bencard Allergy	United Kingdom / Germany
7	EAACI / Jan Lötvall (corresponds to Valovirta & Passalacqua)	
8	Friedrich Horak	Austria
9	GSK Biologicals	Belgium
10	EFPIA	
11	HAL Allergy	Netherlands
12	Schering-Plough	USA
13	Desiree Larenas Lindemann	Mexico
14	Allergopharma	Germany

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
The publication of this draft guidance is welcomed as an opportunity to clarify the requirements for the clinical development of products for specific immunotherapy. We believe that the guideline is an important first step in establishing acknowledged best practices for applicants and regulatory agencies.(**Stallergenes)** The guideline is quite ok and could be improved by implementation or consideration of the comments below (**Allergy Therapeutics & Bencard Allergie)** Regarding the comments see responses below. We found the document very interesting and think that it will significantly help the development of new products for specific immunotherapy. In Europe, well over 20% of the population suffers from symptomatic allergic diseases and medications are unable to control a large proportion of patients. Allergen-specific immunotherapy therefore represents another therapy of interest. With new treatment modalities and new allergenic products, it is essential that a guideline for the clinical development of these products should be issued by CHMP. (**GA2LEN**) We welcome this new guideline because it reflects clinical development of products for SIT according highest standards and the recommendations are based on scientific background. (**Allergopharma**) EFPIA welcomes the drafting of a guideline on specific immunotherapy for the treatment of allergic diseases (SIT). This draft recommendations are already a fair summary of SIT studies developed so far.(**EFPIA**) Many of the aspects touched in the EMEA draft have been taken into consideration in a previous document (Canonica G et al, Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy. Allergy 2007; 62:317-24), although with some differences. This position statement was endorsed by the American Academy of Allergy Asthma and Immunology (AAAAI), the American College of Allergy Asthma and Immunology (ACAAI), the Asian Pacific Association of Allergy and Clinical Immunology (APAACI), the European Academy of Allergy and Clinical Immunology (EAACI) and the Latin-American Society of Allergy Asthma And Immunology (SLAAI). We think that the aforementioned document should be at least quoted in this version of the EMEA guidelines. (**EAACI / Jan Lötvall, Valovirta, Passalacqua)** The document is included in the reference list of the guideline. As stated in the executive summary, the intended purpose of this document is to give guidance on study design, and to address issues of efficacy and safety for allergen extracts and allergenic proteins being developed for specific immunotherapy of allergic diseases. As such it should be clear, concise and cover the relevant points (including stating where there is a need for further information). The document is not always clear: some sections would benefit from re-writing. In addition

important points are absent or left open to doubt.
If this is truly a guideline it would benefit from being evidence based. If evidence is lacking it may be more accurately termed a discussion, directive, or consensus statement (in which case those involved in input should be clearly stated). (**Laboratorios Leti**)

Suggest to give "Point to consider" e.g. in bullet format rather than specific directions in terms of "should"/ "must" wordings.
One example could be in section 4.1.2 page 5 1st line stating that *"…..**should** exclude subject with clinically relevant sensitisations to other allergens….."*. This could be a good advise listed along with other good advises (points to consider). However one could easily image a trial where subjects are treated with several SIT products and the measurements and trial design reflects that situation.
Another example is section 4.1.1 where it reads that "*The history …..… **should** cover at least 2 consecutive years….*" This does not allow for prevention trials or trials in very young children. (**ALK-Abello A/S)**

It is intended to give specific guidance. Therefore, the suggestion to give "Points to consider" in bullet format is not implemented.

- Finally, it would be easier to identify within the guideline, four different main chapters (e.g. population, selection criteria, study design and endpoints) with all their related information so that these topics can be adequately described, and in line with the different potential claims (seasonal and perennial allergic rhinitis, Asthma and Insect venom allergy). (**EFPIA)**

The proposal has partially taken into account (see section 4).

Suggest to make a separate chapter on venoms like the chapter 4.2.5 on food allergy rather than a few sentences on venoms here and there. This will enhance the readability. (**ALK-Abello A/S)**

Since many of the recommendations for SIT in inhalant allergies are also true for insect venom allergies a separate chapter on insect venoms will be highly redundant with other parts of the guideline. Thus insect venom allergy was retained within the different chapters and differences to inhalant allergies were pointed out where necessary.

Some revisions are already proposed for further consideration prior to finalisation:
- It is acknowledged that SIT is the treatment of choice in insect venom allergy. However, assessment is quite different and as a consequence, it is recommended to either delete them from the scope of this guideline or to consider them more in depth in a specific reflection paper (**EFPIA)**

The basic mechanisms of specific immunotherapy are the same regardless whether allergy to inhalational allergens or allergens like insect venoms are addressed. Thus guidance on insect venoms was retained in the guideline.

A *list of definitions* is missing, including: allergen, species, up-dosing.....(**ALK-Abello A/S)**

A list of definitions and abbreviations was included in the revised guideline and harmonised with the corresponding BWP guideline.

A separate section on advice in establishing clinically meaningful effect is called for. One option could be to encourage scientific advice from the competent authorities. (**ALK-Abello A/S)**

It is not in the remit of a regulatory guideline to define a clinically meaningful effect. Such an effect depends on the clinical situation under investigation.

Keywords on Front page: More keywords will be useful both for the applicants and the competent authorities. Add: allergy vaccination, allergic rhinoconjunctivitis, allergic asthma, asthma prevention. (**ALK-Abello A/S)**

Allergy vaccination and allergic rhinoconjunctivitis were added.

The quality and standardization of the allergen should be more thoroughly discussed or referred to in another EMEA guideline.
We think that venom and inhalant-allergen immunotherapy should be considered separately

(**GA2LEN**)

Reference is made to the "Guideline on Allergen Products: Production and Quality Issues (CPMP/BWP/304831/07)". With respect to venom- and inhalant immunotherapy see response above.

In our opinion this guideline does not address adjuvanted vaccines (use of immunostimulants). (**GSK BIOLOGICALS)**

This guideline does address all products for the specific immunotherapy, regardless if an adjuvant is added or not.

Terminology about type of allergen product is not consistent through out the document and should be clarified. Specific examples are given below. (**ALK-Abello A/S)**

In the present draft there seems to be general confusion around the use of words like allergen, extract etc. Extensive use of the word "allergen product" is proposed, with the addition of relevant terms in brackets where relevant, *e.g.* allergen product (extract) or allergen product (allergoid)....(**ALK-Abello A/S)**

In all text, in order to avoid confusions, is better to use the words ***allergen products*** instead allergen extracts, allergen proteins, …. (**Laboratorios Leti)**

Agreed, the term 'allergen products' is now used throughout the guideline.

The term “allergic rhino-conjunctivitis” is used, but not all patients with pollen-induced allergic symptoms have rhino-conjunctivitis. Mites rarely induce ocular symptoms. WHO does not favour this term [2]. (**GA2LEN**)

Agreed, it is now always stated “rhinitis and/or rhino-conjunctivitis”.

Insufficient attention is given to the research of specific Immunotherapy for asthma (**LUIS DELGADO)**

For treatment of asthma refer to the “Note for Guidance on the Clinical Investigation of Medicinal Products in the treatment of Asthma (CPMP/EWP/2922/00)”.

Other subject to take into account is that the guideline should differentiate between:

- Traditional products already on the market for several years, the preclinical/toxicological investigations of which were based on acute and subchronic (repeat dose toxicity testing) toxicity and which have proved to be toxicologically safe after use in many hundred thousands of patients and millions of injections
- Novel medicinal products representing allergen preparations the manufacture of which uses technologies or additional active ingredients which have never been used before and of which no or very limited experience in the use in humans exists

Rationale:

For native, purified, and polymerized extracts the body of toxicological evidence comprises as much as 3 decades and more of experience. Consequently this body of evidence should be taken into account when specifying the package to toxicological investigations to be performed.

We think that this guideline should provide advice on the scope of the preclinical (toxicological) package required depending on the nature of the product(conventional well established products versus novel products resulting from the use novel technologies). (**Laboratorios Leti**)

It is not the scope of this guideline, to give advice to the preclinical package.

Good document. Guideline on dosing specification missing. Safety issues reporting recommendations should be amplified
I think it important to stress that the dose has to be stated exactly: how much allergen is given (if possible in micrograms of mayor allergen, for house dust mite group 1 and 2, for grass group 5, the manufacturer and name of commercial product-if available- have to be stated). Build-up schedule and maintenance dosing quantity and frequency. If it is in drops, tablets, SLIT-swallow or SLIT-spit. If possible total monthly dose in mcg major allergen. (**Larenas Lindemann)**

Up to know, there are no scientifically evidence based recommendations for exact doses for the allergen content in allergen products to achieve efficacious and safe allergen products. Moreover, validated and generally accepted methods to measure the major allergen content in extract and biological reference preparation of major allergen do not yet exist. Thus it is not possible to recommend specific doses.

SPECIFIC COMMENTS ON TEXT		
EXECUTIVE SUMMARY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Allergen Products		
Line 2	Products are developed not extracts and proteins. Thus replace “extracts and allergenic proteins” by “products” **ALLERGY THERAPEUTICS**	Accepted.
Line 3	The title of the guideline includes the scope of clinical development of **products** for specific immunotherapy. Consequently “Allergen extracts and allergenic proteins” is suggested to be replaced by “Allergen products, i.e. based on drug substances of allergen extracts, recombinant allergens, purified allergens, modified allergens, absorbed allergens…”. Proposal “Allergen extracts and allergenic proteins” is suggested to be replaced by “Allergen products, i.e. based on drug substances of allergen extracts, recombinant allergens, purified allergens, modified allergens, absorbed allergens…”. **ALK-Abello A/S**	Accepted.
Line 3	Severity should not be graded, indication is different in different countries Replace “mild allergic asthma” by “allergic asthma” **ALLERGY THERAPEUTICS**	Deleted, the Guideline does not deal with asthma.
Line 3	Even though these are just examples SIT is not only for mild allergic asthma. It could also be developed for moderate to severe asthma or prevention of asthma. Proposal: Delete “mild” in “~~mild~~ allergic asthma”. **ALK-Abello A/S**	See above.

1 INTRODUCTION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Paragraph: 1 Line 6	".. the latter acting independently from any atopic risk" is suggested to be deleted as the wording is not clear and not considered to be relevant in the actual context. Proposal: ".. the latter acting independently from any atopic risk" is suggested to be deleted **ALK-Abello A/S**	The sentence was deleted.
Paragraph: 1 Line 6	Add food to the allergens **LARENAS LINDEMANN**	Accepted.
Paragraph: 2	In the introduction, it is stated that immunotherapy should be considered for the long-term management of allergic diseases, but in venom immunotherapy, it does not take long to react and new studies on pollen allergy have found that the treatment is effective within weeks. **GA2LEN**	The statement is understood; however for a persistent efficacy even immunotherapy with insect venom should be conducted for at least 3 years and the patient should not only benefit from the fast effect but should have a long-lasting effect. Thus there is no discrepancy between the fast onset and the long term management.
Line 3	"… with allergens.." suggested changed to "….with allergen products" and "…allergen extracts or allergens" suggested changed to "the drug substance of the allergen product" as the source of the allergens is not relevant for the definition of specific immunotherapy **ALK-Abello A/S**	The terms were changed.
Line 4	Suggested to read ".. in order by means of immunomodulatory mechanisms to provide sustained relief of symptoms and need for … " **ALK-Abello A/S**	The text has been changed as follows: "Specific immunotherapy with allergen products is the repeated administration of allergens to allergic individuals in order to activate immunomodulatory mechanisms and

		provide sustained relief of symptoms…"
Paragraph 3	The mechanisms of immunotherapy are more complex than those presented. Mast cell and basophil down-regulation exists within a short time and is reversible when immunotherapy is stopped. On the other hand, effects on T-cells occur at a slower rate and are long-lasting after immunotherapy is stopped **GA2LEN**	The view that the mechanisms of immunotherapy are more complex than presented is supported. Moreover, up to now mechanisms are not fully understood. Therefore it is stated "Even if the mechanism of action regarding the clinical effect of specific immunotherapy is up to now not fully understood the underlying mechanisms have been studied, showing that immunotherapy has the potential to modify the course of allergic disease." The following mechanisms are examples and not a complete list of mechanisms. This will be clarified by including "For example, …"
	The changes are only seen in the amount of specific antibodies Proposal: Add 'specific' to antibodies and IgE response. **LARENAS LINDEMANN**	Accepted.
Paragraph: 4	A rephrasing, softening, is suggested. There is not clear one-to-one relationship between immunological markers and clinical outcome, but indications of predictive measures have been seen although not published yet. Proposal: Rewording: However, the mechanism is not such clear that any of the mentioned changes of the immune system is predictive for the clinical outcome. To: At present a relationship between immunological markers and clinical response is not yet fully established. **ALK-Abello A/S**	The passage was rephrased to: "However, up to know the mechanism is not fully understood and at present none of the mentioned changes of the immune response has been shown to be predictive for the clinical outcome. Nevertheless clinical studies to correlate immunological changes to clinical outcome are recommended."
Paragraph 4	Sentence "However, the mechanism is not such clear that any of the mentioned changes of the immune system is predictive of clinical outcomes:" Clinical studies are continuing to assess immunological assessments. The guidance should not limit future assessments. Replace sentence with the following:	Accepted. See response above.

	"Although not currently demonstrated, clinical studies can be conducted to correlate immunological changes to clinical outcome. " **Schering-Plough**	
4th paragraph	'such' sounds out of place Proposal: Change 'such' for 'that' **LARENAS LINDEMANN**	Accepted
6th paragraph	Change "However, up to now…" in "Up to now…".	Accepted
6th paragraph	Sentence "However, up to now there is a wide variety of study designs in terms of e.g. study duration, inclusion criteria, end-points chosen, analysis of data, and control of environmental variables in the evaluation of new preparations for specific immunotherapy." Please include "dosage" in list… **Schering-Plough**	"Dosages" was included in the list.

2 SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Line: 2-5 Paragraph: 2	"allergen preparation" should be "allergen product (e.g. products prepared from extracts, …etc) " and "Application route" should be changed to the regulatory term "route of administration" **ALK-Abello A/S**	Accepted.
Paragraph: 2	The scope could be further clarified to indicate that this guideline does not address adjuvanted vaccines. **GSK BIOLOGICALS**	This guideline does address all products for the specific immunotherapy, regardless if an adjuvant is added or not or which adjuvant is added.
Paragraph 3	"This guideline does not cover atopic eczema/dermatitis" Add "or asthma without established allergen as cause"	The term is added.
Complete section 2	A rewording is thus proposed Proposal: This guideline provides guidance for the development of studies of products for specific immunotherapy to enhance the assessment and comparison of results of such studies. This guideline covers clinical studies on specific immunotherapy, regardless of the affected organ system (e.g. nose, upper and lower airways, eyes, multi organ affection (systemic reaction)), the allergen source (e.g. pollen, mites, animal dander, moulds~~, insect venoms, food~~), the allergen preparation (e.g. extracts, purified allergens, modified allergens, adsorbed allergens) or the application route (e.g. subcutaneous, sublingual). This guideline does not cover atopic eczema/dermatitis, nor food allergies/ intolerance or insect venom allergies. **EFPIA**	The underlying mechanisms of specific immunotherapy are the same regardless if an allergy to inhalational allergens or allergens like insect venoms or food are addressed. Thus insect venoms and foods are retained in this guideline.

3 LEGAL BASIS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	The CPMP/EWP/2455/02 "Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-Conjunctivitis" is included as a Guideline with Directive 2001/83/EC. The text of this guideline states in page 3 that this NfG does not cover the use of specific immunotherapy and anti-IgE agents **LABORATORIOS LETI**	As correctly stated, this NfG was not intended for specific immunotherapy, especially with regard to the suggested study designs. Therefore, a separate guideline for specific immunotherapy was required. Nevertheless, some issues stated in the guideline CPMP/EWP/2455/02 are also valuable for the therapy with specific immunotherapy, therefore these guidelines should be read in conjunction.
	Additional documents and guidelines could be included. E.g. ICH guidelines on safety reporting, clinical study reports, dose-finding and general GCP. Proposal: Include (as a minimum): ICH: Topic E2A, E3, E4 and E6. **ALK-Abello A/S**	The suggestions were included in the revised version.

4 MAIN GUIDELINE TEXT		
4.1 PATIENTS' CHARACTERISTICS AND SELCTION OF PATIENTS		
4.1.1 DIAGNOSIS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.1.1 1st sentence	What is meant by well-documented? Overlapping with *section 4.1.2 Selection of patients* *Proposal:* Suggest to give "Point to consider" e.g. in bullet format rather than specific directions (see General Comments) Points to consider: 1) Classification of rhinoconjunctivities in the past (e.g. last two years) according to ARIA Guidelines 2) Classification of Asthma in the past (e.g. last two years) according to GINA guidelines 3) Duration of allergic disease 4) Previous and current treatment classified into drug classes 5) Concomitant diseases including multiple allergies. **ALK-Abello A/S**	Well documented means a documentation of the allergy by means of need of medication for treatment of symptoms, positive skin prick test and/or specific IgE to the suspected allergen source, documented symptoms etc.. It is not sufficient to state: "The patient was allergic to …" The reasons for this conclusion have to be given and criteria justified. The guideline follows the usual format. Thus, the proposal is not followed.
4.1.1 1st sentence	Sentence "For specific immunotherapy trials patients should have a well-documented history of their allergic conditions before study entry." **Recommendation: removal of 'well-documented'.** Rationale: The experience of the investigator should allow for the screening of subjects such that only patients with convincing histories of clinical allergy who display adequate symptoms to the allergen of interest are enrolled. **SCHERING PLOUGH**	See response above.
4.1.1	The second sentence should read: "The history …. at least 2 consecutive years for seasonal	Accepted.

2nd sentence	allergy and 1 year for perennial allergy …" **ALLERGY THERAPEUTICS**	
4.1.1 2nd sentence	The history of atopic diseases such as allergic rhino-conjunctivitis or allergic asthma should cover at least 2 consecutive years for seasonal allergy **or one year for perennial allergy,** and diagnosis should follow current guidelines [5]. Rationale: For perennial allergy, one year of symptoms should be considered as sufficient to confirm the medical history of the patient. Proposal: The history of atopic diseases such as allergic rhino-conjunctivitis or allergic asthma should cover at least 2 consecutive years for seasonal allergy **or one year for perennial allergy,** and diagnosis should follow current guidelines [5]. **STALLERGENES**	Accepted.
4.1.1 2nd sentence	A two year requirement of symptomatic diseases seems reasonable but this is a criterion for selection of patients not for diagnosis and this sentence should be moved to section 4.1.2. Reference number 5 is the GINA document and refers only to asthma. It doesn't refer to rhino-conjunctivitis Proposal *This reference should be complemented with other reference that covers rhino-conjunctivitis, for instance, the ARIA document, British guidelines for asthma, European guidelines, …* **LABORATORIOS LETI**	The two consecutive seasons are relevant for both, diagnosis and inclusion of patients. Please see also comments to the well-documented history of the allergy. Thus, only properly diagnosed patients can be included and therefore the criterion is well mentioned under "Diagnosis". As the GINA document refers only to asthma other guidelines like the ARIA document were included as well.
	Selection of patients: The guideline proposes to assess only asthma (GINA). There is no mention of rhinitis. We propose that for • Asthma: the new GINA guideline should be used • Rhinitis: the ARIA guidelines should be used. **GA2LEN**	The ARIA document was included.
4.1.1 2nd sentence	"… should cover at least 2 consecutive years" suggested to be deleted because less than 2 years may be relevant for example in children. Proposal: "should cover at least 2 consecutive years" suggested to be deleted	Not agreed: In general a history of 2 consecutive years of allergy to seasonal allergens are necessary to exclude patients which had similar symptoms during a pollen season

	ALK-Abello A/S	but due to other reasons than allergy, or to exclude patients with only minimal symptoms only occurring in seasons with very high pollen load.
4.1.1 2nd sentence	One season is sufficient to determine whether disease severity indicates therapy. Proposal: The history of atopic diseases such as allergic rhino-conjuctivitis or allergic asthma should cover at least **1 year**. **HAL ALLERGY**	See response above.
4.1.1 2nd sentence	The history of atopic diseases such as allergic rhino-conjunctivitis or allergic asthma should cover at least 2 consecutive years, and diagnosis should follow current guidelines. **Recommendation:** add allowance to enrol patients with 1 year of symptoms **Rationale:** symptoms may be minor the next year due to less exposure, travel outside of the region during the season etc. The subject should not be excluded from starting treatment if it is clearly indicated and they have data based on one severe season**.** Proposal: The history of atopic diseases such as allergic rhino-conjunctivitis or allergic asthma should cover at least 2 consecutive years **or 1 season with symptoms not adequately controlled by anti-allergic medication**, and diagnosis should follow current guidelines. **SCHERING PLOUGH**	See response above.
4.1.1 2nd sentence	"Atopic" suggested changed to "IgE mediated" in order to have a specific and agreed understanding – the term "atopic" is not well defined. Proposal: ….."atopic diseases" suggested changed to "IgE mediated diseases" … **ALK-Abello A/S**	Agreed.
4.1.1 2nd sentence	"current guidelines" should be changed to "current international guidelines" in order not to confuse with regulatory guidelines (e.g. CHMP or EU Commission). Proposal: "current guidelines" should be changed to "current international guidelines" **ALK-Abello A/S**	Agreed.
4.1.1	"hymenoptera" suggested to be deleted because other insect venoms may be relevant such	Not agreed:

3rd sentence	as mosquitoes Proposal: “hymenoptera” suggested to be deleted. **ALK-Abello A/S**	The term hymenoptera is correctly mentioned here. All knowledge in this area and the specific issues such as the possibly life-threatening reactions are related only to hymenoptera venoms.

4.1.2 SELECTION OF PATIENTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.1.2 1st paragraph	"…allergens.." suggested to be "…allergen products" **ALK-Abello A/S**	In this case, the individual allergen molecules mediating the reaction are meant, not the allergen product, thus the term „allergens" is correct in this context.
4.1.2 1st paragraph	"…and concordant…" suggested to be "and/or" – and at least to delete "concordant" because the two measurements do not measure the same parameters (blood versus skin prick test). "…and concordant…" suggested to be "and/or" – and at least to delete "concordant". **ALK-Abello A/S**	It is accepted to delete "concordant". For a clinical study the patient panel should be well characterized; thus it is recommended to use both skin prick test and specific IgE for a comprehensive diagnosis. Consequently it is recommended that both tests should be performed. However, in justified cases it may be suitable that only one assay is positive, this has to be justified by the applicant.
4.1.2 1st paragraph	These should be documented by positive skin testing and concordant positive IgE determinations (validated quantitative system for detecting allergen-specific IgE) to the relevant allergen to be studied with specific immunotherapy. Recommendation: add "/or" Proposed change These should be documented by positive skin testing and/or concordant positive IgE determinations (validated quantitative system for detecting allergen-specific IgE) to the relevant allergen to be studied with specific immunotherapy. **SCHERING-PLOUGH**	See response above.
4.1.2 1st paragraph	There is no validated quantitative system available Delete the bracket **ALLERGY THERAPEUTICS**	Not agreed: Several quantitative systems have at least an In-House-Validation. Moreover, for example for the Phadia-CAP-System and other in vitro test systems, national and international collaborative studies are conducted on a regular basis.
4.1.2	There is a contradiction in saying that patients enrolled should at one hand only be sensitised to a limited number of allergen sources and then at the other hand stating that is a	Not agreed. However, to clarify the issue, the chapter

1st paragraph	rare case. Bias should be avoided, i.e. overlapping conditions (allergies) is a point to consider. The patients enrolled should typically support to indication. Proposal: Delete sentence concerning sensitisation to only a limited number of allergen sources. **ALK-Abello A/S**	has been reworded.
4.1.2 1st paragraph	As mentioned in § 4.1.2. "trials… should exclude subjects with clinically relevant sensitisations to other seasonal allergens with overlapping seasons and/or perennial sensitisations". This sentence is more accurate than line 4 'studies should rather include patients with sensitisations to a limited number of allergen sources'. As this latter sentence is redundant we propose to remove it. Proposal: Remove sentence in § 4.1.2. "As a consequence specific immunotherapy studies should rather include patients with sensitisations to a limited number of allergen sources." **GSK BIOLOGICALS**	With regard to the inclusion of polysensitised patients see response above.
4.1.2 1st paragraph	It is acknowledged that recruitment is quite difficult and rather limited as shown in studies published in the literature. Recruiting monosensitised patients is likely to limit the recruitment knowing in addition this will not reflect the real life situation where SIT is used in polysensitised patients, even if SIT is targeting one major allergy based on diagnosis considerations. Recruitment of polysensitised patients is quite possible and relevant as in line with the clinical practice, provided the main responsible for allergic symptoms is identified and targeted. Once appropriately treated, clinical benefit should be obvious. Some revisions are thus proposed. Proposal: To avoid bias of results of clinical studies, specific immunotherapy trials on seasonal allergens should **when possible** exclude subjects with clinically relevant sensitisations to other seasonal allergens with overlapping seasons and/or perennial sensitisations. **If patients with clinically relevant seasonal allergies and/or perennial sensitisations are included in clinical trials with seasonal allergens, specific attention to control periods for collection of efficacy data should be carefully considered.** Trials with perennial allergens should not include patients with clinically relevant other perennial allergies. If patients with clinically relevant seasonal allergies are included in clinical trials with perennial allergens, control periods for collection of efficacy data must	With regard to the inclusion of polysensitised patients see response above. However, it is necessary to exclude patients with clinically relevant sensitisations with overlapping seasons or sensitisations which are clinically relevant in the periods of collecting efficacy data, due to the influence of the symptoms caused by another allergens source and rescue medication use. Thus it is not possible to include "when possible" in this context. If the recommendation "specific attention to control periods for collection of efficacy data should be carefully considered" is fulfilled as such that a bias can be avoided, there is no overlap in the collection data period. This situation is considered by excluding only patients with clinically relevant sensitizations which overlapping seasons and/or perennial sensitizations if relevant in the collection data period. The sentence "if relevant in the period of data collection" was added to enhance clarity.

	not overlap with the season for the seasonal allergens. **EFPIA**	
4.1.2 1st paragraph	○ The first paragraph is poor English and unclear. Concisely stated it includes two points: 1. Sensitisation to the study allergen should be confirmed by skin prick test and/or detection of specific IgE in serum (RAST or CAP): if a consensus can be reached, a required level of sensitisation could be stated here. 2. Many patients are sensitised (have specific IgE) to more than one allergen (or allergen group): multiple sensitisation should be carefully assessed by history, skin test and/or serum specific IgE. Patients who have symptomatic allergic sensitisation to other allergens that are in the environment in the same time as the allergen product under study should not be included in clinical trials of specific immunotherapy, as symptoms due to non-study allergens may confound results. Sensitisation to non-study allergens is acceptable if asymptomatic or occur out of the season of the allergen product under study. **LETI**	The content of the paragraph is correctly summarised. A required level of sensitisation can not be stated. To clarify the issue, the chapter has been reworded.
4.1.2 1st paragraph	Suggest to add "Overall, it is necessary that the causal role of the allergen is documented and that appropriate testing excludes the relevance of other allergens to which the patient is sensitized." **EAACI**	Agreed and included.
4.1.2 1st paragraph	Discussion on seasonal and perennial: I live in Mexico and here we have a sub-tropical climate, as in many southern European countries. This means we have polinization all year long, so pollen is a perennial allergen. Moreover the house dust mites are only present in high levels during the humid time of the years: so the mites and molds are seasonal allergens. People suffering from HDM allergy get worse mostly in july-october, the rainy season. So the concept of seasonal and perennial applies, but the examples are not right. If this doc is to be universal, may be something about this can be said **LARENAS LINDEMANN**	Not accepted. This guideline addresses primarily European issues.
4.1.2 1st paragraph	Most patients with "seasonal" rhinitis due to pollens have persistent symptoms whereas many patients with "perennial" rhinitis have intermittent symptoms. Moreover, for some pollens such as *Parietaria*, symptoms occur for more than 6 months in certain patients. Finally many patients are polysensitized. Over 50% of patients with perennial allergy have intermittent rhinitis[7 , 8] . This is why large numbers of trials with many different medications are negative after 6 weeks of treatment and why the placebo effect becomes very large in one-year trials [9]. Patients with	No differentiation was made regarding persistent or intermittent symptoms by the inclusion of patients neither for seasonal nor for perennial allergies. This is more generally addressed in the statement that "Patients… should experience an appropriate minimum level of symptoms" To clarify the issue, the paragraph was reworded in response to several

	perennial allergens should also have persistent symptoms to show the efficacy of immunotherapy **GA2LEN**	comments.
4.1.2 2nd paragraph	○ The second paragraph states that "Patients with allergic diseases due to inhalational allergens enrolled in specific immunotherapy studies should experience an appropriate minimum level of symptoms during a pre run period or observational phase". Patients with seasonal symptoms (pollen allergy) the observational phase could be considered the historical data of the symptoms of the previous season. ○ An attempt should be made to define what minimum level of symptoms is considered relevant for inclusion The inclusion of a run-in period or season is a priori appealing and has been used in some studies of immunotherapy. However as mentioned later in the document, the variability of seasonal exposure to pollens from season to season is such as to make run-in data of questionable value. A run-in period or season extends the study, in particular it extends the time that treatment is being withheld (particularly from patients subsequently allocated placebo). In well-powered placebo-controlled studies comparison between groups is the main statistical tool, making a run-in period for comparison of the same patient before and after treatment (necessarily non blinded) at best an optional extra. Proposal: This text could be added after the sentence marked by quotation marks": *In patients with seasonal symptoms (pollen allergy) the historical data of the symptoms of the previous season or seasons could be considered and take into account, avoiding an observational phase. The observational phase could be implemented in studies involving perennial allergen products.* *Patients with multiple sensitivities could be studied if the clinical symptomatology due to the allergen product under study is the only symptomatology that occurs when the allergen under study is the environment.* **LETI**	In general, the different comments are considered relevant. However, as stated in chapter 4.2.4 under Study design the scope of a baseline period is not to compare the same patient before and after treatment (e.g. due to the variability of allergen exposure), but to allow the selection of patients with an appropriate minimum level of symptoms. Experience with retrospective scoring in different studies has shown that this is biased by memory of the patients and patients often overrate their symptoms retrospectively. However, due to the limitations of a baseline period this is only a recommendation for an enhanced study design, but not mandatory for each study. This is now clarified in the guideline.
4.1.2 2nd	Suggest to clearly state. "The inclusion of a baseline or run-in period (e.g. a baseline pollen season), although correct in principle is not generally recommended and not considered mandatory. This, due to the unpredictability and variability of exposure to pollens and fluctuations of indoor allergens."	See response above.

paragraph	**EAACI**	
4.1.2 2nd paragraph	Baseline year for seasonal allergy is not recommended "a pre run period or observational phase in perennial allergies" **ALLERGY THERAPEUTICS**	See response above.
4.1.2 2nd paragraph	The request is unclear. Inclusion of a baseline period is not generally recommended (Canonica et al. 2007. Allergy 62(6):668-74.). Proposal: Remove the two first line of this paragraph 'Patients with allergic diseases……retrospective scoring of symptoms' **GSK BIOLOGICALS**	See response above.
4.1.2 2nd paragraph	To include a pre run period or observational phase does not add much information due to variation in allergen exposure. The inclusion of patients should be carefully considered and a list of "points to consider" is suggested. Proposal: Delete: "during a pre run in period or observational phase" **ALK-Abello A/S**	See response above.
4.1.2 2nd paragraph	2nd paragraph beginning with…"Patients with allergic diseases due to inhalational allergens enrolled in specific immunotherapy studies should experience an appropriate minimum level of symptoms during a pre run period or observational period". It is recommended this sentence be deleted and replaced with the proposed change. **Rationale:** The experience of the investigator should allow for the screening of subjects such that only patients with convincing histories of clinical allergy who display adequate symptoms to the allergen of interest are enrolled. Proposed change Patients with allergic diseases due to inhalational allergens who will be enrolled in specific immunotherapy trials should be properly assessed by the investigator and should have a history of symptomatic allergic disease. **SCHERING-PLOUGH**	See response above.
4.1.2	This approach will ensure at study entry a symptom level high enough to recognize	The whole paragraph was reworded. See response

2nd paragraph	relevant changes and is favourable in comparison to retrospective scoring of symptoms. **Rationale:** Patients should be asymptomatic prior to the exposure of the allergen Proposed change This approach will ensure at study entry a symptom level low enough to recognize relevant changes and is favourable in comparison to retrospective scoring of symptoms **SCHERING-PLOUGH**	above.
4.1.2 3rd paragraph	Patients who have received specific immunotherapy **for the tested allergen** in the previous 5 years, **or are receiving immunotherapy to another allergen,** are not eligible for study enrolment. Rationale: The guideline should be more specific about the allergens previously received by immunotherapy. For patients who received immunotherapy with another allergen that the one used for the trial, those who are not under treatment at the time of the trial should be considered as eligible for enrolment. Proposal: Patients who have received specific immunotherapy **for the tested allergen** in the previous 5 years, **or are receiving immunotherapy to another allergen,** are not eligible for study enrolment. **STALLERGENES**	The suggestion was implemented.
4.1.2 2nd paragraph	In the same second paragraph, it is stated that "Patients who have received specific immunotherapy in the previous 5 years or are still receiving this kind of therapy are not eligible for study enrolment" This text should clarify if this is applicable only to the allergen extract under study (patient was or is treated with the same or similar allergen extract or allergen under study) or if patients treated with unrelated allergen extracts or allergens could be included. Proposal: The following text could be added: "*Patients who have received specific immunotherapy with the same allergen product or another cross-reacting allergen product in the previous 5 years or are still receiving this kind of therapy are not eligible for study enrolment*" **LETI**	See response above.

: 4.1.2 2nd paragraph	Patients who have received specific immunotherapy in the previous 5 years or are still receiving this kind of therapy are not eligible for study enrolment. **Recommend** to take these criteria out. **Rationale**: This is too non-specific as this requires that any subject despite the length of treatment (e.g. 1 week vs. 5 years) are not included. This also excludes subjects who were not receiving benefit due to inappropriate dosing or compliance/adherence for reason beyond the control of the subject**.** Replace with If a patient has received allergy immunotherapy in the last 5 years the investigator should assess the length and frequency of treatment and time since last dose. This should be made prior to enrolment. **SCHERING-PLOUGH**	In general, any patient with an immunotherapy to the allergen under question within the last 5 years should be excluded due to the possible modulation of the immune system. Thus the statement is not deleted. However, if properly justified, the applicant can deviate from this requirement.
4.1.2 2nd paragraph	"… in the previous 5 years with the allergen in question … However, patients who had immunotherapy with the allergen in question and benefited but got worse in the meanwhile are eligible." **ALLERGY THERAPEUTICS**	See response above.
4.1.2 2nd paragraph	The inclusion of patients should be carefully considered in accordance with the aim of the study and a list of "points to consider" is suggested. Proposal: "Patients who have received specific imunnotherapy in …. are not eligible for study enrolment" is suggested to be deleted. **ALK-Abello A/S**	See comments above.
4.1.2 3rd paragraph	The third paragraph states that "only patients with mastocytosis should be excluded from clinical trials with insect venoms". Why are patients with mastocytosis in clinical trials with other allergen extracts or allergens not excluded? **This statement should be supported by scientific reference/s.** **LETI**	Up to know mastocytosis is only evaluated in patients with insect venom allergy due the risk of life-threatening reactions after insect sting. This risk is further enhanced by mastocytosis. Therefore, for patients with mastocytosis a lifelong immunotherapy is recommended by current guidelines. However, the risk of adverse events to insect venom immunotherapy is also increased which may bias safety data obtained from clinical trials. This is clarified by rewording the paragraph.

4.1.2 3rd paragraph	I think mastocitosis is contraindication for any SCIT **LARENAS LINDEMANN**	See response above.

4.1.3 CO-MORBIDITY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.1.3.	Change Rhinitis to Rhino(conjunctivitis), as is done below. **LARENAS LINDEMANN**	Agreed.
4.1.3	Rhinitis and asthma do indeed often occur together. Outcomes for both diseases could be measured so long as the study is adequately powered and one is clearly stated as primary outcome and the other disease as a secondary outcome. Proposal: "*Rhinitis and asthma do indeed often occur together. Outcomes for both diseases could be measured so long as the study is adequately powered and one is clearly stated as primary outcome and the other disease as a secondary outcome*". **LABORATORIOS LETI**	It is agreed that rhinitis and asthma often occur together. However, these are two different indications If one plans for a claim in both indications, separate studies for each indication should be performed
4.1.3	Suggest to delete the last two lines and replace with "For a claim of efficacy in asthma, proper primary outcomes should be chosen and clearly stated, and guidance for asthma therapy should be considered. **EAACI**	See the response above.
4.1.3.	Sentence "However, for a claim of efficacy in asthma, separate trials should be conducted and specific guidance for asthma therapy should be considered." Rationale: If designed appropriately to assess the primary endpoints, separate studies should not be required. **Proposed change:** However, for a claim of efficacy in asthma, studies should be appropriately designed to clinically assess asthma. **Appropriate changes in asthma symptoms scores, asthma control using validated asthma control questionnaires in addition to lung function parameters may be appropriate primary end-points.** **SCHERING-PLOUGH**	See response above. For clinical trial in asthma patients the requirements and relevant endpoints are mentioned in a separate Guideline.

4.1.4 CO-MEDICATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.1.4	Co-medication section should address controller medications (e.g. inhaled steroids) for patients with persistent diseases such as asthma and rhinitis, which are clearly recommended as first-line treatments in evidence-based guidelines Proposal: In patients with persistent asthma or rhinitis controller medications, especially anti-inflammatory topical treatments may be prescribed in the lowest recommended dose. As the use of rescue medication might impact study results, the amount and duration of controller medication intake has to be taken into account in the analysis of efficacy. Co-medication does not address anti-inflammatory treatment and other "controller" medications which may limit to much the scope of patients to be included. **LUIS DELGADO**	The section "co-medication" does only comprise medications not to be used to control symptoms of the allergic disease. All medications necessary for the relief of allergic symptoms should be allowed and described as rescue medication. This includes, if necessary, controller medication. This is clarified in the updated GL.

4.2 STRATEGY AND DESIGNS OF CLINICAL TRIALS		
4.2.1 EARLY STUDIES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.1 1st paragraph	"allergen extracts" should be changed to "allergen products". **ALK-Abello A/S**	The term was changed
4.2.1 1st paragraph	1st paragraph beginning with "Classical phase I studies in healthy individuals…". In the 2nd sentence "Non-affected individuals without any hypersensitivity do not react like *allergic* individuals…" change the word 'allergic' to 'sensitized' Non-atopic individuals without hypersensitivity do not react like subjects with clinical allergy and do not carry the risk of the targeted population. Proposed change: Non-affected individuals without any hypersensitivity do not react like sensitized individuals. ~~do not react like allergic individuals.~~ **SCHERING-PLOUGH**	Not agreed: A sensitisation is not predictive for clinical relevant symptoms. Thus the risk for incur an allergic reaction can only properly be assessed in allergic patients.
4.2.1 1st paragraph	line 5: Insert "However, in order to test for irritancy healthy subjects may be investigated." **ALLERGY THERAPEUTICS**	Accepted, the sentence was inserted.
4.2.1 1st paragraph	What is meant by up-dosing here? Up-dosing in the SCIT sense? Or up-dosing as up-titration of cohorts in a phase I trial? Proposal: Passage should be rephrased and/or up-dosing should be included in the "Definitions" list. A reference to more general guidelines concerning Phase I trials might be included here. "The investigational product should be tested at different doses to provide preliminary data on safety and tolerability with regard to the maximal tolerable dose. Dependent on the nature of the product up-dosing may be appropriate to used at all, none or at selected dose levels. The design should be in accordance with relevant guidelines for the conduct of phase I studies.	Accepted. The text was changed to: "The investigational products should be tested at different doses to provide preliminary data on safety and tolerability with regard to the maximum tolerated dose and a suitable dose escalation scheme. Dependent on the nature of the product dose escalation may be necessary or not to reach the maintenance dose. This has to be shown in appropriate trials. The design should be in accordance with relevant guidelines for the conduct of phase I studies."

	ALK-Abello A/S	
4.2.1 1st paragraph	We totally agree with the "early studies" on page 5 indicating that only allergic patients should be included. However, the prevention of allergy trials is now being considered in non-sensitised pre-school children. These studies should be indicated but discussed in a separate document. **GA2LEN**	The statement is accepted, however since this guideline is designed for the development of products for specific immunotherapy for the treatment of allergic disease and not for the prevention, it is not necessary to mention such studies in this guideline.
4.2.1 2nd paragraph	line 8: Strongly crossreactive allergens are immunologically not separatable " If combinations of non-crossreactive different allergens…." **ALLERGY THERAPEUTICS**	Agreed, the word non-crossreactive was inserted.
4.2.1 2nd paragraph	Please see comments to section 4.2.6 regarding definition on purified allergens. **ALK-Abello A/S**	See response to comments to section 4.2.6.
4.2.1 2nd paragraph	It is not practically possible to justify the dose of each allergen in a natural allergen extract, and certainly not in a mixture of extracts. However, for allergoids and recombinant products this requirement might be valid. Proposal: The section should be rephrased with particular attention to these points (and to the seemingly indiscriminate use of the word "allergen"). Natural extracts are by nature a mixture of different allergens. If combinations from different allergen sources are used (e.g. mixtures of allergen extracts or of purified allergens (natural, synthetic, derived from r-DNA technology)) the applicant has to justify the dose/fraction of each allergen source or allergen in case of purified allergens. **ALK-Abello A/S**	Agreed. To clarify this issue the paragraph was rephrased and moved to 4.2.2 Dose-finding studies.

4.2.2 DOSE-FINDING STUDIES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.2	The text states that "Provocation tests (e.g. conjunctival or bronchial provocation……) and/or clinical endpoints may be used as primary endpoints. Nasal provocation tests should be included. Also, skin sensitivity evaluated in dose-response skin prick tests have demonstrated to improve with specific immunotherapy. Proposal: The following text could be changed and read as: "*Since dose-finding studies are of limited duration clinical endpoints may be substituted by relevant surrogate endpoints such as provocation test results, symptom scores provoked by organ specific provocation tests (nasal, ocular or bronchial) or in environmental challenge chambers, or dose-response skin prick tests*". **LABORATORIOS LETI**	Nasal provocation was included. The provocation tests listed in brackets are only examples (see e.g.) thus the applicant may also use the skin sensitivity evaluated in dose-response skin prick tests if justified. However, it is questionable, if skin reactivity improves in short term studies, thus this test was not especially mentioned in the list of tests.
4.2.2	To establish a dose-response relationship for clinical efficacy would require hundreds to thousands of patients in phase 2. Nasal provocation test should not be missed. Immunological parameters and in particular allergen specific antibodies can indicate the immunogenicity of the product and together with the upper tolerated dose range provide an estimate of the suitable dosing. **ALLERGY THERAPEUTICS**	For nasal provocation tests see response above. If provocations tests are used as read out, a limited number of patients would be necessary. Since an estimation of the dose-response should be possible from the outcome of provocation tests, they are accepted in this development phase as to assess dose-dependent effects. As correctly stated, immunological parameters indicate the immunogenicity of the product. This was acknowledged in the section on Pharmacokinetic/Pharmacodynamic studies. However, such tests are not suitable to establish a dose-response relationship unless they are validated and a correlation to the clinical outcome has been established.
4.2.2	Provocation tests cannot replace clinical endpoints, as stated elsewhere in the document. Therefore we suggest to indicate provocation tests as possible secondary endpoints also for dose-finding studies	As correctly stated, a high number of patients will be necessary for dose-finding studies if only clinical endpoints will be allowed as primary endpoint for

	EAACI	dose-finding studies. Since an estimation of the dose-response is possible from the outcome of provocation tests, such tests should be permitted as primary endpoints in this phase of clinical development.
4.2.2	The very sharp distinction between provocation tests (clinical endpoints) and laboratory parameters is questioned. Perhaps a reference to general guidelines would be helpful. Proposal: Perhaps rephrase/soften passage allowing for immunological markers in dose-finding. After establishing a tolerated dose range, studies should be performed to establish a proper dose response relationship. Different techniques and endpoints may be applied and should in each case be justified. Such studies may comprise a short term treatment (e.g. 2-4 months) with different doses in several arms. Provocation test (e. g. conjunctival, nasal or bronchial provocation or allergen exposure in allergen chambers) and/or clinical endpoints may be used. Laboratory parameters such as allergen specific antibodies, T-cell reactivity or cytokines are currently not established as relevant biomarkers for the clinical endpoints and outcome. The use of such endpoints should be justified and generally only provide supportive information regarding the selection of doses for the clinical outcome. **ALK-Abello A/S**	Laboratory parameters can only provide supportive information as long as they are not validated and not correlated to the clinical outcome. Thus such markers may be used in the future if the correlation to clinical symptoms is proven. Therefore, a rewording is not necessary.
4.2.2	"pollen chamber" and "allergen chamber" are not the global term used today [Clin Exp Allergy Reviews 6,2, (March 2006):31-59] Proposal: Use 'Allergen Challenge Chamber (ACC)' **FRIEDRICH HORAK**	Agreed.
4.2.2	For especially food and venom allergens surrogate parameters should still be accepted as primary endpoint in dose-finding studies due to safety concerns with regard to provocation tests Proposal: **For food and venom allergens surrogate parameters may be used as primary endpoints and for other allergens p**rovocation tests (e.g. conjunctival or brionchial provocation or allergen exposure in allergen chambers) and/or clinical endpoints **are recommended.**	For insect venoms a titrated skin test may be a suitable provocation test which reduces the risk of severe adverse events. This test is also recommended before start of immunotherapy to evaluate the suitable initial dose. The same is true for a food challenge with increasing doses, thus there is no need to allow surrogate parameters for these allergies.

	HAL ALLERGY	
4.2.2	Dose-finding studies: If rush immunotherapy is developed, and in the case of venoms, the duration of the study may be shorter than 2 months. **GA2LEN**	Agreed. However the 2-4 months are only an example ("e.g.") thus shorter studies are not prohibited by the guideline. A rewording does not seem to be necessary.
4.2.2	I doubt about the usefulness of these short-term studies (2-4 months) for dose-finding, as the efficacy normally is shown later on: the best result in pollen-immunotherapy is with pre-seasonal start of 4 months before season. In fact, the first 2-3 months symptoms sometimes get a bit worse before they improve, together with the initial IgE rise. So I agree much more with the further discussed need of long-term studies. I would scratch the short-term or prolong it to 6-12 months. **LARENAS LINDEMANN**	It is agreed, that usually clinical efficacy is shown later on; therefore provocation tests are accepted as primary endpoints for such studies. It is unreasonable for the manufacturers to perform long-term studies for dose-finding. However, since studies already have shown dose-depending effects on provocation tests after short term treatment, this seems to be a good compromise to obtain an indication for selection of the suitable dose within an appropriate time frame.

4.2.3 PHARMACOKINETIC / PHARMACODYNAMIC STUDIES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
p 5-6 § 4.2.1 , 4.2.2, 4.2.3	We understand that the pharmacodynamic studies can be combined with the early studies and dose-finding studies. **GSK BIOLOGICALS**	Correct.
4.2.3 2nd paragraph	We respectfully disagree on the second part of the paragraph. In the present form it seems to suggest that T cell response/cytokines indirectly provide information on pharmacokinetics/dynamics. The possibility to assess a pharmacokinetics is excluded in the previous sentence, and the existence of a formal pharmacodynamics for allergens is at least questionable. We suggest to state, more simply that "may represent an indirect measure of the effect of specific immunotherapy on the immune system" **EAACI**	It is acknowledged that formal pharmacodynamics for allergens is questionable, and therefore the mentioned effects on the immune system are regarded as the best compromise to indirectly address pharmocodynamics. In combination with other comments the second part of the paragraph was reworded:
4.2.3. 2nd paragraph	The second paragraph of 4.2.3 states that "Allergen challenge tests may be helpful also in pharmacodynamic studies thus dose-finding studies and pharmacodynamic studies may be combined". Dose-response skin prick tests should also be included in this paragraph Due to the variability of allergen-specific antibody levels during SIT a recommendation should be given which allergen-specific antibodies are considered relevant. Proposal The following text could be changed and read as: "*Specific allergen challenge tests in shock-organ and dose-response skin prick tests may be helpful also in pharmacodynamic studies, thus dose-finding studies and pharmacodynamic studies may be combined*". **LABORATORIOS LETI**	It is not necessary to list all possible end-organs for provocation test, skin prick tests are included in the wording "end-organ specific response (e.g. provocation test)". IgG was implemented to specify the relevant antibodies. See also response above.
4.2.3 2nd paragraph	in 2nd paragraph beginning with "Pharmacodynamic aspects should be addressed using markers such as changes in allergen-specific antibody levels, T-cell responses, and/or cytokine production indicating a specific interaction with the immune response.". **Rationale**: It is recommended that there are other markers which can also be added Please add, "and chemokine"	Cytokine is the umbrella term for chemokines, interleukins, interferons etc. thus chemokines are included in the term cytokine production.

	Pharmacodynamic aspects should be addressed using markers such as changes in allergen-specific antibody levels, T-cell responses, and/or cytokine and chemokine production indicating a specific interaction with the immune response **SCHERING-PLOUGH**	
4.2.3	Not only systemic immune changes have to be documented, but I think also –and especially- local immune changes are of importance, as the anti-allergic effect principally is in the tissues, changes in the blood are just surrogate markers. Something should be added about this to encourage local specific IgA, eosinophyls and their markers, IL-10 etc. production detection and non-specific AND specific bronchial challenges. **LARENAS LINDEMANN**	It is generally mentioned that immunological changes should be measured. It is not specified that this has to be done systematically or as local immune changes. Selection of markers is within the responsibility of the manufacturer and justification of the selection need to be given.

4.2.4 CONFIRMATORY STUDIES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.4	It may be of interest to propose pharmacoeconomic studies. **GA2LEN**	This is not the scope of the guideline.
4.2.4 study design	We agree that randomized, placebo-controlled clinical trials are essential in the assessment of efficacy of specific immunotherapy. However, some surrogate markers may be used to complement clinical efficacy. **GA2LEN**	Biomarkers may be used as secondary endpoints but cannot replace clinical outcomes.
4.2.4 study design	The document states that confirmatory clinical trials on specific immunotherapy should be performed using a randomised placebo-controlled double-blinded design. Should this design be applied to children also? Many Ethics Committees don't accept it. 1. **Comment:** Many studies have demonstrated the superiority of specific immunotherapy vs. placebo. Shouldn't it be possible for investigating some specific clinical issues to demonstrate the superiority of active treatment by comparison to a control group using standard rescue medication? 2. In the first paragraph, the last sentence states that "Since local allergic events are frequent in specific immunotherapy, a placebo preparation with histamine may be considered to keep blinding". One must bear in mind that not all the local reactions (in injected immunotherapy) are due to the intrinsic properties of the allergen extract or allergen. In some cases it is due to the technique of injection. The use of histamine as part of the placebo could bias the safety aspect of the trial. If the allergen extract is hypoallergenic, the placebo could have a higher rate of local reactions. Since histamine per se has an immunological effect it should not be added to placebo. Furthermore, histamine has pharmacologic properties that should be documented and could act as a drug, inducing unwanted responses. Therefore, placebo must contain all ingredients of the active preparation, with the exception of the active ingredient under study. Proposal	Both, the placebo and the verum group of a clinical trail for SIT should always have access to standard rescue medication. This is clearly stated in the guideline. Thus the term "placebo" is only related to the trial medication. It is only stated that a placebo preparation with histamine may be considered. Thus it is only a recommendation and it is the responsibility of the company to decide, if a placebo preparation with or without histamine is more suitable for a specific trial.

	*The Guideline should advise whether the randomised placebo-controlled double-blinded design is considered mandatory in human beings **of all** ages.* *We don't agree in adding histamine to placebo.* *Placebo must contain all ingredients of the active preparation, with the exception of the active ingredient under study.* **LABORATORIOS LETI**	
4.2.4 study design	1st paragraph, line 3: Neither variability in individual clinical response, nor allergen exposure, nor the subjective nature of symptoms assessment make non-inferiority trials impossible, but will at the most effect the sample size. Proposal: Superiority versus placebo or **at least non-inferiority** versus comparator has to be shown. **HAL ALLERGY**	Due to the aspects mentioned in the guideline it is not possible to assess the assay sensitivity (and thus the validity) of a non-inferiority trial in this in area.
4.2.4 study design	Paragraph 1: Use of the wording "not possible" in the sentence concerning non-inferiority trials is not quite true and should be rephrased. The comparator is not active as stated earlier when talking about non-inferiority trials. This should be clear Proposal: Rephrase: "Impractical" or "very difficult" or similar terms might be used instead. Replacement in line 6 of "placebo preparation" with "control preparation" or "comparator preparation" **ALK-Abello A/S**	See above The text already mentions placebo or an active comparator. According to general understanding non-inferiority trials are performed vs. an active comparator. Thus, there is no need for a clarification.
p 6 4.2.4. 1st §	No histamine will be used as a potential placebo preparation Proposal: Remove last sentence of first §. **GSK BIOLOGICALS**	It is only stated that a placebo preparation with histamine may be considered. Thus it is only a recommendation and it is the responsibility of the company to decide, if a placebo preparation with or without histamine is more suitable in a specific trial

4.2.4 study design	Confirmatory studies: placebo (page 6, 1st paragraph)): A histamine placebo may be used but some ethical boards have already prevented its use. Moreover, immunotherapy does not induce the same side effects throughout several months whereas histamine does. Thus, blinding may not be possible. **GA2LEN**	See response above.
4.2.4 study design	The clinical significance of results is always difficult to assess. We think that the allergen arm should be significantly superior to the placebo arm. Furthermore, an expert panel (World Allergy Organisation and European Academy of Allergy and Clinical Immunology) has proposed that an increase of 20% over placebo is necessary. **GA2LEN**	Up to now no scientifically based assessments of an increase, which can be rated as clinically significant, exist, thus the company has to justify which increase is considered clinically relevant in consideration of the special clinical trial and no fixed rates can be mentioned in the guideline. It should be noted too, that the scores used (in particular medication scores) are different and not validated. Therefore, it is not justified to generally define an increase of 20 % over placebo as clinically relevant.
4.2.4 study design	line 10: The sentence is incorrect as there is no "another approved product for treating insect sting allergy" For such condition, only relievers are available (from epinephrine to oral antihistamines). Thus, it would be better to state that all subjects should be provided with proper symptomatic medications. **EAACI**	There are several products with a marketing authorisation for specific immunotherapy of bee or wasp venom allergy (at least at national level). These products have shown over decades an efficacy of about 80-90% of patients tolerating an insect sting after immunotherapy. Thus not only relievers are available but highly efficacious products for immunotherapy can be used for the control group. To clarify the term "another" was deleted.
p 6 § 4.2.4. 3d §	Same comment as p 5 second § Proposal: Remove the two first sentences of that paragraph **GSK BIOLOGICALS**	Retrospective scoring of symptoms is biased by memory, thus a controlled assessment in a baseline period is preferred over retrospective scoring. See also response to comments to Section 4.1.2. However, the paragraph was slightly reworded as done in section 4.1.2.
4.2.4 study design	Paragraph 3 Delete the sentence stating that "*a prospective baseline period is preferred*" (see above). Due to the variation season to season and even with-in subject the baselines does not add much (sometimes even any) information. Proposal:	For baseline period please see response to above. For points of consideration see response to similar

	Delete paragraph 3 in Section 4.2.4. Instead add “points to consider”. Points to consider: 1) Appropriateness of a baseline period 2) Relevance of retrospective scoring as a technique to classify the severity of the disease in the selected study population 3) Use of provocation test to classify the severity of disease in the selected study population 4) Documentation of the allergen exposure during the study unless justified 5) Definition of a period with sufficient allergen exposure for efficacy evaluation or as the baseline In case of perennial allergies minimisation efforts to reduce fluctuations in the level of indoor allergens. Sanitation efforts should be completed before the study period. **ALK-Abello A/S**	issues above.
4.2.4 study design	3rd paragraph beginning with "Since patient with allergic rhino-conjunctivitis or allergic asthma enrolled in specific immunotherapy studies should experience an appropriate minimum level of symptoms a prospective baseline period is preferred and should be included whenever possible.”. -comment that this is contradictory to statement on page 5. Recommendation that an evaluation of patients 2 weeks prior to the peak allergy period for seasonal allergens should be adequate. **Recommended change to: “**Patients with allergic rhinitis/conjunctivitis or allergic asthma who are enrolled in specific immunotherapy studies should experience minimal symptoms prior (e.g. 2 week pre-seasonal) to the start of the study. The investigator screening the subject should enrol patients with convincing histories of clinical allergy who display adequate symptoms to the allergen of interest **SCHERING-PLOUGH**	The statement is not contradictory to the statement on page 5. In both passages a baseline period is recommended to assess symptom severity of patients and to select patients with an appropriate minimum level of symptoms during the season relevant for their disease. For rewording the paragraph please see reply to comment of GSK above. For only assessing the histories by the investigator please see comments and responses to similar issues in Section 4.1.1 and 4.1.2.
4.2.4 study design	On page 6 (3rd paragraph), it is stated that “Provocation tests may be useful for selecting subjects with the desired minimum level of symptoms and for matching study groups”. We do not think that provocation tests would be useful because there are no data supporting their use and the administration of supra-physiological allergen doses	Not supra-physiological doses are meant but titrated provocation tests or for example allergen challenge in an allergen challenge chamber. Such tests are not mandatory. It is noted that they may be useful. The sentence is retained but “Titrated” was included

	GA2LEN	before “provocation test”.
4.2.4 study design	Pollen counts representing the area(s) where the study is performed should always be considered. The sentence on page 6 is unclear. **GA2LEN**	“Important” was replaced with “mandatory” and the second part of the sentence now reads: “…and to define in the study protocol the minimum pollen count which has to be reached to define the evaluation period as well as the baseline period.”.
4.2.4 study design	The recommendation for documentation of exposure level to perennial allergens does not have sufficient scientific and clinical basis. The methods for detection are not sufficiently reliable and they should reflect the overall individual exposure and not the levels of a given location. Moreover, the correlation of exposure and clinical effects are insufficiently documented to be usable in statistical analysis. It increases the costs of the trial and that information is not usable in any rigorous way. Proposal: In addition, exposure level may be documented. Individual exposure to allergens and not levels at a given location should be used. If exposure levels are measured, researchers should explain and justify how the exposure levels were included in the statistical models evaluating the efficacy of the intervention. **DELGADO**	It was not intended to relate the clinical effect to the exposure. Measuring of exposure should be used to control the exposure level and to document the variation especially in evaluation periods. The paragraph was reworded to clarify the issue.
4.2.4 study design	Last sentence states “In addition, the exposure level should be documented”. **Comment:** When should exposure level be documented? During all the study, at baseline, at the end, or other? This statement should be clarified. To document the pollen exposure a suitable and country-wide measurement should be available. This actually not the case for Germany. Quantification of pollen exposure is not possible in general (at any place!). Therefore “artificial exposure models” like the pollen chamber should be allowed as a more general way out of this problem. **LABORATORIOS LETI**	The statement was clarified; see response above. The last sentence is only related to the measurement of indoor allergens. Sampling stations for pollen counts should be distributed all over geographic regions so that it is no problem to provide the pollen count for the region in which the patient is living. This is a generally used and accepted procedure. The allergen challenge chamber can not be used as substitute for measurement of clinical symptoms during the pollen period until the procedure has been validated and a correlation of results obtained in the allergen challenge chamber to the results of measurement of clinical symptoms during the pollen

		period has been established.
4.2.4 study design	Paragraph 5: Documentation of exposure level may be irrelevant if symptoms and positive test (IgE and/or SPT) is present. Also this paragraph is too specific and a list of bullets is suggested. Add to the list that sanitation should not be performed while a trial is ongoing. Proposal: See above **ALK-Abello A/S**	Measuring of exposure should be used to control the exposure level and for documentation of the variation especially in evaluation periods. This was clarified by rewording; see response above. For points of consideration see response to similar issues above. It is clearly mentioned in the draft guideline that sanitation measures should be finished before the start of a clinical trial. However to underline the importance of this issue, the sentence was reworded. .
4.2.4 study design	5th paragraph For trials in the perennial indication it is important to minimise fluctuations in the levels of indoor allergens. Thus, sanitation measures should be finished before the start of a clinical trial and measurement of baseline symptoms should be performed after sanitation. In addition, the exposure level should be documented. . **Rationale**: For trials with perennial allergens it is important to follow real life situations in sanitation. To enforce sanitation measures may be impractical, unrealistic and we are not aware of any system that is validated. Proposed change: For perennial allergens it is also important to document the exposure to the relevant allergens and to define a sufficient allergen exposure level at periodic times through the evaluation period as well as at baseline. Thus, sanitation measures should be **considered.** ~~be finished before the start of a clinical trial and measurement of baseline symptoms should be performed after sanitation. In addition, the exposure level should be documented.~~**"** **SCHERING-PLOUGH**	Sanitation measures should not be enforced, however if sanitation measures are performed they should be finished before the start of a clinical trial. To clarify this, the sentence was reworded; see response above.

4.2.4, study duration	Regarding study design the document states that confirmatory clinical trials on specific immunotherapy should be performed using a randomised placebo-controlled double-blinded design. Regarding the **Study duration** it is stated that depending on the duration, different claims for efficacy are possible. The document should clarify if for all the claims the design of the study must be randomised placebo-controlled double-blinded. Proposal *Depending on the duration of the study which provides 4 different claims for efficacy, clarify for what claims the randomised placebo-controlled double-blinded design is needed and for which claims other designs may be applicable.* **LABORATORIOS LETI**	In general for measurement of efficacy – independent from the length of the period for which efficacy should be demonstrated, a controlled double blind design is necessary. If this is not possible, for example due to ethical reasons, the applicant has to propose and justify another study design. Thus, there is no need for further explanation in the guideline.
4.2.4 study duration p 7 1st §, 1st line	We still believe that one major study should allow to address all the claims that we will propose. Interim analysis could be planned properly via an external advisory board. **GSK BIOLOGICALS**	The guideline does not prohibit assessing several claims within one study, if done methodologically sound and properly justified. However, due to earlier experience the preferred option is to assess different research questions in different trials.
4.2.4 study duration	1st paragraph beginning with "In principle, separate studies should be considered…". "In this context the use of interim data from ongoing trials is strongly discouraged: the dissemination of study information necessary for submission purposes dangers the integrity of the ongoing trial." should be deleted **Rationale**: As in other therapeutic area (e.g. oncology) interim analysis if adequately managed can be acceptable for initial indications (time to progression) and submission. Continuation of these oncology trials for a mortality indication are acceptable if adequately controlled for. This allowance of interim analysis for an initial treatment indication and continuation of a trial for a disease modification indication should be no different for immunotherapy trials, if adequately managed in the trial protocol and statistical analysis plan. Proposed change: In this context the use of interim data from ongoing trials ~~is strongly discouraged~~: should be carefully controlled for and mulitiplicity must be adequately managed. **SCHERING-PLOUGH**	The guideline does not prohibit interim analyses if done properly. However, if results of an interim analysis are used for submission purposes it is the sponsor's responsibility to convince the authority that the necessary dissemination of interim data have no impact the integrity of the later parts of the trial. To control for multiplicity in case of an interim analysis is taken for granted (see ICH E9).

4.2.4 study duration	Points 1. to 4. should be headed with "Study claims" and "5. Prevention of asthma and spread of the sensitisation spectrum" added. **ALLERGY THERAPEUTICS**	No further heading deemed to be necessary. The four claims mentioned are claims for efficacy in therapeutic approaches (relief of symptoms of rhinitis and/or rhinoconjunctivitis). Prevention of asthma and spread of the sensitisation spectrum is an important point to address, but not in this listing, as it is no therapeutic approach but a preventive approach. A sentence addressing this issue has been added to the end of the following paragraph: "However, long-term studies may be planned for showing an additional effect on prevention of asthma and spread of the sensitisation spectrum."
4.2.4 study duration	It would be better to combine points 3 and 4 into a "Long-lasting effect" which simply include the duration of the beneficial effect after the treatment has been stopped. This to maintain an agreement with the current clinical view. **EAACI**	Both points were separated because for claim 3 a clinically relevant relief of symptoms is sufficient whereas for claim 4 a sustained total absence of symptoms is necessary.
4.2.4 study duration	Page 7; Paragraph 3, 1st sentence: Endpoints should be evaluated in each allergen season or several times during the treatment for perennial allergies and at least at end of follow-up. Grammatical correction Endpoints should be evaluated in each allergen season or several times during the treatment for perennial allergies and at least at the end of follow-up **SCHERING-PLOUGH**	Accepted
4.2.4, study duration,	The last but one paragraph of this subchapter (Study duration), states that "Provocation tests performed in parallel as part of clinical studies can support the proof of efficacy, especially in years with low allergen exposure and consequently low or no clinical efficacy but maintained efficacy in provocation tests. Moreover, if the allergen concentration needed to provoke the same symptoms increases over time of the study, this is supportive for the efficacy of the treatment. However, such provocation tests are not validated as surrogate markers for efficacy". **Comment:** This last sentence is incongruent with the first statement and with 4.2.2	Maybe this is a misunderstanding. The last sentence is not incongruent with the first statement and with 4.2.2. Provocation tests can not serve as surrogate markers until they are not validated, they only can support the results of clinical efficacy.

	Proposal: *Provocation tests performed in parallel as part of clinical studies can support the proof of efficacy, especially in years with low allergen exposure and consequently absence of clinical symptomatology, in which the efficacy could be evaluated in provocation tests. Moreover, if the allergen concentration needed to provoke the same symptoms increases over time of the study, this is supportive for the efficacy of the treatment.* **LABORATORIOS LETI**	
4.2.4 study duration Page 7, 2nd paragraph	There are contradictions in this paragraph. Please clarify, on the one hand you say 'provocation tests can support proof-of-efficacy', and on the other hand you say 'provocation tests are not validated as surrogate markers for efficacy'. **GSK BIOLOGICALS**	See response above.
4.2.4 study duration	Page 7; Paragraph 3: Provocation tests performed in parallel as part of clinical studies can support the proof of efficacy, especially in years with low allergen exposure and consequently low or no clinical efficacy but maintained efficacy in provocation tests. Moreover, if the allergen concentration needed to provoke the same symptoms increases over time of the study, this is supportive for the efficacy of the treatment. **Rationale**: Suggested changes provide clarification to the statements. Proposal Provocation tests performed in parallel as part of clinical studies can support the proof of efficacy, especially in years with low allergen or no or minimal demonstrated clinical efficacy. ~~but maintained efficacy in provocation tests~~. Moreover, if the allergen concentration needed to provoke the same symptoms increases over the time of the study, **provocation testing** ~~this~~ is supportive for the efficacy of the treatment**.** **SCHERING-PLOUGH**	No clarification is seen by deleting the part "but maintained efficacy in provocation tests". For the second part, not the provocation testing itself but the result that the allergen concentration increases, is supportive. To clarify "increase" is added after "this".
4.2.4	Rescue medications: This paragraph is very short and it is not clear as to whether intranasal	It is mentioned that rescue medication should

rescue medication	corticosteroids may be accepted or not. Most patients receiving immunotherapy need rescue medications and the WHO consensus on immunotherapy proposed to combine pharmacotherapy and immunotherapy in order to optimally control patients. There may be some information concerning the use of a combined symptom-medication score. **GA2LEN**	generally be provided. This is in full concordance with the WHO position paper. There is no prohibition to use intranasal corticosteroids. Guidance regarding the use of a combined symptom-medication score is given under "Endpoints".
4.2.4. Endpoints	**Comment: ALLERGIC ASTHMA IS NOT INCLUDED** **Proposal:** Include allergic asthma **LABORATORIOS LETI**	Allergic asthma is not in the scope of this guideline. For clinical trials in allergic asthma reference is made to the Note for Guidance on the Clinical Investigation of Medicinal Products in the treatment of Asthma
4.2.4 endpoints	Allergic Asthma is not addressed at all in this document. This should be mentioned and that appropriate changes in asthma symptoms scores, asthma control using validated asthma control questionnaires in addition to lung function parameters may be appropriate primary end-points. Add: Appropriate changes in asthma symptoms scores, asthma control using validated asthma control questionnaires in addition to lung function parameters may be appropriate primary end-points **SCHERING-PLOUGH**	See response above.
4.2.4 endpoints allergenic rhinitis	Page 8: Asthma and prevention endpoints are missing. Especially for HDM allergy treatment of asthma symptoms can be relevant. The prevention of asthma, new sensitisation or even the development of allergy in high risk children are also indications very relevant to address. Proposal: Add text on asthma endpoints and prevention endpoints. Influence on asthma may be determined by evaluating degree of control according to GINA guidelines, evaluation of day and night time symptoms, use of rescue medication, lung function (spirometry), tools like Asthma Control Questionnaires, and the number of exacerbations during the defined study period. In case of prevention studies a well defined definition of presence or absence of asthma will	Regarding asthma, see response above. With regard to prevention of asthma or of new sensitisations, the following sentence was included at the end of the paragraph on secondary endpoints: "In long-term studies prevention of asthma may be addressed as secondary endpoint. For this endpoint, a pre-defined definition of presence or absence of asthma is necessary. In addition the assessment of new sensitisations e.g. by skin prick test may be performed in long-term studies."

	be of paramount importance Other end points may be new sensitisations or primary prevention in terms of development of sensitisations or asthma in high risk children. **ALK-Abello A/S**	
4.2.4, Endpoints	The primary endpoints subsection does not mention asthma. The only indications mentioned are Allergic rhinitis/rhino-conjunctivitis and Insect venom allergy. Moreover, anti-inflammatory medications for persistent diseases should be mentioned in the definition of medication score Proposal Therefore, the primary endpoint has to reflect both, symptom severity as well as the intake of rescue and controller medications. **LUIS DELGADO**	For endpoints regarding asthma see above. Rescue medication comprises all medication which is necessary for the patient to achieve a suitable symptom relief. Thus controller medication is included in the term rescue medication and of course has to be considered in calculation of the medication score. See also reply to your comment to section 4.1.4 Co-Medication.
4.2.4. Endpoints	End points: It would be of interest to differentiate rhinitis and conjunctivitis from asthma since it is mentioned earlier that asthma should be considered separately. It may be indicated that in some studies on a large number of patients asthmatics can be studied but analysed separately in a covariance analysis or in a post-hoc analysis. In the current guideline, it is surprising to read that FEV_1, FVC are proposed as rhino-conjunctivitis end points. Moreover, asthma control tests now appear to be of interest and are easy to administer. **GA2LEN**	This Guideline does not deal with allergic asthma. It is correct that FEV1 and FVC are no secondary endpoints for rhino-conjunctivitis and both were deleted.
4.2.4. endpoints allergenic rhinitis	Last lines of the page 7 and first line of page 8 state that “Up to now, no validated symptoms score exists, but the measurement of symptoms on a 4-point rating scale (i.e. 0 = absent, 1 = slight, 2 = moderate, 3 = severe) is generally accepted”. **Comment:** This scale measures subjective endpoints. Therefore the values included in this scale should be clearly defined. A definition of this scale could be obtained in www.fda.gov/cder/guidance/2718dft.htm in which the symptom scores, although related to rhinitis, are defined as follows and could be applied to any symptom: · 0 = absent symptoms (no sign/symptom evident) · 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated) · 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but	The definitions were included to enhance clarity.

	tolerable) · *3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)* *Proposal* ***Include the definition of the symptom scores as follows:*** · *0 = absent symptoms (no sign/symptom evident)* · *1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)* · *2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)* · 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping) **LABORATORIOS LETI**	
4.2.4 endpoints allergenic rhinitis	Symptom severity as well as the intake of rescue medication is considered as primary endpoint. Whereas, on page 8, the guideline states that other primary endpoints could be considered if clinically justified. The draft guideline states correctly **that no validated symptom neither medication score exists** which is even more important in the light of unpredictable natural pollen exposure. Therefore environmental challenge chambers and provocation tests should be also considered as valuable primary endpoints. Proposal: *Symptom severity as well as the intake of rescue medication should be considered as the primary endpoint, although other primary endpoints could be considered if clinically justified.* **LABORATORIOS LETI**	The commentator is referred to the explanation to allergen challenge chambers under secondary endpoints where is stated why results obtained by allergen challenge chamber studies up to now cannot be accepted as primary endpoints.
4.2.4 endpoints allergenic rhinitis	"pollen chamber" and "allergen chamber" are not the global term used today [Clin Exp Allergy Reviews 6,2, (March 2006):31-59] Proposal: Use 'Allergen Challenge Chamber (ACC)'	Accepted.

4.2.4 endpoints allergenic rhinitis	It is questionable if individual symptoms should / need to be named in this document. No studies evaluated the usefulness of these particular symptoms in comparison with others. They are commonly used in trials and in clinical care but the necessity of explicitly mention these symptoms is not clear. In addition, only ocular and nasal symptoms are identified, lower airways symptoms are not mentioned. Proposal: Delete the sentence: Favourably scored symptoms for allergic rhino-conjunctivitis are: nasal itching, sneezing, rhinorrhoea, nasal obstruction, ocular itching/grittiness/redness and ocular tearing. **LUIS DELGADO**	Assessment of other symptoms is not prohibited, however, the as the commentator correctly stated, the symptoms listed are commonly used in trials and they are mentioned in the "CPMP/EWP/2455/02 Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-Conjunctivitis". Thus, there is broad experience with these symptoms which is the reason to rate them as "favourably". Lower airway symptoms are not mentioned, since only rhinitis/rhinoconjunctivitis symptoms but not asthma symptoms are considered. No changes deemed necessary.
4.2.4 Line endpoints allergenic rhinitis	2 from bottom; Page 7: Symptoms should not necessarily be collected on a daily basis. Firstly, the symptom recording is only required in the period of interest (the efficacy period) – e.g. the grass pollen season – and not year round (outside the season). Secondly, symptom scoring could be highly correlated for the individual subject so that weekly scoring or less might be sufficient to assess efficacy. Proposal: Replace "should" by "could". **ALK-Abello A/S**	It was meant to collect symptoms on a daily basis during the pre-defined assessment period. This is now included for clarification.
4.2.4 endpoints allergenic rhinitis	line 10 : "Such … be collected on a daily basis. Proposal: add "for a pre-defined period" **ALLERGY THERAPEUTICS**	Accepted.
4.2.4 endpoints allergenic rhinitis	Page 8; Paragraph 2: Combining symptom and medication scores are not straightforward as indicated. To begin with the medication scores used are typically not the same from trial to trial. These need to be standardized first. Secondly is the problem with interaction between symptom and medication. Finally a composite endpoint need to prove itself in the individual components	It is correctly stated in the comment that often a standardized combined symptom and medication score will add advantage to the assessment of clinical trials of specific immunotherapy. Therefore, establishing of such a validated score with well defined interaction between symptoms and medication

	coming back to separate symptom and medication scores. Proposal: Rephrase section on combined score. Add reference to: Committee For Medicinal Products for Human Use (CHMP), "Points to Consider on Multiplicity Issues in Clinical Trials," where composite endpoints are addressed with reference to both clinical meaningful effect size as well as separation into individual components – in this case symptoms and medication. **ALK-Abello A/S**	is strongly encouraged by the guideline. As long as such a standardized symptom-medication score is lacking, the sponsor has to justify the calculation of the combined score. Several different possibilities are given, how score can be combined and it is also possible to define symptom score and medication score as co-primary endpoints. No rewording deemed necessary.
4.2.4 endpoints allergenic rhinitis	Primary endpoint: The following is stated in the draft guideline: "Different approaches to combine symptom score and intake of rescue medication are possible… One approach is to combine both scores by a weighted sum of the symptom and medication score respectively. In such a situation the choice of the weights has to be justified… An alternative approach for combining symptom score and intake of rescue medication is the number of days with symptom control, i.e. days without intake of rescue medication and a symptom score below a pre-defined and clinically justified threshold." As this has already been in used in various studies, and to avoid the statistical complexicity of a combined primary endpoint, another endpoint could be considered solely, symptoms score, while its results could be weighed by a main secondary endpoint such as rescue medication. Proposal: Other primary endpoint definitions could be considered if clinically justified, **such as the solely symptoms score, while its results could be weighed by a main secondary endpoint such as rescue medication**. **EFPIA**	It is not agreed to use the symptom score as solely primary endpoint. The primary endpoint has to reflect both, symptom severity as well as the intake of rescue medication, since the use of rescue medication has an impact on symptom severity. However, it is not mandatory to combine the both scores. It is also possible to define the symptom score and the medication score as co-primary endpoints.
4.2.4 endpoints allergenic rhinitis	We support the view that the primary endpoint has to reflect both, symptom severity as well as the intake of rescue medication. The scoring of the medication should be related to their approximated relief of symptoms, as well as the magnitude and duration of effect. **Allergopharma**	Accepted. The following sentence is included: "The scoring of the medication should be related to their approximated relief of symptoms, as well as the magnitude and duration of effect."

4.2.4 endpoints allergenic rhinitis	Page 8; Paragraph 4: Definition of responder impossible for seasonal allergies, since the baseline concept is not meaningful in this context. The two paragraphs should be modified to concern only perennial allergies or deleted, since the "responder definition" is not straightforward for perennial allergies either. Proposal: Delete section on responder **ALK-Abello A/S**	A response definition does not necessarily require baseline values. E.g. a responder could be a patient in whom the outcome score is below a pre-defined threshold or a subject with minimal symptoms and no rescue medication.
4.2.4 endpoints allergenic rhinitis	Page 8; Paragraph 8: What is clinically meaningful from EMEA's point of view? General guidance from the EMEA or invitation for discussion with competent authorities is asked for. Proposal: Provide more guidance on clinically meaningful effect size. According to Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. Am J Med 2004 Mar 1;116(5):338-44 a difference between treatment and placebo of 10% in symptom score is considered to be clinically relevant. **ALK-Abello A/S**	It is not within the scope of a regulatory guideline to define clinically relevant effects.
4.2.4. endpoints allergenic rhinitis Secondary endpoints	**Comments:** 1. Medication free days and symptom+medication free days should be included. These endpoints, together with symptom free days could be considered as primary endpoint. Nasal provocation test should be included Proposal: *Include:* o *nasal provocation tests* o *Medication free days*	The definition is the responsibility of the sponsor and needs to be pre-defined and justified. Symptom and medication free days are already included. The corresponding paragraph reads: "An alternative approach for combining symptom score and intake of rescue medication is the number of days with symptom control, i.e. days without intake of rescue medication and a symptom score below a pre-defined and clinically justified threshold". Since i. e. is stated in the paragraph an additional combination with medication free days is possible if it is considered necessary by the investigator. Nasal provocation was added

	○ *Symptom + medication free days* *The concept of "free" should be established (daily mean symptom score <= 1?; and the same for medication and symptom+medication?)* **LABORATORIOS LETI**	
4.2.4 endpoints allergenic rhinitis Secondary endpoints	Page 8; Paragraph 10: Too restrictive – supportive studies where the primary endpoint is QoL or FEV_1 are conceivable. Proposal: Rephrase (soften) section. Secondary Endpoints: In specific cases some of the below mentioned endpoints may actually be the primary endpoint in a supportive clinical trial but cannot be accepted as the primary endpoint in a confirmatory study aiming at documenting the effect of SIT **ALK-Abello A/S**	The primary endpoints are described under "confirmatory studies" thus they are valid for pivotal studies. If the sponsor wants to perform additional supportive studies, he is free in the choice of the primary endpoint, but these studies would not be accepted as pivotal studies for the assessment of efficacy for example in applications for marketing authorisation. To give guidance for suitable pivotal studies, no softening of the section on primary endpoints is possible.
4.2.4 endpoints allergenic rhinitis Secondary endpoints	Secondary endpoints (skin, eye, nose, bronchi, pollen chamber) **ALLERGY THERAPEUTICS**	Nasal provocation was added.
4.2.4 endpoints allergenic rhinitis Secondary endpoints	Objective measures: again add 'specific' Provocation tests: add 'nasal' and 'specific and non-specific' bronchial challenge. Might add some remarks about 'cat chamber' **LARENAS LINDEMANN**	Specific was added: "(e.g. changes in allergen-specific IgE and IgG levels, cytokines, other inflammatory markers)" Nasal provocation was added. Up to know, there is limited experience with cat chambers, especially not in providing a constant allergen exposure level. Thus cat chambers cannot be considered in the guideline.

4.2.4 endpoints allergenic rhinitis Secondary endpoints	Pharmacoeconomics should be added as possible secondary endpoint. **GSK BIOLOGICALS**	This is not within the scope of the guideline.
4.2.4 endpoints insect venom	Insect venom allergy may not only be evaluated by *controlled sting provocation* but also by *field stings.* Field stings may contribute very important information regarding assessment of efficacy of therapy. Proposal: Add field stings as being clinically relevant information that may be collected with respects to evaluation of efficacy of venom allergy immunotherapy. **ALK-Abello A/S**	It is acknowledged that field stings can support the assessment of efficacy of therapy. However, since field stings are never controlled and often the evaluation is biased or impossible because the stinging insect may not be identified or falsely identified (e.g. wasp instead of bee), field stings cannot be regarded as primary endpoint for efficacy.
4.2.4 endpoints insect venom	<u>Insect venom allergy:</u> - It is acknowledge that SIT is the treatment of choice in insect venom allergy. However, assessment (limited number of controlled studies, no placebo group usually used…) is quite different and as a consequence and therefore it is recommended to either delete them from the scope of this guideline or to consider them more in depth in a specific reflection paper to be issued later. However, some statement should be included in the scope. **EFPIA**	The basic mechanisms of specific immunotherapy are considered the same regardless whether allergy to inhalational allergens or allergens such as insect venoms is addressed. Therefore guidance on insect venoms allergy is retained in the guideline. The specific issues regarding therapy of insect venom allergy are addressed in the guideline. No need to release a specific reflection paper on insect venom allergy is seen.
4.2.4 Methodological issues	Page 8; Last paragraph: According to ICH E9 the statistical analysis should be clearly described in a Statistical Analysis Plan finalized before breaking the blind and analyzing the data. This however, is not special for immunotherapy but applies to all therapeutically areas. Proposal: Suggestion: Add that the detailed analytical consideration could be outlined in a Statistical Analysis Plan (SAP). E.g. reference to ICH E9. "When planning a specific immunotherapy-study all relevant and current ICH and CHMP guidelines should be consulted. The detailed analytic consideration should in accordance with ICH E9 be -outlined and pre-	The comment is correct. However, due to regulatory experience in this area it seems important to mention these aspects explicitly.

	specified in a Statistical Analysis plan (SAP). As well a detailed analytic section in the study protocol……” **ALK-Abello A/S**	

4.2.5 FOOD ALLERGY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.5	1st paragraph, line 6: Please rephrase Proposal: "., scientific advice *should be requested* by competent authorities…" suggested to be ".. it is *recommended to request* scientific advice by competent authorities …" **ALK-Abello A/S**	The proposal is accepted.
4.2.5	In our opinion, this section related to food allergy considerations although quite important should be considered in a specific document as already mentioned in the above-mentioned general comments. In addition, although DBPCFC said to be the gold standard, is mainly used for clinical trials whereas not any more in use in the clinical practice mainly in children. This should be reflected in the guideline as to ease the recruitment and completion of clinical studies. **EFPIA**	The basic mechanisms of specific immunotherapy are considered the same regardless whether an allergy to inhalational allergens or allergens such as food is addressed. Therefore guidance on food allergy is retained in the guideline. The specific issues regarding therapy of food allergy are addressed in the guideline. No need to release a specific reflection paper on insect venom allergy is seen.

4.2.6 PURIFIED ALLERGENS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.6	The text states that "…..Due to the sensitisation frequency in allergic subjects these different allergens are regarded as major (> 50% IgE prevalence) or minor (< 50% IgE prevalence) allergens". The text should read as: "…..*Due to the sensitisation frequency in allergic subjects these different allergens are regarded as major (> 50% **specific** IgE **binding** prevalence) or minor (< 50% **specific** IgE **binding** prevalence) allergens* *Proposal:* *Change the text as follows: "…..Due to the sensitisation frequency in allergic subjects these different allergens are regarded as major (> 50% **specific** IgE **binding** prevalence) or minor (< 50% **specific** IgE **binding** prevalence) allergens".* **LETI**	Accepted, the text was changed.
4.2.6	A clear and consistent definition of "purified allergen" is requested (please also refer to 4.2.1 page 5 and 4.2.7 last paragraph). Proposal: Please define purified allergens. **ALK-Abello A/S**	"Purified allergens" was defined.
4.2.6	Line: 9-11: Further justifications for the selected study population should not be required if the relations between the purified allergens are similar to the relation between the natural allergens. This presupposes that the product of purified allergens imitate a product form natural allergens. Proposal: Suggested changed to: *Thus the applicant has to justify the selected allergens and has to define and justify the selection of the study population in regard to the included allergens if these do not imitate natural non-purified allergens..*	As it is not entirely clear which of the properties of an allergen extract are essential for the therapeutic effect, demonstration of similarity of a panel of purified allergens with an extract is very difficult and would have to take into consideration IgE-reactivity, T cell reactivity, the relevance of isoforms and other factors. A justification of the allergen selection was already required by the original text. The intention was that the applicant would have to provide evidence that the selection of purified allergens is relevant for the study

	ALK-Abello A/S	population and appropriate for treatment of the allergic disease in that group. This kind of evidence may be generated without proof that the allergen panel fully mimics an extract. Therefore the original phrase was kept.
4.2.6	Last sentence: We find this sentence very stringent, we like to have it modulated a little bit. Proposal: 'If possible we should try…' in stead of 'has to…' in the last sentence. **GSK BIOLOGICALS**	It is not suitable to weaken this sentence. Due to the fact that the allergen spectrum in purified allergens is reduced in comparison to natural extracts, it has to be shown that the selected study population at least has the chance to benefit from the therapy which is not the case, if patients are included, who are not sensitized to the purified allergen under investigation. Thus the sentence is retained.
4.2.6	In our opinion, this section related to CMC considerations should be deleted as neither relevant nor informative for this clinical guideline. **EFPIA**	Not agreed: This section is not related to CMC considerations but the composition and the selection of the suitable study population has a high impact on clinical studies with purified allergens.
4.2.6	It is correct that by using allergen extracts the patient is treated with a broad variety of allergens of the allergenic source, but this does not necessarily mean that this is important for the treatment or improves efficacy. Minor allergens may not be important for a patient, but they are still included in an extract of natural allergen source material. In addition the concentration of important allergens may be limited in natural allergen extracts relative to the total protein content so that they are insufficient to achieve the desired clinical efficacy. Proposed change: By using allergen extracts the patient is treated with a broad variety of allergens of the allergenic source, this may or may not be relevant for her/his individual allergy. By using purified allergens the spectrum of allergens is reduced, but in contrast to extracts from natural allergen source the allergens can be chosen according to their importance and included in a dose that is adequate to achieve the desired clinical improvement. **Allergopharma**	The statement of the company is endorsed, but more in addition to the already stated facts than as change. The proposal was included in the following way: "By using allergen extracts the patient is treated with a broad variety of allergens of the allergenic source, enhancing the chance that the patient is treated with all allergens which are relevant for her/his individual allergy, even if not all included allergens may be relevant for her/his individual allergy. By using purified allergens the spectrum of allergens is reduced, but in contrast to extracts from natural allergen sources the allergens can be chosen according to their importance and included in a dose that is adequate to achieve the desired clinical improvement Thus, the applicant has to justify the selected allergens and has to define and justify the selection of study population regarding the included allergens (e.g. measurement of individual sensitization patterns)."

4.2.6	For studies with purified allergens, a positive control group should consist of the whole allergen extract. **GA2LEN**	The benefit of always including a positive control group with the whole allergen extract is not seen. If the purified allergen/s are efficacious and safe in double-blind, placebo-controlled studies, there is no general need to compare the efficacy with that of allergen extracts. In some cases, such a comparison may be suitable but according to the principles of the European regulatory system it is not mandatory.

4.2.7 CROSS-REACTING ALLERGENS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.7	This section (the so-called taxonomic family) could be considered in the scope section where useful examples could be added given that would be of major interest for development purposes. **EFPIA**	The taxonomic family concept is not used anymore and has been replaced by the concept of homologous groups which is based on scientific criteria. Inclusion of the concept in the scope of the guideline was not considered necessary.
4.2.7	The concept of homologous group is not clearly defined. Proposal: Please explain further or refer to guideline on allergen products: production and quality issues **ALK-Abello A/S**	Unfortunately the old Note for Guidance on Allergen Products was cited whereas the concept on homologous groups is defined in the new quality guideline. The Paragraph was corrected: "The concept of cross-reacting allergens ("allergen families" or "homologous groups") as defined in the "Guideline on Allergen Products: Production and Quality Issues (CPMP/BWP/304831/07) can be adopted for the evaluation of efficacy…"
4.2.7	Line: 7: If the natural allergens are homologous the allergens are not less homologous by being purified. Proposal: Please delete the sentence *The concept of "homologous group" is not applicable to purified allergens (native/recombinant/synthetic peptides).* **ALK-Abello A/S**	As stated in the "Guideline on Allergen Products: Production and Quality Issues (CPMP/BWP/304831/07) the concept of homologous groups not only considers the similarity of major allergens. It is written in the draft of the guideline that "The grouping should be based on the following criteria: • Comparable physicochemical and biological properties of the source material • Cross-reactivity/structural homology of the allergens • Identical formulation of the finished product • Identical production process of the allergen extract and of the finished product." Thus the concept is only designed for native extracts not for single allergens. Therefore the authors retain the sentence "The concept of "homologous groups" is not

		applicable to purified allergens (native/recombinant/synthetic peptides).”
4.2.7	The concept of “allergen families” or “homologous groups” is extremely important. It has a profound scientific background (high cross-reactivity between the different allergens of an allergen family, comparable efficacy in post marketing surveillance studies, no safety problems in long-term market experience) and is of economic and practical importance (product development in this small market segment is not realistic because of cost and the availability of patients). There is absolutely no reason why the “concept of homologous groups” is not applicable to purified allergens (native/recombinant/ synthetic peptides) as long as efficacy can be shown with a major allergen of this “homologous group” and preparations contain the same allergens existing in all allergens of this “homologous group”. For example, if efficacy can be demonstrated with the birch pollen allergen Bet v 1 this data can be extrapolated to a preparation of the highly homologous hazel pollen allergen Cor a 1. Proposed change: If the concept of cross-reacting allergens should be applied to allergens which do not belong to a “homologous group”, then the applicant has to provide a justification for the suggested grouping. The sentence “The concept of “homologous groups” is not applicable to purified allergens (native/recombinant/synthetic peptides)” should be deleted. **Allergopharma**	See response above.
4.2.7.	We believe that the 'homologous group' concept is applicable even when using recombinant allergens. This is in contradiction with the last sentence of that paragraph. Therefore we propose to remove this sentence. Proposal: Remove last sentence of § 4.2.7. **GSK BIOLOGICALS**	See response above.

4.2.8 COMPARABILITY STUDIES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.8	If products are physically changed in vivo efficacy studies have to be done in my opinion. Just in vitro equivalence will not be enough **LARENAS LINDEMANN**	The section on Comparability studies is based on the respective EMEA guidance documents and it is pointed out that these documents should be taken into consideration and that the chosen approach has to be justified by the applicant. In cases in which the product was profoundly changed in vivo efficacy studies will have to be performed.

4.2.9 DIFFERENT ROUTES OF APPLICATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.2.9	"routes of application" should be changed to "routes of administration" **ALK-Abello A/S**	Accepted.
4.2.9	The title would need to be changed to better reflect the clinical reality. In addition, one sentence would need revision as a placebo group does not seem adequate (and ethical) in a setting where a double dummy design is considered. Proposal: Different routes of ~~application~~ **administration**. To compare the efficacy of different routes of application a double-blind, double-dummy design~~, also involving a placebo group~~ is required **EFPIA**	Accepted: "routes of administration" Not accepted: deletion of placebo group: The statement, that a placebo-group is not necessary is correct in cases where efficacy of the single allergen products was already proven in placebo-controlled studies. But even then, to compare the efficacy of different routes, studies without placebo-group have to be designed to show superiority of one route of administration, since non-inferiority trials are not possible as the principal requirement for this (i.e. assay sensitivity) can not be fulfilled. However, the sentence was slightly reworded: To compare the efficacy of different routes of application a double blinded, double dummy design is required and inclusion of a placebo group is normally needed

4.3 EFFICACY IN CHILDREN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.3	Safety should be demonstrated in children. There is no rationale, however, that the mechanism of action is any different in children compared to adults. Therefore efficacy studies in children seem to be unnecessary and consequently unethical. **ALLERGY THERAPEUTICS**	It is known that the immune system maturates during childhood. Up to now, there is no evidence that SIT acts similarly in the immature and the mature immune system. Moreover, several studies for immunotherapy in the paediatric population lacked efficacy. Therefore it is considered necessary to demonstrate efficacy and safety in the paediatric population. Moreover it is referred to the European regulations for this vulnerable population, especially to the European Paediatric Board which decides on basis of submitted paediatric investigation plans, whether clinical studies in children can be waived for specific products or not.
4.3	Although it recognised that there is a need to gather separate safety data for children, there is no clinical or immunological rationale for establishing separate efficacy data for children Proposal: Therefore, the **safety for children** of products for specific immunotherapy has to be evaluated **HAL ALLERGY**	See response above.
4.3	We strongly suggest that in addition for efficacy and safety studies in children there is a need for studies evaluating long-term efficacy and preventive capacity (development of asthma in children with allergic rhinitis and development of new sensitivities in children sensitized and allergic to a single allergen). **EAACI**	The necessity for such studies in general is now implemented in the section 4.2.4 of the guideline. Study duration.
4.3	Definitions of adolescents and young children/children are missing. Suggest to use ICH/CHMP guidelines on age classification. Proposal: Add definitions of adolescents and young children/children to precise and references: Children: 2 – 11 years Adolescents: 12 – 17 years	It is referred to the ICH E11 guideline in which the age classification is defined. There is no obvious reason to repeat these definitions in this guideline.

	(Ref. ICH/CHMP guidelines) **ALK Abello A/S**	
4.3	As per ICH E11, the paediatric age groups include: • Preterm newborn infants • Term newborn infants (0 to 27 days) • Infants and toddlers (28 days to 23 months) • Children (2 to 11 years) • Adolescents (12 to 16-18 years (dependent on region)) **Rationale**: Clinical study of seasonal immunotherapy in paediatric patients below the age of 2 years should be waived as this age group may not have had adequate exposure to demonstrate symptoms. Studies of perennial allergens should be assessed based on ICH E11. Proposal: In general, European regulations regarding this specific vulnerable population (e. g. ICH Topic E11, European Paediatric Board, etc.) should be followed. Studies should not be required in patients under the age of 2 years of age for seasonal allergens. Study of perennial allergens should be assessed following ICH E11. **SCHERING-PLOUGH**	It is not within the scope of the guideline to define in which paediatric populations clinical studies can be waived. This is the responsibility of the Paediatric Board.
4.3	Efficacy in children: It seems that children should be divided into 3 age groups: below 5 years (guidelines do not currently recommend immunotherapy) with a specific target on safety, 5-11 years (as in the US Asthma guidelines) and 12 years and over 12. We appreciate that, in the guideline, this latter age group can be studied with adults. **GA2LEN**	Not accepted. The definition of age groups has to follow European regulations.
4.3	As it is usual requirement, we would prefer to use “validated” instead of “special” questionnaire Proposal: If Quality of Life Questionnaires should be used as secondary endpoints it should be considered that ~~special~~ **validated** Quality of Life Questionnaires are available for children suffering from allergic rhino-conjunctivitis or asthma. **EFPIA**	Accepted.

4.3	A PIP ‘paediatric investigation plan’ could be proposed. **GSK BIOLOGICALS**	It is referred to the European regulations regarding the paediatric population, thus a PIP has to be submitted for each allergen product submitted for marketing authorisation after the 26th of July 2008.

4.4 SAFETY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.4	The guideline recommends the use of the grading system of the European Academy of Allergy and Clinical Immunology (LUIS DELGADO). The grading system of the LUIS DELGADO only grades the reactions related to the allergenicity. Although using this grading system, adverse events should be classified according the severity (none, mild, moderate, severe), and this severity should be defined. **Comments:** 1. One must bear in mind that some local reactions are not due to the intrinsic properties of the allergen extract or the extract. Some local reactions are due to the injection technique and the characteristics of the needle. 2. The untoward events related to treatment should be distinguished into local and systemic: a clear definition of local and systemic is needed. Local side reactions are those that occur where the dose is administered, whereas systemic reactions don't occur in this place. This is especially important in the case of sublingual administration, where the dose is administered under the tongue, and sometimes reactions that take place in the digestive system are classified as local. 3. Untoward events related to treatment, besides to be distinguished into local and systemic, should be distinguished into immediate (onset of the reaction during the first 30 min after the administration of the dose) and delayed (onset of the reaction after 30 min). 4. Untoward local events related to treatment should be evaluated as the length of the diameter of the erythema or the induration (it should be defined). Local immediate reactions with a diameter of less than 5 cm and delayed of less than 10 cm could be considered as clinically irrelevant. 5. The text states that "Other safety parameters which should be addressed are vital signs, routine laboratory haematology, biochemical tests and urinalysis". There is	It is stated in the guideline that the grading system of the EAACI should be used for grading reactions related to the allergenicity of the product. To make this clearer, the words "For systemic allergic reactions…" were added. It is sufficient to refer to this grading system, a complete listing is not necessary. Immediate and delayed type reactions were added and defined, local and systemic was defined. The listing of other safety parameters were retained since it is necessary for each new medicinal product to fulfil these minimal safety criteria. In addition, other comments were taken into consideration. The reworded chapter reads: "In general the existing guidelines on safety have to be followed. All adverse events should be documented, classified as mild, moderate or severe and assessed for relationship to study medication. The adverse events should be coded using MedDRA terminology. Untoward events specifically related to treatment and serious adverse events must be described in detail. Expected allergic side effects should be distinguished into immediate or delayed effects according to the time of appearance (immediate when the onset of the reaction is during

	no reference in the scientific literature about if immunotherapy with the existing allergen extracts doesn't modify these parameters, thus the checking for these parameters may be omitted. Proposal *Reactions related to the intrinsic properties of the allergen-allergen extract should be classified as:* 1. *immediate or delayed according the time of appearance (immediate when the onset of the reaction is during the first 30 minutes after the administration) and delayed (when the onset id after the first 30 minutes of the administration)* 2. *Local or systemic according the site of the appearance of the reaction. Local when the reaction takes place in the administration site and systemic when the reaction takes place far from the administration site.* *Systemic reactions related to the intrinsic properties of the allergen-allergen extract should be graded following the grading system of the LUIS DELGADO* [1] o ***Grade 0: No symptoms or non-specific symptoms.*** o ***Grade I: Mild systemic reactions****. Symptoms: Localized urticaria, rhinitis or mild asthma (PF < 20% decrease from baseline).* o ***Grade II: Moderate systemic reactions****. Symptoms: Slow onset (>15 min) of generalized urticaria and/or moderate asthma (PF < 40% decrease from baseline).* o ***Grade III: Severe (non-life-threatening) systemic reactions.*** *Symptoms: Rapid onset (<15 min) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).* o ***Grade IV: Anaphylactic shock****. Symptoms: Immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension etc.* *Systemic reactions classified as "non-specific symptoms" and reactions non-related to the intrinsic properties of the allergen-allergen extract should be classified as mild, moderate or severe, according to the definitions described in "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* **LABORATORIOS LETI**	the first 30 minutes after the administration and delayed when the onset is after the first 30 minutes of the administration) and into local and systemic effects according the site of the appearance of the reaction (local when the reaction takes place in the administration site and systemic when the reaction takes place far from the administration site) and reported separately. For systemic allergic reactions the severity grading of systemic effects of the European Academy of Allergy and Clinical Immunology (EAACI) may be used. Other safety parameters which should be addressed are vital signs, routine laboratory haematology, biochemical tests and urinalysis."

4.4	"The severity of grading of systemic effects of the European Academy of allergy and Clinical Immunology may be used. " Proposal: The severity of grading of systemic effects of the European Academy of allergy and Clinical Immunology Systemic reactions may be graded according to the EAACI system or another accepted system may be used." **SCHERING-PLOUGH**	As it is stated "The severity grading of systemic effects of the EAACI **may** be used" other accepted systems are not prohibited. No change of wording seems necessary.
4.4	A complete rewording is suggested to be more in compliance with general safety reporting. Especially for sublingual immunotherapy the distinction between local and systemic reaction is unclear, e.g. throat irritation could be classified as one or the other. It is also important to collect all AEs also those not regarding local or systemic. By using the standing MedDRA coding comparisons within a drug and between drugs is made easier. In special cases, if part of the trial purpose, the LUIS DELGADO severity grading can be added as a supplement to the safety reporting. Proposal: Complete rewording is suggested: ***4.4 Safety*** In general the existing guidelines on safety have to be followed. All adverse events should be documented and assessed for relationship to study medication. The adverse events should be collected as individual diagnosis and symptoms and coded using MedDRA terminology including what has previously been considered local and systemic IgE-mediated reactions (anaphylactic reactions). Specifically regarding sublingual immunotherapy, the distinction between local and systemic reactions may be unclear. Therefore, In order to have a standardized way of assessing the reported reactions for systemic reactions it is suggested to use the Standard MedDRA query (SMQ) for Anaphylaxis. Anaphylactic reactions should be presented as A) those not leading to any intervention, B) those where symptomatic medication is used and C) those that are considered life-	The chapter was reworded; see response above.

	threatening and require extensive measures. The timing of anaphylactic reactions to initiation of treatment, to each application and to total duration of treatment should be considered in the presentation. **Abello A/S**	
4.4	The adverse events should be described using the MedRA (Medical Dictionary for Regulatory Activities) and the European Academy of Allergology and Clinical Immunology (EAACI) proposals **GA2LEN**	Accepted, see response above.
4.4	The whole section is related to AEs rated and documented in regards to clinical studies. Although it is stated, “In general the existing guidelines on safety have to be followed”, there is no specific reference to any Risk Management Plan. It would be appreciated to have some guidance. **EFPIA**	Only clinical trials are within the scope of the guideline, thus Risk Management Plans are not considered
4.4	Safety: adverse events should be reported per dose given and per patient. In SLIT ‘local’ AE are mouth symptoms, and some regard GI symptoms also as ‘local’. However, nasal and eye symptoms (in some studies regarded as ‘local’) are systemic, in SLIT as well as in SCIT. **LARENAS LINDEMANN**	Accepted, see comment above.

REFERENCES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	No 3 should be updated with Linda Cox, JACI Sept. 2007 **ALLERGY THERAPEUTICS**	It is not possible to include an extensive literature list in a guideline. Thus only very few references were selected.
	Many of the aspects touched in the EMEA draft have been taken into consideration in a previous document (Canonica G et al, Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy. Allergy 2007; 62:317-24), although with some differences. This position statement was endorsed by the American Academy of Allergy Asthma and Immunology (AAAAI), the American College of Allergy Asthma and Immunology (ACAAI), the Asian Pacific Association of Allergy and Clinical Immunology (APAACI), the European Academy of Allergy and Clinical Immunology (EAACI) and the Latin-American Society of Allergy Asthma And Immunology (SLAAI). We think that the aforementioned document should be at least quoted in this version of the EMEA guidelines. **EAACI / Jan Lötvall**	Accepted.

	Some other relevant references could be added such as:
	- Canonica GW, Baena-Cagnani CE, Bousquet J et all. Recommendations for standardization of clinical trials with Allergen Specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy 2007: 62: 317–324
	- The ARIA (Allergic Rhinitis and its Impact on Asthma) WHO recommendations - http://www.whiar.org/docs/ARIA_Glance_WM.pdf
	- Some reference to validated Health related Quality of Life questionnaire for rhino-conjunctivitis in adults and children, such as
	  - E. Juniper- http://www.qoltech.co.uk/Rhinocon.htm
	  - Juniper EF. Quality of life in adults and children with asthma and rhinitis. Allergy 1997: 52; 971-977.
	
	EFPIA
	
	Add the following references:
	• Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-334.
	• Bousquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases. A comprehensive approach. Global Alliance against Chronic Respiratory Diseases. World Health Organization. ISBN 978 92 4 156346 8. 2007:148 pages.
	• Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy. 2007 Mar;62(3):317-24.
	• Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy. 2006;61 Suppl 82:1-20.
	• Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. J Allergy Clin Immunol. 2007 Apr;119(4):881-91
		See response above.
		
		The WAO and the ARIA recommendations were added.

GA2LEN

[1] Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-334.

[2] Bousquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases. A comprehensive approach. Global Alliance against Chronic Respiratory Diseases. World Health Organization. ISBN 978 92 4 156346 8. 2007:148 pages.

[3] Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy. 2007 Mar;62(3):317-24.

[4] Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy. 2006;61 Suppl 82:1-20.

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[7] Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy. 2003 Jul;58(7):672-5.

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[10] Bousquet J, Calvayrac P, Guerin B, Hejjaoui A, Dhivert H, Hewitt B, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. I. In vivo and in vitro parameters after a short course of treatment. J Allergy Clin Immunol. 1985;76(5):734-44.

[11] Bousquet J, Lockey R, Malling H. WHO Position Paper. Allergen Immunotherapy: TherapeuticVaccines for allergic diseases. Allergy. 1998;53, suppl 54.

[12] Expert panel report 3: Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program. National Heart, Lung and Blood Institute. US Department of Health and Human Services. 440 pages. 2007.