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Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the development of a guideline on consumer safety of active substances of immunological veterinary medicinal products acting against endogenous targets

Draft agreed by CVMP Safety Working Party	March 2025
Adopted by CVMP for release for consultation	15 May 2025
Start of public consultation	23 May 2025
End of consultation (deadline for comments)	31 August 2025

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	Consumer safety, immunologicals, endogenous targets

1. Introduction

This concept paper addresses the need for a guideline on evaluation of consumer safety of biological active substances of immunological veterinary medicinal products (IVMPs) intended to produce active immunity, e.g. antibodies against endogenous targets, e.g., cytokines, in food-producing species. Similar endogenous targets may be present in the body of the consumer, and these could be targeted upon ingestion of foodstuff from treated animals containing residues of the active substance of the IVMP or its effectors (e.g. antibodies). Although the risk to the consumer is likely to be very low, it needs to be considered as part of the safety evaluation.

The statement in Article 1(2)(a) of Regulation (EC) No 470/2009 exempting certain active substances of biological origin from the requirement of MRL '*active principles of biological origin intended to produce active or passive immunity or to diagnose a state of immunity, used in immunological VMPs*' includes substances targeting endogenous targets. Immunologically active substances inducing immunity against endogenous targets are thus legally exempted from MRL considerations. Therefore,

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they are not covered by the Commission Regulation (EU) 2018/782 establishing methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009, nor the guideline on determination of the need for an MRL evaluation for chemical-unlike biological active substances. Both refer to Article 1(2)(a) of Regulation (EC) No 470/2009 and clarify that they apply to 'biological substances other than immunologicals'. The evaluation of consumer safety of IVMPs with active substances acting against endogenous targets is thus addressed during marketing authorisation application (MAA) of the IVMPs.

Annex II of Regulation (EU) 2019/6 (IIIb.3A.(1)(b), IIIb.3F) allows for adequate assessment of consumer safety for IVMPs as part of MAA but does not provide any specific requirements regarding the documentation needed and there is currently no guidance elsewhere on this matter. Further guidance on the evaluation of consumer safety of IVMPs with active substances acting against endogenous targets are therefore considered necessary. This concept paper describes and discusses the basis for this new guidance.

2. Problem statement

Based on a scientific approach agreed by SWP-V, NTWP and CVMP, the consumer safety of active substances of IVMPs acting against endogenous targets needs to be carefully evaluated as the targets for the antibodies produced may be present in the body of the consumer.

Monoclonal antibodies (mAbs) against endogenous target have been classified as 'biologicals other than immunologicals' and are therefore covered by the scope of the guideline on determination of the need for an MRL evaluation for chemical-unlike biological substances ('chemical-unlike biological non-immunological substances') in line with Regulations (EU) 2018/782 and (EC) No 470/2009.

Active substances of IVMPs acting against endogenous targets are however, legally exempted from the requirement of MRL (Article 1(2)(a) of Regulation (EC) No 470/2009). They are therefore not covered by the scope of Regulation (EU) 2018/782 (Sections I.6 and 1.7 of Annex I; biological substances other than immunologicals); or the guideline on determination of the need for an MRL evaluation for chemical-unlike biological substances ('chemical-unlike biological non-immunological substances'). Consequently, the consumer safety of active substances of IVMPs acting against endogenous targets is not evaluated in the context of MRL applications but in the context of MAA of the IVMPs. This reconciles the scientific and legal sides and is consistent with what has been done earlier for IVMPs.

According to Section IIIb of Annex II to Regulation (EU) 2019/6 on requirements in MAA for IVMPs, the safety documentation shall be adequate for the assessment of the potential harmful effects to man of residues of the IVMP or substance in foodstuffs obtained from treated animals (IIIb.3A.(1)(b)). Further consideration is provided on study of residues (IIIb.3F.(1)) and withdrawal period (IIIb.3F.(4)). However, Annex II does not define specific requirements for active substances of IVMPs acting against endogenous targets. The guidance to be developed intends to clarify the scientific expectations regarding the documentation needed and to identify the appropriate approach for the assessment of consumer safety of the active substances of IVMPs acting against endogenous targets to be udertaken in the context of MAA.

3. Discussion (on the problem statement)

The guidance to be developed intends to focus on the following items:

- A definition of active substances of IVMPs acting against endogenous targets and examples of such substances will be provided. In the target animal, these biological active substances are intended

to act against an endogenous target by the production of antibodies neutralising the endogenous target.

- For consumer safety, the active substance in the IVMP administered to the animal, the antibodies produced by the animal, and the potential effects on the consumer upon consumption of foodstuff containing residues of them should be evaluated.
- Identification of the information that would be required to conclude on consumer safety of IVMPs with active substances acting against endogenous targets. Studies of the IVMP will consider the effect of excipients and adjuvants on absorption and distribution of the active substance into tissues/other commodities (milk etc.).
- Identification of an adequate assessment procedure. It may be appropriate to develop guiding questions and criteria in terms of a decision tree, allowing applicants and assessors to identify the data needed to address consumer safety in a tiered risk-based approach. The requirements could be different depending on the active substance. These differences will be taken care of by the decision tree.

Technical guidance on the conduct of the studies recommended for assessment of the consumer safety of active substances of IVMPs acting against endogenous targets is not within the scope of this guideline. The need for such technical guidance may be identified based on the experience gained and lessons learnt from the implementation of this guideline and will be dealt with in follow-up guidance.

4. Recommendation

The Committee for Medicinal Products for Veterinary Use (CVMP) recommends that the Safety Working Party (SWP-V) in collaboration with the Immunological Working Party (IWP) and the Novel Therapies and Technologies Working Party (NTWP) drafts a guideline to address the problem above.

5. Proposed timetable

23 May 2025	Concept paper released for public consultation.
31 August 2025	End of consultation of the concept paper (deadline for comments).
September 2025 – 2Q 2026	Discussion of the draft guideline in SWP-V, IWP and NTWP.
3Q 2026	Draft guideline adopted by CVMP and released for 3-month consultation.
4Q 2026	End of consultation of the guideline (deadline for comments).
2Q 2027	Final guideline adopted by CVMP and published.

6. Resource requirements for preparation

The development of the new guideline will involve the SWP-V (including a drafting group composed of 3-4 SWP-V members), the IWP, the NTWP and the CVMP.

The SWP-V drafting group will meet virtually as required (e.g. 2-3 virtual meetings). Comments will be sought from IWP and NTWP. The guideline is foreseen to be discussed at 3 plenary meetings of the SWP-V.

7. Impact assessment (anticipated)

The guidance will clarify for applicants and for assessors the approach to assess consumer safety for immunological substances acting against endogenous targets during MAA of the IVMPs and what specific data are required in order to make that assessment. This approach will encourage predictable decisions.

8. Interested parties

Veterinary pharmaceutical industry, EU competent authorities, consultants.

References to literature, guidelines, etc.

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN

Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) 726/2004 of the European Parliament and of the Council https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0470

Commission Regulation (EU) 2018/782 of 22 May 2018 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0782&from=EN

Guideline on determination of the need for MRL evaluation for chemical-unlike biological substances

Guideline on determination of the need for an MRL evaluation for biological substances (europa.eu)