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Reflection paper on the application of Article 40(5) of Regulation (EU) 2019/6 for certain categories of variations

Potential criteria to support the demonstration of a reduction in the antimicrobial or antiparasitic resistance, or an improvement of the benefit-risk balance

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1. Introduction

For variations involving a change to the pharmaceutical form, administration route or dosage, Article 40(5) of Regulation (EU) 2019/6, envisages four years of protection of technical documentation to the results of the concerned pre-clinical studies or clinical trials assessed to have demonstrated:

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

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

Whereas Article 40(5) provides the abovementioned high-level criteria (a) and (b), it is appropriate to elaborate more detailed scientific criteria to ensure a clear and consistent interpretation. This reflection paper aims to provide an overview of the CVMP's considerations to date, taking into account the comments received during the public consultation of the concept paper preceding this reflection paper (20 July to 21 September 2020), as well as during a workshop with stakeholders held by the EMA on 15 October 2020.

Regulatory considerations beyond the abovementioned scientific criteria will not be included in this reflection paper, except where necessary to explain the rationale.

2. Definition of terms

In respect of Article 40(5), the following definitions of terms apply:

'Variation' refers to a variation requiring assessment according to Article 62, that has been approved in accordance with Article 67;

'Antimicrobial' is defined by Article 4(12) as "any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals";

'Antimicrobial resistance' is defined by Article 4(11) as "the ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species";

'Antiparasitic' is defined by Article 4(13) as "a substance that kills or interrupts the development of parasites, used for the purpose of treating or preventing an infection, infestation or disease caused or transmitted by parasites, including substances with a repelling activity";

In the absence of a definition of 'antiparasitic resistance' within Regulation (EU) 2019/6, the following working definition is used for the purpose of this document: "antiparasitic resistance is defined as the genetically transmitted loss of sensitivity in a population of parasite species that were previously sensitive to the same substance when used according to label recommendations";

'Benefit-risk balance' is defined by Article 4(19) as "an evaluation of the positive effects of the veterinary medicinal product in relation to the following risks relating to the use of that product:

- Any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;
- Any risk of undesirable effects on the environment;
- Any risk relating to the development of resistance";

'Pre-clinical study' is defined by Article 4(18) as "a study not covered by the definition of clinical trial which aims to investigate the safety or efficacy of a veterinary medicinal product for the purpose of obtaining a marketing authorisation or change thereof";

'Clinical trial' is defined by Article 4(17) as "a study which aims to examine under field conditions the safety or efficacy of a veterinary medicinal product under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof".

3. General considerations

Articles 38-40 of Regulation (EU) 2019/6 lay down the provisions for protection of technical documentation ('data protection'). While this document predominantly focuses on chemical-based veterinary medicinal products, protection of technical documentation is applicable to all types of veterinary medicinal products. For the purpose of applying Article 40(5), it is to be understood that variations referred thereto are 'variations requiring assessment', according to Article 62 of Regulation (EU) 2019/6, for which the procedural aspects are described in Articles 66-68. Depending on the scope of the product development the changes may be submitted as a group of variations. This reflection paper does not include in its scope the procedure or dossier requirements in general for variations requiring assessment. Meeting one of the criteria of Article 40(5) is considered an additional element to be assessed, within the procedure for the variation requiring assessment, in cases where the marketing authorisation holder claims the applicability of the protection of technical documentation under Article 40(5).

Pursuant to Article 40(5), the "change to the pharmaceutical form, administration route or dosage" must be a factor leading to (a) a reduction in antimicrobial or antiparasitic resistance, or (b) an improvement of the benefit-risk balance of the veterinary medicinal product. For the protection of technical documentation foreseen under Article 40(5) to apply, it will always be necessary to justify how the change to the pharmaceutical form, administration route or dosage contributes to the claimed improvement of the benefit-risk balance and/or the reduction of resistance.

It is not excluded that a change of pharmaceutical form, administration route or dosage may also be associated with another variation. However, protection of technical documentation foreseen under Article 40(5) only applies to the results of the pre-clinical studies and/or clinical trials provided in parts 3 and 4 of the dossier in support of a variation to change the pharmaceutical form, administration route or dosage and where a reduction in the antimicrobial or antiparasitic resistance or an improvement of the benefit-risk balance of the veterinary medicinal product is accepted by the relevant competent authority. Consequently, the protection of technical documentation under Article 40(5) would not cover data in support of other variations submitted in association with the variation to change pharmaceutical form, administration route or dosage, or quality data in part 2 of the dossier. Therefore, this reflection paper does not provide any considerations in respect of quality data.

In order to meet the criteria within Article 40(5), in addition to the usual documentation required to support the variation requiring assessment, it should be adequately shown within the variation application that one or more of the following criteria are met:

- The proposed change(s) leads to a reduction in the antimicrobial or antiparasitic resistance, as compared to the already authorised product; or
- The benefit is increased by the proposed change(s), as compared to the already authorised product (with no resulting undue increase in any risk); or

- The risk relating to the use of the product is decreased by the proposed change(s), as compared to the already authorised product (with no resulting undue decrease in efficacy or increase in another risk).

4. Criterion (a) of Article 40(5): "reduction in the antimicrobial or antiparasitic resistance"

4.1 Antimicrobial veterinary medicinal products

Types of antimicrobials

According to Article 4(12), antimicrobials comprise antibiotic, antiviral, antifungal and antiprotozoal substances. The reflections in this section have been developed primarily with VMPs containing antibacterial substances in mind, but in principle could be applied at high level to veterinary products containing other types of antimicrobial substances. VMPs containing antiviral and antifungal substances will not be covered in any detail in this reflection paper due to lack of antiviral and only a limited number of antifungal authorised VMPs. In relation to antiprotozoal products, considering that their resistance profile bears more similarity to antiparasitic products than to antimicrobial VMPs, the information included in section 4.2 below on antiparasitic resistance generally equally applies to antiprotozoal products.

Approaches to demonstrate a reduction in antimicrobial resistance

In accordance with Article 40(5)(a), a reduction in the antimicrobial resistance should be demonstrated. As the Article refers to prospective applications the applicant can also demonstrate a 'reduction in the *risk of development of* resistance', rather than an absolute 'reduction in resistance'.

Variations to an antimicrobial VMP involving a change to the pharmaceutical form, route of administration or dosage in respect of which the applicant claims a reduction in antimicrobial resistance might be expected to have an impact on the antimicrobial risk assessment for the product.

According to Article 62(2)(b) of Regulation (EU) 2019/6, variations requiring assessment shall contain "data referred to in Article 8 relevant to the variation". Article 8(2)(a) states that where an application concerns an antimicrobial VMP, documentation should be provided on the risks to public or animal health or to the environment of the use of the product in animals. In this regard, the CVMP considers it relevant that the applicant's claimed reduction in antimicrobial resistance should be integrated within the antimicrobial risk assessment.

Reference is made below to guidance related to the antimicrobial risk assessment, that can be relevant to the assessment of a reduction in risk of development of antimicrobial resistance.

Current guidance:

a) Reduction in the antimicrobial resistance risk to public health

The framework for the assessment of the antimicrobial resistance risk to public health due to use of antimicrobial veterinary medicinal products in food-producing animals is laid out in the CVMP guideline (EMA/CVMP/AWP/706442/2013, 2025) and in VICH GL 27 (CVMP/VICH/644/01, 2004). The outlined methodology (hazard identification, release, exposure, consequence assessment) could be extrapolated for antimicrobial use in companion animals. The microbiological hazards of concern originating from companion animals are identified in the CVMP reflection paper on the risk of antimicrobial resistance transfer from companion animals (EMA/CVMP/AWP/401740/2013, 2015). In addition, the environment as a potential vehicle for spreading the risk of antimicrobial resistance to humans shall be addressed within marketing authorisation applications in accordance

with Article 8(2) of Regulation (EU) 2019/6 as well as relevant sections in Annex II to this regulation. The CVMP is currently working on the development of guidance providing more information on the data requirements to address the risk of antimicrobial resistance for humans emanating from the use of veterinary medicines via the environment.

b) Reduction in the antimicrobial resistance risk to animal health

The CVMP guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.2, 2025) identifies data on resistance that may characterise the potential for an antimicrobial veterinary medicinal product to select for resistant bacteria of concern to animal health, although not fully setting these in the context of a risk evaluation.

The applicant should provide a comparative risk assessment between the proposed new product development and the currently authorised product to demonstrate a more beneficial outcome i.e. a lower risk estimation for the new pharmaceutical form, administration route or dosage, using the available guidelines. Thus, an applicant could make use of the frameworks outlined above, focussing on the areas of difference between the currently authorised product and the proposed new product development.

In particular cases it may be possible to base the demonstration of reduction in antimicrobial resistance risk on established and well substantiated models or concepts, duly justified through scientific evidence. However, following a comparative approach to demonstrate a reduction of the risk of development of resistance should not preclude the applicant to provide additional quantitative data supporting an absolute reduction in resistance (e.g. MIC studies, or novel approaches), as these can be part of the suite of studies that support the overall risk estimation.

The AMEG (Antimicrobial Advice Ad Hoc Expert Group) proposed a list of routes of administration and formulations ranking from those with a lower effect on the selection of antimicrobial resistance to those that would be expected to have higher impact on resistance (EMA/CVMP/CHMP/682198/2017, 2019). When following the AMEG's ranking as a basic principle, (scientific) evidence should be provided to demonstrate that such an approach will be relevant to the new product development, in comparison to the previous (unchanged) product.

4.2 Antiparasitic veterinary medicinal products

Similarly, as for antimicrobials, this reflection paper focuses on the possibility to address a 'reduction in antiparasitic resistance' in the context of an assessment of the 'reduction in the *risk of development of* resistance'.

The resistance genes responsible for the loss of sensitivity are initially rare in the natural population of a parasite. There are different factors which can promote the selection of parasites carrying resistance genes that will fail to respond to a standard dose of an active substance when used as recommended, e.g. frequent or insufficient exposure of that population to an active substance or class of substances with the same mode of action.

Types of antiparasitics

In the context of this document, the antiparasitic products referred to are both anthelmintics and ectoparasiticides, including products with repelling activity. As outlined in the section above (4.1), this section generally also applies to antiprotozoals considering that their resistance profile bears more similarity to antiparasitic products than to antimicrobial products.

Relevant parasites

In line with the Annex II of Regulation (EU) 2019/6, the demonstration of a reduction in the risk relating to the development of antiparasitic resistance is relevant to the target parasites of the already-authorised indications of the veterinary medicinal product in the respective target animal species.

Applicants should justify why the new product development is likely to select less rapidly for resistance in target parasites in the respective target animal species than the authorised product and consequently, why it is likely to lower the future rate of resistance development.

Approaches to demonstrate a reduction in antiparasitic resistance

Data from published literature

One option to substantiate a decrease in the risk of development of antiparasitic resistance is for the applicant to provide appropriate bibliographic data relevant to the specific case.

According to published literature, there are some general concepts associated with the pharmaceutical form, administration route or dosing regimen of a product that could predict a beneficial impact on development of resistance.

Notably, the reviews of Leathwick and Luo (2017), Lifschitz et al. (2017), and Lanusse et al. (2018) emphasise the direct relationship between exposure of an endoparasite to an active substance, the variability in the dose reaching the targeted parasites, the antiparasitic efficacy of the concerned formulation, and the probability of an increase in the frequency of resistant parasites.

From these reviews and a series of other publications, it appears for example that:

a) In general, increased availability of the active substance at the site of infection is associated with a decrease in the risk of resistance selection, which is partly due to a less variable parasite exposure to the active substance.
b) Pour-on formulations in farm animals are usually associated with an increased risk of resistance development in target endoparasites because of a more variable bioavailability of the active substance, sometimes intensified by extrinsic factors (e.g. dirty fur, rain). Some orally administered anthelmintic products may have a more favourable bioavailability profile against gastro-intestinal nematodes.
c) Underdosing, inappropriate dosing frequency or timing of treatment, or poor administration techniques, can lead to a lack of efficacy and thereby to the selection of resistance, in both ecto- and endoparasites.
d) In case a long-acting formulation has a long tail of decreasing exposure, it may be associated with an increased risk of resistance selection.

These principles may, however, not be applicable to all possible scenarios and combinations of active substances, routes of administration, pharmaceutical forms, parasites and target species. A claim for reduction of the risk of development of antiparasitic resistance should be duly justified; theoretical considerations alone cannot be accepted. For example, proposing a theoretically more favourable pharmaceutical form or an increase in the recommended dose cannot be assumed to automatically result in a decrease in the risk of development of resistance. Unless convincing scientific support in terms of literature data relevant to the specific case is presented, the beneficial impact of the product development in relation to development of resistance should be confirmed by product-specific data, allowing a comparison of the proposed changes with the already authorised product.

Product-specific data

The gold standard to confirm a reduction in the risk of development of resistance would consist of a prospective study(ies) directly comparing the rate or frequency of emergence of resistance and showing that resistance develops to a lesser extent, or more slowly, in parasite populations exposed to the new product development when compared to the already authorised product in the relevant target animal species. This should ideally be assessed in an appropriately designed clinical trial, and the risk of resistance development when using the already authorised product should be considered. It is, however, acknowledged that the conduct of such studies will be difficult since this is likely to require substantial time and investment and, at present, there is limited availability of validated analytical methods or models.

Therefore, the actual monitoring of treatment-related resistance development under field conditions could be replaced by the demonstration of an increased level of efficacy, which would be considered as correlated to a reduced risk of resistance selection. An essential issue, however, would be to determine the appropriate efficacy thresholds or minimum relevant differences in relation to these endpoints.

The following approaches, used alone or in combination, could be considered to support an increased efficacy level, and which may be accepted as an indicator for a decrease in the risk of development of resistance:

a) Although it is recognised that this is currently not well developed in the field of antiparasitics, *Pharmacokinetic/Pharmacodynamic (PK/PD) integration* could be a relevant approach. Where it has been established that the antiparasitic concentration at a given site or in a given matrix correlates to antiparasitic efficacy, and where thresholds predicting optimal efficacy have been validated, it could be acceptable to demonstrate that the PK/PD criteria are more favourable with the new product development than with the currently approved product. Antiparasitic concentrations within parasites and the time of parasite exposure to the active substance could also constitute potential endpoints. The variability of parasite exposure could also be part of a PK/PD criterion.

b) The results of *laboratory efficacy studies or clinical trials in susceptible isolates or strains* (in accordance with current scientific guidelines) could be considered relevant where it is demonstrated that the efficacy level of the proposed product variation is higher than that of the currently authorised product, this being considered correlated to a reduced risk of resistance selection in the respective approved target animal species and parasite.

c) *Laboratory efficacy studies or clinical trials using specific parasite isolates or strains* with decreased susceptibility also constitute a possible approach. Comparison of efficacy of antiparasitic products in animals infected with a worm isolate with documented decreased susceptibility has been reported in the literature and could, in some circumstances, be a useful method to demonstrate an increase in efficacy of a product development and, consequently, a reduced risk of resistance selection.

d) *Alternative/innovative ways* of demonstrating a reduction of the risk of resistance can be contemplated and will be considered on a case-by-case basis. The list of methods and approaches proposed above is not exhaustive, and any future guidance should remain open to alternative endpoints and study designs.
Among alternative approaches, the use of mathematical modelling e.g. of the frequency of resistance determinants, could be appropriate to compare the performance of the new product development against the currently authorised product, provided that it is clearly shown that the used model is sufficiently validated and that the underlying assumptions are realistic or worst-case.

5. Criterion (b) of Article 40(5): "an improvement of the benefit-risk balance"

The CVMP's 'Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products' (EMA/CVMP/55240/2025 – Rev.1) provides the basis for the reflections regarding the criterion on "improvement of the benefit-risk balance" within Article 40(5)[1]. A key principle is that the benefit-risk analysis of a veterinary medicinal product is based on the intended use of that product.

As defined in the above-referred CVMP Guideline, the *direct benefits* linked to the intended use of a product are those predominantly taken into account for the purpose of the benefit-risk evaluation. These are generally therapeutic or diagnostic benefits in line with the legal definitions of a veterinary medicinal product (Article 4(1) of Regulation (EU) 2019/6).

Any change of pharmaceutical form, administration route or dosage leading to an improvement of the direct benefit of the product could be examined under criterion (b) of Article 40(5). An improvement of direct benefit would mean that the extent and significance of the improvement can be clearly demonstrated and is considered as meaningful, with no resulting undue increase in risk. This could be the case, for instance, when the dosage of a product is changed in a way that the proportion of cured animals is increased when used at the new dosage.

The CVMP guideline on evaluation of the benefit-risk balance (EMA/CVMP/55240/2025 – Rev.1) explains that *additional benefits* are positive effects that are not specifically captured by the indication of the product but are associated to the use of the product in accordance with the terms of the marketing authorisation. These can be general benefits for the animal, the veterinarian, the farmer, the user, or relate to particular properties of the product and shall be relevant to the use of the product in the indications that have been specifically authorised. For an improvement of the benefit-risk balance via an additional benefit to be sufficient in the context of Article 40(5) it should be meaningful and not result in an undue increase in risk.

As regards 'change in dosage' it is clarified that a change in the volume of the dose which is required due to differences in body weight (ranges) of animal species or animal subcategories is not considered a 'change in dosage' and therefore does not qualify as an Art. 40(5) variation.

In general, economic factors (such as cost-effectiveness of a veterinary medicinal product) are not considered to be benefits that fall within the framework for the evaluation of the benefit-risk balance of a veterinary medicinal product.

A reduction of risks to the user, environment or target animal might be demonstrated in cases where e.g. a change in the pharmaceutical form, administration route or dosage leads to a decrease in the exposure of the user, the environment or the target animal to any active ingredient or excipient of the product exerting a harmful effect.

A decrease of a given risk should not be counterbalanced by a decrease in the efficacy or an increase of another risk such that the overall benefit-risk balance is reduced or remains unchanged. The decrease in the risk should be substantiated and based either on data (e.g. pre-clinical studies, clinical trials), published literature or other appropriate information (e.g. pharmacovigilance). A valid decrease of the risk to the user, environment or the target animal could be defined as a meaningful decrease of the exposure to a harmful ingredient. To be considered as meaningful, this decrease should preferably be associated with tangible consequences such as, for instance, the deletion or easing of precautionary measures or contra-indications stated in the product information regarding the user, the environment

[1] Note: The contents of this Reflection Paper are without prejudice to the content of the CVMP Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products (EMA/CVMP/248499/2007-Rev.1) and should therefore always be read in conjunction with it.

or the target animal. Demonstration that a variation leads to a meaningful decrease in the prevalence of adverse effects could also be a valid approach. For example, a formulation requiring multiple administrations further developed as a single-dose formulation could be considered to meaningfully improve the benefit-risk balance with respect to target animal safety by reducing the need for animal handling, reducing local tolerance issues or reducing the risk in gaps in effectiveness due to a potential lack of owner compliance, provided the level of efficacy is not impaired.

In certain cases, in particular for products with a narrow safety margin that is known and documented a change in pharmaceutical form leading to improvement in accuracy of dosing, thereby reducing this risk in the target species, could be considered as relevant in the context of criterion (b) of Article 40(5). It will be necessary to justify that the improvement in accuracy of dosing is of a sufficient magnitude to have a real impact on the safety of the product for the target species.

In relation to variations affecting withdrawal periods, the risk for consumers is already fully controlled with the authorised withdrawal period stated in the product information or with the regulatory withdrawal periods in the case of use under the cascade. Given that an authorised product is not expected to pose a risk to the consumer when the VMP is used according to the SPC recommendations, a change to the withdrawal period is not considered to be a risk that could be reduced.

When evaluating the overall benefit-risk balance, in cases where the benefit is clearly improved without an undue increase in risk or when the risk is clearly decreased without compromising the benefit, a conclusion on an improved benefit-risk balance is expected to be straightforward. However, in the case where the improved benefit is associated with an increase in one or several risks, the conclusions regarding the improvement of the benefit-risk balance will be made on a case-by-case basis, and will depend on the type of risk, its magnitude and also on the level of improvement of the benefit.

6. Conclusions

This reflection paper is aimed to provide an overview on the CVMP's considerations to-date on the development of scientific criteria to support the practical application of Article 40(5) of Regulation (EU) 2019/6.

In order to meet the criteria within Article 40(5), it should be justified with the variation application that the change to the pharmaceutical form, administration route or dosage is a factor leading to (a) a reduction in antimicrobial or antiparasitic resistance, or (b) an improvement of the benefit-risk balance of the veterinary medicinal product.

When a reduction in antimicrobial resistance is claimed to fulfil the criteria of Article 40(5), the applicant should integrate this claimed reduction within the antimicrobial risk assessment, taking into account available guidance. The comparison should demonstrate a more beneficial outcome, i.e. a lower risk estimation, for the new pharmaceutical form, administration route or dosage, and should focus on the areas of difference between the currently authorised product and the proposed new product development.

When reduction in the risk to develop antiparasitic resistance is claimed, the applicant should justify why the new product development is likely to select less rapidly for resistance in target parasites than the authorised product and consequently, why it is likely to lower the future rate of resistance development.

An improvement of the benefit(s) of the VMP would mean that the extent and significance of the improvement can be clearly demonstrated and is considered as meaningful, with no resulting undue increase in risk.

A valid reduction of the risk could be defined as a meaningful decrease of the exposure of the target animal, the user, or the environment to an ingredient with a harmful effect. The decrease in the risk should be substantiated and be confirmed as a known risk prior to the new product development. A decrease of a given risk should not be counterbalanced by a decrease in the efficacy or an increase of another risk such that the overall benefit-risk balance is reduced or remains unchanged.

In order for a variation submitted in support of a product development to be approved, the benefit-risk balance of the veterinary medicinal product must remain overall positive. In addition, for a variation involving a change to the pharmaceutical form, administration route or dosage and citing Article 40(5)(b), the overall benefit-risk balance of the veterinary medicinal product must be superior when compared to before the variation.

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