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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for the development of a reflection paper on criteria for the application of Article 40(5) of Regulation (EU) 2019/6

Agreed by CVMP Drafting Group on Article 40(5) of Regulation (EU) 2019/6	1 July 2020
Adopted by CVMP for release for consultation	16 July 2020
Start of public consultation	20 July 2020
End of consultation (deadline for comments)	21 September 2020

Comments should be provided using this template. The completed comments form should be sent to mailto:Vet-Guidelines@ema.europa.eu

Keywords	NVR Article 40(5)/40.5, data protection, variations, reduction antimicrobial resistance, reduction antiparasitic resistance, improvement benefit-risk balance

1. Introduction

Recital 36 of Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products('the Regulation') reasons that "*the protection of technical documentation should be applied to new veterinary medicinal products, as well as to data developed for supporting innovations of products with or referring to an existing marketing authorisation. In that case, the variation or marketing authorisation application may refer partly to data submitted in a former marketing authorisation or variation applications, and should include new data specifically developed to support the required innovation of the existing product*".

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Article 40(5) of the Regulation confers 4 years of data protection for variations involving a change to the pharmaceutical form, administration route or dosage assessed as having demonstrated:

a) a reduction in the antimicrobial or parasiticide resistance, or

b) an improvement of the benefit-risk balance of the veterinary medicinal product (VMP).

The data protection applies to the results of the pre-clinical studies or clinical trials provided in support of the variation.

The CVMP 2020 workplan foresees the development of scientific criteria to support the practical application of Article 40(5). This concept paper has been prepared with the aim to develop a reflection paper on the types of criteria that could be developed for the application of Article 40(5) via all routes of authorisation: centralised, decentralised, mutual recognition or nationally.

2. Problem statement

Article 40(5) gives the high-level criteria to be fulfilled to gain the 4-year period of protection for the (pre-)clinical data submitted in support of the variation. It is necessary to elaborate more detailed scientific criteria to ensure a clear interpretation and consistent implementation of the provisions.

The scope of Article 40(5) is broad and potentially covers all types of veterinary medicinal products, particularly with respect to improvement of the benefit-risk balance.

A balance is needed between defining criteria that are clear enough to enable consistent decision-making and establishing a framework that is too rigid in areas where there is not yet sufficient understanding, which would hold back innovation.

Whilst a definition exists for antimicrobial resistance under Article 4(10) of the Regulation, and although a definition of antiparasitic was introduced in Article 4(13) of the Regulation, antiparasitic resistance is not currently defined in the Regulation.

3. Discussion on the problem statement

Preliminary CVMP discussions have identified the following points to be considered when developing the scientific criteria to support the application of Article 40(5):

1. Data protection is predominantly relevant for pharmaceutical veterinary medicinal products due to their established relationship with generic products. Therefore, at this initial stage, it is not foreseen to develop criteria for biological or immunological veterinary medicinal products.

2. The data protection period conferred by Article 40(5) is relatively substantial and therefore the nature and scale of (pre-)clinical data to be submitted in support of eligible variations should be better defined, taking into account the shorter periods of data protection conferred by other parts of the Article e.g. Article 40(1).

3. In all cases, the impact of a variation on the overall benefit-risk balance of the product concerned must be considered. The benefit-risk balance therefore forms the overarching framework of Article 40(5).

4. Within the scope of variations falling under Article 40(5) (changes to the pharmaceutical form, administration route or dosage), consideration should be given as to what types of product development could meet the high-level criterion (b) of improving the benefit-risk balance of the veterinary medicinal product.

5. The wording of Article 40(5), 'reduction' or 'improvement' implies a comparative approach against the product profile prior to the development that is the subject of the variation. The aim would be to establish specific criteria, but a more general approach would be outlined where this is not possible, to avoid unduly restricting the application of Article 40(5).

6. It is considered necessary to establish a working definition of 'antiparasitic resistance'.

7. Where relevant, a consistent approach is required when seeking to define a reduction in antimicrobial and antiparasitic resistance, whilst taking into account the differences in availability of data and methodologies used.

8. Criteria to demonstrate a reduction in the antimicrobial or antiparasitic resistance will be explored. It is necessary to reflect on whether a reduction in the *risk* relating to the development of resistance, per the definition of the benefit-risk balance in Article 4(19), could be sufficient to meet criterion (a) of Article 40(5).

9. It is necessary to consider relevant currently applicable guidance or guidance under development within the different fields covered by Article 40(5).

10. Regulatory considerations beyond the abovementioned scientific criteria will not be included in the proposed reflection paper. They would, if necessary, be captured in an accompanying 'question and answer' document which could be adapted quickly as practical experience on use of Article 40(5) is gained.

4. Recommendation

Taking the above points into account, the purpose of the reflection paper would be to explore and reflect on the state of knowledge in the fields addressed by Article 40(5), particularly as regards criteria demonstrating a reduction of resistance, as a preliminary step towards an eventual guideline. Types of product development falling within the scope of Article 40(5) that could meet the criterion of improving the benefit-risk balance of the veterinary medicinal product will also be considered. The reflection paper will further consider whether any existing guidance would benefit from being updated due to the provisions of Article 40(5).

5. Proposed timetable

Timelines for development of the reflection paper will be determined in more detail following review of comments received on the concept paper. The aim is to release the draft reflection paper for consultation in early 2021 and to finalise it by July 2021.

6. Impact assessment (anticipated)

The intended reflection paper will provide an opportunity for the CVMP to reflect on the appropriate avenues for implementation of Article 40(5) and for stakeholders to feed into those reflections. This will allow the most effective use of Article 40(5), taking into account the aims of the Regulation. It will facilitate the practical application of Article 40(5) for both regulatory authorities and industry.

7. Resource requirements for preparation

The reflection paper will involve the CVMP Drafting Group on Article 40(5) of Regulation (EU) 2019/6, the EMA secretariat and the CVMP. The Drafting Group is composed of six members[1] representing expertise from across the different scientific disciplines covered by the scope of the Article.

As discussion progresses and as a function of comments received during public consultation, additional expertise may be sought on an *ad hoc* basis.

A workshop involving relevant stakeholders is foreseen for the later part of 2020 to allow for discussion of written comments received during the public consultation on this concept paper.

8. Interested parties

Pharmaceutical industry, consultants, EU national competent authorities, researchers

9. References

Legislation

Regulation (EU) 2019/6 of the European Parliament and the Council on veterinary medicinal products and repealing Directive 2001/82/EC

Existing guidance on benefit-risk balance of veterinary medicinal products

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

Existing guidance on antimicrobial resistance

VICH GL27 Guidance on the pre-approval information for registration of new veterinary medicinal products for food-producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-Final)

Draft guideline on the assessment of 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)

Categorisation of antibiotics in the European Union (EMA/CVMP/CHMP/682198/2017)

Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP 627/2001)

Existing guidance on antiparasitic resistance

Reflection paper on anthelmintic resistance (EMA/CVMP/EWP/573536/2013)

Draft reflection paper on resistance in ectoparasites (EMA/CVMP/EWP/310225/2014)

VICH GL7 Efficacy of anthelmintics: general requirements (CVMP/VICH/832/1999)

EU note for guidance on demonstration of efficacy of ectoparasiticides (7AE17a)

Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3)

[1] CVMP members/Chairs of CVMP Working Parties and the CMDv Chair

Draft guideline on data requirements for veterinary medicinal products for the prevention of transmission of vector borne diseases in dogs and cats (EMA/CVMP/EWP/278031/2015)

Draft guideline for the demonstration of efficacy for veterinary medicinal products containing anticoccidial substances (EMA/CVMP/EWP/755916/2016)

Guideline on specific efficacy requirements for ectoparasiticides in cattle (EMEA/CVMP/625/03/Final)

Guideline on specific efficacy requirements for ectoparasiticides in sheep (EMEA/CVMP/411/01-Final)

Guideline on demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish (EMA/CVMP/EWP/459868/2008)

Guideline on veterinary medicinal products controlling Varroa destructor parasitosis in bees (EMA/CVMP/EWP/459883/2008)

Guideline on the summary of product characteristics for anthelmintics (EMEA/CVMP/EWP/170208/2005)