EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

The Director General

Brussels,
SANTE/E5/CS/mcd 379717
Sent by e-mail only

Dear Prof Rasi,

Subject: Establishment of the criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans in order to preserve the efficacy of those antimicrobials, as required under Article 37(4) of Regulation (EU) 2019/6 on veterinary medicinal products[1]

On 7th 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 28th January 2022.

The Commission strongly supports the fight against antimicrobial resistance (AMR) in the EU and at global level. In June 2017, it adopted a second action plan against AMR, pursuing the One Health Approach, which recognises the interconnection between human health, animal health and the environment. It clearly underlines the Commission's commitment to step up its actions to tackle the huge challenge of antimicrobial resistance.

The misuse or overuse of antimicrobials in a veterinary setting can create an important source of antimicrobial resistant bacteria that can spread to humans through various channels. For this reason, improving the management of the use of antimicrobials in animals is paramount, in particular managing the use of those antimicrobials, which are essential for human medicine in order to help preserve the efficacy of those antimicrobials for people.

In this setting, a cornerstone of the new VMP Regulation is that the use of certain antimicrobials will be reserved for the treatment of certain infections in humans, thereby excluding their use in a veterinary context (Article 37, paragraph 3; Article 107, paragraph 5).

[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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The list of these antimicrobials or groups of antimicrobials will be laid down by the Commission through implementing acts (Article 37, paragraph 5), based on specific criteria, which will be defined in delegated acts to be adopted by the Commission (Article 37, paragraph 4). In accordance with Article 153(2) these delegated acts shall be adopted at the latest by 4 months before the date of application of the VMP Regulation.

Establishing clear and pertinent criteria to adequately designate those antimicrobials or groups of antimicrobials, which are to be reserved for human use in order to preserve their efficacy, is paramount to the implementation of the new VMP Regulation. For example, not only will these criteria set the basis for the designation itself of these antimicrobials, but they will also impact imports of animals and products of animal origin from Third Countries into the EU, which will also have to respect these restrictions (Article 118, paragraph 1).

To establish these criteria, the Commission shall take into account scientific advice from the Agency and take into account any relevant advice from EFSA and other relevant EU Agencies (Article 37 paragraph 6).

In this context, I would ask the Agency to describe the criteria to designate those antimicrobials to be reserved for human use; to this end, the Agency shall:

- Liaise with relevant EU bodies (including EFSA and ECDC).
- Use relevant external experts, where necessary, in order to collect their input and to discuss with them, in a coordinated fashion, the best basis to establish the abovementioned criteria.
- Consider the work of relevant international agencies, bodies or organisations (such as OIE, WHO and FAO); organise a scientific workshop with those international agencies, bodies or organisations in order to exchange visions and share expertise on the scientific evidence which may guide the EU in its approach to establishing those antimicrobials to be restricted to human use.
- When establishing those criteria, consider the elements listed in Article 107, paragraph 6, including that sufficient availability needs to be ensured for antimicrobials essential in a veterinary setting, while endeavouring to secure animal health.
- Consider examples of Third Countries with relevant experience in the establishment of criteria serving a similar purpose.
- Based on the above information, provide a report, which will include recommendations to the Commission as to which criteria should be used to determine those antimicrobials to be restricted to human use.

Additional useful elements to be taken into account while preparing this scientific advice are provided in Annex I. Relevant excerpts from the VMP Regulation are included in Annex II for your convenience.

In light of the strict timeline set for the adoption of the required delegated acts, as specified in Article 153(2), we would kindly ask for the Agency's advice by end of October 2019. We would also ask that the Agency update our services on the main progress of its work on a monthly basis.

I would like to thank you for your collaboration.

Yours sincerely,

Anne Bucher

Encl. : Annex I – Annex II

ANNEX I

Please note that the elements below are not exhaustive and that the Agency shall complete the list with whatever other necessary elements that would improve the quality of its recommendations.

- WHO's Critically Important Antimicrobials for Human Medicine (5th Revision)
  http://apps.who.int/iris/bitstream/handle/10665/255027/9789241512220-eng.pdf;jsessionid=02474C67040DBB2DFAA9B988A4C31C2C?sequence=1

- WHO guidelines on use of medically important antimicrobials in food-producing animals
  http://apps.who.int/iris/bitstream/handle/10665/258970/9789241550130-eng.pdf?sequence=1

- OIE List Of Antimicrobials Of Veterinary Importance
  https://www.oie.int/doc/ged/D9840.PDF

- Codex Alimentarius Code Of Practice To Minimize And Contain Antimicrobial Resistance
  www.fao.org/input/download/standards/10213/CXP_061e.pdf

- EU Guidelines for the prudent use of antimicrobials in veterinary medicine
  https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf

- EU Guidelines for the prudent use of antimicrobials in human health
  https://ec.europa.eu/health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf

- 'JIACRA' Reports
  https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/analysis-antimicrobial-consumption-resistance-jiacra-reports

- Categorization of Antimicrobial Drugs Based on Importance in Human Medicine in Canada
  https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html

- Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern (CVM GFI #152)
  https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf

- FDA_Guidance for Industry_Judicious Use of MIA drugs in food producing animals (CVM GFI #209)
  https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf

- Control of the Development and Prevalence of Antimicrobial Resistance in Bacteria of Food Animal Origin in Japan: A New Approach for Risk Management of Antimicrobial Veterinary Medicinal Products in Japan; Foodborne Pathogens and Disease, Vol. 11, No. 3 | Review; https://www.liebertpub.com/doi/full/10.1089/fpd.2013.1649#B8

ANNEX II

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.

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 118

Animals or products of animal origin imported into the Union

1. Article 107(2) shall apply, mutatis mutandis, to operators in third countries and those operators shall not use the designated antimicrobials referred to in Article 37(5), insofar as relevant in respect of animals or products of animal origin exported from such third countries to the Union.

2. The Commission shall adopt delegated acts in accordance with Article 147 in order to supplement this Article by providing the necessary detailed rules on the application of paragraph 1 of this Article.

Article 153

Transitional provisions regarding delegated and implementing acts

1. The delegated acts referred to in Article 118(2) and the implementing acts referred to in Articles 37(5), 57(4), 77(6), 95(8), 99(6) and 104(7) shall be adopted before 28 January 2022. Such delegated and implementing acts shall apply from 28 January 2022.

2. Without prejudice to the date of application of this Regulation, the Commission shall adopt the delegated acts referred to in Article 37(4) at the latest by 27 September 2021. Such delegated acts shall apply from 28 January 2022.

3. Without prejudice to the date of application of this Regulation, the Commission shall adopt the delegated acts referred to in Articles 57(3) and 146(2) and the implementing acts referred to in Articles 55(3) and 60(1) at the latest by 27 January 2021. Such delegated and implementing acts shall apply from 28 January 2022.

4. Without prejudice to the date of application of this Regulation, the Commission shall adopt the delegated acts referred to in Article 109(1) and the implementing acts referred to in Articles 17(2) and (3), 93(2), 109(2) and 115(5) at the latest by 29 January 2025. Such delegated and implementing acts shall apply at the earliest on 28 January 2022.

5. Without prejudice to the date of application of this Regulation, the Commission is empowered to adopt delegated and implementing acts provided for in this Regulation as from 27 January 2019. Such delegated and implementing acts, unless otherwise provided in this Regulation, shall apply from 28 January 2022.

When adopting the delegated and implementing acts referred to in this Article, the Commission shall allow sufficient time between their adoption and their start of application.