EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2024
EMA/CVMP/SWP/46749/2024
Committee for Veterinary Medicinal Products

Overview of comments received on Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6 (EMA/CVMP/SWP/32027/2022)

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

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

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	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).	Cruelty Free Europe is thanked for the comments. It is noted that, the primary purpose of the limited market guidelines is to improve availability, not to address 3Rs. However, the CVMP indeed supports the 3Rs principles and acknowledges that these principles should be always considered in the interest of animal welfare. Therefore, a new sentence on this regard has been added in the Legal basis section: *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) laid down in Directive 2010/63/EU on protection of animals used for scientific purposes.* Reference to Regulation 2019/6 is made because it cross-refers to Directive 2010/63/EU. 3Rs reference documents have been also included in the References section.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
113-114	1	Comments: Currently, there are no mechanisms for MAHs to check if the MRL-related data is protected or not.	The comments from Access VetMed are appreciated. Article 40(4) of Regulation 2019/6 states that: *Where an applicant for a marketing authorisation for a veterinary medicinal product or for a variation to the terms of a marketing authorisation submits an application in accordance with Regulation (EC) No 470/2009 for the establishment of a maximum residue limit, together with safety and residues tests and pre-clinical studies and clinical trials during the application procedure, other applicants shall not refer to results of those tests, studies and trials for a period of five years from the granting of the marketing authorisation for which they were carried out.* It is acknowledged that there is not a direct mechanism for MAH to confirm if the MRL data are protected. In this context, we refer to the Guidance to Applicants - Veterinary Medicinal Products (C/2024/1443), in particular the section on 'Responsibility of applicants and role of competent authorities'.
121-122	1	Comments: It would be useful to have more specific guidance about the requirements of using scientific literature to support the dossier. In this way, the number of SA would be reduced.	Not accepted. In Annex II, section II.3(2) of Commission Regulation (EU) 2019/6 further information on the use of bibliographical references is given: *Published studies may be accepted if they contain a sufficient amount of data and sufficient details to allow an independent assessment. The experimental techniques shall be described*

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			in such detail as to allow them to be reproduced, and the investigator shall establish their validity. Summaries of studies for which detailed reports are not available shall not be accepted as valid documentation. When the substance has been previously evaluated for the establishment of maximum residues limit ("MRL") to address certain safety requirements reference may be made to the European public MRL assessment reports ("EPMARs"). Where reference to EPMAR is made there is no need to submit studies already evaluated as part of the MRL evaluation; only new studies not available for the MRL assessment shall be provided. If the route of exposure (for example, for the user) is not identical to the route used in accordance with Commission Regulation (EU) 2018/782 (5), new studies might be necessary. In general, a bibliographic reference is considered of high reliability when it has been published in a source of renowned prestige and the methodology and description of the study are in accordance with the corresponding guidelines. It is recognised that, scientific literature do not always satisfy the required criteria but may provide nonetheless valuable information. Therefore, the assessment of the validity of the scientific literature to support the dossier is made on a case-by-case basis. However, as stated in the regulation, the applicant should ensure that, the references provided allow the derivation of the relevant toxicological endpoints.
171-173	1	Comments:	Accepted.

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		It is not entirely clear what the CVMP wants to say in this paragraph. Is this still referring to local effects or toxicological effects in general? Is CVMP referring to anticipated exposure levels in animals or users? It is not clear when the scenario "If such information is not available, ..." would apply. Proposed change: Suggest rewording for clarification	The section has been reworded for clarification.
174-178	1	Comments: Data from human use of, for instance, an active ingredient (e.g. therapeutic human doses and human use safety profile) also provides relevant information for a user safety assessment. Proposed change: To be included in this section.	Partly accepted. It is acknowledged that data from human use and adverse effects may provide additional information on tolerable intake levels that may be useful to complete the user safety assessment. Indeed, according to the User Safety Guideline (EMEA/CVMP/543/03), '*if the active substance has been used in human medicines, then any available data including company data as well as published data, relating to observations in humans and adverse reaction data should be available and submitted in the dossier*.' However, it is noted that the therapeutic human doses cannot be considered as relevant toxicological reference values to assess the user safety of a veterinary medicinal product because they are subject to a benefit/risk assessment where some levels of risk can be accepted due to the benefit for an individual patient. Regarding safety data sheets of the product, the data included in those documents are a compilation made by the applicant and have not undergone any scientific assessment by a competent authority. Therefore, these values cannot be considered reliable TRVs. A new sentence on this has been added in this section

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181	1	Comment: The reference "IPCS/WHO, 2005" is not quoted in section "References" Proposed change: Reference to be added in "references" section	Accepted.
259	1	Comment: The reference "EMA/CVMP/016/2000" is not quoted in section "References" Proposed change: Reference to be added in "references" section	Accepted.
2. Scope Lines 79-101	2	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 principles (replacement, reduction and refinement), and which should be applied to all testing involving animals".*	. Not accepted. The primary purpose of the limited market guidelines is to improve availability, not to address 3Rs. However, the guideline mentions the need to comply with Directive 2010/63/EC and with 3Rs principles: *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) laid down in Directive 2010/63/EU on protection of animals used for scientific purposes.* Reference to Regulation 2019/6 is made because it cross-refers to Directive 2010/63/EU. 3Rs reference documents have been also included in the References section.
3. Legal basis 102-106	2	Comment: Reference to Directive 2010/63/EC should be included in the 'Legal basis' section of the guideline. Proposed change:	Partly accepted. Specific reference to Directive 2010/63/EU has been included in the 'Legal basis' section but the proposed wording has been slightly amended as follows:

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		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 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) laid down in Directive 2010/63/EU on protection of animals used for scientific purposes.* Reference to Regulation 2019/6 is made because it cross-refers to Directive 2010/63/EU.
4.1.1. Pharmacological data Lines 128-130	2	"Pharmacological studies conducted in experimental animals and target species, or reliable bibliographic data adequately describing the mechanism of action and the fate of the active substance and its metabolites must be included". Comment: the use of existing data should be prioritised over tests on animals. Proposed change: ~~Pharmacological studies conducted in experimental animals and target species, or~~ *R*eliable bibliographic data adequately describing the mechanism of action and the fate of the active substance and its metabolites must be included*. When there is no bibliographic data available, pharmacological studies conducted in experimental animals and target species should be included.*	Partly accepted. The proposal of prioritising existing data over tests on animals is appreciated. However, the following wording is considered more appropriate: *Reliable bibliographic data adequately describing the mechanism of action and the fate of the active substance and its metabolites must be included. When there is no bibliographic data available or, these data do not contain a sufficient amount of data and details to allow an independent assessment (Annex II, section II.3(2) of Commission Regulation (EU) 2019/6) pharmacological studies conducted in experimental animals and target species should be included.*