EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

The Director-General

Brussels,
SANTE/E5/JS/AJT/DT/ih (2020)1029506

**Sent by e-mail only**

Dear Prof. Rasi,

**Subject:** **Implementing measures under Article 107(6) of Regulation (EU) 2019/6 on veterinary medicinal products[1], regarding the establishment of a list of antimicrobials, which shall not be used in accordance with Articles 112, 113 and 114 or which may be used in accordance with these articles subject to certain conditions.**

On 7 January 2019, the new Regulation on Veterinary Medicinal Products ('VMP Regulation') was published.

In accordance with its Article 160, it will start applying 3 years from its entry into force, i.e. on 28 January 2022.

The Commission strongly supports the fight against antimicrobial resistance (AMR) in the EU and at global level. The misuse or overuse of antimicrobials in veterinary settings can create an important source of antimicrobial resistant microorganisms that can spread across animal species, as well as between animals, humans and the environment in various ways. For this reason, improving the management of the use of antimicrobials in animals is paramount.

To ensure a well-rounded approach to fighting AMR, the new Regulation lays down that certain antimicrobials may be reserved for treatment of certain infections in humans (Article 37(5)). In addition, it envisages that the use of certain antimicrobials under Articles 112, 113 and 114 ('cascade use') may not be allowed or be subject to certain restrictions in order to help preserve their efficacy for humans and/or animals.

[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, OJ L 4, 7.1.2019, p. 43.

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Article 107(6) stipulates that the Commission may, by means of implementing acts, establish a list of antimicrobials, which shall not be used in accordance with Articles 112, 113 and 114 or which may be used in accordance with these articles subject to certain conditions, while taking account of the following criteria:

(a) risks to animal or public health if the antimicrobial is used under the 'cascade';

(b) risks for animal or public health in case of development of AMR;

(c) availability of other treatments for animals;

(d) availability of other antimicrobial treatments for humans;

(e) impact on aquaculture and farming if the animal affected by the condition receives no treatment.

In this context, I would ask you to provide us with the Agency's scientific advice for the establishment of such a list.

The VMP Regulation does not foresee a deadline by which the implementing acts under Article 107(6) are to be adopted. However, the Commission considers it beneficial to align this strand of work with the establishment of the list of antimicrobials to be designated in the EU as reserved for treatment of certain infections in humans (Article 37(5)), which is to be adopted by 28 January 2022.

To ensure the coherence and complementarity of both lists, the scientific assessment of whether specific antimicrobials or types of antimicrobials should be placed or not on either of them should be facilitated by allowing the Agency's expert groups to work on these lists in parallel and by supporting a clear and timely communication between the groups. Taken together, the lists should help achieve the overall objective of the VMP Regulation as regards fighting AMR and promoting a prudent use of antimicrobials.

While preparing the advice requested here, we would invite you to take due account of the fact that sufficient availability of antimicrobials needs to be ensured to secure animal health, including for limited markets and exceptional circumstances.

In particular, due account should be taken of the *OIE List of Antimicrobial Agents of Veterinary Importance*[2] updated in July 2019, while bearing in mind that the latter addresses only antimicrobial agents authorised for use in food-producing animals, and that it does not include antimicrobial classes/subclasses only used in human medicine. You may note that the OIE *ad hoc* Group on AMR, in its recommendations on the use of that updated list, underlines that among the Veterinary Critically Important Antimicrobial Agents (VCIA) cited, some are considered critically important both for human and animal health (Fluoroquinolones, third and fourth generation of Cephalosporins, Colistin). For these, the Group recommends specific restrictions on their use.

At the same time, the *WHO list of Critically Important Antimicrobials for Human Medicine*[3] *(also known as WHO CIA list)* and the *AWaRe classification of antibiotics of*

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[2] https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/A_OIE_List_antimicrobials_July2019.pdf

[3] https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf?ua=1

*WHO's Essential Medicines Lists*[4] classify antimicrobials by priorities and make recommendations as to their use, in order to help preserve their efficacy. These should be considered while reflecting on possible restrictions for 'cascade use' in animals of antimicrobials authorised for human use.

Some elements considered in the Agency's '*Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union*'[5], which was adopted by the CVMP at the end of 2018 may also be of interest.

Finally, elements from the Agency's paper '*Categorisation of antibiotics in the European Union*'[6], adopted by the CVMP in December 2019, may be useful to consider during the preparation of your scientific advice, bearing in mind however: 1) that the original mandate for such categorisation was not designed for the specific purpose of listing antimicrobials reserved for human use only or listing antimicrobials that should see their use under 'the cascade' banned or restricted, and 2) that divergences exist between this categorisation and WHO's CIA list[7].

Besides, please note that in contrast to the list of antimicrobials to be reserved for treatment of certain infections in humans, the bans or restrictions on the 'cascade use' of certain antimicrobials shall not apply to animals or products of animal origin to be imported into the EU from third countries.

We would therefore kindly ask for your scientific advice by end of February 2021.

Relevant excerpts (non-exhaustive list) from the VMP Regulation are included in Annex I for your convenience.

We would also ask that the Agency updates Commission's services on the main progress of its work on a monthly basis.

We would like to thank you for your collaboration.

Yours sincerely,

Anne Bucher

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4 https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1&ua=1 ;
https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1&ua=1

5 https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-label-use-antimicrobials-veterinary-medicine-european-union-first-version_en.pdf

6 https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf

7 *e.g.* macrolides are classified under WHO's CIA list as of the 'highest priority' under the 'critically important antimicrobials', while only falling under 'category C- Caution' under EMA's updated categorisation for the EU.

## ANNEX I

*Article 107*

**Use of antimicrobial medicinal products**

1. Antimicrobial medicinal products shall not be applied routinely nor used to compensate for poor hygiene, inadequate animal husbandry or lack of care or to compensate for poor farm management.

2. Antimicrobial medicinal products shall not be used in animals for the purpose of promoting growth nor to increase yield.

3. Antimicrobial medicinal products shall not be used for prophylaxis other than in exceptional cases, for the administration to an individual animal or a restricted number of animals when the risk of an infection or of an infectious disease is very high and the consequences are likely to be severe.

In such cases, the use of antibiotic medicinal products for prophylaxis shall be limited to the administration to an individual animal only, under the conditions laid down in the first subparagraph.

4. Antimicrobial medicinal products shall be used for metaphylaxis only when the risk of spread of an infection or of an infectious disease in the group of animals is high and where no other appropriate alternatives are available. Member States may provide guidance regarding such other appropriate alternatives and shall actively support the development and application of guidelines which promote the understanding of risk factors associated with metaphylaxis and include criteria for its initiation.

5. Medicinal products which contain the designated antimicrobials referred to in Article 37(5) shall not be used in accordance with Articles 112, 113 and 114.

6. The Commission may, by means of implementing acts, and taking into consideration scientific advice of the Agency, establish a list of antimicrobials which:

(a) shall not be used in accordance with Articles 112, 113 and 114; or

(b) shall only be used in accordance with Articles 112, 113 and 114 subject to certain conditions.

When adopting those implementing acts, the Commission shall take account of the following criteria:

(a) risks to animal or public health if the antimicrobial is used in accordance with Articles 112, 113 and 114;

(b) risk for animal or public health in case of development of antimicrobial resistance;

(c) availability of other treatments for animals;

(d) availability of other antimicrobial treatments for humans;

(e) impact on aquaculture and farming if the animal affected by the condition receives no treatment.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 145(2).

7. A Member State may further restrict or prohibit the use of certain antimicrobials in animals on its territory if the administration of such antimicrobials to animals is contrary to the implementation of a national policy on prudent use of antimicrobials.

8. Measures adopted by the Member States on the basis of paragraph 7 shall be proportionate and justified.

9. The Member State shall inform the Commission of any measure it has adopted on the basis of paragraph 7.

*Article 37*

**Decisions refusing marketing authorisations**

1. Decisions refusing marketing authorisations referred to in Article 5(1) shall be taken on the basis of the documents prepared in accordance with Article 33(1) and shall be duly justified and include the reasons for refusal.

2. A marketing authorisation shall be refused if any of the following conditions are met:

(a) the application does not comply with this Chapter;

(b) the benefit-risk balance of the veterinary medicinal product is negative;

(c) the applicant has not provided sufficient information on the quality, safety or efficacy of the veterinary medicinal product;

(d) the veterinary medicinal product is an antimicrobial veterinary medicinal product presented for use as performance enhancer in order to promote the growth of treated animals or to increase yields from treated animals;

(e) the proposed withdrawal period is not long enough to ensure food safety or is insufficiently substantiated;

(f) the risk for public health in case of development of antimicrobial resistance or antiparasitic resistance outweighs the benefits of the veterinary medicinal product to animal health;

(g) the applicant has not provided sufficient proof of efficacy as regards the target species;

(h) the qualitative or quantitative composition of the veterinary medicinal product is not as stated in the application;

(i) risks to public or animal health or to the environment are not sufficiently addressed; or

(j) the active substance within the veterinary medicinal product meets the criteria for being considered persistent, bioaccumulative and toxic or very persistent and very bioaccumulative, and the veterinary medicinal product is intended to be used in food-producing animals, unless it is demonstrated that the active substance is essential to prevent or control a serious risk to animal health.

3. A marketing authorisation for an antimicrobial veterinary medicinal product shall be refused if the antimicrobial is reserved for treatment of certain infections in humans as provided for in paragraph 5.

4. The Commission shall adopt delegated acts in accordance with Article 147 in order to supplement this Regulation by establishing the criteria for the designation of the antimicrobials which are to be reserved for treatment of certain infections in humans in order to preserve the efficacy of those antimicrobials.

5. The Commission shall, by means of implementing acts, designate antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 145(2).

6. The Commission shall, when adopting the acts referred to in paragraphs 4 and 5, take into account the scientific advice of the Agency, the EFSA and other relevant Union agencies.