EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for medicinal products for veterinary use (CVMP)

Concept paper on the revision of the CVMP Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/2007)

Adopted by CVMP for release for consultation	4 November 2021
Start of public consultation	12 November 2021
End of consultation (deadline for comments)	28 February 2022

The proposed guideline will replace the current "Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/2007)"

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

Keywords	**Veterinary medicinal products, Benefit-risk balance, CVMP**

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1. Introduction

The CVMP recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/2007) was drafted in 2006-2009 and included two rounds of public consultations with stakeholders, before it came into effect in November 2009. The document outlines the different scenarios (pre- and post-authorisation) and methodology when carrying out a benefit-risk balance evaluation for a veterinary medicinal product, including an annex with examples of structure and sentences that may be included in a benefit-risk balance.

2. Problem statement

As for any existing guidance, the CVMP recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/2007) will need to be reviewed at regular intervals, taking into account the scientific and regulatory updates. The current guidance also states this ("*It is envisaged that the CVMP will review the recommendation within a few years in light of experience gained*").

With the implementation of Regulation (EU) 2019/6[1], some aspects regarding the benefit-risk balance have changed, and CVMP agreed that the current guidance document (EMEA/CVMP/248499/2007) would need to be updated accordingly.

Over the years, additional CVMP documents have been developed that address particular aspects for the CVMP to take into account within the benefit risk balance evaluation, mainly in regard to particular product application types such as antimicrobials or antiparasitics, or veterinary medicinal products used in particular species[2].

3. Discussion (on the problem statement)

Possible topics to take into consideration for such a revision are:

- **References to legal requirements**

The current guidance makes explicit reference to sections in Directive 2001/82/EC and Regulation (EC) 726/2004, and to the appropriate wording thereof. Any legal reference needs to be thus reviewed and amended, as appropriate. This is in particular relevant in regard to the "Summary of the benefit-risk evaluation approaches in relation to the basis for marketing authorisation applications" referring to the articles in Directive 2001/82/EC (currently Annex III of the CVMP recommendation (EMEA/CVMP/248499/2007)).

- **Alignment with Regulation (EU) 2019/6**

Regulation (EU) 2019/6 defines the benefit-risk balance in Article 4(19) and includes additional or new aspects, which might require changes or additions to the current guidance. Some examples for these are listed below:

[1] 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.
[2] For example: Guideline on the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals (EMA/CVMP/AWP/706442/2013), reflection paper on anthelmintic resistance (CVMP/EWP/573536/2013); concept paper on the development of a guideline on the environmental risk assessment of veterinary medicinal products intended to be used in aquaculture (EMA/CVMP/ERA/173026/2021), concept paper on the environmental risk assessment for parasiticide veterinary medicinal products used in companion animals (EMA/CVMP/ERA/55512/2020).

a) The definition of benefit-risk balance has been revised under Regulation (EU) 2019/6 and as a result:

- includes risk of development of resistance as an additional risk relating to the use of the product, and
- removes the word 'therapeutic' with regard to 'effects of the veterinary medicinal product'. Instead of '***positive therapeutic effects*** *of the veterinary medicinal product'* as stated in the definition of benefit risk balance in Article 1(20) of Directive 2001/82/EC, Article 4(19) of Regulation (EU) 2019/6 refers to the '***positive effects*** *of the veterinary medicinal product'.*

The CVMP will explore the impact of these changes, taking into account the definition of a veterinary medicinal product as provided by Article 4(1) of Regulation (EU) 2019/6 and the criteria for refusing marketing authorisations provided by Article 37 of Regulation (EU) 2019/6.

b) Regulation (EU) 2019/6 introduced a number of specified "new" risks that should be considered, in particular the development of resistance (antimicrobial and antiparasitic), and the risk of PBT[3] substances as regards environmental safety. Whilst these risks already formed part of the assessment in the past, they are now specifically listed in the legislation. (Note: This *may* also affect generics, since Annex II formally requires generic applicants to provide information on resistance and, where relevant, an environmental risk assessment).

c) A new legal basis (Article 23) has been introduced for products for "limited markets", which affects the overall benefit-risk assessment, and the current guidance will need to be reviewed to ensure that this is in line with Regulation (EU) 2019/6.

d) A more precise legal basis (Article 25) has been defined for marketing authorisation applications in exceptional circumstances, which outlines specific considerations with respect to the benefit-risk evaluation.

e) Changes brought in by Regulation (EU) 2019/6 relating to pharmacovigilance.

- **Experience gained over the years**

Some sections in the current guidance might benefit from improvement, based on the experience gained over the years.

- **Alignment with other CVMP guidance documents**

CVMP has discussed several particular situations where a specific benefit-risk assessment would be applied, and specific guidance has been developed, which might need to be taken into consideration in the revision of the CVMP recommendation on the evaluation of the benefit-risk balance[4].

- **Quantitative versus qualitative assessment**

CVMP has also discussed on occasions whether or not the approach of the benefit-risk assessment should be reviewed, e.g. in regard to the use of a semi-quantitative assessment. (Note: currently, only a qualitative benefit-risk assessment is undertaken).

[3] Persistent, bioaccumulative and toxic, with reference to Article 37(2)(j) of Regulation (EU) 2019/6
[4] For example: Draft CVMP guideline - Assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals | European Medicines Agency (europa.eu)

- **Other aspects**

Other aspects, not covered by the above, or other emerging concepts might need to be taken into account (e.g. "big data", unmet medical need).

4. Recommendation

The Committee recommends revising the current "Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/2007)", taking into account the issues identified above.

5. Proposed timetable

Released for consultation:	November CVMP 2021
Deadline for comments:	28 February 2022
Discussion in the CVMP benefit-risk subgroup:	March 2022 – December 2022
Discussion at CVMP:	January 2023
Proposed date for release of draft guideline:	February 2023
Expected deadline for comments:	August 2023
Focus Group meeting with Interested parties –	*date(s) to be confirmed*
Re-discussion in CVMP benefit-risk subgroup –	*date(s) to be confirmed*
Expected date for adoption by Committee - –	*date(s) to be confirmed*

6. Resource requirements for preparation

The revision would need to create a small drafting group of 4-6 CVMP members, who would meet at least at monthly intervals (virtual meetings only).

Additional experts and/or a workshop/interested parties meeting is considered necessary.

7. Impact assessment (anticipated)

The existing guidance is routinely used by assessors when assessing initial marketing authorisation applications and more significant post-authorisation product developments or referrals.

It is also a reference for applicants for regulatory strategic planning purposes during product development.

The changes introduced within Regulation (EU) 2019/6, as described in section 3 above, require careful consideration to ensure an agreed clear and consistent implementation within the regulatory network.

Training of the assessors using/applying the revised guideline is expected to be required.

8. Interested parties

Assessors at national competent authorities, pharmaceutical industry/consultants

9. References to literature, guidelines, etc.

Regulation (EU) 2019/6