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Committee for Veterinary Medicinal Products (CVMP)

Concept paper for the development of a reflection paper on the assessment of public health risks related to antimicrobial resistance acquired via the environment, resulting from the use of a veterinary medicinal product

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

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1. Introduction

Following the use of antimicrobial[1] veterinary medicinal products (VMPs), residues of the active substance(s) (antimicrobial residues – 'ARs'), including their microbiologically active metabolites as well as antimicrobial-resistant bacteria selected on/within the animal subsequent to VMP use, including their antimicrobial resistance genes (generally referred to as AMR for the purpose of the present concept paper), may enter the natural environment. The presence of antimicrobials in the environment can lead to further development, selection and spread of AMR. All this may lead to an increase of human exposure to AMR via the environment. This should be addressed as part of the globally recognised 'One Health' approach (European Commission , 2017; United Nations, 2016). In line with this, Regulation (EU) 2019/6[2] governing the authorisation of VMPs in the European Union outlines the following dossier data requirements for the authorisation of antimicrobial VMPs:

- Article 8(2)(a): Documentation on the direct or indirect risks to public or animal health or to the environment of use of the antimicrobial veterinary medicinal product in animals;
- Article 8(2)(b): Information about risk mitigation measures to limit antimicrobial resistance development related to the use of the veterinary medicinal product;
- Details regarding the above requirements are further addressed in Section II.3A4.3 and IIIa.3A4.3 of Annex II ('Development of resistance and related risk in humans'), which clarifies that resistance in the environment shall be addressed.
- Annex II further outlines the specific requirements for generics and hybrid applications:
  - Section IV.1.3: "For a generic veterinary medicinal product application containing an antimicrobial substance, information about the level of resistance, as known from bibliographic data, shall be provided."
  - Section IV.2.2.(b) pertaining to applications for hybrid veterinary medicinal products: "[...] New data shall include a user safety risk assessment and an environmental risk assessment in accordance with Article 18(7), if applicable. In addition, for relevant products (for example, antimicrobials, antiparasitics) the risk of development of resistance shall be addressed, if applicable."

In relation to the risk for humans exposed to AMR in the environment originating from the use of VMPs, a CVMP reflection paper ('Reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products') was published in 2021[3]. At the time of writing that document, it was concluded that there was too limited information to robustly define a methodology modifying the current approach for the environmental risk assessment (ERA) to include the risks posed by the emission of ARs and AMR to the environment from the use of these VMPs. Consequently, no guidance is available yet on how to fulfil the above-mentioned dossier requirements in relation to the risk for humans exposed to AMR via the environment originating from the use of VMPs.

[1] In the context of this concept paper antimicrobial substances are considered substances that are used to treat bacterial as well as fungicidal infections.
[2] 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, OJ L 4, 7.1.2019, p. 43–167.
[3] EMA/CVMP, ' Reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products, EMA/CVMP/ERA/632109/2014, 2021. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-antimicrobial-resistance-environment-considerations-current-and-future-risk-assessment-veterinary-medicinal-products-first-version_en.pdf (accessed on 26 February 2025).

The new reflection paper to be developed will support a harmonised assessment among VMPs and should help the future development of a guideline on the assessment of AMR risks to humans via the environment originating from the use of VMPs. As such, it is to be understood that the risk for public health is to be assessed, in which the environment acts as a potential vehicle for exposing humans to AMR. The present concept paper intends to describe and discuss the scientific approach as a basis for the reflection paper to be developed. Furthermore, other relevant documents and guidance will also be considered for the purpose of the reflection paper being developed, for example the CVMP '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 animal species'[4], the WHO background document 'Evidence synthesis for deriving PNECs for resistance selection' (World Health Organisation, 2024) and the EFSA publication on the 'Role played by the environment in the emergence and spread of antimicrobial resistance (AMR) through the food chain' (Koutsoumanis et al., 2021).

2. Problem statement

In Regulation (EU) 2019/6, no further guidance is given on how to fulfil the above-mentioned data requirements on addressing the role of the environment in the development, selection and spread of AMR to humans following the use of VMPs. Consequently, there is no guidance for applicants/marketing authorisation holders on how to fulfil these legal requirements.

Especially, the question of what type of information should be submitted is not clear. The generation of new data on AMR is not excluded by the text in Regulation (EU) 2019/6, except for generic marketing authorisation applications for which reference to bibliographic data is mandated. A specification of the data to be submitted, including an overview of potentially relevant test methods that could be applied for the generation of new data is envisaged to be included in the reflection paper.

The focus of the present paper is based on the dossier requirements outlined in sections II.3A.4.3 and IIIa.3A.4.3 of Annex II to Regulation (EU) 2019/6 ('Development of resistance and related risk in humans'). As dossier requirements pertaining to AMR are not only relevant for VMPs for food-producing animal species, considerations on the risk assessment of VMPs for companion animals will also be addressed. Currently, there is no established method to attribute specific portions of environmental AMR to different sources. This challenge is complicated by a lack of quantitative data on both the amplification of AMR within the environment and the potential environmental harm caused by the use of antimicrobial VMPs. All this may ultimately contribute to AMR-related risks for humans. Considering all limitations, the assessment will follow the current risk assessment methodology (i.e. hazard identification, release assessment, exposure assessment, consequence assessment and risk estimation), but the reflection paper will focus on the potential pathways and probabilities of a VMP-related release into the environment and exposure to humans via the environment (i.e. the release and exposure steps, for further explanation see section 3 below).

3. Discussion

For the reflection paper to be developed, it is proposed that, for antimicrobial VMPs for food-producing animal species, the approach as developed for the risk assessment of AMR following the use of antimicrobial VMPs in food-producing animal species[4] serves as a basis to develop guidance on the assessment of the risk for humans exposed to AMR via the environment originating from the use of

[4] EMA/CVMP, '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 animal species', EMA/CVMP/AWP/706442/2013, 2025. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/final-guideline-assessment-risk-public-health-antimicrobial-resistance-due-use-antimicrobial-veterinary-medicinal-product-food-producing-animal-species_en.pdf (accessed on 26 February 2025).

antimicrobial VMPs. This approach covers the hazard identification, the release, exposure and consequence assessment for humans from which an overall risk estimation is established for each of the hazards identified. For now, in relation to the risk for humans, it is considered that the hazards that will be identified following the aforementioned guideline on AMR risk assessment for VMPs used in food-producing animal species[4] will be also the most relevant in terms of exposure of humans via the environment. This also accounts for the consequences resulting from exposure to an identified hazard. Therefore, the guidance that will be developed shall, at first, only focus on the release to the environment and exposure of humans via the environment, as these are the steps in the risk assessment process that require the most attention where exposure via the environment is concerned (Lepper et al., 2022). Ultimately, regarding the above, the reflection paper would need to be adapted to new scientific developments on hazards and consequences related to release/exposure to AMR via the environment. Furthermore, the consequences resulting from exposure to AMR via the environment should be reflected upon in the frame of the overall risk estimation for AMR.

It is planned that a general guideline on the risk to public health from antimicrobial resistance due to antimicrobial use in companion animals will be developed for VMPs for companion animals[5]. This guideline is intended to be similar to the previously mentioned guideline for antimicrobial VMPs in food-producing animal species[4]. The approach for companion animals as planned will also cover hazard identification, release, exposure and consequence assessment for humans. Once this general risk assessment guideline for companion animals is finalised, human exposure to AMR via the environment originating from the use of VMPs related to companion animals can also be addressed by a complementary assessment of release and exposure. Therefore, also the release and exposure of antimicrobial VMPs authorised in companion animals will be addressed in the reflection paper to be developed.

As part of the above considerations, it should be noted that, within the exposure assessment, the microbiologically active residues of VMPs entering the environment can, depending on their concentration, apply a selective pressure on microorganisms present in the environment as well as AMR already developed in the treated animals and released together with these residues and, as such, affect their abundance and diversity in the environment. A review on this has been presented by Murray et al. (2021).

Human exposure to antimicrobial resistance acquired via the environment due to the use of VMPs for food-producing and companion animals will be addressed in the reflection paper as follows:

- For food-producing terrestrial animals, release of AMR and residues from the treated animal[6];
- For companion animals, release of AMR and residues from the treated animal[6];
- For aquatic animals (e.g. aquaculture), release of AMR and residues to the aquatic compartment[6];
- Only exposure to AMR originating from treated animals and entering the environment via multiple pathways (e.g. direct excretion or through slurry and manure), conferring resistance against the active substance in the antimicrobial VMP being assessed should be considered;
- Distribution of AMR between environmental compartments;

[5] EMA/CVMP, 'Work plan for the Committee for Veterinary Medicinal Products (CVMP) Antimicrobials Working Party (AWP) 2025', EMA/CVMP/AWP/341740/2024, 2024. Available at: https://www.ema.europa.eu/en/documents/work-programme/work-plan-committee-veterinary-medicinal-products-cvmp-antimicrobials-working-party-awp-2025_en.pdf (accessed on 26 February 2025).

[6] Where the release of residues to the environment is sufficiently addressed in separate CVMP guidance, only reference will be made to the separate guidance and it will not be further addressed in the reflection paper.

- Development, selection and spread of AMR in the environment due to residues of the VMP (selective pressure), including an overview of available potential test methods and interpretation of their results;
- Routes of human exposure via the environment.

Risk related to direct contact will be considered within the global frame of the risk assessment guidelines, but not as part of the assessment of human exposure via the natural outdoor environment.

Definitions for 'environment' and 'human' in the context of this paper:

Within the framework of the present paper, 'environment' is understood as being the outdoor environment, and not the home, clinical or work environment. The latter aspects are considered as representing part of the direct contact with the animal, an aspect which is covered within the CVMP '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 animal species'[4]. Exposure of humans via the environment considers people that have no direct contact with the treated animal(s) (or its/their excrements).

- For food-producing animal species, this includes, for instance, exposure via meadows and agricultural fields where manure is applied or exposure via recreational water sources contaminated with antimicrobial residues via leaching from a field where manure has been applied.
- For companion animals, the same approach is followed and includes e.g. exposure via swimming lakes, while the natural outdoor environment excludes the home environment as well as veterinary clinics.

4. Recommendation

The Committee recommends the development of a reflection paper outlining the methodology for the performance of a risk assessment for the risk for humans exposed via the environment to AMR developed or spread in relation to the use of antimicrobial VMPs. Considering the fast evolution of knowledge related to exposure of humans to AMR via the environment, the current intention is that the reflection paper will not be directly followed by a guidance document. The reflection paper will be timely updated and, only once it is decided that there is sufficient knowledge and methodology for robust guidance, a guideline will be developed on the basis of the approach outlined in the latest version of the reflection paper.

The developed methodology will apply to full marketing authorisation applications for antimicrobials according to Article 8 of Regulation (EU) 2019/6 and, where applicable, marketing authorisation applications for hybrid VMPs, as well as variations which can lead to increased risk of AMR to humans via the environment.

5. Proposed timetable

- April 2025: Release of concept paper for public consultation.
- October 2025: Deadline for receipt of comments.
- December 2026: AWP and ERAWP to endorse the draft reflection paper.
- February 2027: CVMP to adopt the draft reflection paper for public consultation.
- August 2027: Deadline for receipt of comments.

- February 2028: AWP and ERAWP to endorse final reflection paper.
- March 2028: CVMP to adopt final reflection paper for publication.

6. Resource requirements for preparation

The ERAWP and the AWP would jointly develop the reflection paper. A rapporteur from each working party will be nominated. Adequate time for discussions at both working parties will be required. The EMA will coordinate the consultation and communication between the working parties as well as the public consultations. Time at CVMP plenary meetings will be required to discuss and adopt the various drafts of the reflection paper.

7. Impact assessment (anticipated)

The reflection paper would be beneficial for both industry and regulators, as it would promote the use of a consistent and scientifically justifiable approach on the assessment of AMR risks to humans via the environment originating from the use of VMPs.

An assessment of human exposure to AMR via the environment due to the use of VMPs would be required for all full marketing authorisation applications for antimicrobials, and, where applicable, marketing authorisations applications for hybrid VMPs, as well as variations thereto which can lead to increased risk of AMR to humans via the environment. In those cases where a high risk for humans is identified, risk mitigation measures should be proposed.

8. Interested parties

Pharmaceutical industry, academia and researchers (e.g. environmentalists), regulatory bodies (e.g. environmental agencies) and environmental non-governmental organisations (NGOs). In addition, information supplied can be useful for veterinary practitioners and the public at large.

9. References

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