18 October 2024
EMA/CVMP/IWP/53315/2024
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on Guideline on safety and efficacy data requirements for applications immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6 (EMA/CVMP/IWP/224724/2022)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope
2	Access VetMed
3	Cruelty Free Europe

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on this draft guideline and seeks clarity on the hierarchy of expected level of requirements for IVMPs, being our understanding that the minimum requirements should be those for IVMPs intended for limited markets (art. 4[29]) meeting article 23, followed by this guideline (IVMPs intended for limited markets (art. 4[29]) but not meeting Art. 23, and never losing the flexibility already built in Annex II to RE 2019/06 and/or European Pharmacopoeia monographs, which should remain. Conflicting recommendations have been highlighted through the individual comments, as it would not seem logical that a guideline intended to create further flexibility would be more restrictive than already existing legislation or guidance applicable to a broader range of IVMPs.	Noted and updated where necessary.
1	Moreover, as the requirement reduction proposals in the current proposal are so nuanced compared to Annex II or to the 'article-23' requirement reduction guideline, that this new proposed guideline cannot really help for shaping a pre-clinical and clinical development plan, leaving Applicants with two possibilities: fully follow Annex II or submitting a scientific advice, which by itself is a rather complex procedure. The requirements/flexibilities coming from already existing texts should be either entered in a dedicated column or removed, in order to better understand where the flexibility lies for limited markets. It would be welcome to follow the same format as that proposed in Table 1 of the Quality guideline (for biologicals meeting limited markets but not meeting article 23), with a dedicated column on the possible	The table was updated considering the comment.

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	reduction (see also next comment). This table's division into "Data requirements" and "Comments on possible reduction" is clearer and more understandable.	
1	The title of Table 1 "Possible flexibility concerning safety and efficacy data requirements for IVMPs in Annex II" should be updated as: • It includes specific comments for limited markets (and not for all IVMPs) • It includes requirements and flexibilities from Annex II but also from general chapters of Pharmacopeia or EMA guidelines, and it includes specific comments for limited markets A reminder that the process for request of limited market classification and confirmation of eligibility for a MA for limited market (art.23) is common and described on EMA website should be included in this guideline. Although this scientific guideline does not address procedure points, it is to note that the absence of fee incentives for products under limited markets, but not eligible to Art.23 (including for scientific advice request) is considered as a limiting factor and contradictory with the aim of enhancing availability of veterinary medicinal products, including for limited markets.	The title of Table 1 was amended. A reminder was added. Noted, but fees are not in the scope of this guideline.
2	Access VetMed welcomes the CVMP initiative to establish guidance on how Annex II flexibility could be applied to VMPs intended for limited markets but not eligible for authorisation under Art 23, so that certain studies can be omitted. It is hoped this will have a critical and positive effect on the availability of new MAs and also on existing MAs for use in minor species or for uncommon conditions that were before eligible for MUMS/Limited market classification. Time will be needed for MAHs to implement this new guideline; possibly further comments may pop up once experience is gained.	Noted.

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	Our main comment is that the document provides general guidance and further details and comments in the table would be welcome. As the text reads now, clarity to applicants is expected to be provided via Scientific Advice to a greatest extent.	
3	Cruelty Free Europe welcomes the publication of this new guideline, which introduces clearer guidance on the circumstances under which the data requirements for limited market veterinary products can be reduced. However, the guideline does not explicitly state that reduced data requirements also come with the added benefit of reducing animal testing. In Europe there is a legal obligation to use alternatives to animal tests if available (i.e. Directive 2010/63) and to take the principles of the 3Rs into consideration – both of which should be clearly mentioned in the guideline (as they are in a similar separate draft guideline on 'safety and residue requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/16'). We urge the CVMP to reference legislation relating to the protection of animals used for scientific purposes, and to incorporate the principles of the 3Rs into the revised guideline where appropriate in the interests of animal welfare. This is in line with the goals set out in the EMA's published strategic reflection (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf).	Noted and considered.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
37-39	1	**Comment:** The described aim of the guideline is IVMPs classified as limited markets in line with Article 4(29) which is more general than the title and scope which is limited to IVMPs intended for limited markets but not eligible for Art. 23. The described aim of the guideline should therefore be clarified and aligned with the title and scope and never result in more stringent requirements than those in Annex II to RE 2019/06 or European Pharmacopoeia monographs. See also **general comment**. **Proposed change:** The general aim of this guidance is to define acceptable data requirements for the demonstration of safety and efficacy of immunological veterinary medicinal products (IVMPs) classified as limited markets in line with Article 4(29) of Regulation (EU) 2019/6**, but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6.**	The purpose of the guideline has been clarified. No change to the title of the guideline is considered necessary. The proposed change in the text is accepted.
Introduction 51-57	1	**Comment:** The scope and applicability of the guideline should be better explained to avoid any confusion, as it was done in the concept paper on scientific guidelines for limited market products deemed not eligible for authorisation under Article 23 of Regulation 2019/6 (EMA/CVMP/435071/2021). **Proposed change:** "Article 23 of the Regulation states that comprehensive safety or efficacy documentation, as defined in Annex II of the Regulation, shall not be required for limited markets applications, provided that the two conditions contained in that same provision are met. **Guidance on the safety and efficacy requirements for limited market products deemed eligible for consideration under Article 23 does exist (Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - 58 (EMA/CVMP/59531/2020)).**	Partially Accepted. The last sentence of the proposed text was not included (too detailed).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		However, not all products that satisfy criteria to be classified as 'intended for a limited market' are automatically eligible for consideration under Article 23. Additionally, an applicant is required to show that the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided (Article 23(1)(a)). Products meeting the 'limited market' definition in Article 4(29) of the Regulation but not meeting the conditions for limited markets application listed in Article 23 will require, by default, a comprehensive set of safety and efficacy documentation in accordance with the requirements in Annex II of the Regulation."	
54-55	1	**Comment:** No comprehensive safety and efficacy 'data package' needs to be submitted when **both** conditions **1a** and **1b** of Article 23 are met. **Proposed change:** Products meeting the 'limited market' definition in Article 4(29) of the Regulation but not meeting **all** the conditions for limited markets application listed in Article 23 will require, by default, a comprehensive set of safety and efficacy documentation in accordance with the requirements in Annex II of the Regulation.	Accepted.
58-59	1	**Comment:** The described aim of the guideline is IVMPs classified as limited markets in line with Article 4(29) which is more general than the title and scope which is limited to IVMPs intended for limited markets but not eligible for Art. 23. The described aim of the guideline should therefore be clarified and aligned with the title and scope and never result in more stringent requirements than those in Annex II to RE 2019/06 or European Pharmacopoeia monographs. See also **general comment**. **Proposed change:** There is a practical need for specific scientific guidance describing how the general data requirements in Annex II can be adapted to products that meet the definition of limited market in Article 4(29), **but not**	The purpose of the guideline has been clarified. No change to the title of the guideline is considered necessary. The proposed change in the text is accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		eligible for authorisation under Article 23 of Regulation (EU) 2019/6, due to the characteristics of these products.	
65-67	1	**Comment:** The purpose described in line 65-67 focus on products that meet the definition of limited market in Article 4(29) due to the characteristics of these products. This is more general than the title and scope (line 71-73) which is limited to IVMPs intended for limited markets but not eligible for Art. 23. We suggest clarifying and align the purpose with the title and scope and never result in more stringent requirements than those in Annex II to RE 2019/06 or European Pharmacopoeia monographs. See also **general comment**. **Proposed change:** The purpose of this scientific guidance is to indicate how the general flexibilities **around the requirements** provided within Annex II can be applied to **immunological** veterinary medicinal products defined as limited market by Article 4(29) of the Regulation **but not eligible for authorisation under Article 23 of the Regulation,** due to the characteristics of these products.	Partially Accepted. The text has been amended as follows: '*The purpose of this scientific guidance is to indicate how the general requirements provided within Annex II can be applied with flexibility to immunological veterinary medicinal products defined as limited market by Article 4(29) of the Regulation but not eligible for authorisation under Article 23 of the Regulation, due to the characteristics of these products.*'
2. Scope Lines 64-73	3	Comment: In the 'Scope' section of the guideline it would be beneficial to note that the guideline also has a 3Rs benefit in offering reduced data requirements for limited market veterinary products. Proposed change: Add the following text to the end of this section. **"This guideline also presents several opportunities to waive animal testing requirements for veterinary products intended for limited markets, which is in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Directive 2010/63/EU on protection of animals used for scientific purposes, and the 3R**	Not accepted. A reference to compliance with 3Rs principles has already been included in section 3, last paragraph.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		principles (replacement, reduction and refinement), and which should be applied to all testing involving animals".	
3. Legal basis 74-83	3	Comment: Reference to Directive 2010/63/EC should be included in the 'Legal basis' section of the guideline. Proposed change: Add the following test to the end of the Legal basis section (this is similar to the language that was used in previously adopted MUMS/limited market guidelines): **"Directive 2010/63/EU on the protection of animals used for scientific purposes should also be considered in relation to the conduct of all testing involving animals".**	In general, accepted. The following text has been included: In accordance with Annex II of Regulation (EU) 2019/6, all experiments on animals should be conducted taking into account the 3Rs principles (replacement, reduction and refinement) as laid down in Directive 2010/63/EU on protection of animals used for scientific purposes.
75-76	1	**Comment:** Article 4(29) should also be specified in line 75-75. **Proposed change:** This guideline should be read in conjunction with Regulation (EU) 2019/6, in particular **Article 4(29),** Article 8, Article 23 and Annex II.	Accepted.
80-82	1	**Comment:** The described aim of the guideline is more general than the title and scope. The text in line 80-82 should be aligned with the title and scope and never result in more stringent requirements than those in Annex II to RE 2019/06 or European Pharmacopoeia monographs. See also **general comment**. **Proposed change:** This guidance aims to highlight where such general flexibility exists and how this flexibility may be applied to marketing authorisation applications for **immunological** veterinary medicinal products intended for limited markets **but not eligible for authorisation under Article 23 of the Regulation,** where scientifically justified.	It is not agreed that the aim of the guideline is more general than the title and scope. The change in the wording is accepted.
101	1	**Comment:** It should be considered to include the information in line 101 in the scope of the guideline.	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: please add "**For IVMPs containing a GMO, this guideline is only applicable for efficacy requirements**" in section 2 "scope".	
106-108	1	**Comment:** It should be specified that the flexibilities described in Table 1 are applicable to products not eligible for authorisation under Article 23 and never result in more stringent requirements than those in Annex II to RE 2019/06 or European Pharmacopoeia monographs. See also **general comment**. **Proposed change:** In Table 1, possible flexibilities concerning safety and efficacy data requirements as described in Annex II are highlighted and commented how this flexibility may be applied to marketing authorisation applications for **immunological** veterinary medicinal products intended for limited markets **but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6.**	Accepted.
125-126	1	**Comment:** Please align wording with Annex II of RE 2019/06. IIIb.3.A. (6). IIIb.4.A. (1) (a). **Proposed change:** ~~Safety and efficacy studies shall be in line with the general and, where applicable, specific Ph. Eur. requirements. Deviations shall be justified.~~ **The efficacy studies shall be in line with the general European Pharmacopeia requirements. Deviations shall be justified. The safety studies shall be in line with the relevant European Pharmacopeia requirements. Deviations shall be justified.**	Partially accepted. Text slightly reworded: Safety and efficacy studies shall be in line with the Ph. Eur. requirements. Deviations shall be justified.
127-130	1	**Comment:** The following flexibility could be added from paragraph IIIb.4.a: **Proposed change:** Appropriate parameters for the evaluation of efficacy should be established. The applicant should test for treatment differences using appropriate statistical methodology. It should be possible in all cases to demonstrate a benefit of treatment. The practical limitations of data collection for a limited market product will be taken into consideration.	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		In general, pre-clinical studies shall be supported by trials carried out in field conditions. When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required.	
145-154	1	**Comment:** References 4 and 5 cover non-immunological veterinary medicinal products and are not relevant for this guideline. **Proposed change:** Please delete references in lines 145-154.	Accepted.
191- 200	1	**Comment:** These definitions can be removed as already entered in the definitions above (164-174).	Accepted.
Table 1 section 3.A/4.A	1	**Comment:** It is unclear why the No. of section mentions 3.A/4.A while the comments seem only related to the general requirements of the safety part, as there is also a section later about 4A repeating this information. It is confusing when reading the table. **Proposed:** 3.A~~/4.A~~	Accepted.
Table 1, 3A/4A General requirements, footnote 1	1	**Comment:** General texts state; The use of pilot scale/R&D batches that are representative for the manufacturing process described in the marketing authorisation application is possible. The footnote should be adjusted according to the wording in the general text which is considered more appropriate. **Proposed change:** Pilot batch: small scale industrial batch, ~~but in full compliance with~~ **representative of** the production process described in the licensing dossier. R&D batch: batch produced under laboratory conditions but ~~in full compliance~~ **representative of** the production process described in the licensing dossier	Accepted.
3.A General requirements	1	**Comment:** Clarification is needed on the passage level requirement: Is passage level requirement from EP 5.2.6 lifted for live IVMPs (Limited markets not meeting Art.23)?	The text has been removed.
Table 1 section 3.B.2.	1	**Comment:** The text come from Annex II, whatever the product status (even if not eligible for limited market). The additional comment "Possible data reduction concerning used routes of administration" should be clarified.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Table 1 section 3.B.4.	1	**Comment:** It is not clear what are the additional flexibilities for this section 3.B.4. According to Ph. Eur. 5.2.6. : "If the reproductive safety studies are not performed, an exclusion statement appears on the label, **unless a scientific justification for absence of risk is provided**.". Ph 5.2.6 allows for more flexibility than the last sentence included in the Table. The interest of this last sentence and impact on flexibility is unclear and seems even to erase the flexibility allowed by the general requirement of the Ph. Eur. **Proposed**: **If no studies performed or scientific justification for absence of risk on reproductive performance provided, it needs to be clearly stated in the product information."**	Acceptable. The proposal has been slightly re-worded. "If such studies are not performed relevant warnings should be given in the product information, unless a scientific justification for absence of risk is provided.
Table 1 section 3.B.5.	1	**Comment:** The last sentence: "If it is usually unlikely for classical IVMP to affect the immune system, studies are normally not required." does not come from Annex II. It is unclear what is a classical IVMP or scientific background for such positioning. In addition, it doesn't bring an additional flexibility compared to Annex II unless it is more clearly defined what is a classical IVMP and on which scientifically ground this sentence is based. If necessary, relevant warnings should be given in the SPC." does not bring any added flexibility. **Proposed:** ~~"If it is usually unlikely for classical IVMP to affect the immune system, studies are normally not required. If necessary, relevant warnings should be given in the SPC."~~**For inactivated vaccines data reduction should be applied. For live vaccines where the pathogen is known to be immunosuppressive, a study should be conducted, if live pathogen but not known to be immunosuppressive there is no need for study and this should not be reflected on the SPC.**	Accepted. The text proposal has been slightly re-worded and re-organised: "For inactivated vaccines, studies for the examination of immunological functions may be omitted. If necessary, relevant warnings should be given in the product information. For live vaccines where the pathogen is known to be immunosuppressive, a study should be conducted; based on the results of the study, relevant warnings should be given in the product information. If a live pathogen is not known to be immunosuppressive there is no need for study, and this must not be reflected in the product information."

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Table 1 section 4A Line 3	1	**Comment:** Clarification is needed on the passage level requirement: Is passage level requirement from 5.2.7 lifted for live IVMPs (Limited markets not meeting Art.23)? The sentence "The minimum titre should be adequately justified' is not understood. It doesn't seem to bring any additional flexibility to the requirements from regulation or Pharmacopeia but rather a constraint. It should also be in alignment with the section 3A Line 4. **Proposed:** Please add: "**According to Ph. Eur. 5.2.7, a batch or batches of vaccine containing virus/bacteria at the most attenuated passage level that will be present in a batch of vaccine, should be used. For live IVMPs / limited market, no passage requirement in Annex II (except for reversion to virulence test).**"	The text has been removed from the guideline.
Table 1 section 4A Line 4	1	**Comment:** The sentence "If studies for duration of immunity are omitted, it must be made clear in the SPC that the data are not available." should be worded the same way as in the guideline for limited markets under article 23, for the sake of clarity regarding the flexibility. **Proposed**: ~~If studies for duration of immunity are omitted, it must be made clear in the SPC that the data are not available.~~ **Omission of studies such as duration of immunity is acceptable, provided that it is made clear in the SPC that the data are not available.**	Accepted. The text has been moved to section 4.B.
Table 1 section 4A Line 5	1	**Comment:** The sentence 'If such studies are omitted, it must be made clear in the SPC that the data are not available.' should be worded the same way as in the guideline for limited markets under article 23, for the sake of clarity regarding the flexibility. **Proposed**: ~~If such studies are omitted, it must be made clear in the SPC that the data are not available.~~ **Omission of studies such as effect of maternally derived antibodies (MDA), are acceptable, provided that it is made clear in the SPC that the data are not available, and it should be scientifically justified.**	Accepted. The text has been moved to section 4.B.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Table 1 section 4A	1	**Comment:** In parallel to the mention in Table 1 section 3.A Line 4, the possibility to combine safety and efficacy studies for inactivated IVMPs and therefore to use standard batches should be made. **Proposed**: **Efficacy studies for inactivated IVMPs may be combined with safety studies, and therefore, standard batches may be used with no requirements to demonstrate the efficacy with batches with batches formulated with minimum antigen content.**	Accepted.
Annex 1 Section 4.B	2	Comment: It is not clear what is the marked flexibility for live vaccines, since from the text it seems that the batch with the minimum titre should still be used.	Agreed. The text has been deleted.