European Medicines Agency
*Pre-Authorisation Evaluation of Medicines for Human Use*

London, 20 November 2008
Doc. Ref.: EMEA/CHMP/BWP/596200/2008

# OVERVIEW OF COMMENTS RECEIVED ON THE DRAFT GUIDELINE "ALLERGEN PRODUCTS: PRODUCTION AND QUALITY ISSUES"

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

| | Name of Organisation or individual | Country |
|---|---|---|
| 1 | AFSSAPS Pharmaceutical Working Group on Biological Allergen Products | France |
| 2 | ALK-Abelló A/S | Denmark |
| 3 | Allergopharma Joachim Ganzer KG | Germany |
| 4 | Allergy Therapeutics (UK) Ltd (ATL) | The United Kingdom |
| 5 | European Allergen Manufacturers Group (EAMG) | Denmark |
| 6 | GlaxoSmithkline Biologicals (GSK) | Belgium |
| 7 | HAL Allergy BV | The Netherlands |
| 8 | Laboratorios LETI | Spain |
| 9 | College ter Beoordeling van Geneesmiddelen - Medicines Evaluation Board (CBG-MEB) | The Netherlands |
| 10 | Stallergenes S.A. | France |
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| GENERAL COMMENTS - OVERVIEW |
| --- |
| **AFSSAPS:**<br>Considering that most of the regulatory text or technical documents do not apply or exclude allergen products, the characteristics required for allergen products (for example, sterility) should be defined according to the route of administration claimed (in particular when the product is entering into the skin for skin-prick tests but also for provocation tests).<br>*Response to comment:*<br>*The corresponding regulations and definitions are laid down in the Ph. Eur. monograph on allergen products or other relevant monographs and do not need to be specified here.* |
| **ALK-ABELLÓ:**<br>IgE binding test is not necessarily the same as Total allergenic activity testing, as IgE binding can also be performed on major allergens. We recommend that the wording is more specific by using "Total allergenic activity" or "Major allergen activity" where appropriate.<br>*Response to comment:*<br>*The expression "competitive IgE-binding test" is used throughout entire document and a definition will be given in the section "Definitions". It is made clear that this term generally applies to experiments with extracts, while it will be specifically mentioned if IgE binding to individual allergens is meant.*<br><br>This guideline must be aligned with the final wording of the updated EP monograph on Allergen Products, to be published in the next issue of Pharmeuropa.<br>*Response to comment:*<br>*Consistency and complementarity between the two documents has been assured.* |

**ALLERGOPHARMA:**

It is important that the Guideline should make clear distinctions between the requirements for diagnostic preparations and those for allergen specific immunotherapy.

*Response to comment:*

*This guideline covers therapeutic as well as test allergen preparations. The majority of the requirements are applicable to both products, but it is accepted, that numerous test allergen preparations cannot be standardised. In those cases the guidance for non-standardised allergen extracts shall be applied.*

Homologous groups of allergens: The new concept which is now proposed does not fit the existing regulatory grouping, and therefore it could only be applied to new product registrations and not implemented retrospectively for products already on the market. The scientific rationale for this new concept is not officially available because the paper referred to (Lorenz, 18) is not published, and therefore it cannot be implemented at the moment due to lack of background information. In order to comment on the homologous group concept the scientific material must be available.

*Response to comment:*

*The publication on the suggested new grouping of the allergens is now published. This issue was discussed separately during an informal consultation with manufacturers during the 12th International Paul-Ehrlich-Seminar (September 24th, 2008). The guideline defines requirements for allergen products of the basis of the state of the art knowledge in the field In general the new guideline applies to new marketing authorisations only.*

This Guideline is not intended to address the subject of efficacy and therefore it is not appropriate to include criteria for addressing this subject.

*This guideline only describes the concept of he homologous group and gives reference to the corresponding GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES (CHMP/EWP/18504/2006). It does not specify any clinical requirements.*

The prospect of using mixtures of recombinant allergens that have their origins in different allergen sources is not addressed. The arguments used to justify the use of homologous groups in respect of allergen extracts of natural source materials should not apply as the individual recombinant proteins are fully defined entities.

*Response to comment:*

*The concept of homologous groups is limited to allergen extracts only as indicated in the corresponding section (e.g. identical production process of the allergen extract).*

The draft Guideline contains no mention of allergens that have traditionally been categorized as 'foods'. This definition has its short-comings, not least because it encompasses a very broad range of plant and animal materials. Therefore we suggest that two further categories, 'Plant derived allergens (excluding pollens)'and 'Animal derived allergens (excluding mites and epithelia)' should be introduced. This will take account of potential plant products such as latex, peanut, apple etc., and animal products such as fish allergens which are not recognised in the current draft.

*Response to comment:*

*The general requirements also apply to food allergens. Therefore the criteria laid down in section 4.2.3.1 "Control of source materials for allergen extracts" are applicable and no separate section will be included. The suggested grouping does not fulfil the scientific criteria for homologous groups. However, additional homologous groups may be formed for groups of foods, provided that the criteria are met. In addition, many food extracts may be categorised as non standardised extracts for which rules are described in the guideline.*

**ALLERGOPHARMA:**

Additional comments:

- There is no mention of the use of preservation agents, e.g. phenol, and no requirement concerning testing or the adequacy of preservation.

*Response to comment:*

*The specific requirements are laid down in the corresponding Ph. Eur. Monographs (e.g. monographs for preservatives, parenteral preparations).*

- The draft Guideline fails to address the matter of safety testing, specifically the toxicological testing of allergen products. It is imperative that this subject should be addressed in an additional section. Experience in various Scientific Advice Meetings with Authorities has shown that they are often not in a position to give clear guidance.

*Response to comment:*

*Safety testing is not in the scope of this guideline.*

**ALLERGY THERAPEUTICS (UK):**

The terminology used for the allergen products are inconsistent and not clear. The terms should clearly defined and harmonised with the terms used in the European Pharmacopeia. i.e. Allergen, allergen extract and allergen product. A definition of the term "active substance" should also be provided.

When the term "allergen mixtures" is used it should be made clear if the meaning is related to mixture of allergens from the same species, from different species or from closely related cross reactive allergen sources.

*Response to comment:*

*The term "active substance" is defined in the common European regulations and is specified in section 4.2.1. No further definition is assumed to be necessary. Concerning allergen mixtures, it is defined that mixtures are prepared from allergen extracts from single source materials, which may be different species.*

**College ter Beoordeling van Geneesmiddelen - Medicines Evaluation Board (CBG-MEB):**

- In case the potency has not been determined on the final container, the company should have an alternative method to verify the label claim, e.g. to establish the correct dilution.

*Response to comment:*

*This comment is covered by the guideline text.*

- The proposed guideline requires biological standardisation of IHRP on basis of the skin test reactivity. However, reference preparations should preferentially be investigated in blinded controlled clinical trials.

*Response to comment:*

*The guidance is based on existing documents on biological standardisation of allergen extracts. None of these documents requires standardisation of the IHRP in a blinded clinical trial. It remains unclear why blinded testing could result in a different biological potency of the IHRP.*

**EAMG/LETI:**

Homologues groups of allergens: This new concept will not fit the existing regulatory grouping, why this should only be applied for new product and not implemented for products already granted marketing authorisation in one or more member states. The scientific rationale for this new concept is not officially available and the paper referred to (Lorentz, 18) is not published why the concept is not prepared for implementation. In order to comment on the homologous group concept the scientific material must be available. The guideline mentions that there are no homologues groups for moulds. We recommend using *Alternaria alternata* as the representative allergen as this was described earlier. Please see enclosed expert report from Dr. Samson, Utrecht specifically on the taxonomic relationship within the moulds.

*Response to comment:*

*The guideline gives recommendations for allergen products of the basis on the state of the art knowledge in the field. The publication on the suggested new grouping of the allergens is now published. This issue was discussed separately during an informal consultation with manufacturers at the 12th International Paul-Ehrlich-Seminar (September 24th, 2008).*

*Grouping of moulds into a homologous group would require a justification as described in the corresponding section of the guideline.*

The updated guideline should not automatically apply to existing products i.e. to the products already authorised in any EU/EEA member state.

*Response to comment:*

*The guideline gives recommendations for allergen products of the basis on the state of the art knowledge in the field. The guideline should be used for any new application regardless whether or not the product is already authorised in the EU (Directive 2001/83/EC, as amended).*

With regard to the allergen products the terminology used in this guideline is inconsistent and not clear. The terms have to be clearly defined and harmonized with the terms used in the European Pharmacopeia. i.e. Allergen, allergen extract and allergen product and also a definition of the term "active substance" must be defined.

*Response to comment:*

*The term "active substance" is defined in common European regulations and is specified in section 4.2.1. No further definition is necessary.*

When the term "allergen mixtures" is used it should in each case be made clear if the meaning is related to mixture of allergens from the same species, from different species, from closely related cross reactive allergen sources or from species from different homologous groups.

*Response to comment:*

*Concerning allergen mixtures, it is defined that mixtures are prepared from allergen extracts from single source materials, which may be different species.*

**EAMG/LETI:**

In situations where it for confidentiality reasons is not possible for the allergen product manufacturer to get access to needed information from raw material suppliers, a procedure similar to the Active Substance Master File or Drug Master File have to be considered in order that the Authorities will have the complete information and the MAH (Marketing Authorisation Holder) or the manufacturer) will have only access to the open part of the complete Drug Master File.
*Response to comment:*
*The establishment of a "Drug Master File" for allergen source material and active substance was discussed, but no legal basis is currently available for the implementation of a master file approach. Therefore, it was impossible to include such an approach into the guideline.*

Some of the quality issues should be applicable only to allergen products for treatment, not those only used for diagnostic. A more clear distinction between allergens only used for diagnostics and allergens used for both diagnostics and treatment is needed.
*Response to comment:*
*This guideline covers therapeutic as well as test allergen preparations. The majority of the requirements are applicable to both products, but it is accepted, that numerous test allergen preparations cannot fulfil all requirements applicable for the therapeutic preparations (e.g. biological standardisation). In this case the guidance for non-standardised allergen extracts shall be applied. These cases would have to be justified on a case by case basis by the applicant. No separate quality requirements for test allergen preparations are defined in this guideline.*

It should be pointed out that several issues raised in this document are clinical issues and should be omitted. This Guideline is not intended to address the subject of clinical efficacy and/or safety even if both is related to the quality of the allergen products.
*Response to comment:*
*This guideline provides the principle of the homologous groups, which also applies to clinical and preclinical aspects as described in the corresponding guideline. Therefore, for clarification, reference was made to these topics even though the guideline applies only to quality issues in general.*

Biological potency estimates based on IgE assays should be termed IgE-binding assays since this terminology will cover the different methodologies implemented for potency estimates.
*Response to comment:*
*The expression "competitive IgE-binding test" will be used throughout entire document and a definition will be given in the section "Definitions". It will be made clear that this term generally applies to experiments with extracts, while it will be specifically mentioned if IgE binding to individual allergens is meant.*

**STALLERGENES:**

The guideline introduces the new concept of homologous groups which replaces previous taxonomical families. However, the scientific rationale for the grouping is not available (Lorentz, reference 18). As long as we have no information about the criteria used for grouping, it is not possible to comment on this concept. Furthermore such a change in grouping of allergen products cannot be implemented for marketed products.

*Response to comment:*

*The paper is now published. This issue was discussed separately during an informal consultation with manufacturers at the 12th International Paul-Ehrlich-Seminar (September 24th, 2008).*

In addition, extrapolation of data gained on the representative allergen product to non-representative members is too limited. More possibilities to extrapolate are needed to make the concept of homologous groups fully useful.

*Response to comment:*

*See section on homologous groups. Without any scientific justification extended extrapolation cannot be accepted.*

The guideline also introduces the new concept of « relevant allergen ». This new concept deserves more explanations. We suggest a specific paragraph at the beginning of the document.

*Response to comment:*

*A definition of the expression "relevant allergen" is now provided in the section "Definitions".*

Quality and production issues related to hymenoptera venoms are mentioned in some paragraphs but are missing in others. Whether the other paragraphs do apply or not to venoms should be made clear.

*Response to comment:*

*Specific requirements for individual allergens like hymenoptera venoms are only mentioned if there is a difference from the requirements for allergen extracts in general. Therefore, if no specific requirements are given, the guidance also applies to venoms.*

| SPECIFIC COMMENTS ON TEXT | | |
|---|---|---|
| **GUIDELINE SECTION TITLE** | | |
| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| **EXECUTIVE SUMMARY** | | |
| Page 4<br>Line 3 – Line 21<br>(Allergopharma) | The allergen extracts themselves are not of natural origin.<br><br>Proposed rewording:<br>*"…..allergen extracts from natural* ***~~origin~~ source materials*** *and allergens produced...."* | Change into "allergen extracts derived from natural source material" is acceptable. |
| **1. INTRODUCTION** | | |
| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 4<br>Lines 7-10<br>(Allergopharma) | The definition of allergy needs to be re-worded:<br>***"Allergy is a disease that is a consequence of Type I hypersensitivity reactions which are vigorous responses of the immune system triggered by the interaction of allergens with specific IgE antibodies leading to the release of inflammatory mediators including histamine, cytokines and lipid mediators."*** | The definition provided by Allergopharma is accepted. |

| 2. SCOPE | | |
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| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 4<br>Line 19<br>(EAMG)<br>(LETI) | The scope of the guideline needs more clarification.<br>The guideline should only apply to new therapeutic allergen products and to the most common test allergen products. For some rare but clinical relevant diagnostic test allergens it will not be possible to comply.<br><br>Proposed text to be added:<br>***"The guideline is covering quality requirements for not already marketed allergen products used for specific immunotherapy (SIT) and for the most common diagnostic allergen products"***. | See previous comment concerning scope of the guideline.<br>Because no clear distinction of common and not-common/rare test allergens can be made, no such differentiation should be included. It may be recognised that if some quality requirements cannot be fulfilled because of the rareness of such test allergens, this has to be justified. For further explanations please see comments in the overview section. "Rare" allergens may be dealt with as non standardised on a case by case basis if justification is provided by the applicant. |
| Page 4<br>Line 26<br>(Allergopharma) | Various allergen derivatives or variants produced through the use of recombinant DNA technology are being tested or are in development, e.g. recombinant allergen fragments, genetically engineered 'mutant' allergens. It should be made clear that these also fall within the scope of the Note for Guidance.<br><br>Proposed rewording:<br>*"...conjugates or allergens* ***and allergen variants*** *(e.g. mutants or variants generatedby physiochemical treatment) manufactured using…."* | Allergen variants are now included into the definition of recombinant allergens (see section "Definitions") and therefore need not to be mentioned in this section. |
| Page 4<br>Line 31<br>(Allergopharma) | Repetition of 'use / used'.<br><br>Proposed rewording:<br>*"... (IHRP)* ~~***, which are used***~~ *for quality control, including…"* | This comment is accepted. |

| 4.1.1. GENERAL CONCEPTS – HOMOLOGOUS GROUPS | | |
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| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Pages 4-5<br>(Allergopharma) | **Homologous Group Chapter**<br>The statement that the concept of homologous groups 'retains the flexibility needed' is a matter of debate. The system of taxonomic classification has a sound scientific basis that provides an hierarchical grouping of living organisms on the basis of their similarities. The proposal presented in this draft Guideline, and it can be seen as nothing more than a proposal at this stage, would impose far greater restrictions than those provided for in the existing Note for Guidance (CPMP/BWP/243/96).<br><br>Explanation/rationale for the proposed changes/amendments<br>(1): A more precise use of the term "allergen" is needed. An allergen extract may contain a variety of allergen proteins.<br>(2): the concept of taxonomic allergen groups/exemplar allergens, as described in the Note for Guidance "Allergen Products" (CPMP/BWP/243/96) was introduced in 1992 by the first issue of the Note for Guidance (CPMP III/9271/90). Since then it has proved its applicability in every day practice. In Germany it found its extension by a classification system introduced by the Paul Ehrlich Institute in 2000 by also grouping the food allergens and at the same time introducing the concept of quality categories over the whole range of allergens with a stepwise increase of quality demands according to the clinical importance of the test allergens.<br>(3): The concept of homologous groups has not yet been published in detail. Evaluation of the impact of the new concept on all aspects of elaborating data about safety, efficacy, and stability of allergen products is premature. Stipulating that the new concept limits the extrapolation of data and at the same time postulating that it retains the flexibility is a contradiction in itself.<br>Taking the proposed groups contained in the annex for granted, a rough estimate came to the result that the theoretical number of studies that would be required by strict application of the draft proposal would be at least about tenfold the number necessary under the current Note for Guidance, not | The publication (" The Principle of Homologous Groups in Regulatory Affairs of Allergen Products – A Proposal) on the suggested new grouping of the allergens is published (A.R. Lorenz et al, Int. Arch. Allergy Immunol., 2009, 148: 1-17)(published online 2008). This issue of group formation (Annex I) was discussed separately during an informal consultation with manufacturers during the 12th International Paul-Ehrlich-Seminar (September, 24th, 2008). |

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| | withstanding the fact that a reasonable number of allergens will drop out of the existing groups, thus calling for additional studies. Taking into account the fact that many test allergens already have marketing licences, it would be highly questionable from an ethical point of view to start additional clinical trials for the new allergen groups or for the drop out allergens. In this respect it will only be realistic to apply a modified group classification in respect of new product registrations and not to expect retrospective studies for those allergens which were covered by the existing accepted grouping, but not by any new classification that may be adopted.<br>Extending the new grouping principle also to biotechnologically produced allergens is at the moment premature, but needs to be considered for the future when more such allergens may become available which will call for data about safety, stability, and efficacy. It should be noted that CHMP/EWP/18504/2006 specifically excludes the concept of homologous groups for purified/recombinant allergens and synthetic peptides.<br>(4): A more precise assignment of the grouping parameters to their function in grouping the allergens seems appropriate. Combining cross-reactivity with physicochemical structures would provide a more practical approach for grouping and soften the need for creating groups on a sheer theoretical approach as proposed.<br>(5): (Page 5, L.12) 'Limited extent' has to be defined or an alternative wording substituted. We suggest the latter option whilst including the additional statement '***provided that there is an adequate rationale***.'<br>Annex 1: the allergen groups 'Plant derived allergens (excluding pollens)' and 'Animal derived allergens (excluding mites and epithelia)' should be added with the grouping instead of "Food stuffs" as proposed by the Paul Ehrlich Institute in 2000.<br><br>It is proposed that the following revised text should replace page 4, line 39 to page 5, line 20 inclusive. Numbers in brackets refer to individual comments):<br>***"Due to the high number of ~~allergens~~ allergenic proteins (1) in an allergen extract or in an allergen extract mixture and the cross-reactivity of the individual components, it is impossible to determine all relevant parameters for ~~the allergens~~ each individual allergen/protein within a given extract or a defined allergen extract mixture. ~~Therefore in the previous Note for~~*** | |

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| | ~~*Guidance on 'Allergen Products' (CPMP/BWP/243/96)*~~<br>***The large number of allergen products prepared for allergy testing or immunotherapy and the limited number of suitable patients or test material (sera) mean that it is impossible to test each single allergen preparation for efficacy, safety and stability. In order to circumvent this problem the first issue of the Note for Guidance on Allergen Products (CPMP/BWP/243/96) in 1992 introduced the concept of taxonomic allergen groups [(2)]. It stipulated that tests for stability (§7), safety (§8) and efficacy (§9) may be performed with one member of a taxonomic group (exemplar allergen) and the data obtained may be extrapolated to other members of that group, provided that the manufacturing process is comparable. The extrapolation has to be discussed and justified. This concept has become well established and has proved its applicability and worth.***<br>***However, the extrapolation of stability, safety and efficacy data among members of taxonomic families were defined in a very broad sense*** ~~***and used by applicants***~~***. The concept of homologous groups introduced here*** ~~***replaces***~~ ***therefore redefines the concept of taxonomic families. As in modern taxonomy, the homologous groups [(3)] should take account of phylogenetic relationships by taxonomy and structure, and physicochemical structure of allergens by homology. The homology principle can also be applied to biotechnologically derived allergens. This*** ~~***new concept***~~ ***change*** ~~***limit***~~***s the extrapolation to groups defined and justified by scientific criteria whilst at the same time*** ~~***it retains***~~ ***retaining the flexibility needed.***<br>***Allergen extracts prepared from different species, different genera or different families, and finished products which are derived from these allergen extracts*** ~~***and for which clinical experience already exists***~~ ***may be grouped, if justified, into homologous groups.***<br>***The grouping should be based on the following criteria [(4)]:***<br>• ***Comparable physicochemical and biological properties of the source material (taxonomy)***<br>• ***Cross-reactivity and/or physicochemical structure*** ~~***/structural homology***~~ ***of the allergens (clinical experience and/or homology)***<br>• ***Comparable*** ~~***identical***~~ ***formulation of the finished product***<br>• ***Comparable*** ~~***identical***~~ ***production process of the allergen extract*** | |

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| | ***and the finished product***<br>***One member of a homologous group is selected as the representative allergen. This choice should be justified, taking into consideration <u>all ~~for example geographical differences in the sensitization patterns and other~~</u> relevant factors.***<br>***~~To a limited extent~~ Data on stability, safety and efficacy can be extrapolated from the representative <u>(exemplar)</u> allergen to other members of the homologous group <u>provided that there is an adequate rationale</u> [(5)]. For allergens that cannot be included into one homologous group, the data for quality, safety and efficacy have to be provided on a single-product basis.***<br>***~~Detailed~~ Safety studies are only requested for the representative allergen, while post-marketing safety reports will be requested for non-representative allergens of the same group. Extrapolation of clinical data is addressed in the separate EWP guideline[1].***<br>***<u>Proposed</u> ~~accepted~~ homologous groups are listed in Annex I. If justified, the applicant may define other groups or introduce new members into an existing group provided the above-mentioned criteria are fulfilled."*** | |
| Pages 4-5<br>(EAMG)<br>(LETI) | Homologous groups of allergens: This new concept will not fit the existing regulatory grouping, why this should only be applied for new products and not implemented for products already on the market in one or more EU/EEA member states.<br>The scientific rationale for this new concept is not officially available, and the paper referred to (Lorentz, 18) is not published. In order to comment on the homologous group concept the scientific material must be available, otherwise it should not be implemented.<br><br>Proposed text to be added:<br>***"This new concept should only be implemented for new products, not already on the market in any EU/EEA member state."*** | The guideline defines requirements for allergen products on the basis of the state-of-the-art knowledge in the field. In general, the new guideline applies to new marketing authorisations only. |
| Page 4 lines 39-46<br>Page 5 lines 1-20<br>(Stallergenes) | The scientific material describing the criteria used for the grouping is not available. Therefore it is not possible to comment on this concept. | The publication on the suggested new grouping of the allergens is published. This issue was discussed during an informal consultation with manufacturers during the 12th International Paul-Ehrlich-Seminar (September, 24th, 2008). |

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| Page 4,<br>Lines 43-46<br>(ALK-ABELLO) | The concept of homologous groups should only be required for new marketing authorisation applications, meaning the first marketing authorisation application for a given product in EU. The requirement should come into effect from the date stated in the final version of the guideline | The guideline defines requirements for allergen products on the basis of the state-of-the-art knowledge in the field. In general, the new guideline applies to new marketing authorisations only. |
| Page 5,<br>(ALK-ABELLO | As long as the scientific background for this grouping is not officially available and the paper referred to (Lorentz[18]) is not published, it is not possible to comment on the homologous groups. | The publication on the suggested new grouping of the allergens is published. This issue was discussed during an informal consultation with manufacturers during the 12th International Paul-Ehrlich-Seminar (September, 24th, 2008). |
| Page 5<br>Lines 4-7<br>(AFSSAPS) | Hierarchy should not be considered for criteria used to define homologous groups. Consequently, it should be clearly specified that the four criteria used to define homologous groups should be considered simultaneously.<br><br>*"The grouping should be based* ~~***on***~~ ***considering simultaneously*** *the* ***four*** *following criteria:*<br>*• Comparable physicochemical and biological properties of the source material*<br>*• Cross-reactivity/structural homology of the allergens*<br>*• Identical formulation of the finished product*<br>*• Identical production process of the allergen extract and of the finished product."* | No hierarchy was intended. For clarification the text will be revised as follows, so that it is specified that all four criteria have to be met:<br><br>*"The grouping should be based following criteria:*<br>*• Comparable physicochemical and biological properties of the source material and*<br>*• Cross-reactivity/structural homology of the allergens and*<br>*• Identical formulation of the finished product and*<br>*• Identical production process of the allergen extract and of the finished product*<br>*For group formation all four criteria have to be fulfilled."* |
| Page 5<br>Lines 4-8<br>(LETI) | Clarification of the criteria is needed to know if all the requirements have to be complied or only some of them. | See comment from AFSAPPS above. |

<table>
<tr>
<td>Page 5<br>Line 9<br>(LETI)</td>
<td>Allergen and allergen extract are not the same concept.<br><br>Proposed rewording:<br>“One member of a homologous group is selected as the representative allergen extract”.</td>
<td>According to the annex I, representative allergen sources have been defined and not individual allergens (molecules). The sentence will be reworded accordingly.<br>“One member of a homologous group is selected as the representative allergen source”.</td>
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<tr>
<td>Page 5<br>Line 9<br>(Stallergenes)</td>
<td>The term « allergen » should only be used for a molecule (cf. definitions). In this sentence (and others in the document), the term “allergen product” would be more accurate (cf. Ph. Eur. 1063).<br><br>Proposed rewording:<br>“One member of a homologous group is selected as the representative allergen <u>product</u>.”</td>
<td>According to the annex I, representative allergen sources have been defined and not individual allergens (molecules). The sentence will be reworded accordingly.<br><br>See comment from LETI above.</td>
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<tr>
<td>Page 5<br>Lines 12-15<br>(Allergopharma)</td>
<td>The requirement to provide separate efficacy data for those allergens that cannot be included in an homologous group, or indeed those which would fall into a new group as a result of the introduction of a new grouping system would inevitably lead to a reduction in the number of new allergen products that would be made available for practitioners in the future, in particular for in vivo diagnostic products.<br>In this regard, the system currently operated by the Paul Ehrlich Institute whereby in vivo diagnostic preparations are divided into four categories depending on the extent of their characterization, standardization and extent of efficacy testing has proven its worth.<br>Test allergens: Categories of Quality as proposed by PEI (05/2000)<br><br>This is a cover-to-cover translation of a paper issued by the Paul Ehrlich Institute in 2000 in order to establish certain common quality standards throughout the whole range of test allergens covered by marketing licences in Germany.<br><br>
<table>
<tr><td>A</td><td>Test allergens for which potency test can be done with high titer human IgE sera from allergic patients</td></tr>
<tr><td></td><td></td></tr>
<tr><td>B</td><td>Test allergens for which potency test can be done either with IgE sera from humans (limited availability) or animal anti-sera or monoclonal</td></tr>
</table>
</td>
<td>The proposal of Allergopharma concerning the quality standards cannot be accepted because they represent only nationally valid requirements.<br>This guideline covers therapeutic as well as test allergen preparations. The majority of the requirements are applicable to both types of products, but it is accepted that numerous test allergen preparations cannot fulfil all requirements applicable to therapeutic preparations (e.g. standardisation). In this case the guidance for non-standardised allergen extracts shall be applied. Deviations from the guideline have to be justified by the applicant on a case-by-case basis. No separate quality requirements for test allergen preparations will be defined in this guideline.</td>
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| | antibodies. |
| | |
| C | Test allergens for diagnosis of rare allergens for which anti-sera of human or animal origin for test of potency are not available in sufficient quantities. |
| | |
| D | Test allergens for diagnosis of very rare allergens for which anti-sera of human or animal origin for test of potency are not available at all. |

Application of the concept of quality categories for marketing licence dossiers and product batch control

| Category: | Dossier | | | | Batch control | | | |
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| | A | B | C | D | A | B | C | D |
| Determination of total protein (provided there is no test of potency) | + | + | + | + | + | + | + | + |
| Protein profile by IEF, SDS-PAGE ... | + | + | + | + | + | + | + | + |
| Potency test or allergen/antigen profile | + | either | - | - | + | either | - | - |
| Antigen profile or individual antigens w. animal anti-sera or monoclonal antibodies e.g. CIE, immunoblot or ELISA | | or | | | | or | | |
| Clinical trials | + | - | - | - | | | | |
| Statistical evaluation of “Skin test charts” | - | + | either | - | | | | |

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| | 2 -3 case reports giving the numbers of patients tested, provided that anamnesis has been proven by testing with the allergen in question | - | - | or | - | |

Whilst it might be appropriate to apply the concept of homology to achieve a more restricted group classification for the purposes of ensuring the quality of allergen products, a broader approach is justified with regard to clinical efficacy. Allergy is one disease with many triggers. There is good reason to believe that the mechanisms of immunotherapy for inhalant allergens are the same for each allergen. (It might be argued that some additional factors have to be taken into account in the case of insect venoms). Provided that the quality of the products can be ensured, there is no reason to doubt that they can all be equally efficacious. Consequently clinical development programs for additional members of a particular group could be restricted to addressing issues of tolerance and safety.

**For test allergens the criteria for demonstrating quality of the extracts may be less stringent provided adequate justification is given.**

Comment: A broader grouping for the purposes of demonstrating clinical efficacy would be welcomed.

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| Page 5<br>Lines 12-15<br>(EAMG)<br>(LETI) | This guideline is covering product quality assurance and should not include safety and clinical issues. Then safety and efficacy should be deleted.<br><br>Proposed rewording:<br>*"To a limited extent data on stability, ~~**safety and efficacy**~~ can be extrapolated from the representative allergen to other members of the homologous group. For allergens that cannot be included into one homologous group, the data for quality, ~~**safety and efficacy**~~ have to be provided on a single-product basis."* | This guideline only describes the concept of the homologous group and gives reference to the corresponding GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES (CHMP/EWP/330611/2008). It does not give any further guidance on efficacy issues. Because no specific guideline on non clinical studies for allergen preparations does exist yet, basic information on the extrapolation of safety data within one homologous group is given in this guideline. The wording |

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| | | has been approved by the CHMP Safety Working Party. Therefore the section will not be changed. |
| Page 5<br>Lines 12-18<br>(AFSSAPS) | The concept of homologous groups is debatable and subject to constant evolution depending on the acquired knowledge in molecular and biological research. Especially, from efficacy/safety point of view, their definition and grouping may be reconsidered with respect to the acquired data regarding the identification of major allergens and the results from future clinical investigations and studies.<br>This guideline is aimed at addressing production and quality issues but it is not the place for any recommendation or statements regarding safety and efficacy. Therefore, we propose that any recommendation and statement on efficacy and safety points be deleted from this guideline.<br><br>Therefore, the following sentences (from line 12 to 18) should be reworded by deleting safety and efficacy statements:<br>"*To a limited extend data on stability, ~~safety and efficacy~~ can be extrapolated from the representative allergen to other members of the homologous group. For allergens that cannot be included into one homologous group, the data for quality, ~~safety and efficacy~~ have to be provided on a single-product basis.*<br>***~~Detailed safety studies are only requested for the representative allergen, while post marketing safety reports will be requested for non representative allergens of the same group.~~*** *Extrapolation of clinical data is addressed in the separate EWP guideline.*" | See response to comment from EAMG and LETI above. |
| Page 5<br>Lines 19-20<br>(AFSSAPS) | Considering that the opinion article defining the homologous groups is only submitted at the moment and consequently not fully validated by the scientific community, it should be preferable to consider the annexe I as a | The proposal is accepted. |

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| | proposal of homologous groups.<br>Moreover, the annexe 1 should be updated according to the state of the art and the scientific knowledge.<br><br>Proposed rewording:<br>***"~~Accepted~~ Proposed*** *homologous groups are listed in Annex I. If justified, the applicant may define other groups or introduce new members into an existing group provided the above-mentioned criteria are fulfilled.*<br>***The annex I should be updated according to the state of the art and the scientific knowledge."*** | |
| **4.1.2. ALLERGEN EXTRACT MIXTURES** | | |
| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 5<br>Line 22<br>(AFSSAPS) | Mixtures could be considered at the source material step if justified and validated.<br><br>Proposed rewording:<br>*"**Unless justified <u>and</u> validated by scientific and experimental data**, allergen extract mixtures should be prepared from individual extracts from single source materials."* | Generally, if justification and validation by scientific and experimental data are provided, applicants can deviate from guidelines. Therefore the comment is not agreed and the section is not changed. |

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| Page 5<br>Lines 22-23<br>(Allergopharma) | A clear distinction should be made between allergen extract mixtures of unrelated species and those of closely related species. In the case of grass pollen allergy, for example, diagnosis is made currently using representative allergens. Subjects are normally exposed to pollen from a great variety of grass species and the sensitisation they develop is a collective response. The use of grass pollen mixtures has found widespread application because it achieves an allergen profile that is more likely to reflect the natural exposure.<br><br>Proposed rewording:<br>*"Allergen extract mixtures have to be prepared from individual extracts* ***~~from single source materials. Therefore the~~*** *Different source materials should not be mixed prior to extraction* ***unless otherwise justified****."* | See response to comment from AFSAPPS above. |
| Page 5<br>Lines 22-28<br>(EAMG) | It is not generally clear what is meant by an "*allergen mixture"*. Are mixed allergens within a homologous group a mixture? The potency testing issue for each individual active substance before mixing is unclear.<br>Does the meaning refer to individual allergens, extracts of individual species or allergens of different origin?<br>It is common practise to mix the source materials for related cross reacting species like grasses. Because grasses are the homologous group of source materials and cross-reactive we consider this acceptable. Clinical practise is available for these products for decades. The guideline should leave room for this general accepted practise.<br>Should be rewritten and terminology made clear.<br><br>Proposed rewording:<br>"***Unless justified, allergen extract mixtures have to be prepared from individual extracts from single source material."*** | The exact wording of the paragraph is "allergen extract mixture" and not "allergen mixture". The regulation concerning mixtures according to the draft ensures consistency in the manufacture of allergen extract mixtures. The statement in line 32 – 33 "If in a mixture the allergens do not belong to the same homologous group, the combination of the components should be justified" clearly indicates that mixed allergens within a homologous group are regarded as mixture. The main concern related to the simultaneous extraction of pollen from different species is that the presence of equal amounts from the different source materials cannot be ensured, in particular in the case of cross reacting allergens because measurement of the individual components is not possible.<br><br>See response to comment from AFSAPPS above. |

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| Page 5<br>Lines 22-23<br>(Stallergenes) | It is common practice to mix the source materials for related cross reacting species. For example we consider this acceptable for grasses belonging to the same homologous group and cross-reacting with each other. Clinical practice is available for these products for decades. The guideline should leave room for this general accepted practise.<br><br>Proposed rewording:<br>*"**Unless justified,** the different source materials should not be mixed prior to extraction."* | See response to comment from AFSAPPS above. |
| Page 5<br>Lines 22-25<br>(ATL) | ATL formulates a number of preparations for which mixtures of e.g. 12 different pollens from a homologous group are extracted. The pollens are mixed before extraction i.e. as a dry pollen mix.<br>ATL conducts testing of the raw materials to show their acceptability for protein profile and other quality parameters by performing an extraction on lab scale before release of the raw material for production use. The lab extract analysis prior to production renders the need to prepare separate extracts unnecessary. Furthermore it has to be pointed out that patients are naturally exposed to dry pollen mixtures, not to pollen extract mixtures.<br><br>Proposed rewording:<br><br>*"Allergen extract mixtures have to be prepared from individual extracts from single source materials. Therefore, the different source materials should not be mixed prior to extraction **unless justified**. Since extracts are considered as active substances (see section 4.2), each individual extract should be considered as an active substance of its own."* | See response to comment from AFSAPPS above |

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| Page 5<br>Lines 26-29<br>(Allergopharma) | There is a difference between the total allergenic potency of an allergen mixture (i.e. birch/alder/hazel) determined by a birch-system or an alder-system or a hazel-system. Only the cross reactive part, but not the total allergenic potency of the cross-reactive allergens in the mixture is determined by a single-allergen test-system. Any mixed-allergen test system applied for a certain mixture (of a specified combination) can determine only the cross reactive parts of the single allergens. Therefore a higher total potency results for a mixture compared to the single allergen results.<br><br>Proposal to delete the following sentence:<br>~~***"If the testing of the individual active substances in the finished product is not possible due to cross reactivity of the constituents the total potency of the finished product should be determined by an IgE-inhibition test."***~~ | It is clearly indicated in the guideline that the potency of the individual extracts before mixing should be determined using sera pools with specific reactivity for the corresponding species. If this is not possible in the finished product e.g. due to cross-reactivity of the species used, a pool should be used that allows determination of the total allergenic activity of the mixture. In that case, the solid phase antigen would be a mixture too, and no higher total potency would result from the testing.<br><br>The comment was not accepted. |
| Page 5<br>Line 28<br>(EAMG) | Specific IgE can be measured by IgE inhibition binding test or IgE competition binding test.<br>Change "*IgE inhibition*" to "*IgE binding*". | The wording will be changed into "competitive IgE-binding test". |
| Page 5<br>Lines 28-29<br>(LETI) | Biological potency of the extracts can be also analyzed by competition experiments. IgE-binding test is more accurate because both methods (inhibition and competition) are included in this term.<br><br>Proposed rewording:<br>*"[…] the total potency of the finished product should be determined by an IgE-* ***binding*** *test."* | The wording will be changed into "competitive IgE-binding test". |
| Page 5<br>Lines 30-38<br>(EAMG)<br>(LETI) | The issues mentioned in lines 30-38 are clinical issues and should not be included in this document. | The issues mentioned in the lines 30-38 are not clinical but a clinical / immunological justification of quality requirements and should therefore remain in the guideline. |
| Page 5<br>Lines 30-33<br>(ALK-ABELLO) | This section is also of clinical relevance and not only quality related as the need for mixing is due to clinical reason and the limitation of the number of mixes allowed should be related to safety and efficacy and based on clinical practice | The issues mentioned in the lines 30-38 are not clinical but a clinical / immunological justification of quality requirements and should therefore remain in the guideline. |

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| Page 5<br>Line 30-32<br>(ALK-ABELLO) | It is not clear why five species are selected as the maximal number in a mix.<br><br>Proposed rewording:<br>*"The number of allergen extracts in a mixture should be kept at a minimum regardless of homology and cross-reactivity of the individual allergen* ***~~Combinations containing more than five individual allergen extracts~~ and the combination*** *should be justified."* | No justification of the maximum number of five can be given and therefore the proposal was accepted. The section will be reworded as follows:<br><br>Number and relative proportion of the individual active substances should be justified. |
| Page 5<br>Lines 31-32<br>(Allergopharma) | No scientific reasons for an arbitrary number (five).<br><br>Proposed rewording:<br>*"Combinations* ***~~containing more than five individual~~ of*** *allergen extracts should be justified."* | No justification of the maximum number of five can be given and therefore the proposal was accepted. |
| Page 5<br>Lines 32-33<br>(Allergopharma) | This sentence can be deleted as it is covered by the previous suggested change.<br>Furthermore, it should be remembered that most of the therapies currently prescribed involve the use of mixtures. If patients have to be treated with several single extract preparations they will be burdened with considerably more injections. As a result their compliance with the treatment comes into question. By denying the possibility to use mixtures there is a risk of encroaching on the medical privilege concerning the freedom of prescription.<br>Proposal to delete the following sentence:<br>***~~"If in a mixture the allergens do not belong to the same homologous group, the combination of the components has to be justified."~~*** | The guideline does not exclude the possibility of using allergen mixtures (but gives guidance on their manufacture and quality control). The original text acknowledges similarity of the members of one homologous group, so that no justification has to be given for mixing members of the same homologous group.<br>The proposal was not accepted. |
| Page 5<br>Line 37<br>(Allergopharma) | A mixture of *Vespula germanica* and *Vespula vulgaris* is the most commonly prescribed wasp venom immunotherapy in Europe. A differential diagnosis of sensitisation is not possible because of extensive cross-reactivity. It would be reasonable to stipulate that venoms from different genera should not be mixed, e.g. Vespula with Apis, or Polistes with Vespula, but not venoms from the same genus.<br><br>Proposed rewording:<br>*"Venoms from different* ***~~species~~ genera*** *should not be mixed."* | The proposal was accepted. |

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| Page 5<br>Lines 37-38<br>(ALK-ABELLO) | Please refer to comment on page 5, 4.1.2, line 22. | Please see comment on page 5, 4.1.2, line 22. |
| **4.1.3. COMPARABILITY** | | |
| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 5<br>Lines 44-49<br>(ALK-ABELLO) | It is the company's position that reference to the ICH Q5E guideline gives the appropriate information.<br><br>Proposed rewording:<br>*"Applicants should take into consideration the step-by-step approach according to ICH Q5E; CPMP/ICH/5721/03* ~~***EU guidance***~~*considering not only the characterisation studies at the level of the active substance, but also the validation of the manufacturing process as well as in-process controls and stability data.*<br><br>~~***"Comparability studies must be performed if the changes have been introduced after initiation of the critical studies (for example stability, non-clinical or pivotal phase II/III studies). If the changes were introduced at the very early stages of development, no comparability studies have to be performed"***~~ | Reference is only made to the EU guidance, because it includes both ICH and CHMP guidance. It is agreed that the referenced guidelines provide all necessary information. It was accepted to delete the last paragraph because it does not specifically deals with allergens. |
| Page 5<br>Line 47<br>(Allergopharma) | Not all changes justify comparability studies and the nature of the change will determine whether or not such studies are necessary.<br><br>Proposed rewording:<br>*"*<u>***The necessity for***</u> *comparability studies* ~~***must be performed***~~ <u>***should be considered***</u> *if the changes have been introduced. ''* | See above. Comment not accepted. |

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| Page 5<br>Lines 47-49<br>(EAMG)<br>(LETI) | Minor changes should be possible without comparability studies. Proposed text is included:<br>*"Comparability studies ~~must be performed~~ **should be considered** if the changes have been introduced after initiation of the critical studies (for example stability, non-clinical or pivotal phase II/III studies). **If not performed, justification should be provided**. If the changes were introduced at very early stages of development, no comparability studies have to be performed."* | See above. Comment not accepted. |

| 4.2.1. ACTIVE SUBSTANCE – GENERAL INFORMATION | | |
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| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 6<br>Lines 4-6<br>(ATL) | The adsorption of excipients onto allergen extracts is described in line 6 as formulation step. However the adsorption is a physical modification as stated in the Ph. Eur. monograph on Allergen products (Producta allergenica) 01/2008: 1063. The paragraph concerning the adsorption is quoted below: "The modification may be achieved by chemical processes (chemical conjugation) or physical processes (physical adsorption onto different carriers, for example, aluminium hydroxide, calcium phosphate or tyrosine. …"<br>Furthermore both the WHO and EACCI position papers on immunotherapy[1,2] and the more recently published "Standards for Practical Allergen – Specific Immunotherapy"[3] refer to the adsorption as physical modification of the allergen extract.<br><br>1 **WHO Position Paper** Allergen immunotherapy: therapeutic vaccines for allergic diseases. Bousquet J, Lockey RF, Malling HJ.Allergy 1998; 53 Suppl 44.<br>2 **EAACI Position Paper on Immunotherapy**. Malling HJ, Weeke B. Allergy 1993;48 Suppl 14:9-35.<br>3 Standards for Practical Allergen – Specific Immunotherapy. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Allergy 2006; 61 Suppl 82.<br><br>Proposed rewording:<br>*"The active substance can be an unmodified allergen extract,* ***an allergen extract physically modified by adsorption, an allergen extract chemically modified (allergoid), an allergen extract both physically and chemically modified,*** *a conjugate as well as a purified natural or recombinant protein. Preferably, the active substance is a stable preparation at the latest step before mixing or formulation."* | The comment was accepted and therefore the sentence was changed into: "an allergen extract, as well as a purified natural or recombinant protein, all of which can be unmodified or modified (e.g. physically and/or chemically as allergoid or conjugate)" |

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| Page 6<br>Lines 9-10<br>(ALK-ABELLO) | A number of approved allergen products are manufactured in w/v and therefore not standardised.<br><br>Proposed rewording:<br>*"(…) concentrations of individual allergens in such extract may vary and standardisation is therefore very important**, if possible**."* | Despite the fact that some older products are approved in w/v, standardisation remains very important. Therefore the suggestion was not accepted. |
| Page 6<br>Lines 12-13<br>(EAMG)<br>(Stallergenes) | The requirements for the standardisation of recombinant products are not clearly defined. The guideline should mention that standardisation in mass units is preferable to skin test reactivity. The statement should also be reported in paragraph 4.3.<br><br>Proposed rewording:<br>*"The quantity and structure of these polypeptides can be determined and these products should be standardised **~~like other biological products consisting of purified proteins~~** **as defined in the guidelines relevant for biotechnological products**."* | The comment was accepted. |

**4.2.2. ACTIVE SUBSTANCE - MANUFACTURE**

| Page no. + Line no. | Comment and Rationale | Outcome |
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| 4.2.2.1.<br>Page 6<br>Line 17<br>(AFSSAPS) | Add freeze-drying step : critical step:<br><br>*"The production process including pre-treatment, extraction, filtration, dialysis or concentration **and freeze-drying step** should be described in detail and validated."* | The comment was accepted. |
| 4.2.2.1.<br>Page 6<br>Lines 17-23<br>(Stallergenes) | Extrapolation of process validation data gained on the representative allergen product to non-representative allergen product of the same homologous group should be allowed.<br><br>Proposed rewording:<br>*"The production process including pre-treatment, extraction, filtration, dialysis or concentration should be described in detail and validated **for the*** | Even if the members of a homologous group have to share properties, a general extrapolation of the validations cannot be accepted within one homologous group. Therefore the proposal cannot be accepted. Nevertheless it may be acceptable that to a limited extent, validation data for the representative allergen are extrapolated to the validation program of non-representative allergens, if justification is |

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| | ***representative allergen product. Data can be extrapolated to the non-representative allergen products of the same homologous group provided that the manufacturing process is identical**."* | provided.<br>Section 4.4.2 (1st paragraph) has been reworded accordingly. |
| 4.2.2.1.<br>Page 6<br>Line 23<br>(Allergopharma) | It is important to indicate that this comment concerns the production process.<br><br>Proposed rewording:<br>*"...Intermediates in the **production** process should be identified and controlled."* | The comment was generally accepted, but the word "production" was replaced by "manufacturing". |
| 4.2.2.2.<br>Page 6<br>Lines 30-31<br>(Stallergenes) | "*This includes but is not restricted to…"* is not specific enough.<br><br>Proposed rewording:<br>*"Therefore, a detailed characterisation of the cell lines used and the manufacturing process is required~~. This includes but is not restricted to a detailed examination of the expression constructs in the cell lines~~ as described in the relevant regulations."* | Because the proposed wording is less specific compared to the draft guideline text, the comment was not accepted. |
| 4.2.2.2.<br>Page 6<br>Line 32<br>(Allergopharma) | Again the scope has to be extended beyond recombinant allergens alone.<br><br>Proposed rewording:<br>*"For the production of recombinant allergens **and allergen variants**, all guidelines…"* | The comment was not accepted. See above. |

| 4.2.3. ACTIVE SUBSTANCE – CONTROL OF MATERIALS | | |
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| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| 4.2.3.<br>Pages 6-8<br>(Allergopharma) | The requirements for documentation of raw materials are unrealistic, and a more pragmatic proposal has to be agreed.<br>With regard to the sentence *"Details concerning the cultivation, collection, pre-treatment and storage should be supplied for each separate source material"* this information should appear in the source material manufacturer's basic documentation and in case not publicly available included in a Drug Master File.<br><br>Proposed rewording:<br>*"**In case raw material suppliers do not publish information's needed regarding raw material production issues, this information should be made available to the registration authorities in a Drug Master File"*** | Because a Drug Master File for allergen source material does not exist and cannot be developed due to regulatory reasons (lack of a legal basis), the proposal was not accepted. |
| 4.2.3.<br>Pages 6-7<br>(ATL) | ATL would like to receive details on the definition of impurities of allergen solutions. | The general concept of impurities is addressed in the quality guidelines for biological and biotechnological products.<br>Information on expected impurities for pollen source material is given in this guideline. |
| 4.2.3.<br>Page 6<br>Lines 36-38<br>(Allergopharma) | *"Protein"* should be substituted for *"allergen"* in order to cover both allergens and allergen variants:<br>*"….and cell substrates for the production of recombinant **~~allergens~~ proteins**)…"* | The proposal was generally accepted. The guideline was modified accordingly. |
| 4.2.3.<br>Page 6<br>Line 40<br>(EAMG)<br>(LETI)<br>(Stallergenes) | Traceability is detailed depending on the source material in the subsequent lines. Therefore, traceability issue should be removed from this paragraph for clarity purpose.<br>Remove: ***~~"Traceability should be provided for these materials"~~*** | The proposal was accepted. |

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| 4.2.3.1.<br>Page 6<br>Line 46<br>(AFSSAPS) | Add irradiation of allergenic source material issue when performed:<br>▪ validation of the method,<br>▪ irradiation dose,<br>▪ limit of contamination (before defining the need of irradiation step and expected after irradiation),<br>▪ maintain of the allergenic quality of the allergenic source material should be demonstrated<br><br>Proposed rewording:<br>*"Details concerning the cultivation, collection, pre-treatment* ***for example irradiation step*** *and storage should be supplied for each separate source material.* ***Concerning irradiation step, the following data should be submitted:***<br>▪ ***validation of the method,***<br>▪ ***irradiation dose,***<br>▪ ***limit of contamination (before defining the need of irradiation step and expected after irradiation),***<br>▪ ***preservation of the allergenic quality of the allergenic source material should be demonstrated."*** | Irradiation is considered as part of the pre-treatment of the allergenic source material. Because the applicants have to provide data on the pre-treatments, this includes the data concerning irradiation. Therefore, this extra section is considered not to be necessary and was not be included into the guideline. |
| 4.2.3.1.<br>Page 6<br>Lines 45-47<br>(EAMG)<br>(LETI) | With regard to the sentence: *"Details concerning the cultivation, collection, pre-treatment and storage should be supplied for each separate source material"*, this information should appear from the source material manufacturer's basic documentation and in case it is not possible to disclose all details to the applicant should be included and based on a "Starting Material Master File" similar to the "Active Substance Master File".<br><br>Suggestion to add the text proposed:<br>*"Details concerning the cultivation, collection, pre-treatment and storage should be supplied for each separate source material.* ***In case raw material suppliers are not able to disclose all relevant details regarding raw material production issues, this information should be made available to the Authorities as a "Starting Material Master File" and to the applicant as an open part of this "Starting Material Master File".***" | Because a Starting Material Master File for allergen source material does not exist and cannot be developed due to regulatory reasons (lack of a legal basis), the proposal cannot be accepted. |

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| 4.2.3.1.<br>Page 6 Line 48<br>Page 7, Line 1<br>(EAMG)<br>(Stallergenes) | "*moreover acceptance limits have to be defined*"<br>This proposal is not applicable to this process step.<br><br>Remove**: *~~"moreover acceptance limits have to be defined"~~***. | No justification is given for this proposal. Since the acceptance criteria are considered to be applicable and have to be defined for any specification, this proposal was not accepted. |
| 4.2.3.1.<br>Page 7<br>Line 9<br>(ALK-ABELLO) | It is unclear what is meant with "qualified"<br><br>Proposed rewording:<br>*"Each individual source material has to be **~~qualified~~** **characterised** regardless on whether it belongs to the same homologous group."* | The word "qualified" is clear and unambiguous. Therefore the proposal was not accepted. Qualification is different from characterisation. |
| 4.2.3.1.<br>Page 7<br>Lines 13-26<br>(Allergopharma) | The intention of the GACP-Guideline is to ensure appropriate and consistent quality of medicinal plant/herbal substances. In case of herbal preparations the production and primary process has a direct influence on the quality of the API. Also herbal substances should be harvested when they are at the best possible quality for the proposed use.<br>For most plant material (leaves, flowers, stem, roots) it is therefore appropriate to follow the GACP guideline. However, it is more difficult to do so in the case of pollens.<br>In many cases wild plants are the best source of pollen for the purpose of producing allergen extracts. In such cases it is not realistic to restrict collection to one site. This aspect has been considered in the proposed new text. In those cases, the plant biotope instead of the geographical location should be described.<br>The restriction to a specific geographical location can also present problems with cultivated plants. Circumstances can arise when it is not possible to supply raw material from a specified location, for example if a harvest fails because of poor weather conditions. It should then be possible to substitute raw material from another soured provided that it can be shown to be of comparable quality<br><br>For some (rare) pollen species requirements in L 13/14 cannot be fulfilled because they are collected at many locations.<br><br>New Text: | The guideline enables applicants to give relevant information also if the pollens are collected from wild plants. If the pollens are collected from wild plants, this should be indicated and consequently information on field characteristic and seed used will be very limited. In this case, it may also be possible that the GACP guideline will not be applicable. These possibilities are considered in the guideline and therefore the proposal was not accepted.<br>*"The principles of the Guideline on Good Agricultural and Collection Practice (GACP) for Starting Material of Herbal Origin [9] and other relevant guidelines for the source material of plant origin should be followed **where applicable**."* |

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| | ***"Pollens***<br>***Pollens are obtained from either cultivated or wild plants.–Collection in wild habitats may require special consideration. In most cases the growing conditions for pollinating wild plants, which will ensure a yield of optimal source material for allergen extracts, are species specific.***<br>~~***Geographic location and nature of the fields and seeds used, field characteristics, treatments, visual control, way of collection and random sampling procedures should be described. The variety of the plants used should be given including transgenic plants if used. The use of transgenic plants has to be justified.***~~ *The principles of the Guideline on Good Agricultural and Collection Practice (GACP) for Starting Material of Herbal Origin [9] and other relevant guidelines for the source material of plant origin should be followed where applicable****, e.g. if pollen are obtained from cultivated plants [10,11,12]. In those cases where pollen are collected from wild plants, these guidelines are more difficult to apply.***<br>*Growing conditions, information on the collection area (geomorphic and climatic conditions), nature of the field and seeds used, field characteristics, treatments, visual control, way of collection and random sampling procedures should be described* ***as far as applicable and useful. In case of wild plants a description of the normal habitat of these plants should be sufficient. If possible*** *the variety of the plants used should be given including transgenic plants if used. The use of transgenic plants has to be justified. Test methods……included."* | |
| 4.2.3.1.<br>Page 7<br>Line 13<br>(EAMG)<br>(LETI)<br>(Stallergenes) | The nature of the seeds used cannot be indicated in the case of wild species. "Field characteristics" does not refer to any particular information. The treatments applied to the fields are discussed in lines 21-22. Therefore, these requirements should be removed from the sentence.<br><br>Proposed rewording:<br>*"Geographic location and nature of the fields* ~~***and seeds used, field characteristics, treatments***~~*, visual control, way of collection and random sampling procedures should be described."* | The guideline enables applicants to give relevant information also if the pollens are collected from wild plants. If the pollens are collected from wild plants, this should be indicated and consequently information on field characteristic and seed used will be very limited. In this case, it may also be possible that the GACP guideline will not be applicable. These possibilities are considered in the guideline and therefore the proposal was not accepted. |

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| 4.2.3.1.<br>Page 7<br>Lines 13-14<br>(ALK-ABELLO) | Not all pollens are grown on fields i.e. tree pollen.<br><br>Proposed rewording:<br>*"Geographic location and nature of the fields and seeds used, field characteristics, treatments, visual control, way of collection and random sampling procedures should be described.*<br>***If pollen is harvested from a natural resource the collection area and possible treatments should be defined."*** | The guideline enables applicants to give relevant information also if the pollens are collected from wild plants. If the pollens are collected from wild plants, this should be indicated and consequently information on field characteristic and seed used will be very limited. In this case, it may also be possible that the GACP guideline will not be applicable. These possibilities are considered in the guideline and therefore the proposal was not accepted. |
| 4.2.3.1.<br>Page 7<br>Lines 14-15<br>(Stallergenes) | Description of the variety is not a critical parameter. Many varieties are not genetically stable and the supplier has to change its varieties over time. Furthermore some pollens do not have any variety.<br><br>**Remove *"The variety of the plants used should be given including transgenic plants if used."*** | If some pollens do not have any variety, this should be stated. Otherwise the information concerning the varieties is considered necessary and the sentence was not removed. |
| 4.2.3.1.<br>Page 7<br>Lines 16-18<br>(LETI) | Proposed rewording:<br>*"The principles of the Guideline on Good Agricultural and Collection Practice **(GACP)** for Starting Material of Herbal Origin and other relevant guidelines for the source material of plant origin should be followed where applicable."* | The comment was accepted. |
| Page 7<br>Lines 21-22<br>(Allergopharma) | The provision of the original guideline CPMP/BWP/243/96 should be retained as permanent monitoring of all pollen harvests is impossible due to the large amounts of material needed and what would be prohibitively high costs.<br><br>Proposed rewording:<br>*"The content of relevant **representative** pesticides~~, **heavy metals**~~ lead and solvents should be ~~measured~~ monitored on a limited number of representative pollen batches, in order to demonstrate that their level**s are** ~~is~~ kept to a minimum in the allergen~~ic~~ source material."* | The wording "monitoring" was chosen because it is not expected that every lot of source material is controlled for these impurities. No reason is given why there is no need to monitor the content of heavy metals other than lead. Therefore the proposal was not accepted. |

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| Page 7<br>Line 21<br>(EAMG) | "*The content of relevant pesticides, heavy metals and solvents should be monitored in order to demonstrate that their level is kept at a minimum in the allergenic source material"* would normally require that validated assays are available. On the other hand as now described it is left to the manufacturer to decide how to manage.<br><br>Either details about validated assays to be used should be included or the subject should be excluded from this document. The content of representative pesticides and lead should be measured on a limited number of pollen batches. This should be combined with a wash-out period for cultivated plants. | It is not in the scope of this guideline to give details on the validation of assays. Moreover, many contract laboratories are accredited for analysis of heavy metals or pesticides in biological materials. In addition, please see comment above. |
| 4.2.3.1.<br>Page 7<br>Lines 21-22<br>(LETI) | The content of representative pesticides and lead should be measured on a limited number of pollen batches, such as indicated in the current guideline.<br><br>Proposed rewording:<br>"*The content of relevant pesticides, heavy metals and solvents should be ~~monitored~~* ***measured in a limited number of pollen batches*** *in order to demonstrate that their level is kept at a minimum in the allergenic source material."* | The wording "monitoring" was chosen, because it is not expected, that every lot of source material is controlled for these impurities. |
| 4.2.3.1.<br>Page 7<br>Lines 21-22<br>(ALK-ABELLO) | It is unclear if the solvent content should be measured in the final source material or if the content of solvent should be controlled during the process?<br><br>Proposed rewording:<br>"*The content of relevant pesticides, heavy metals and solvents should be monitored* ***on a regularly basis~~ in order to demonstrate that their level is kept at a minimum in the allergenic source material~~****."* | Since the statement is included in the section 4.2.3.1 "Control of source material for allergen extracts", it is obvious that the content should be determined in the source material. Information concerning the depletion of solvents during the manufacturing process should be reflected in the specifications for the impurities in the pollen. Therefore the proposal was not accepted. |
| 4.2.3.1.<br>Page 7<br>Line 31<br>(EAMG)<br>(Stallergenes) | A process validation approach cannot be implemented for cultivation method for moulds.<br><br>Remove: ***~~"the cultivation method should be validated"~~***. | In response to the comment, the word "validated" has been replaced by "described in detail and key parameters (e.g. temperature) justified". |

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| 4.2.3.1.<br>Page 7<br>Lines 31-32<br>(ATL) | ATL proposes to change the wording as the absence of mycotoxins cannot be demonstrated as in general assays do have a detection limit.<br><br>Proposed rewording:<br>*"The cultivation method should be validated and evidence should be provided that no mycotoxins* ***<u>can be detected; using the appropriate measurement systems</u>.*** *"* | It is obvious and well accepted that all analytical methods have a detection limit, which has to be determined during validation of the system. As response to the comment, the paragraph was reworded as follows: "no detectable amounts of mycotoxins are produced by the moulds". |
| 4.2.3.1.<br>Page 7<br>Lines 31-39<br>(EAMG)<br>(Allergopharma)<br>(LETI) | As many mould strains produce mycotoxins, emphasis should be put on highly toxic mycotoxins such as aflatoxins and ochratoxins and on the ability of the process to remove other types of mycotoxins.<br><br>Proposed rewording:<br>*"~~Strains which produce mycotoxins such as aflatoxins or ochratoxins should not be used unless justified and their mutagenic potential should be evaluated. In this case, the amount of relevant mycotoxins should be quantified before processing and its removal through processing should be implemented and validated. Appropriate measures have to be implemented to avoid contamination by other mould strains.~~*<br>***<u>Evidence should be provided that no aflatoxins or ochratoxins are produced. Reduction to safe levels of other types of mycotoxins through processing should be implemented. Details on the composition of the cultivation medium and the media components should be submitted. Synthetic media i.e. media free of animal-derived material or allergen-free media should be preferably used. In case of mycotoxin producing moulds evidence should be provided that no mycotoxins are produced. Details on the composition of the cultivation medium and the media components should be submitted by the applicant or separately by the supplier</u>.*** *"*<br><br>**Remove lines 35-39.** | The comment of the companies is exactly reflected in the paragraph lines 35-39 and therefore no change was necessary. |
| 4.2.3.1.<br>Page 7<br>Lines 31-39<br>(Stallergenes) | These sentences are confusing. As many mould strains produce mycotoxins, emphasis should be put on highly toxic mycotoxins such as aflatoxins and ochratoxins and on the ability of the process to remove other types of mycotoxins.<br>Proposed rewording: | The guideline emphasizes that preferentially strains not producing mycotoxins should be used. Clear guidance is also given for the scenario where strains producing mycotoxins have to be used. There are other highly toxic mycotoxins than aflatoxins or ochratoxins, e.g. trichotecenes. Therefore the |

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| | *"Evidence should be provided that no* ***~~mycotoxins~~ aflatoxins or ochratoxins*** *are produced. (…)"*<br>**Remove lines 35-39.** | guideline text is not confusing and the corresponding section was not changed. |
| 4.2.3.1.<br>Page 7<br>Lines 35-36<br>(ALK-ABELLO) | Proposed rewording:<br>*"Strains which produce mycotoxins such as aflatoxins or ochratoxins should not be used* ***for treatment products*** *unless justified"* | Because even in low doses these mycotoxins have a potential mutagenic effect, these substances should also be avoided in medicinal products for test purposes. If these strains are used in such products, the small amount of substance (and therefore mycotoxins) applied to the subjects should be considered in the evaluation of the mutagenic potential. |
| 4.2.3.1.<br>Page 7<br>Lines 41-42<br>(LETI) | Not strains but species.<br>The taxonomic classification of domestic mites, if it is performed by an expert acarologist, is sufficient to guarantee a correct identification.<br><br>Proposed rewording:<br>*"The* ***~~strain~~ species*** *of mite should be specified. Morphology and/***or** *other parameters (for example biochemical or genetic properties) for the identification of the mites should be specified."* | The comment was accepted. |
| 4.2.3.1.<br>Page 7<br>Line 41<br>(ALK-ABELLO) | The term "strain" in this context meaning?<br><br>Proposed rewording:<br>*"The* ***~~strain of~~*** *mite* ***species*** *should be specified."* | The comment was accepted. |
| 4.2.3.1.<br>Page 7<br>Line 41<br>(Allergopharma) | Mite 'strains' are not defined, i.e. there is no official classification. It would be appropriate to provide information regarding the origin of a mite culture.<br><br>Proposed rewording:<br>*"The* ***~~strain~~*** *species of mite should be specified."* | The comment was accepted. |
| 4.2.3.1.<br>Page 7<br>Line 41<br>(AFSSAPS)<br>(EAMG)<br>(Stallergenes) | Mite species not strain | The comment was accepted. |

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| 4.2.3.1.<br>Page 7<br>Lines 45-46<br>(ALK-ABELLO) | Proposed rewording:<br>*"Synthetic and consequently free of animal derived material allergen free media should be preferably used.* ***However, when substrates of human or animal origin are used in the medium, the absence of risk of transmission of infectious diseases should be demonstrated.****"* | It is already stated in section 4.2.3 "when substances of animal or human origin are used as source or as raw material, viral safety and compliance with TSE requirements should be demonstrated." Therefore this comment is already covered by the guideline. |
| 4.2.3.1.<br>Page 7<br>Line 47<br>(EAMG)<br>(Allergopharma) | *"validated"* should be replaced by "*defined*":<br>***"The conditions of culture and the time of harvest should ~~must be validated~~ defined."*** | The comment was accepted and "validated" was replaced by "and the key parameters should be defined". |
| 4.2.3.1.<br>Page 7<br>Line 47<br>(LETI) | Suggested text to substitute "validated" to "described", such it is required in the current guideline.<br><br>Proposed rewording:<br>*"The conditions of culture and the time of harvest* ***~~must~~ should be ~~validated~~ described****."* | The comment was accepted and "validated" was replaced by "and the key parameters should be defined". |
| 4.2.3.1.<br>Page 7<br>Line 48<br>(ALK-ABELLO) | In some cases it is favourable to mix mites and mite faeces<br><br>Proposed rewording:<br>*"…mite faeces only,* ***~~or~~*** *whole mite culture* ***or mixes hereof****."* | The proposal was accepted. |
| 4.2.3.1.<br>Page 7<br>Line 49<br>(LETI) | The term aeroallergen is more correct because describe any of various airborne particles that can cause an allergic response. The allergic symptoms associated with epithelia are produce after inhalation of airborne particles. The use of "allergens" could be mixed up because include the proteins/allergens present in foods, responsible for the allergy after contact or ingestion.<br><br>Proposed rewording:<br>*"Animal* ***aero****allergen"* | The section 4.2.3.1 describes requirements for various source materials and does not specify which part of the source material (e.g. hair or airborne particles) would cause the disease. In addition, it covers also the sourcing of non-aeroallergens e.g. for diagnostic use. Therefore the comment was not accepted. |

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| 4.2.3.1.<br>Page 8<br>Line 1<br>(Allergopharma) | The term healthy animal is difficult to define. Therefore we propose a more pragmatic approach.<br><br>Proposed rewording:<br>*"Only **apparently** healthy animals should be used**, and the collectors should certify that the animals used were apparently free from detectable skin diseases.**"* | As response to the comment, thr following rewording was introduced: "Only healthy animals should be used and certificates from the collector concerning their health status should be provided where possible". It was accepted that it may not be always possible to provide a certificate concerning the health status of the animals used (e.g. fish or insects used for test allergens). |
| 4.2.3.1.<br>Page 8<br>Lines 3-4<br>(ALK-ABELLO) | The sentence starting with: "Morphology…" is irrelevant and should be deleted. | The sentence was not regarded as irrelevant and should remain. Therefore the comment was not accepted. |
| 4.2.3.1.<br>Page 8<br>Line 6<br>(Allergopharma) | Excluding contaminations in materials of natural origin is often unrealistic and therefore a more pragmatic wording is suggested.<br><br>Proposed rewording:<br>*"Any possible contamination with mites and moulds, for example, should be addressed and **~~avoided~~** **minimized**."* | The comment was generally acceptable; the corresponding section was changed into "avoided as far as possible". |
| 4.2.3.1.<br>Page 8<br>Lines 6-7<br>(ALK-ABELLO) | The live animals are in contact with plants, dust etc implying that they are in contact with both mites and moulds. It is therefore not possible to "avoid" contamination. We suggest aligning with the coming version of the EP monograph for Allergen Products.<br><br>Proposed rewording:<br>*"Any possible contamination with mites or moulds for example should be addressed **~~and avoided~~."*** | See comment above. |

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| 4.2.3.1.<br>Page 8<br>Lines 6-7<br>(LETI) | The microscopic checking of a sample will not guarantee the complete absence of moulds or mites.<br>"Animal allergens", as natural source materials, are not sterile and are not further processed to eliminate mites. If certificated healthy animals are used, they will have not infestation by parasitic mites.<br><br>Proposed rewording:<br>*"Any possible* ***macroscopic contamination with*** ~~*mites and*~~ ***moulds*** *for example should be addressed and avoided."* | No distinct proposal should be made for the method used for the investigation. Because of the high allergenic potential contaminations by mites should be addressed and therefore the section was not changed as proposed. |
| 4.2.3.1.<br>Page 8<br>Lines 7-8<br>(Stallergenes) | Requirement that *"The collector should certify that the animals used have not recently been treated with antiparasitics or other drugs"* cannot be implemented.<br><br>Remove sentence. | Because no justification is given and the usage of such materials is expected to be relevant for the source material, the comment was not accepted. |
| 4.2.3.1.<br>Page 8<br>Lines 14-15<br>(EAMG)<br>(Allergopharma)<br>(LETI) | The quantities of venom that would be required make this proposal totally unrealistic, and therefore we see no alternative than to suggest that this sentence should be deleted:<br>~~***"The content of relevant pesticides should be monitored and acceptance criteria should be defined."***~~ | The comment is generally agreed and the section was reworded as follows:<br>"Evidence should be provided that the amount of relevant pesticides is kept at a minimum. This may include a certificate, that no pesticides were used in the hymenoptera culture." |
| 4.2.3.1.<br>Page 8<br>Lines 14-15<br>(Stallergenes) | Hymenoptera venoms are coming from different suppliers across the world. It would be impossible to monitor any possible relevant pesticide. Besides contamination of the venom sac by pesticides is unlikely. Therefore determination of pesticide content is not scientifically sound.<br><br>Remove: ~~***"The content of relevant pesticides should be monitored and acceptance criteria should be defined."***~~ | See comment from EAMG, LETI and Allergopharma above. |

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| 4.2.3.1.<br>Page 8<br>Lines 14-15<br>(ALK-ABELLO) | It is not clear why pesticides should be monitored and acceptance criteria defined? Insects are collected alive. They must be collected alive to preserve the integrity of the venom sac. A statement from collectors that no pesticides are used in the collection process is relevant. It can be demonstrated that a hypothetical worse case cumulative dose of pesticides received from immunotherapy is much lower than the Acceptable Daily Intake of pesticides listed in USP/EP.<br><br>Proposed rewording:<br>"~~*The content of relevant pesticides should be monitored and acceptance criteria should be defined.*~~<br>***Collectors of hymenoptera insects must certify that no pesticides are used in the collection process.***" | It is not expected that collectors use pesticides during the collection process, but the problem of pesticides collected as impurity of the venom should be addressed. First, pollen and other materials collected by hymenoptera may contain pesticides. Second, at least bee cultures are frequently treated against mite pests for example. Therefore the comment was not accepted. |
| 4.2.3.3.<br>Page 8<br>Line 21<br>(ALK-ABELLO) | It is not clear what is meant with: *If any allergenic components are used in the culture medium, their removal should be demonstrated.*<br><br>Proposed rewording:<br>*"If any allergic components are used in the culture medium, their* ~~***removal***~~ ***content and insignificance*** *should be demonstrated* ~~***The content of relevant pesticides should be monitored and acceptance criteria should be defined.***~~*"* | For clarification, the following rewording was introduced: "If any allergenic components are used in the culture medium, their removal in the manufacturing process should be demonstrated" |

**4.2.4. ACTIVE SUBSTANCE – CHARACTERISATION AND CONTROL OF THE ACTIVE SUBSTANCE**

| Page no. + Line no. | Comment and Rationale | Outcome |
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| 4.2.4.1<br>Page 8<br>Lines 28-29<br>(ALK-ABELLO) | Proposed rewording:<br>*"… and* ~~***test results***~~ ***these acceptance criteria*** *should be considered as in-process acceptance criteria and included in the* ***release*** *specifications of the active substance."* | This proposal was accepted. |

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| 4.2.4.1<br>Page 8<br>Lines 29-31<br>(ALK-ABELLO) | Proposed rewording:<br>*"Generally, the following tests and acceptance criteria are applicable: appearance and description, identity, purity and impurities,* ***~~potency and quantity~~ total allergenic activity and major allergen determination****."* | The proposal was accepted. |
| 4.2.4.1.<br>Page 8<br>Line 30<br>(Allergopharma) | Impurities should be defined and determination of purity is generally not possible at this stage.<br>"*Purity*" has to be deleted | All parameters listed are important for the quality of the extract and should be taken into consideration. The proposal was therefore not accepted. |
| 4.2.4.1.<br>Page 8<br>Lines 30-31<br>(LETI) | Due to the complex nature of these biological products, it's suggested to remove "impurities":<br><br>*"[…] appearance and description, identity, purity* ***~~and impurities~~****, potency, and quantity."* | All parameters listed are important for the quality of the extract and should be taken into consideration. The proposal was therefore not accepted. |
| 4.2.4.1<br>Page 8<br>Lines 30-31<br>(EAMG)<br>(Stallergenes) | Please specify which impurities have to be considered. | The impurities are dependent on the source material and therefore have to be determined by the applicant individually. |
| 4.2.4.1<br>Page 8<br>Line 31<br>(ALK-ABELLO) | "*Quantity*" is in this context not defined. | "Quantity" has been replaced by "total allergenic activity", which is defined in the section "Definitions". |
| 4.2.4.1.<br>Page 8<br>Line 34<br>(EAMG)<br>(Allergopharma)<br>(LETI)<br>(Stallergenes) | **Remove *"mass spectrometry"***. The use of mass spectrometry for the characterization of complex protein extract has not been demonstrated yet. It is too early to mention it in this guideline. | Mass spectrometry is mentioned as an option only. It is a state of the art method for characterisation of proteins or protein mixtures. There is no obligation for applicants to use this method compulsively. However, it provides some unique possibilities. Therefore, the mention of mass spectrometry remains in the text and the proposal was not accepted. |

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| 4.2.4.1.<br>Page 8<br>Line 37<br>(Allergopharma) | Due to the biologic origin of the allergen preparations it is impossible to have a complete matching ("corresponding") of protein and/or allergen profiles between allergen product and IHRP. At best "comparability of the profiles" can be achieved.<br><br>Proposed rewording:<br>*"…The protein profile should be* ***comparable*** ~~***correspond***~~ *…"* | "Corresponding" does not mean "identical" here. However, the relevant bands have to be identified, specified and included in the acceptance criteria. "Comparable" in this context is highly subjective and cannot be accepted for a biological medicinal product. Therefore the proposal was not accepted. |
| 4.2.4.1.<br>Page 8<br>Line 39<br>(Allergopharma) | How are 'safety concerns' to be defined? Is the risk of inducing new sensitizations a safety concern? If so it might be argued that it is necessary to quantify everything. Data on the possible induction of new sensitizations under therapy are scare and far from convincing. We suggest that a more pragmatic and realistic wording should be sought and any requirements should be restricted to therapeutic preparations | Induction of new sensitizations is not meant here. There is evidence that sensitisation to minor allergens may correlate with severe side effects during SIT. (Duffort O, Palomares O, Lombardero M, Villalba M, Barber D, Rodríguez R, Polo F. Variability of Ole e 9 allergen in olive pollen extracts: relevance of minor allergens in immunotherapy treatments. Int Arch Allergy Immunol. 2006;140(2):131-8.)<br>If this is true, these allergens have to be quantified to provide data on the safety profile of the drug product. Therefore the guideline text was not changed. |
| 4.2.4.1.<br>Page 8<br>Lines 39-40<br>(AFSSAPS) | To complete and for better understanding:<br><br>Proposed rewording:<br>*"If* ***significant part of activity*** ***or*** *safety concerns arise from other (for example minor) allergens, these have to be quantified as well."* | The proposal was accepted, the section was reworded as follows:<br>*"If a significant part of the total allergenic activity or safety concerns arise from other (for example minor) allergens, these have to be quantified as well."*. |
| 4.2.4.1.<br>Page 8<br>Line 39-40<br>(EAMG)<br>(LETI) | The discussion about what is a major and what is a minor allergen is to be avoided. Any allergen that is under suspicion for creating allergic side effects should be investigated in relation to the patient population.<br><br>Safety concerns should be investigated whichever will be the origin of the concern. Safety is a clinical issue and should not be implemented in this guideline.<br>Remove the sentence:<br>~~***"If safety concerns arise from other (for example minor) allergens, these have to be quantified as well."***~~ | No discussion about what is a major and what is a minor allergen is raised in the draft guideline.<br>Batch-to-batch consistency provides the molecular basis for both efficacy and safety of biological products. For efficacy, the relevant allergens are determined. If safety concerns arise from other allergens, these molecules have to be determined too in order to provide evidence on the safety of the products. Clinical issues are only mentioned here in case there are implications for quality. The only alternative would be quantification of all allergens. Therefore the sentence was not removed from the guideline text. |

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| 4.2.4.2.<br>Page 8<br>Lines 44-46<br>(Stallergenes) | The tests proposed here are carried out during characterisation. As the paragraph refers to characterisation **and** control it should be clearly mentioned.<br><br>Proposed rewording:<br>"***<u>During characterisation</u>*** *emphasis should be put (…)"* | Because the parameters mentioned in the corresponding sentence may provide information of importance for the consistency of production, it may be necessary to perform these tests for quality control too. The proposed wording may be misleading and the sentence was not changed. |
| 4.2.4.2.<br>Page 8<br>Lines 44-47<br>(GSK) | This paragraph cannot be applied to all recombinant allergens, as we may wish to modify the structural integrity to achieve reduction of allergenic activity.<br>Remove the first paragraph | Because the structural integrity and potential modification of recombinant proteins are key characteristics, it is obvious that these parameters have to be determined. Therefore, this paragraph is essential and was not removed from the guideline text. Low IgE binding variants will be addressed in a separate paragraph. |
| 4.2.4.2.<br>Page 8<br>Lines 44-46<br>(Allergopharma) | Investigation of post translational modifications such as glycosylation should be considered when appropriate.<br><br>Proposed rewording:<br>*"Emphasis should be put on the structural integrity****, ~~post-translational modifications~~*** *and consistency of folding....immunotherapy****. <u>Investigation of post-translational modifications such as glycosylation should be considered when appropriate.</u>*** *"* | This proposal was accepted. |
| 4.2.4.2.<br>Page 9<br>Lines 4-6<br>(EAMG)<br>(Stallergenes) | Some impurities cannot be quantified because of trace amounts. Identification and quantification of impurities depends on safety concerns and likeliness of being detected.<br><br>Proposed rewording:<br>*"Special attention should be given on impurities from the media or host cell components. ~~**These impurities should be identified and quantified and their**~~* ***Their*** *potential in giving rise to undesirable and potentially allergic reactions should be estimated.* ***If there is a cause for concern these impurities should be identified and quantified****."* | The guideline text reflects the requirements of the corresponding ICH guidelines for recombinant products. Moreover, it is not clear how a cause for concern should be defined. Therefore the proposal was not accepted. |

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| 4.2.4.2.<br>Page 9<br>Lines 4-6<br>(Allergopharma) | Alternative wording suggested to provide a more practical approach.<br><br>Proposed rewording:<br>*"**~~Special~~** Attention should be given **~~on~~** **to potential** impurities from media or host cell components. **~~These~~** Such impurities should be **~~identified and~~** quantified and...."* | The word "Special" has been removed. |
| 4.2.4.2<br>Page 9<br>Lines 7-15<br>(AFSSAPS) | Recombinant allergens are not mentioned in the section 4.2.4.4. Potency assays. In order to be more relevant, the paragraph from line 7 to line 15 of the previous section 4.2.4.2. Characterisation and control of recombinant allergens should be moved to section 4.2.4.4. Moreover, in the section 4.4.3. Control of finished product, a cross-reference is performed for the control of recombinant allergens to the chapter 4.2.4.4.<br><br>***4.2.4.2. Characterisation and control of recombinant allergens***<br>*(...)*<br>***~~Recombinant allergens should be characterised and quantified by techniques appropriate for recombinant proteins. The content should be expressed in weight per volume whenever possible. The correlation between the quantity of the individual recombinant allergens and the corresponding biological (for example allergenic) activity should be shown in validation studies. For recombinant allergen molecules, ELISA methods with specific animal antibodies may be used as potency assays as long as a correlation with the IgE binding has been demonstrated. For recombinant allergens with a reduced IgE reactivity, potency tests should preferably consist of a discriminatory test to distinguish between molecules with high and low IgE binding capacities (for example by quantification in ELISA systems) and an assay to determine the lack of IgE reactivity.~~***<br><br>***4.2.4.4. Potency assays***<br>*The following potency tests should be performed for the different kinds of active substances:*<br>▪ *For allergen extracts and purified allergens without structural modification, the IgE inhibition test should be performed.*<br>▪ *Relevant individual allergens may be determined by immunological methods (for example ELISA) with specific animal antibodies as long* | For a better understanding of the special properties of recombinant allergens in contrast to allergen extracts, the sections on characterisation and control of recombinant allergens should be retained in a separate paragraph. Therefore the guideline text was not changed. |

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| | *as a correlation with the IgE binding has been demonstrated.*<br>▪ *For allergoids, potency tests should consist of a discriminatory test to distinguish between native and modified molecules (for example by quantification in ELISA systems or mediator release assay) and an assay to determine the lack of IgE reactivity. As an alternative to a discriminatory immunoassay, other techniques (for example mass spectrometry) may be used to demonstrate the presence of the relevant allergens.*<br>▪ *For conjugates, the potency testing should consider the immuno-modulating properties of the specific modifications.*<br>▪ ***For recombinant allergens: Recombinant allergens should be characterised and quantified by techniques appropriate for recombinant proteins. The content should be expressed in weight per volume whenever possible. The correlation between the quantity of the individual recombinant allergens and the corresponding biological (for example allergenic) activity should be shown in validation studies. For recombinant allergen molecules, ELISA methods with specific animal antibodies may be used as potency assays as long as a correlation with the IgE binding has been demonstrated. For recombinant allergens with a reduced IgE reactivity, potency tests should preferably consist of a discriminatory test to distinguish between molecules with high and low IgE binding capacities (for example by quantification in ELISA systems) and an assay to determine the lack of IgE reactivity.*** | |
| 4.2.4.2<br>Page 9<br>Lines 11-13<br>(GSK) | We suggest modifying the word 'potency assay' in this case, as it characterizes IgE-binding activity.<br><br>Change 'potency assay' into 'IgE-reactivity' assay. | The wording was changed into "competitive IgE-binding assay". |
| 4.2.4.2.<br>Page 9<br>Line 15<br>(Allergopharma) | The lack of IgE reactivity cannot be determined.<br><br>Proposed rewording:<br>*"....and an assay to determine****/verify*** *the* ~~***lack of***~~ ***reduction in*** *IgE-reactivity."* | The proposal was accepted. |

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| 4.2.4.2<br>Page 9<br>Lines 16-18<br>(AFSSAPS) | Per analogy with recommendations performed for allergen extracts mixtures (Paragraph 4.1.2. Allergen extract mixtures), add issues that should be taken into consideration for mixtures of recombinant allergens as rules concerning:<br>- number of allergens,<br>- combinations of the components according to homologous groups, proteolytic activity.<br><br>Proposed rewording:<br>*"For mixtures of different recombinant allergens, the content of the individual allergens should be determined by adequate quantification methods, for example ELISA just prior to mixing and in the mixture, unless otherwise justified.****[Rules concerning mixtures of recombinant allergens should be added here.]"*** | The proposal was accepted and the following sentence was added to the paragraph:<br>"The general rules given in section 4.1.2 (Allergen mixtures) should be considered where applicable." |
| 4.2.4.3<br>Page 9<br>Lines 20-22<br>(EAMG) | There is a need for further justification for this statement. | No need is seen for a justification. The drug substance has to be characterised and demonstration of the reduction of allergenicity is not sufficient. |
| 4.2.4.3<br>Page 9<br>Lines 20-22<br>(ATL) | In modified allergens like allergoids native epitopes are no longer present in the original form and cannot be measured reliably with specific antibody assays. An appropriate method to identify the previous native allergens in their multiple crosslinked forms is not available.<br><br>Proposal to delete the following sentence:<br>***"~~For modified allergens (for example denatured or chemically-modified allergoids or conjugates), antibody based assays or other appropriate test methods have to be established to identify the relevant allergens in the modified form.~~"*** | Some specific methods have already been developed ( e.g. Gelhar et al., Int Arch Allergy Immunol. 2005;136:311-9) and preliminary data have been presented at scientific meetings. Therefore, the proposal was not accepted. There is an obvious need to provide data on the composition and consistency of allergoids. It is not requested to identify native epitopes in allergoids. |

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| 4.2.4.3.<br>Page 9<br>Lines 20-22<br>(HAL Allergy) | For chemically-modified allergens (allergoids), there are no appropriate test methods available to identify the relevant allergens in the modified forms.<br><br>Proposed rewording:<br>***"~~For modified allergens (for example denatured or chemically-modified allergoids or conjugates), antibody-based assays or other appropriate test methods have to be established to identify the relevant allergens in the modified form.~~*** *When certain control tests cannot be applied to the finished product, for instance in the case of modified allergens (for example denatured or chemically-modified allergoids or conjugates), quality specifications should be defined for the product just prior the modification, dilution, etc."* | Some specific methods have already been developed ( e.g. Gelhar et al., Int Arch Allergy Immunol. 2005;136:311-9) and preliminary data have been presented at scientific meetings. Therefore, the proposal was not accepted. There is an obvious need to provide data on the composition and consistency of allergoids. |

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| 4.2.4.3.<br>Page 9<br>Lines 20-22<br>(LETI) | The chemical process of polymerization (amino terminal groups of proteins/allergens) has been widely investigated and different published papers have demonstrated that polymerization is a reproducible method, obtaining products with similar characteristics and structure and containing peptide sequences from individual allergens[1,2].<br>Consistency and characterization (identification of relevant allergens) demonstrated in IHRP or in two or three different lots, using antibody-based assays or by peptide mapping should be enough.<br>If it is not possible to do it in the modified form, do it in the unmodified form. We propose to identify the allergens in the previous step (unmodified allergen extract)<br>[1]John W. Payne Polymerization of proteins with glutaraldehyde. Soluble molecular-weight markers Biochem J. 1973 December; 135(4): 867–873.<br>[2]J. Carnés, M.T. Gallego, M. Himly, V. Iraola, M. Casanovas, P. Briza, F. Ferreira. Physicochemical Characterization Of Polymerized Extracts. J Allergy Clin Immunol 2008 (Vol. 121, Issue 2, Page S176).<br><br>Proposed rewording:<br>"*For modified allergens (for example denatured or chemically-modified allergoids or conjugates), antibody-based assays or other appropriate test methods ~~have to~~* **may** *be established to identify the relevant allergens in the modified form* ***and when it is not possible then the relevant allergens should be identified in the unmodified allergen extract.***" | Some specific methods have already been developed ( e.g. Gelhar et al., Int Arch Allergy Immunol. 2005;136:311-9) and preliminary data have been presented at scientific meetings. Therefore, the proposal was not accepted. There is an obvious need to provide data on the composition and consistency of allergoids. |

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| 4.2.4.3.<br>Page 9<br>Lines 20-25<br>(Allergopharma) | It is unrealistic to develop a test for identification of modified allergens in chemically modified allergen extracts, although this may be realistic for modified pure allergens or recombinant allergen variants. Quality control of a native allergen extract ensures that all relevant allergens are present. The allergoiding process establishes inter- and intra-molecular cross links ensuring that no allergens are lost. If there are doubts about this, this matter has to be checked in course of the product development, but not in the routine.<br>For chemical modification, which is a complex process, the "degree of polymerisation" cannot be determined as for plastics, for example, which are prepared from defined monomers, because allergen extracts are complex heterogeneous protein mixtures.<br><br>Proposed rewording (line 22):<br>*"…..in the modified form.* ***If certain control tests cannot be applied to the modified form then it may be appropriate to test at the unmodified stage****. Other assays should…"* | Some specific methods have already been developed ( e.g. Gelhar et al., Int Arch Allergy Immunol. 2005;136:311-9) and preliminary data have been presented at scientific meetings. Therefore the proposal was not accepted. There is an obvious need to provide data on the composition and consistency of allergoids. |
| 4.2.4.3.<br>Page 9<br>Lines 24-25<br>(LETI) | Other methods are available to use. Suggestion of amending the text as proposed:<br>*"[…] the modification process, for example by peptide mapping by mass spectrometry, or size-exclusion chromatography to determine the degree of polymerization* ***or other methods to determine the degree of polymerization (as presence of amine groups).****"* | This proposal was accepted. |
| 4.2.4.4.<br>Page 9<br>Lines 27-39,<br>(EAMG)<br>(Stallergenes) | Please specify which potency assay has to be used for recombinant allergens. | The potency tests used have to be justified by the applicant individually. For further information, please see section 4.2.4.2 and ICH Q6B. No further explanation was considered necessary. |

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| 4.2.4.4.<br>Page 9<br>Lines 28-29<br>(Allergopharma) | The supply of sera of acceptable quality is limited to a small number of allergens, and consequently this restricts the use of RAST/EAST inhibition or allergen profiling. In the case of test allergens we propose that the PEI concept of graduated quality standards should be adopted (see above under P.5/L 12 – 15). This concept of "quality categories" was introduced in 2000 and led to an overall improvement in the quality of the whole range of test allergens. It was possible to retain some less well characterized test allergens associated with rarer sensitisations. These would otherwise have been withdrawn from the market thus denying a proper diagnosis to those patients with sensitizations to rarer allergens.<br><br>Proposed rewording:<br>*"....the IgE inhibition test should be performed**, if appropriate**."* | In case that for a specific allergen, no sufficient numbers of patients for preparing a serum pool are available, the paragraph on "non-standardised allergen extracts" in section 4.4.3 applies. Therefore, no change in the guideline was considered as necessary. |
| 4.2.4.4.<br>Page 9<br>Lines 28-32,<br>(ALK-ABELLO) | Proposed rewording:<br>• *For allergen extracts and purified allergens without structural modification,* ***Total allergenic activity by an*** *IgE* ***assay*** ~~***inhibition test***~~ *should be performed.*<br>• *Relevant individual allergens may* ***in addition to the total allergenic activity*** *be determined by immunological methods (for example ELISA) with specific animal antibodies****.*** ~~***as long as a***~~ ***A*** *correlation with the* ***total allergenic activity*** ~~***IgE binding has been***~~ ***should be*** *demonstrated* ***at time of release in order to ensure batch to batch consistency.***<br>• ***In case relevant individual allergens are measured without measuring total allergenic activity a correlation should be demonstrated both at release and during stability."*** | Proposed rewording:<br>• For allergen extracts and purified allergens without structural modification, the total allergenic activity should be determined by a competitive IgE-binding test. If the product is defined on the basis of relevant allergens, a correlation with the total allergenic activity has to be demonstrated.<br>• Relevant individual allergens may be determined by immunological methods (for example ELISA) with specific animal antibodies.<br><br>The proposed change to the last bullet point ("In case (…) stability" was not accepted because it is already reflected in the second bullet point. |
| 4.2.4.4.<br>Page 9<br>Lines 28-29<br>(LETI) | Biological potency of the extracts can be also analyzed by competition experiments. IgE-binding test is more accurate because both methods (inhibition and competition) are included in this term.<br><br>Proposed rewording:<br>"*For allergen extracts and purified allergens without structural modification, the IgE* ~~***inhibition***~~ ***binding*** *test should be performed*." | The introduced rewording is "competitive IgE-binding assay". |

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| 4.2.4.4.<br>Page 9<br>Lines 33-37<br>(LETI) | The sentence is unclear and only one test is needed. The same assay can distinguish between native and modified molecules and determine the lack of IgE reactivity.<br><br>Proposed rewording:<br>*"For allergoids, potency tests should consist of a discriminatory test to distinguish between native and modified molecules (for example by quantification in ELISA systems or mediator release assay) and* ~~***an assay***~~ *to determine the lack of IgE reactivity. As an alternative to a discriminatory immunoassay, other techniques (for example mass spectrometry) may be used to demonstrate the presence of the relevant allergens."* | Indeed two tests are required. Lack of IgE reactivity is important for the safety of the product, but is not acceptable as potency test. However, an additional test demonstrating consistency and activity of the product or presence of the relevant allergens is required too. |
| 4.2.4.4.<br>Page 9<br>Lines 33-37<br>(Allergopharma) | The proposals are not feasible in respect of molecules in chemically modified allergen extracts. It is unrealistic to have a test discriminating between native and modified allergen and testing potency of the modified allergen as well. Methods such as mass spectrometry are not appropriate for identifying relevant allergens in chemically modified allergen extracts since individual modified allergens may occur in conjugates with several different proteins.<br>The methods as suggested would be applicable to recombinant allergen variants.<br><br>Proposed rewording:<br>*"For allergoids,* ~~***potency tests should consist of a discriminatory test to distinguish between native and modified molecules (for example by quantification in ELISA systems or mediator release assay) and an assay to determine the lack of IgE reactivity.***~~ *a potency test for determination of its antigenic properties using animal anti-sera and an assay to determine the reduction in IgE reactivity by comparison with the unmodified allergen extract should be established and performed.* ~~***As an alternative to a discriminatory immunoassay, other techniques (for example mass spectrometry) may be used to demonstrate the presence of the relevant allergens."***~~ | Some specific methods have already been developed ( e.g. Gelhar et al., Int Arch Allergy Immunol. 2005;136:311-9) and preliminary data have been presented at scientific meetings. Therefore, the proposal should not be accepted. There is an obvious need to provide data on the composition and consistency of allergoids. |

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| 4.2.4.4<br>Page 9<br>Lines 33-37<br>(ATL) | In modified allergens like allergoids native epitopes are no longer present in the original form and cannot be measured reliably with specific antibody assays. An appropriate method to identify the previous native allergens in their multiple crosslinked forms is not available.<br><br>Proposed rewording:<br>*"For allergoids, potency tests should consist of a discriminatory test to distinguish between native and modified molecules (for example by quantification in ELISA systems or mediator release assay) and an assay to determine the lack of IgE reactivity. **~~As an alternative to a discriminatory immunoassay, other techniques (for example mass spectrometry) may be used to demonstrate the presence of the relevant allergens~~**."* | Mass spectrometry is named as an example only, indicating that other methods may be applied as well. Therefore the proposal was not accepted. |
| 4.2.4.4.<br>Page 9<br>Lines 33-39<br>(EAMG) | The issues must be justified and further described if to be included in this document. | No justification is given for this comment on potency test for allergoids and conjugates and therefore it was not considered as relevant. |
| 4.2.4.4.<br>Page 9<br>Lines 33-39<br>(HAL Allergy) | Antibody based tests, like ELISA, can not make a distinction between an allergen and an allergoid. Furthermore, mediator release essays are hard to validate. Moreover, mass spectrometry to prove the presence of relevant allergens has not been demonstrated yet. Further development of these methods is necessary before they can be implemented in the guideline<br><br>Omit lines 33-39 of page 9. | Indeed ELISA methods can be used for this purpose depending on the specificity of different sets of antibodies. Mass spectrometry is named as an example only, indicating that other methods may be applied as well. Therefore the proposal was not accepted. |
| 4.2.4.4.<br>Page 9<br>Line 41<br>(ALK-ABELLO) | Proposed rewording:<br>*"In addition to the **~~potency~~ total allergenic activity**, the relevant individual allergens should be identified and the…."* | The proposed rewording was not accepted. |

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| 4.2.4.4.<br>Page 9<br>Lines 41-43<br>(Stallergenes) | It is stated here that relevant allergens should be identified and major allergens should be quantified. The opposite statement can be found elsewhere in the guideline (relevant allergens should be quantified: page 8 line 35 and page 10 line 35).<br>Please clarify | No opposite statement can be seen in the corresponding section, indicating that normally the major allergens are identical with the relevant ones. For clarification the section was reworded as follows:<br>"In addition to the potency, the relevant individual allergens should be identified and their content should be measured." |
| 4.2.4.4<br>Page 9<br>Lines 43-44<br>(AFSSAPS) | As already stated above, to complete and for better understanding:<br><br>*"If **significant part of activity <u>or</u>** safety concerns arise from other (for example minor) allergens, these have to be quantified as well."* | The introduction of the word "activity" was accepted, the wording "significant part" is not unambiguous to be used in the guideline. |
| 4.2.4.4<br>Page 9<br>Lines 43-44<br>(Allergopharma) | This sentence should be deleted as a rational is not given:<br>*"~~**If safety concerns arise from other (for example minor) allergens, these have to be measured as well**~~."* | This proposal was not accepted. See also comment from AFSSAPS above. |

**4.2.5. ACTIVE SUBSTANCE - STABILITY**

| Page no. + Line no. | Comment and Rationale | Outcome |
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| Page 9<br>Lines 47-49<br>(Stallergenes) | Guidelines ICH Q1E (evaluation of stability data) should be applicable to allergen extracts, Q5C (stability testing of biotechnological/biological products) to recombinant allergens and Q1D (bracketing and matrixing designs) to both.<br>Insert references to these guidelines. | The first paragraph has been reworded as follows :<br>"If the active substance is stored, stability data should be obtained according to the relevant guidelines (e.g. ICH Q1A) to provide information concerning the allowed maximum storage period. The general principles defined in ICH Q5C for biological/biotechnological products should also be considered for allergen extracts." |
| Page 9<br>Line 49<br>(EAMG) | Should be ICH Q5**<u>C</u>** guideline | See above. |
| Page 10<br>Lines 1-3<br>(Allergopharma) | For test allergens we propose that the concept of "quality categories" as published by the German PEI (see comments under Page 5 /Lines 12 – 15 and Page 9, Lines 28-29) should also be applied for stability testing. | The concept of "quality categories" was not included into this guideline (see above). |

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| Page 10<br>Lines 1-11<br>(EAMG)<br>(LETI) | Full extrapolation of stability data gained on the representative allergen extract or product to non-representative allergen product of the same homologous group should be allowed. Indeed according to the guideline, representative and non-representative allergen extracts or products of a group share physicochemical and biological properties and identical formulation and process.<br><br>Proposed rewording:<br>*"Regarding the homologous groups, a full set of data should be presented for the "representative" allergen of the particular homologous group. For the "non-representative" allergens, stability studies* ***can be extrapolated from data gained on the representative allergen extract*** ~~***may be performed on an ongoing basis for the overall shelf life of the active substance. If these data are not available at the time of submission of a marketing authorisation application, a commitment should be made to continue the stability studies after approval. The marketing authorisation application should contain a detailed protocol of the stability studies of the "non-representative" allergens. If justified, some stability data may be extrapolated from the "representative" allergen. The extrapolation of the results from the "representative" allergen" should be discussed and justified, taking into account data concerning the activity of those enzymes (such as proteases) which might impact on the structure of the individual molecules. In case of mixtures of members of different homologous groups, an extrapolation is not acceptable.***~~***"*** | It is stated in the draft, that extrapolation of stability data may be performed if justified, but it was considered that an extrapolation may not be possible for all allergens. Therefore the guideline text was not changed and the proposal was not accepted. |

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| Page 10<br>Lines 1-11<br>(Stallergenes) | Full extrapolation of stability data gained on the representative allergen product to non-representative allergen product of the same homologous group should be allowed. Indeed according to the guideline, representative and non-representative allergen products of a group share physicochemical and biological properties and identical formulation and process.<br><br>Proposed rewording:<br>*"Regarding the homologous groups, a full set of data should be presented for the "representative" allergen of the particular homologous group. For the "non-representative" allergens, stability studies* ***can be extrapolated from data gained on the representative allergen product*** ~~***may be performed on an ongoing basis for the overall shelf life of the active substance. If these data are not available at the time of submission of a marketing authorisation application, a commitment should be made to continue the stability studies after approval. The marketing authorisation application should contain a detailed protocol of the stability studies of the "non-representative" allergens. If justified, some stability data may be extrapolated from the "representative" allergen. The extrapolation of the results from the "representative" allergen" should be discussed and justified, taking into account data concerning the activity of those enzymes (such as proteases) which might impact on the structure of the individual molecules.***~~*"* | |
| Page 10<br>Lines 1-11<br>(Allergopharma) | Full extrapolation of stability data gained on the representative allergen product to non-representative allergen product of the same homologous group should be allowed. Indeed according to the guideline, representative and non-representative allergen products of a group share physicochemical and biological properties and identical formulation and process.<br><br>Proposed rewording:<br>*"Regarding the homologous groups, a full set of data should be presented for the "representative" allergen of the particular homologous group. For the "non-representative" allergens, stability studies* ***<u>can be extrapolated from data gained on the representative allergen product</u>*** ~~***may be performed on an ongoing basis for the overall shelf life of the active substance. If these data are not available at the time of submission of a marketing authorisation***~~ | **See comment above.** |

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| | ~~***application, a commitment should be made to continue the stability studies after approval. The marketing authorisation application should contain a detailed protocol of the stability studies of the "non representative" allergens. If justified, some stability data may be extrapolated from the "representative" allergen. The extrapolation of the results from the "representative" allergen" should be discussed and justified, taking into account data concerning the activity of those enzymes (such as proteases) which might impact on the structure of the individual molecules. In case of mixtures of members of different homologous groups, an extrapolation is not acceptable.***~~ " | |
| Page 10<br>Lines 9-10<br>(Stallergenes) | Data concerning activity of proteases are not relevant for stability.<br><br>**Remove *"taking into account data concerning the activity of those enzymes (such as proteases) which might impact on the structure of the individual molecules."*** | The activity of proteases may degrade the proteins and thereby affects the stability of the products. Therefore this comment was not accepted. |

**4.3. STANDARDS AND REFERENCE MATERIALS**

| Page no. + Line no. | Comment and Rationale | Outcome |
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| Page 10<br>(Stallergenes) | Should not apply to recombinant allergens.<br>Add the following wording:<br>***"For recombinants allergens IHRP should be characterised by in vitro tests. Standardisation should be based on mass units of major allergen whenever possible."*** | A new paragraph on reference materials consisting of recombinant proteins has been added. It was made clear that the existing text applies to extracts only. |
| Page 10<br>(Stallergenes) | Should not apply to hymenoptera venoms.<br>Add the following wording:<br>***"For hymenoptera venoms IHRP should be characterised by in vitro tests and standardised based on relevant enzymatic activity."*** | Because no justification was given for this suggestion, the proposal was not accepted. |

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| Pages 10-11<br>(AFSSAPS) | Recombinant allergens seem to not be concerned by this section. Consequently, a reference standard should be defined for recombinant allergens in order to establish the correlation between the mass units and the total allergenic activity (by clinical studies), and in order to perform a comparison between this standard and the corresponding allergen extract.<br>In the same way, standard reference should be defined for allergoids and conjugates. | The total allergenic activity is determined in IgE-inhibition assays, whereas the efficacy of the finished product is determined in clinical studies. No reason is seen to compare a recombinant product with the corresponding extract, which may be impossible to be defined exactly. No IgE-inhibition assays can be performed with allergoids and conjugates. Therefore the comment was not accepted. |
| Page 10<br>Line 13<br>(GSK) | This is not applicable to recombinant proteins.<br>Mention that this applies to extracts only. | The proposal was accepted (see comment above). |
| Page 10<br>Lines 14-15<br>(ALK-ABELLO) | Proposed rewording:<br>*"Individual company's established IHRP should only be used* ***as the primary IHR*** *as long as no official standards with confirmed and monitored content of the major allergens and* ***Total allergenic activity*** ~~***potency***~~ *are available.* ***When an official IHRP is established the company should calibrate the individual IHRPs against the official IHRP by defined in vitro methods.****"* | The proposal was accepted and the wording was changed. |
| Page 10<br>Lines 14-15<br>(Allergopharma) | This statement implies that some Authority will be in a position to supply reference material in sufficient quantities for routine use by all manufacturers. If and when this is the case then we cannot envisage that more than a handful of official standards will become available. In reality such official standards will only be available so that manufacturers can use them to calibrate their own IHRP. Therefore IHRP will continue to be used.<br><br>Proposed rewording:<br>*"*~~***Individual company's established IHRP should only be used as long as no***~~ ***When*** *official standards with confirmed and monitored content of the major allergens and potency* ***are available, these should be used to calibrate IHRPs."*** | There is no substantial new information in this proposal taking into consideration the comment above. Therefore this proposal was not accepted. |

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| Page 10<br>Lines 16-19<br>(EAMG)<br>(ATL) | Lines 16-19 seem unnecessary as it is a statement about manufacturers and comparability which does not provide any substance to the draft guideline.<br><br>Proposal to delete the following sentence:<br>***~~"Allergen extracts are potentially different between manufacturers and, due to the variability of biological source materials, may even vary to a certain extent from one batch to another within a single company. These characteristics represent a problem with regard to any further harmonisation between products from different manufacturers."~~*** | This section provides the justification for the establishment of the IHRP and should therefore remains in the guideline text. |
| Page 10<br>Line 22<br>(Allergopharma) | An IHRP may be produced from more than one batch and furthermore IHRPs are likely to have to be replaced as they are exhausted in the course of time. The wording should allow for these eventualities.<br><br>Proposed rewording:<br>*"The IHRP is derived from* ***~~a~~ typical*** *production* ***~~run~~*** *batches following the manufacturing process as defined in the dossier;…"* | It is obvious that an IHRP may expire and needs to be replaced by another IHRP. It is generally indicated by the existing text that any IHRP is manufactured as identical to a regular batch, regardless whether it is the first or second IHRP for a given product. In addition, since it is not clear what is meant by "typical production batches" this proposal was not accepted. |
| Page 10<br>Lines 24-25<br>(Allergopharma) | Due to biological origin of the allergens a certain variability is inherent the requirement "match" is unrealistic.<br><br>Proposed rewording:<br>*"Therefore, the qualitative and quantitative composition of regular production batches should* ***~~match the~~ be comparable to*** *the IHRP."* | Because it is expected that the IHRPs are qualified using acceptance criteria, "comparable" is not the correct wording. For clarification, the section was reworded as follows:<br>*"Therefore, the qualitative and quantitative composition of regular production batches should meet predefined acceptance criteria when compared with the IHRP. These criteria have to be justified."* |
| Page 10<br>Line 26<br>(Allergopharma) | Delete this part of sentence and see for explanation page10, line 38:<br>***~~"….and its specific allergenic activity shall be established"~~*** | Because the total allergenic activity is a main characteristic of the IHRP, the wording was not changed. |
| Page 10<br>Lines 27-28<br>(ALK-ABELLO) | It is unclear what is meant by carbohydrate composition. In general it is not possible to measure in allergen extracts due to inadequate methods. It is therefore recommended to change the sentence.<br><br>Proposed rewording:<br>*"Data should be provided on protein****~~, and whenever possible, carbohydrate composition~~****"* | Methods are established to determine the carbohydrate composition in extracts. Therefore, the justification for the change is not adequate and the deletion was not accepted. |

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| Page 10<br>Lines 27-28<br>(LETI) | Eliminate carbohydrate. It has been described that carbohydrate moieties of glycoproteins determine the IgE binding. However, the capacity of individual carbohydrates to bind IgE, present in the allergenic extracts, has not been demonstrated. The presence of carbohydrates in the allergenic extracts is not relevant considering immunological aspects, so, its determination do not affect the final quality or the biological potency of the extracts.<br><br>Proposed rewording:<br>*"Data should be provided on protein* ~~***and, whenever possible, carbohydrate composition."***~~ | It is known that carbohydrates may also act as immuno-modulators. Therefore, it may be required to determine their content and the proposal was not accepted. |
| Page 10<br>Lines 29 and 35<br>(Allergopharma) | How are 'relevant allergens' to be defined? | Please see section "Definitions". |
| Page 10<br>Lines 38-46<br>(Allergopharma) | Implication that ALL IHRP should be biologically standardized.<br>Methods of Turkeltaub and Nordic Council of Medicines should only be cited as examples.<br>Implication, that IHRP's need to be established for all allergens.<br>For therapeutic preparations the assignment of biologic units as derived from the application of the Nordic guideline on Allergen Products creates a serious risk. There are no international reference preparations which have been standardized according to the Nordic Guideline. Therefore, every company has the need for standardizing their own In-House reference preparations, prepared by different protocols, clinically tested by different practitioners and with different cohorts of patients. It is evident, that biological units created under such non-standardized conditions are by no means comparable between companies.<br>The idea of having biologic units on the labels of therapeutic preparations was borne from the wish of the Authorities and the practitioners to have a comparative measure for evaluating preparations of different origin with regard to safety and efficacy and to substitute the preparations whenever it seems appropriate. Such substitutions create serious safety risks for the patients. Furthermore the current knowledge regarding the mechanisms of allergen specific immunotherapy clearly contradicts the use of biological | The expression "if practicable" is not specific enough to be used in a guideline. The wording was changed into "using methods such as those described ...". |

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| | units for therapeutic preparations in that it indicates the importance of the T-cell modulatory activity rather than IgE antibody reactivity. The latter is of relevance in the case of test preparations.<br>There is evidence that therapeutic preparations standardized to the same level of biologic units show allergen specific mean tolerated doses in immunotherapy differing by up to 1 : 10 between allergens! (Basomba A., Proc. XII Int. Congr. Allergy Immunol., Washington D.C. (1985), 335 -340, see attachment). Current allergoid preparations are highly effective in immunotherapy despite their extremely reduced biologic activity.<br>For test allergens the "Points to consider on the evaluation of diagnostic agents" (CPMP/EWP/1119/98) as effective since November 2001 describes in detail how test allergens should be evaluated. The provision of that Guideline totally abolish the need for biological standardization of test allergens.<br>Proposed rewording for line 43:<br>*"If* ***practicable*** *the IHRP should be biologically standardised by appropriate methods on the basis of skin test* ***reactivity using methods such as those described by [****Turkeltaub[15] and Nordic Council of Medicines[16]****]."* | |
| Page 10<br>Line 41<br>(LETI) | Biological potency of the extracts can be also analyzed by competition experiments. IgE-binding test is more accurate because both methods (inhibition and competition) are included in this term.<br><br>Proposed rewording:<br>*"[…] (for example IgE-* ***~~inhibition~~*** **binding** *or cellular mediator release assays*)." | "Competitive IgE-binding" test is the wording used throughout the guideline due to reasons described above. Therefore the comment was not accepted. See revised definitions section. |
| Page 10<br>Lines 43-44<br>(EAMG)<br>(LETI) | These references should be omitted from the document and as usual each manufacturer should describe their methodologies for biological standardization. Alternatively, the references should be mentioned as potential examples for biological estimates of allergen potency.<br><br>Proposed rewording:<br>*"The IHRP should be biologically standardised by appropriate methods on the basis of skin test reactivity* **such as** *Turkeltaub[15] and Nordic Council of Medicines[16] ".* | See comment above. |

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| Page 10<br>Lines 43-44<br>(ALK-ABELLO) | We suggest that this is only relevant for establishing the IHRP for skin-prick testing products (diagnostica).<br>For treatment products (SLIT and SCIT) the clinical trials have established the relevant strength for the given product using the relevant way of administration and formulation.<br><br>Proposed rewording:<br>*"**For diagnostic products,** the **1st** IHRP should be biologically standardised by appropriate methods on the basis of skin test reactivity **at the time of establishment of the IHRP. Future IHRPs can be demonstrated to be equivalent and approved by in vitro techniques.**"*<br>***For treatment products where the product strength is based on results from clinical trials, a correlation between the biological activity of the drug product and the 1st IHRP has been demonstrated. In that case the following IHRPs can be demonstrated to be equivalent using in vitro techniques.**"* | The biological potency has to be established for the IHRPs of all products to provide a proof for batch-to-batch consistency. Therefore this comment was not accepted. |
| Page 10<br>Lines 43-46<br>(ATL) | As there are further methods to conduct skin test reactivity, the references provided (15 and 16) should be deleted: | See comment above. |
| Page 10<br>Lines 48-50<br>(ALK-ABELLO) | We suggest aligning with the coming version of the EP monograph for Allergen Products.<br><br>Proposed rewording:<br>*"This standardisation should be performed using a predefined set of in vitro methods**~~, but in vivo standardisation procedures may also be included~~**"* | There is no scientific reason for the deletion of this sentence. Therefore the comment was not accepted. |
| Page 11<br>Lines 3-4<br>(AFSSAPS) | Delete "s" for "Sera pools" since there is only one serum used:<br>*"Specific sera pool**~~s~~** should be established for batch control and for the qualification of individual IHRP."* | The proposal was accepted. |

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| Page 11<br>Lines 4-5<br>(EAMG)<br>(Stallergenes) | The same pool of sera, and not 2 different pools, is used for batch control and qualification of the IHRP.<br><br>Proposed rewording:<br>*"**~~Specific sera pools~~** **A sera pool** should be established for batch control and for the qualification of individual IHRP.* | The proposal was accepted. |
| Page 11<br>Lines 5-12<br>(EAMG) | In this case there is a risk that the sera pool will not be representative anymore because of the numerous and strict criteria for the selection of individual sera. Sera recognising carbohydrate epitopes and sera from patients who had a previous SIT treatment with the respective or cross-reactive allergen should not be included in the pool.<br><br>**Delete lines 5-12.** | Guidance on the selection and characterisation of the individual sera used for the composition of the pools is considered as necessary. Evidence has to be provided, that the pool is representative and relevant allergens are detected. Therefore, the comment was not accepted. If criteria are considered too strict for one pool, it may be considered to establish two separate pools to cover geographic differences for example. |
| Page 11<br>Lines 5-12<br>(Stallergenes) | The sera pool will not be representative anymore because of the numerous and strict criteria for the selection of individual sera. Moreover, for allergen products for which not so many sera are available, these criteria could not be fulfilled.<br>Qualification should be predominantly carried out on the pool rather than on individual sera.<br><br>**Remove lines 5-12.** | Guidance on the selection and characterisation of the individual sera used for the composition of the pools is considered necessary. Evidence has to be provided, that the pool is representative and relevant allergens are detected. Therefore, the comment was not accepted. If criteria are considered too strict for one pool, it may be considered to establish two separate pools to cover geographic differences for example. |

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| Page 11<br>Lines 4-9<br>(EAMG)<br>(ATL) | Both the consideration of geographically different sensitisation patterns and the composition of sera from 10 to 15 individuals are extremely difficult to achieve.<br>Commercial sources only supply a maximum of six individuals and a definition of different geographical locations is not possible.<br><br>ATL:<br>The use of hospitals as source for sera pools would provide for a higher number of individuals however it will be an issue to ascertain HIV and Hepatitis B testing. Thus ATL is limited to obtain their sera pools from commercial sources.<br><br>Proposed rewording:<br>EAMG/ATL:<br>*"Specific sera pools should be established for batch control and for the qualification of individual IHRP.* ***~~The problem of geographically different sensitisation patterns should be taken into consideration in the preparation of the pools.~~*** *For the used sera, the frequency of IgE-recognition of different allergens as well as the content of allergen-specific IgE antibodies and the clinical relevance of sensitisation should be taken into account when preparing the pool."*<br>ATL:<br>*"The pool should be composed of sera from* ***4~~10~~ to 6~~15~~*** *individuals."* | Guidance on the selection and characterisation of the individual sera used for the composition of the pools is considered necessary. Evidence has to be provided, that the pool is representative and relevant allergens are detected. Therefore, the proposal was not accepted. If criteria are considered as too strict for one pool, it may be considered to establish two separate pools to cover geographic differences for example. |

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| Page 11<br>Lines 5-9<br>(LETI) | Both the consideration of geographically different sensitisation patterns and the composition of sera from 10 to 15 individuals are very difficult to achieve.<br>Commercial sources only supply a few number of individuals sera and a definition of different geographical locations is not possible.<br><br>Proposed rewording:<br>***~~"The problem of geographically different sensitisation patterns should be taken into consideration in the preparation of the pools.~~*** *For the used sera,* ***~~the frequency of IgE-recognition of different allergens as well as~~*** *the content of allergen-specific IgE antibodies* ***~~and the clinical relevance of sensitisation~~*** *should be taken into account when preparing the pool.* ***~~The pool should be composed of sera from 10 to 15 individuals."~~*** | See comment form EAMG and ATL above. |
| Page 11<br>Lines 8-9<br>(ALK-ABELLO) | The blood volume that can be/is drawn from different patients varies and it is therefore necessary to extend the range of individuals included.<br><br>Suggested rephrased to:<br>*"The pool should be composed of sera from* ***a defined number of individuals, preferably*** ***~~10~~*** ***5*** *to* ***20*** ***~~15~~*** *individuals"* | Because the inclusion of more than 15 individuals may lead to a dilution of the reactivates of the individual sera, the number of individuals should not be changed and the proposal was not accepted. |
| Page 11<br>Lines 8-9<br>(Allergopharma) | It may be necessary to include more than 10 to 15 sera in order to achieve a realistic total volume, particularly as it has become increasingly difficult to obtain large volumes from individual patients.<br><br>Proposed rewording:<br>*"The pool should be composed of sera from* ***<u>at least</u>*** *10 to 15 individuals."* | The proposal was not accepted.<br><br>See comment above. |
| Page 11<br>Lines 9<br>(ALK-ABELLO) | We do not understand this statement as some allergens are glycoproteins.<br><br>Suggested rephrasing:<br>*"Sera* ***~~recognising carbohydrate epitopes and sera~~*** *from patients who had a previous SIT treatment with the respective or cross-reactive allergens should not be included in the pool."* | Because IgE-sera recognizing carbohydrate epitopes are extremely cross-reactive and not specific for individual allergen sources (see e.g. Fötisch K, Vieths S: N- and O-linked oligosaccharides of allergenic glycoproteins. Glycoconjugate J 2002, 18: 373-390) they should not be included into the pools to provide specificity. Therefore the proposal was not accepted. |

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| Page 11<br>Lines 9-11<br>(LETI) | Proposed rewording:<br>*"Sera recognising carbohydrate epitopes and sera from patients who had a previous SIT treatment with the respective or cross-reactive allergen should not be included in the pool,* ***unless that a method that avoid IgG interferences is used.****"* | The comment is unclear and not justified in any way. The scientific rationale is not given. Therefore the proposal was not accepted. |
| Page 11<br>Lines 11-12<br>(ALK-ABELLO) | It is necessary to be able to use a serum pool containing IgE against milk protein in order to prepare a milk extract for diagnosing milk allergy.<br><br>Proposed rewording:<br>*"In addition, sera containing IgE antibodies against serum albumin, milk proteins or gelatine could cause experimental problem and should therefore be avoided in the pool* ***unless otherwise justified.****"* | The proposal was accepted. |

| 4.4.1. FINISHED PRODUCT – DESCRIPTION AND COMPOSITION OF THE FINISHED PPRODUCT | | |
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| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 11<br>Line 17<br>(Allergopharma) | A distinction must be made between test allergens and therapeutic preparations as done in the Ph.Eur. Allergen Monograph, as requirements as to the extent of quality measures to be taken clearly differs.<br><br>New text:<br>***"Destinction has to be made between test allergens and allergen preparations for specific immunotherapy. In general, test allergen preparations contain native unmodified allergens, having their inherent IgE-binding capacity in order to provide a sensitive and relevant test. Therapeutic allergen products are often prepared as physically or/and chemically modified allergen products in which the original IgE binding capacity is reduced in order to minimise the risk of allergic side effects when administered to sensitized individuals. Therefore the methods of standardisation have to take the characteristics of the product into consideration."*** | The proposal does not provide any new information. Therefore the comment was not accepted. |

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| Page 11<br>Lines 19-22<br>(Allergopharma) | A more concise wording is suggested and reference to formulation is deleted as it is covered in lines 29-30.<br><br>Proposed rewording:<br>***"A detailed description of the finished product should be given, ~~If the finished product consists of a mixture of active substances, a complete list of all the active substances used should be given.~~ naming the contained allergen drug substance(s), excipients and the physical, biochemical and immunological properties. The function of the different components should be described. The rationale for the specifications should be given. ~~In general, adsorption and addition of excipients are regarded as formulation, and these steps should be described in the manufacturing process of the finished product.~~"*** | The comment was not accepted because the proposal deals with specifications which are outside the scope of this paragraph. |

**4.4.2. FINISHED PRODUCT - MANUFACTURE**

| Page no. + Line no. | Comment and Rationale | Outcome |
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| Page 11<br>Lines 24-28<br>(Stallergenes) | Extrapolation of process validation data gained on the representative allergen product to non-representative allergen product of the same homologous group should be allowed.<br><br>Proposed rewording:<br>*"Description, documentation, and results of the validation of the manufacturing process should be provided* ***for the representative allergen product. Data can be extrapolated to the non-representative allergen products of the same homologous group provided that the manufacturing process is identical****."* | The proposal was discussed and the corresponding section was reworded, even if a general extrapolation of the validation data was not accepted. |

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| Page 11<br>Line 23<br>(AFSSAPS) | ▪ Add sterility issue: discuss need of sterility for the finished product according to the route of administration (diagnosis (skin prick test, provocation test), treatment).<br>▪ Method of sterilization.<br>▪ Bioburden issue. | The requirements for the manufacturing and quality parameters for sterile products are defined in the relevant Ph. Eur. Monographs and other guidance documents. The specific requirements for sterile products should not be included into this guideline and therefore the proposal was not accepted. |
| Page 11<br>Line 24<br>(ALK-ABELLO) | Proposed rewording:<br>*"The **~~production~~ manufacturing** process…"* | The proposal was accepted. |

**4.4.3. FINISHED PRODUCT – CONTROL OF FINISHED PRODUCT**

| Page no. + Line no. | Comment and Rationale | Outcome |
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| Page 11<br>Lines 40-42<br>(ALK-ABELLO) | Proposed rewording:<br>*"In such cases, test results should **comply with ~~be considered as~~ the** acceptance criteria **defined in the finished product specification ~~and included in the specifications of the finished product~~. The characteristics of the finished product should ideally be documented for all strengths (dilutions). Where appropriate testing is not possible due to methodological limitations, this should be justified.** In addition, (…)"* | The proposal was accepted, but the word "ideally" was deleted. |
| Page 11<br>Lines 41-43<br>EAMG)<br>(LETI)<br>(Stallergenes) | The sentence *"In addition, aspects described in previous parts that are also relevant to the control of the finished product should be taken into account"* is not specific enough.<br><br>Remove the sentence | For clarification, the section was reworded as follows:<br>"Guidance provided in previous parts of this guideline that are also relevant to the control of the finished product should be taken into account" |
| Page 11<br>Line 44<br>(ALK-ABELLO) | Proposed rewording:<br>*"Control of **standardised** non-modified allergen preparations:"* | Because a separate section is in the guideline for non-standardised products and competitive IgE-binding tests are described here, it is obvious that the requirements described here apply to standardised products. Therefore the proposal was not accepted. |

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| Page 11<br>Line 44<br>(LETI) | Add "*biological standardized*" to better understanding of the paragraph:<br>"*Control of non-modified allergen* ***biological standardized*** *preparations."* | See above. |
| Page 11<br>Line 45<br>(ALK-ABELLO) | Proposed rewording:<br>"***Total allergenic activity*** ~~*IgE-binding*~~ *tests* ***by an IgE assay*** *are required"* | The rewording is as follows: "**Total allergenic activity determined by a competitive IgE-binding test** is required". See revised definitions. |
| Page 11 line 46 to Page 12 line 3<br>(Allergopharma) | IgE binding assays play different roles for test allergens and therapeutic allergens. For test allergens they ensure consistent IgE reactivity. The efficacy of therapeutic allergens is not dependent on IgE activity but the ability to modulate the T-cell response.<br><br>Proposed rewording:<br>*"IgE-binding tests are required for the standardization and batch control of finished products containing non-modified allergens* ***and which are intended for in vivo diagnosis. These tests are also relevant to ensure the safety of therapeutic products.*** ~~***Consequently***~~ *The labelling should be indicated in* ~~*potency units*~~ *relevant units of standardization.*<br>*If safety concerns arise from individual minor allergens, these have to be measured as well,* ***if test systems are available.****"* | According to the draft of the revised Ph. Eur. Monograph on "Allergen Products", all finished products covered by this guidance document, including therapeutic allergen preparations, have to be tested for total allergenic activity.<br>The proposal was not accepted. |
| Page 11<br>Line 46<br>(ALK-ABELLO) | Proposed rewording:<br>"*Consequently, the labelling should be indicated in* ***biological activity*** ~~***potency***~~ *units* ***unless otherwise justified****"* | This proposal was not accepted. |
| Page 11 Lines 46-48<br>Page 12 Lines 1-3<br>(ATL) | ATL agrees to perform the quantification of individual allergens with test systems validated in international standardisation programs for inclusion of the content of individual allergens in the SPC.<br>However ATL is unaware of such international standards and would appreciate if they could be provided by the European Union. | The development of such standards (biological reference preparations) is in progress and coordinated by EDQM. |
| Page 11<br>Line 48<br>(ALK-ABELLO) | Do "*individual allergens*" correspond to relevant allergens here?<br>Please clarify. | Individual allergens mean single allergens. See revised definition section. |

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| Page 12<br>Lines 4-8<br>(Allergopharma) | See also chapter 4.1.2, page 5, lines 26 -29:<br>There is a difference between the total allergenic potency of an allergen mixture (i.e. birch/alder/hazel) determined by a birch-system or an alder-system or a hazel-system. Only the cross reactive part, but not the total allergenic potency of the cross-reactive allergens in the mixture is determined by a single-allergen test-system. Any mixed-allergen test system applied for a certain mixture (of a specified combination) can determine only the cross reactive parts of the single allergens. Therefore a higher total potency results for a mixture compared to the single allergen results.<br><br>Proposed rewording:<br>*(…) cross reactivity of the constituents**, the potency of the constituents should be determined prior to mixing.**"* | Please see comment on page 5, line 26 – 29. |
| Page 12<br>Line 5<br>(ALK-ABELLO) | Proposed rewording:<br>*"For allergen mixtures, potency testing, **i.e. major allergen content,** should be performed for each individual ~~**allergen**~~ active substance in the mixture"* | Guidance on potency testing is given in section 4.2.4.4 and should not be repeated here. Therefore the proposal was not accepted. |
| Page 12<br>Line 8<br>(LETI) | Biological potency of the extracts can be also analyzed by competition experiments. IgE-binding test is more accurate because both methods (inhibition and competition) are included in this term.<br><br>Proposed rewording:<br>*"[…] should be determined by an IgE- ~~**inhibition**~~ **binding** test."* | The common wording in this guideline is "competitive IgE-binding assay". This term is defined in the section "Definitions" of the revised guideline. |
| Page 12<br>Lines 9-12<br>(Stallergenes) | *"For adsorbed products, the stability of the adsorption has to be determined by measuring the amount of total soluble protein and/or the presence of IgE-binding components in the supernatant or by using other relevant methods at release and at the end of the shelf life period."* belongs to a different paragraph. Information specific to the control of adsorbed product should be inserted instead. | The paragraph was reworded as follows: "efficacy and stability of the adsorption". Otherwise it is considered that this paragraph directly applies to the control of finished products containing adsorbed allergen preparations. |
| Page 12<br>Line 10<br>(AFSSAPS) | Proposed rewording to be more understandable:<br><br>*"Control of adsorbed products:*<br>*For adsorbed products, the ~~**stability**~~ **efficiency** of the adsorption has to be ~~**determined**~~ **assessed** by measuring the amount of total soluble protein and/or* | The last sentence was added to the text. The proposal was accepted. |

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| | *the presence of IgE-binding components in the supernatant or by using relevant methods at release and at the end of the shelf life period.*<br>***These parameters should be followed during the stability studies performed for adsorbed products.****"* | |
| Page 12<br>Lines 13-16<br>(Allergopharma) | The recombinant hypoallergenic variants have to be acknowledged.<br><br>Proposed rewording:<br>***"The potency as described in chapter 4.2.4.4. should be determined. A determination of the content of purified protein should be considered when possible and appropriate."*** | The proposal was agreed. The section 4.2.4.4 was changed accordingly. |
| Page 12<br>Lines 20-21<br>(EAMG)<br>(Stallergenes) | The range of *in vitro* methods applicable for non-standardized allergen products strongly depends on the tools available. For some allergen products, the choice is limited.<br><br>Proposed rewording:<br>*"In this case, a range of* ***pertinent*** *in vitro methods should be applied for the control of the finished product."* | The comment is reflected by an additional sentence at the end of the paragraph:<br>"If one of the above-mentioned parameters is not tested, a justification has to be given". |
| Page 12<br>Line 21<br>(ALK-ABELLO) | Proposed rewording:<br>*"(…) may be applied for the control of the finished product.* ***However, for non-standardised allergen extracts for diagnostic use, testing for protein content and protein profile should be considered as sufficient.****"* | The comment is reflected by an additional sentence at the end of the paragraph:<br>"If one of the above-mentioned parameters is not tested, a justification has to be given". |
| Page 12<br>Lines 29-46<br>(EAMG)<br>(LETI) | Full extrapolation of stability data gained on the representative allergen product to non-representative allergen product of the same homologous group should be allowed. Indeed according to the guideline, representative and non-representative allergen products of a group share physicochemical and biological properties and identical formulation and process. The same approach should be considered for the mixtures of allergen extracts that belong to the same homologous group.<br><br>Proposed rewording:<br>EAMG/LETI:<br>*"For the non-representative allergens* ***~~some~~*** *stability data* ***can*** *be* | It is stated in the guideline that extrapolation of some stability data may be performed if justified. But it was considered that an extrapolation may not be possible for all allergens (e.g. differences in enzymatic activities). Therefore the guideline text was not changed and the proposal was not accepted. |

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| | *extrapolated from* ***data gained on*** *the "representative" allergen* ***product****.* ~~***Therefore, only a limited number of parameters may be tested in these studies. The applicant should justify the choice of these parameters. The extrapolation of the results from the "representative allergen" should be discussed and justified. This justification should include experimental evidence that the relevant enzymatic pattern of the non representative allergens is equivalent to the enzymatic pattern of the representative allergen. The data for the non representative allergens may be obtained in ongoing real time stability studies after granting of a marketing authorisation. If the data are not available at the time of submission of a marketing authorisation, a commitment should be made to continue the stability studies after approval. The marketing authorisation application should contain a detailed protocol of the stability studies of the "non representative" allergens."***~~<br>LETI:<br>*"If the finished product consists of a mixture of allergen extracts not belonging to the same homologous group, stability studies have to be performed for the mixture considering each individual active substance.*<br><br>*If the individual extracts in a mixture belong to the same homologous group* ***the stability data of the representative allergen product can be extrapolated to the mixture*** ~~***and therefore cross-reactivity occurs between the relevant allergens, it may not be possible to determine the activity of the individual active substances. In such cases (for example a mixture of grass pollen extracts), an overall potency testing by IgE inhibition may be appropriate.***~~*The selected testing strategy should be described in detail and justified by the applicant."* | |
| Page 12<br>Line 45<br>(LETI) | Biological potency of the extracts can be also analyzed by competition experiments. IgE-binding test is more accurate because both methods (inhibition and competition) are included in this term.<br><br>Proposed rewording:<br>*"[…] overall potency testing by IgE-* ~~***inhibition***~~ ***binding*** *may be appropriate."* | The wording was changed. See comments in active substance section. |

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| Pages 11-12<br>(EAMG)<br>(Stallergenes) | There is no recommendation for the control of venoms in this section. Such recommendations should be considered. | Hymenoptera venom preparations are considered as regular allergenic products. No reason is given why specific recommendations are required. Therefore the comment was not accepted. |
| Page 13<br>Lines 7-9<br>(EAMG)<br>(LETI)<br>Move to 4.4.5 of this overview | The "*in vivo* immunogenicity test" would require a large amount of laboratory animals. The statement should be deleted or reconsidered.<br><br>Proposed rewording:<br>*"If it is not possible to perform potency tests, for example in the case of adsorbed material, **~~in vivo immunogenicity tests or~~** validated alternative in vitro tests should be performed at the beginning and end of the stability study to provide evidence on the stability of the product."* | Animal-based tests should only be considered, if no other validated in vitro test is established. As this has to be performed only at two time points, the use of laboratory animal will be limited. Therefore the proposal was not accepted. |

| 4.4.4. FINISHED PRODUCT – CONTAINER CLOSURE SYSTEM | | |
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| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 12<br>Lines 22-23<br>(AFSSAPS) | The volume of the container should be in accordance with the intended use and the stability after first opening.<br><br>Proposed rewording:<br>***"4.4.4. Container closure system***<br>*The container closure system(s) used for the various strengths should be described in detail.* ***The volume of the container should be in accordance with the intended use and the stability after first opening.***<br>*Additionally, all other parts of the final medicinal product including for example solvents for reconstitution or syringes have to be described."* | The concerns for prick tests were acknowledged, but this statement is too obvious to be considered in the guideline. In addition, the comment as written was not understandable. Therefore the proposal was not accepted. |
| **4.4.5. FINISHED PRODUCT STABILITY** | | |
| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Pages12-13<br>(Allergopharma) | This request will lead to a significant increase in the number of stability studies and will have a high impact on the size of an allergen portfolio. | The point here is well recognized, but the improvements through the revision of the guideline are considered as necessary to reflect the actual state of the art in pharmaceutical manufacturing and testing. |
| Page 12<br>Line 28<br>(AFSSAPS) | Proposed rewording:<br>*"Stability testing should be performed as real-time stability studies as indicated in the relevant guidance documents (e.g. 4, 14).* ***The analytical methods used during the stability studies should be stability indicating.****"* | This is an obvious statement that has also been reflected in ICH Q1A guideline, so there is no need to repeat this statement in this guideline. |

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| Page 12<br>Lines 29-39<br>(EAMG)<br>(Allergopharma)<br>(Stallergenes) | Full extrapolation of stability data gained on the representative allergen product to non-representative allergen product of the same homologous group should be allowed. Indeed according to the guideline, representative and non-representative allergen products of a group share physicochemical and biological properties and identical formulation and process.<br><br>Proposed rewording:<br>*"For the non-representative allergens* ~~***some***~~ *stability data* ***<u>can</u>*** *be extrapolated from the "representative" allergen.* ~~***Therefore, only a limited number of parameters may be tested in these studies. The applicant should justify the choice of these parameters. The extrapolation of the results from the "representative allergen" should be discussed and justified. This justification should include experimental evidence that the relevant enzymatic pattern of the non representative allergens is equivalent to the enzymatic pattern of the representative allergen. The data for the non representative allergens may be obtained in ongoing real time stability studies after granting of a marketing authorisation. If the data are not available at the time of submission of a marketing authorisation, a commitment should be made to continue the stability studies after approval. The marketing authorisation application should contain a detailed protocol of the stability studies of the "non representative" allergens.***~~ *"* | See comment above. |
| Page 12<br>Lines 30-31<br>(AFSSAPS) | Even if simplify stability studies could be accepted for non-representative allergens on an on going basis. At minima, relevant parameter should be followed during these stability studies in order to conclude on a relevant shelf-life.<br><br>Proposed rewording:<br>*"Therefore, only a limited* ***<u>but</u> relevant*** *number of parameters may be tested in these studies."* | According to the following sentence, the applicant has to justify the choice of these parameters. It is then up to the regulatory body to decide if the justifications for parameters are sufficient or other parameters should have been included. Therefore the expression "but relevant" was not included. |

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| Page 12<br>Lines 33-34<br>(AFSSAPS) | The sentence on the enzymatic pattern is not understandable and should be clarify or deleted:<br>~~***"This justification should include experimental evidence that the relevant enzymatic pattern of the non representative allergens is equivalent to the enzymatic pattern of the representative allergen."***~~ | The comment was accepted and this sentence was deleted. |
| Page 12<br>Lines 33-34<br>(Stallergenes) | Comparison of the enzymatic profiles is not relevant for stability.<br><br>Remove: ~~***"This justification should include experimental evidence that the relevant enzymatic pattern of the non representative allergens is equivalent to the enzymatic pattern of the representative allergen."***~~ | The comment was accepted and this sentence was deleted. |
| Page 12<br>Lines 47-48<br>(ALK-ABELLO) | If the stability of the active substance is well documented based on stability studies following the ICH Q1A guideline and the end of shelf life specification for the active substance is identical to the release specification for the active substance, it should not be necessary to perform stability studies of finished products manufactured with active substance at the end of its shelf-life.<br><br>Proposed rewording:<br>"*For allergen extracts, stability studies of the finished products manufactured with active substance at the end of its shelf-life should be* ***considered*** ~~***performed on an ongoing basis after marketing approval.***~~<br><br>***If performed, the study should be initiated once during development or a commitment should be given to initiate such a study after marketing approval."*** | The proposed approach will generate data indicating the stability of the finished product in a worst case scenario, e.g. using a drug substance at the end of its shelf life. Therefore the guideline text was not changed an the proposal was not accepted. |
| Page 13<br>Lines 7-9<br>(ALK-ABELLO) | Proposed rewording:<br>*"If it is not possible to perform potency tests, for example in the case of adsorbed material, in vivo immunogenicity tests or validated alternative in vitro tests should be performed at the beginning and end of the* ***proposed shelf-life period. The*** *stability study* ***should be initiated during development,*** *to provide evidence of the stability of the* ***finished*** *product."* | The comment was accepted and the wording was changed accordingly by addition of "in the stability studies" for clarification. The last sentence of the proposal was not included in the guideline because this is an obvious statement. |

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| Page 13<br>Lines 7-9<br>(EAMG) | This would require a large amount of laboratory animals.<br>The statement should be deleted or reconsidered. | Animal-based tests should only be considered if no other validated in vitro test is established. As this has to be performed only at two time points, the consumption of laboratory animal will be limited. Therefore the guideline text was not changed. |
| Page 13<br>Lines 7-9<br>(Stallergenes) | The reference to *in vivo* immunogenicity tests is not understood.<br>Please clarify. | Tests in laboratory animals are meant here. |
| **DEFINITIONS** | | |
| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
| Page 13<br>(AFSSAPS) | Cross-reactivity issue should be defined.<br>Indeed, the approach used to define proposed homologous groups should be explained, considering that at the moment the opinion article: *(18) A.R. Lorenz, D. Lüttkopf, S. May, S. Scheurer, S. Vieths. The Principle of Homologous Groups in Regulatory Affairs of Allergen Products – A Proposal. Int.Arch.Allergy Immunol. Submitted* is not available. | The article is published. *This issue was discussed separately during an informal consultation with manufacturers at the 12th International Paul-Ehrlich-Seminar (September 24th, 2008).* |
| Page 13<br>Lines 19-20<br>(Stallergenes) | Demonstration of a clinically relevant effect for relevant allergens is not always available. Therefore, additional data that are indicative of a clinically relevant effect can be exploited instead. We propose that binding to a significant amount of IgE for a significant proportion of the allergic patients as compared to the amount of IgE binding to the corresponding allergen source is also a significant parameter for the definition of a relevant allergen.<br><br>Proposed rewording:<br>*"Relevant allergens are allergens causing **either** a clinically relevant effect in a significant proportion of the allergic patients, **or binding to a significant amount of IgE for a significant proportion of the allergic patients, as compared to the amount of IgE binding to the corresponding allergen source.**"* | Since the *in vivo* clinically relevance and not the *in vitro* IgE-binding capacity is the main attribute to these allergens, the comment was not accepted. The "relevance" should be described on a clinical basis only, if possible. |

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| Page 13<br>Lines 26-27<br>(Allergopharma) | Change in definition of homologous groups:<br>Old 1:… the composition and physiochemical biochemical properties…<br>Old 2: …the cross-reactivity/structural homology of allergens…<br><br>See also 4.1.1 Homologous Groups<br><br>Proposed rewording:<br>New 1: *" …the composition, the physicochemical ~~biochemical~~* ***and/or biological*** *properties…."*<br>New 2: *"…the cross-reactivity/structural homology of allergen* ***proteins…."*** | The wording is clear and no change was introduced. |

**REFERENCES (scientific and/or legal)**

| **Page no. + Line no.** | **Comment and Rationale** | **Outcome** |
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| Pages 13-14<br>(EAMG) | We recommend to use the expert report below specifically related to homology issues within the mould allergen extracts as a potential reference in the guideline:<br>R.A. Samson. The taxonomic relationships of the allergen group "moulds" and a proposal for the selection of *Alternaria alternata* as representative allergen of this group". Centraalbureau Voor Schimmelcultures - Fungal Biodiversity Centre - Institute of the Royal Netherlands Academy of Arts and Sciences, 2008. | No mould homologous group is defined by the guideline. If a mould homologous group is intended to be defined by an applicant, the corresponding literature may serve as supportive data. |

| ANNEX 1 – Accepted homologous groups | | |
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| **Page no. + Line no.** | | |
| Pages 15-17 (Allergopharma) | Castanea satavia and Fagus sylvatica should be added to the 'birch group' that would be better named 'Fagales'.<br>We propose that two additional group headings should be included 'Plant derived allergens (excluding pollens)'and 'Animal derived allergens (excluding mites and epithelia)' as an alternative to the previous ill-defined category Food Stuffs | The homologous group was extended for Castanea satavia and Fagus sylvatica and the group was named 'birch group' or ´fagales group´ . |
| Page 15 (AFSSAPS) | Delete "Suggested representative allergen sources for each group", in order to let the choice to the applicant. | This comment was accepted. |
| Page15 (ALK-ABELLO) | ➢ Plantago sp. Can be included in the Oleacea group because the main allergen, Pla l 1, belongs to the Ole e 1 familly<br>➢ Cryptomeria japonica can be included in the Cypress group since the major allergen is homologous.<br>➢ The mite species Acarus siro, Glycyphagus domesticus, Lepidoglyphus destructor and Tyrophagus putrescentiae can form a homologous group since they have a similar allergenic composition: They all lack group 1, group 2 being the major allergen, and intermediate to high cross-reactivity at the level of group 2.<br>Foods are not addressed. | The grouping was discussed by the authors, but the proposals were not accepted. However, this does not exclude the formation of the groups as suggestion, if comprehensive justifications are provided by the applicant. |

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| Page 17<br>Lines 23-24<br>(AFSSAPS) | To be more understandable and to be consistent throughout the document.<br>The following sentence:<br>~~***: The relevance of geographical differences should be taken in consideration for the individual products***~~<br>should be deleted and replaced by the sentence at lines n°9, 10, 11 of the paragraph 4.1.1. Homologous groups, as follows:<br>***One member of a homologous group is selected as the representative allergen. This choice should be justified, taking into consideration for example geographical differences in the sensitization patterns and other relevant factors.*** | This comment was accepted. |
| Pages 15-17<br>(LETI) | See General comments and point 4.1.1. Homologous groups. | See comments there. |