

1 22 July 2022

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- 2 EMA/CVMP/EWP/222080/2022
- 3 Committee for Veterinary Medicinal Products (CVMP)

# Concept paper on the revision of the guideline for veterinary medicinal products for zootechnical purposes

Initial concept paper agreed by the Efficacy Working Party (EWP-V) September 2016 Adopted by the Committee for Medicinal Products for Veterinary Use 8 December 2016 (CVMP) for release for consultation Start of public consultation 16 December 2016 End of consultation (deadline for comments) 31 March 2017 Revised concept paper agreed by the EWP-V June 2022 Adopted by the CVMP for release for consultation 14 July 2022 22 July 2022 Start of public consultation End of consultation (deadline for comments) 31 October 2022

The proposed guideline will replace the current "Guideline for veterinary medicinal products for zootechnical purposes" (NtA Volume 7, 7AE7a).

Comments should be provided using this  $\underline{\text{template}}$ . The completed comments form should be sent to  $\underline{\text{vet-guidelines@ema.europa.eu}}$ 

Keywords	veterinary medicinal products for zootechnical purposes, embryo transfer,
	oestrus synchronisation, fixed time artificial insemination, animal
	husbandry, farm animal management, reproduction management, animal
	welfare

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#### 1. Introduction

- 16 The current guideline for veterinary medicinal products for zootechnical purposes (7AE7a) was adopted
- in March 1992 and came into force in September 1992, and the CVMP already proposed in 2016 a
- 18 revision of the guideline. Comments received from stakeholders during this consultation supported a
- 19 revision.

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- 20 However, as work by the EWP-V on the topic had to be discontinued for an extended period, and in the
- 21 meantime new veterinary legislation (Regulation (EU) 2019/6) came into effect, further considerations
- 22 have been added to the scope of the revision. Therefore, a revised concept paper has been prepared
- 23 (resulting in a second publication). Comments received from the stakeholders on the previous concept
- paper have been taken into account when drafting the present concept paper.

### 2. Problem statement

- 26 The current guideline concerns the documentation to support the safety and efficacy of veterinary
- 27 medicinal products (VMPs) related to the reproductive system of healthy animals, focussing on food-
- 28 producing animals. Overall, the recommendations included in the existing guideline are still relevant.
- 29 Based on regulatory experience and current scientific knowledge it is, however, observed that the
- 30 recommendations are not sufficiently detailed regarding, e.g. requirements for the conduct of the
- 31 studies according to current quality standards (Good Clinical Practices/Good Laboratory Practices), the
- 32 number of pre-clinical studies and clinical trials and their study design and statistical evaluation; also,
- 33 legal references need to be amended to align with Regulation (EU) 2019/6.
- 34 Moreover, in 2015 the CVMP, through EWP-V, answered a question from the CMDv about the necessity
- 35 and acceptability of adding oestrus synchronisation protocols onto Summary of Product Characteristics
- 36 (SPCs) of cattle hormonal products. The discussion around this issue highlighted a need for
- 37 harmonised requirements for the addition of treatment protocols to product literature, including those
- 38 where different products are used sequentially.
- 39 Given that the guideline only addresses veterinary medicinal products that are related to the
- 40 reproductive system and are administered to healthy animals, particular attention should be given to
- 41 the justification that the target animal safety and animal welfare are not adversely affected by the use
- 42 of the product.

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- 43 The main focus in the current guideline is on veterinary medicinal products modifying the physiological
- 44 function of the reproductive system in farm animals. However, such VMPs are also increasingly used in
- 45 companion animals.
- 46 Furthermore, the guideline refers to "zootechnical" products but is restricted to indications affecting the
- 47 reproductive system only. It is therefore proposed to change the name of the guideline, e.g. to
- 48 "Guideline on data requirements for veterinary medicinal products used for non-pathological, non-
- 49 therapeutic indications related to the reproductive system".

# 3. Discussion (on the problem statement)

- The current guideline refers to "zootechnical" products as defined by Directive 96/22/EC, Art 1(2)(c),
- 52 i.e. the guideline is restricted to indications affecting the reproductive system only. As "zootechnical" is
- not defined in Regulation (EU) 2019/6, it is proposed to clarify the scope and to re-name the guideline
- 54 to e.g. "Guideline on data requirements for veterinary medicinal products used for non-pathological,
- 55 non-therapeutic indications related to the reproductive system".

- 56 The current guideline is focused on the use of VMPs in production animals; however, other species
- 57 (e.g. companion animals) should also be addressed. Consequently, the scope of the guideline should
- 58 be broadened.
- 59 The recommendations for pre-clinical studies addressing pharmacology should be further detailed,
- 60 including a reference to the Guidelines for the conduct of pharmacokinetic studies in target animal
- 61 species (EMEA/CVMP/133/99).
- 62 The minimum data necessary to obtain a claim should be further detailed, in terms of dose
- 63 determination, establishment of treatment regimen, and dose confirmation under laboratory and/or
- 64 field conditions.
- 65 Currently it is recommended to conduct pre-clinical efficacy studies according to GLP or GCP, as
- 66 appropriate (depending on the nature of the studies). If GLP or GCP are not applied, the traceability,
- 67 accuracy, integrity and correctness of data should be ensured, and the use of such data in pivotal
- 68 studies should be justified. For clinical trials, compliance with established principles of GCP is required,
- 69 unless otherwise justified. Statistical principles for clinical trials for veterinary medicinal products
- 70 should be followed (see guideline CVMP/EWP/81976/2010). The guideline should therefore be updated
- 71 with regard to current requirements on the conduct of pre-clinical studies and clinical trials.
- 72 The requirements in the current guideline to demonstrate target animal safety (TAS) are not detailed
- 73 enough, and more guidance should be provided for pre-clinical TAS studies and clinical trials on
- 74 suitable parameters and pharmacological end-points that have to be considered and reported to
- 75 confirm the clinical safety of the product according to species. The guideline text may also benefit from
- 76 clarification on the suitability of and requirements for parameters focussing on animal welfare or
- 77 pharmacological end-points to be considered when designing the pre-clinical studies and clinical trials.
- 78 The guideline should also be in alignment with current recommendation for 3Rs testing approaches.
- 79 Where the concerned VMP is used in combination with other pharmacologically active substances, the
- 80 CVMP considered in its answer to CMDv that hormonal protocols should be mentioned in section 3.9 of
- 81 the SPC ('Administration routes and dosage') and that they have to be supported by appropriate data,
- 82 e.g., peer reviewed literature or proprietary study data. Such recommendations could be included in
- 83 the revised guideline. The extent to which the efficacy of those protocols that are to be mentioned in
- 84 the SPC should be documented has to be specified in more detail and the possibilities of extrapolation
- 85 between different formulations and molecules of the same class should be addressed.

#### 4. Recommendation

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- 87 The CVMP recommends the revision of the existing guideline in order to provide clearer guidance and
- 88 to align the guideline with current scientific and regulatory requirements, as outlined above.

# 5. Proposed timetable

90	22 July 2022	Revised concept paper released for consultation
91	31 October 2022	Deadline for comments from interested parties
92 93	Q1-Q2 2023	Expected date for adoption of the draft revised guideline by CVMP for release for consultation $% \left( 1\right) =\left( 1\right) \left( 1\right) $
94	Q3-Q4 2023	Expected end of consultation on the draft revised guideline
95	Q4 2023-Q1 2024	Expected date for adoption by CVMP and publication of the revised guideline

## **6. Resource requirements for preparation**

- 97 Revision of the guideline will involve two EWP-V rapporteurs and two co-rapporteurs.
- 98 Preparation of the draft revised guideline will require discussion at two EWP-V plenary meetings.
- 99 Drafting group meetings (virtual) will be organised, as needed.

# 7. Impact assessment (anticipated)

- 101 The revision of the guideline is expected to improve the guidance for applicants as well as for
- 102 regulatory authorities. It is not intended to increase the requirements for marketing authorisation
- 103 applications for veterinary medicinal products.

## 8. Interested parties

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- Veterinary pharmaceutical industry and consultants;
- EU regulatory authorities involved in the assessment of marketing authorisation applications for veterinary medicinal products;
- Veterinary organisations and professional bodies;
- Scientific veterinary associations.

## 9. 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
- 113 Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation
- 114 (EU) 2019/6 of the European Parliament and of the Council
- 115 Guideline for Veterinary Medicinal Products for Zootechnical Purposes (NtA Volume 7, 7AE7a)
- 116 Council Directive 96/22/EC of 29 April 1996 concerning the prohibition on the use in stockfarming of
- certain substances having a hormonal or thyrostatic action and of beta-agonists, and repealing
- 118 Directives 81/602/EEC, 88/146/EEC and 88/299/EEC (see <u>link</u>)
- 119 CVMP guideline on statistical principles for clinical trials for veterinary medicinal products
- 120 (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)
- 121 Good Laboratory Practice (GLP) (see Directive 2004/9/EC and Directive 2004/10/EC)
- 122 VICH Topic GL9 (GCP): Guideline on Good Clinical Practices (CVMP/VICH/595/1998)
- Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement)
- testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)
- 125 Question and answer document on requirements for pre-clinical studies submitted in support of a
- marketing authorisation application for a veterinary medicinal product (EMA/CVMP/565615/2021)