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2 EMA/CVMP/SWP/564861/2023
3 Committee for Veterinary Medicinal Products (CVMP)

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

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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

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Keywords	Consumer safety, immunologicals, endogenous targets
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11 **1. Introduction**

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

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



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

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

37 **2. Problem statement**

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

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

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

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

62 **3. Discussion (on the problem statement)**

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

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

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

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

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

84 **4. Recommendation**

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

88 **5. Proposed timetable**

89	23 May 2025	Concept paper released for public consultation.
90	31 August 2025	End of consultation of the concept paper (deadline for comments).
91	September 2025 – 2Q 2026	Discussion of the draft guideline in SWP-V, IWP and NTWP.
92	3Q 2026	Draft guideline adopted by CVMP and released for 3-month
93		consultation.
94	4Q 2026	End of consultation of the guideline (deadline for comments).
95	2Q 2027	Final guideline adopted by CVMP and published.

96 **6. Resource requirements for preparation**

97 The development of the new guideline will involve the SWP-V (including a drafting group composed of
98 3-4 SWP-V members), the IWP, the NTWP and the CVMP.

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

102 **7. Impact assessment (anticipated)**

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

107 **8. Interested parties**

108 Veterinary pharmaceutical industry, EU competent authorities, consultants.

109 **References to literature, guidelines, etc.**

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

113 Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying
114 down Community procedures for the establishment of residue limits of pharmacologically active
115 substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and
116 amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC)
117 726/2004 of the European Parliament and of the Council [https://eur-lex.europa.eu/legal-](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0470)
118 [content/EN/TXT/PDF/?uri=CELEX:32009R0470](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0470)

119 Commission Regulation (EU) 2018/782 of 22 May 2018 establishing the methodological principles for
120 the risk assessment and risk management recommendations referred to in Regulation (EC) No
121 470/2009 <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0782&from=EN>

122 Guideline on determination of the need for MRL evaluation for chemical-unlike biological substances
123 [Guideline on determination of the need for an MRL evaluation for biological substances \(europa.eu\)](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0782&from=EN)