21 July 2023
EMA/CVMP/IWP/530940/2019
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline on requirements for the quality (production and control), safety and efficacy of allergen products for use in horses, dogs and cats' (EMA/CVMP/IWP/170689/2016)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1.	Ceva santé animale & Ceva Biovac
2.	ECEIM past president Prof. Dr. René van den Hoven Dip ECEIM, Dip ECVFT
3.	Cruelty Free International
4.	Laboratorios LETI, S.L.U. (LETI)
5.	EGGVP – European Group for Generic Veterinary Products

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2.	This is a well-designed document that certainly helps manufacturers to have their products easier developed and accepted by EMA. Relevant for horses are the products used for skin prick tests and those for de-sensitizing therapy.	Noted
3.	In Europe there is a legal obligation to use alternatives to animal tests if available (i.e. Directive 2010/63/EU) and to take the principles of the 3Rs into consideration. Cruelty Free International therefore encourages the EMA to reference legislation relating to the protection of animals used for scientific purposes, and to clearly define the principles of the 3Rs in this revised guideline, and all future guidelines, so as to further encourage their implementation. This is in line with the EMA's ongoing commitment to support the implementation of the 3Rs principles: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001916.jsp&mid=WC0b01ac0580d52a5e.	Agree and to be included (in legal basis-point 3)
4.	Although there is limited information about the allergenic profile of these animals (horses, dogs and cats), some studies show a different pattern of recognition to specific allergens across species. In this sense, Specific Immunotherapy (SIT) can improve the efficacy of the vaccines through direct patient targeting.	To be taken into consideration in the text. This will be assessed on a case by case basis. Safety and Efficacy should be adequately demonstrated.

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	Furthermore, since allergic animals in these species are usually polysensitised (sensitised to a high number of different allergens), SIT combining several allergenic sources in each treatment is indeed needed, leading to hundreds of different vaccine formulations. However, given that safety and efficacy field studies conducted with each individual allergenic extract is not a feasible alternative (due to the difficulties to enrol the necessary population to implement them), use of clinical data support based on bibliography and on daily use data (Real Word Data) to demonstrate product safety and efficacy should be considered acceptable.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
52	1.	Comments: Treatment for Specific Immunotherapy There is no definition given for SIT Proposed change (if any): Include a definition line 664	The acronym is defined in the executive summary. There is no specific proposal made (and no specific definition found in human guidelines) See proposal in page 11 of these comments and in the section Definitions.
102-107	1.	Comments: The scope define that all listed products are industrially prepared following method 2001/82. Add a precision of the out of scope. Proposed change (if any): After "It applies to all allergen products and their intermediates prepared industrially by a method involving an industrial process as defined by Directive 2001/82/EC", add the following It does not apply to allergens products specially prepared for an animal from a prescription by a veterinarian (ie not prepared industrially).	Partially accepted. As indicated in the revised sentence, and in line with the Regulation EU 2019/6: It applies to all allergen products and their intermediates prepared industrially by a method involving an industrial process as said in article 2(1) of Regulation (EU) 2019/6 of the European Parliament and of the Council. But about the addition of the new proposed text, there is no need for further explanations (see also comments about proposals of definitions)
118-119 Section 3. Legal basis, page 4	3.	Comments: Reference to Directive 2010/63/EU on the protection of animals used for scientific purposes should be included in the 'legal basis' section. Proposed change (if any):	Accepted

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		Add the following document to the list: **Directive 2010/63/EU (regarding the protection of animals used for experimental and other scientific purposes).**	
134-135	1.	Comments: "The concept of homologous groups introduced in the guideline for human allergens MEA/CHMP/BWP/304831/2007 replaces the concept of taxonomic families." We understand the statement, but as in the state of the veterinary knowledge no homologous group is defined or definable according to the criteria except to make a homology by extrapolation of the human, can we say that the homologous groups are added to the notion of taxonomic family and replace them only if a group can be defined? In the absence of taxonomic family, the concept can be kept. Proposed change (if any):	**Not accepted** What is intended with this paragraph is a that the homologous group should be defined by the company based in the criteria indicated in the section 4.1. We are not looking for a direct "extrapolation" from human defined homologous groups. The companies could follow also the "taxonomic families" for each animal species (horse, dogs, cats) if they follow the criteria indicated : • Comparable physicochemical and biological properties of the source material; • Cross-reactivity (between the group)/structural homology of the allergens; • Identical formulation of the finished product; • Identical production process of the allergen extract and of the finished product.
156-158	5.	Comments: The idea of a homologue group is that the allergens within the group are essentially similar and that data can be extrapolated between allergens within a group based on data of the representative allergen. It is understood that the idea behind defining homologue groups is to reduce the number of safety and efficacy	**Not accepted** As the homologous groups will be defined by each company, this paragraph has been kept open, as a case by case decision, depending on the data/ bibliography sent to support these groupings

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		studies needed to be conducted and this is highly appreciated. However, it is also mentioned that post-marketing safety and efficacy data could be requested for non-representative allergens of the same homologous group which seems to be in contradiction with the previous text. Proposed change (if any):	It is also said in the text*: The choice of the relevant allergen components must be justified. If a significant part of the total allergenic activity or safety concerns arise from other (for example minor) allergens, these have to be studied as well.*
165	1.	Comments: What will be the processus to change the Annexes I & II ? Proposed change (if any):	Partly accepted. As other guidelines, the guideline will be revised when some experience are gained at EU level with these authorisations. Nevertheless when data and/or bibliography presented by the companies gives enough input to change these Annexes
166	1.	Comments: Need to add "Allergen mixtures" in Definitions 664 Proposed change (if any):	Accepted (but no specific proposal is given). See proposal in page 11 of the comments and in page 19 of the final guideline (Definitions).
304	1.	Comments: water or loss on drying? Proposed change (if any): Only for dehydrated forms (lyo).	Partially accepted: In line with Ph. Eur. monograph 1063 Water or loss of drying ("if applicable")
309	1.	Comments: Aluminium? when Calcium phosphate is used as absorbent Proposed change (if any):	Partially accepted. In line with Ph. Eur. monograph 1063 Aluminium: When aluminium hydroxide or aluminium phosphate is used as adsorbent Calcium: When calcium phosphate (is used as adsorbent)

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388 – 390 (Now 390-92)	4.	Comments: Due to the current number of allergens and the number of animal species involved, a different and justified approach should be accepted. Proposed change (if any): Reference standard materials should be established and characterised for all types of allergen products and for each target species. If not possible, a different and justified approach may be used.	**Not accepted** The text proposed now in the draft guideline is flexible enough. In Section 5.1.4. Characterisation and control of active substance, 5.1.4.1 Characterisation and control of allergen extracts: The content of relevant allergens should be measured by validated assays using certified reference standards or biological reference preparations and assays validated in international standardisation programmes **whenever possible.** In section 5.2: Standards and reference materials, we do not see this option "not to have reference materials", as is the basis for the standardisation of the manufacturing of the product. In addition, as indicated in the guideline (and monograph), there is also included the possibility to have in house reference preparations and sera pools. Moreover in the proposal there is no clear explanation of what kind of different approach could be proposed.
531-534 Section 5. Safety and efficacy testing, page 15	3.	"*Furthermore, GLP safety studies in unsensitised animals have little relevance for the safety profile of the SIT in the target group of sensitised animals in the interests of the 3Rs such studies should only be conducted if there are specific concerns related to the use of the SIT in non-allergic animals".* Comment and proposed change:	Accepted (see proposal in section 6 of the guideline).

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		The 3Rs are mentioned here without having been previously described or defined in the draft guideline. We therefore suggest that both the 3R principles and the obligations of Directive 2010/63/EU be clearly defined at the beginning of this section. The following text has been accepted into the final versions of several other recently published guidelines: **In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on the protection of animals used for scientific purposes), the 3R principles (replacement, reduction and refinement) should be applied.**	
582	1.	Comments: Loco-regional reactions are possible (e.g. enlargement of lymph nodes). Proposed change (if any): Add monitoring of loco-regional reactions.	Accepted, as an example. Not accepted to include as "loco-regional reactions" in line with general IVMP texts (only local and systemic reactions are included).
593	1.	Comments: Is it possible to clarify what does "immunological functions" refer to and what kind of warnings might be necessary. Proposed change (if any):	**Not accepted:** Please see Annex II of Regulation EU 2019/6 (COMMISSION DELEGATED REGULATION (EU) 2021/805: SECTION IIIb REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

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606	1.	Comments: Superiority or non-inferiority studies versus authorized products should be authorized whenever possible. Proposed change (if any):	**Not accepted.** Please see also other guidelines applicable to safety and efficacy studies with IVMP, as for example EMA/CVMP/IWP/260956/2021Guideline on clinical trials with immunological veterinary medicinal products and VICH GL-9 Good clinical practices (CVMP/VICH/595/1998)
645	1.	Comments: The most frequently prescribed immune-modulating agent in atopic dogs is oclacitinib. So, Janus kinase inhibitors should also be included in the list. Proposed change (if any):	Accepted.
656-658	1.	Comments: It is not clear how the demonstration of specificity and sensitivity of in vivo tests can be done in absence of gold standard (reference tests with known performances). Proposed change (if any): The use of surrogate tests could be suggested if appropriately justified.	**Not accepted.** Is difficult to understand the proposal of "surrogates tests" without examples, but it seems that what is suggested here is to use for example in vitro tests "as IgE measurement in sera" as surrogates. There is enough flexibility already included in the guideline. In section 6.3 of the guideline, it is stated that '*Taking into account the different formulation and in general different administration routes between therapy and "in vivo" diagnosis products, safety and efficacy studies already performed for SIT allergens from the same manufacturer could be appropriate to demonstrate safety and could be supportive for the efficacy of the same allergens used for in vivo diagnosis (skin test allergen).'*

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			And in section 6.2 Efficacy studies with veterinary allergen products for immunotherapy: '*Further surrogate parameters for efficacy might be acceptable if a correlation can be demonstrated between the specific parameters and protection induced by the treatment. A follow up of these surrogate parameters might be considered sufficient to substantiate the efficacy claim.'*
664	1.	Comments: Include new definitions for the following: - SIT :Specific Immuno Therapy - Allergen prepared industrially and an allergen prepared for a single animal. - Allergen mixtures Proposed change (if any):	**Partly accepted: new definitions** Even if no specific proposals are made, and no specific definitions are included in EMA human guidelines /Ph. Eur. texts , the following could be included: <u>Allergen/Specific Immuno Therapy (AIT/SIT):</u> Is an allergen/ specific treatment of allergic diseases in animals, reducing the degree of sensitization using allergen extracts. <u>Allergen mixtures:</u> Mixtures of allergen extracts. These should be prepared from individual extracts from single source materials. **Not accepted to include the next definitions**: <u>Allergen industrially prepared:</u> It is already indicated in the Scope of the guideline that this guidelines apply to :Allergen products and their intermediates prepared industrially or by a method involving

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			an industrial process and intended to be placed on the market; as defined by Regulation (EU) 2019/6-and already in Directive 2001/82/EC; therefore, there is no need to indicate this again in the guideline. About veterinary prescriptions for individual animals or allergens for a single animal (similar to human "NPPs") for veterinary use, we want to indicate that the regulatory framework for rare allergens in humans (NPPs) is currently under revision. The present guideline should focus on the most common allergens in horses, dogs and cats, and these products should fulfil minimum quality standards in order to generate evidence for their efficacy and to ensure their safety.