EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

**Director-General**

Brussels,
SANTE/E5/DB/mcd Ares (2017) 3584639

Dear Professor Rasi, dear Guido,

**Subject: Request for an update of the advice on the impact on public health and animal health of the use of antibiotics in animals (categorisation of antimicrobials and early hazard characterisation)**

On request of the European Commission in April 2013, the European Medicines Agency (EMA) provided in 2014 the scientific advice on the impact on public health and animal health of the use of antibiotics in animals. This advice included a categorisation of critically important antimicrobials from the World Health Organisation list, based on their degree of risk for public health due to resistance development following use in animals, as assessed by the Antimicrobial Advice Ad Hoc Expert Group (AMEG). The updated advice on colistin, published by the EMA in 2016, resulted in a re-classification of this substance.

Furthermore, the EMA recommended that risk assessment of new antimicrobial substances for use in food-producing species should be reinforced by introducing e.g. an early hazard characterisation assessment prior to the submission of a marketing authorisation application.

You have recently informed me (your letter ref. EMA/139924/2017) about the need to revise the AMEG categorisation of antimicrobials and to further elaborate on the proposed early hazard characterisation, indicating the need for a mandate for EMA to reinstate the AMEG to revise the EMA advice of 2014 accordingly. I also acknowledge the problem statement provided, in which the Committee for Medicinal Products for Veterinary Use and the Committee for Medicinal Products for Human Use scientifically justify the need for such a revision.

Therefore, I would like to request the EMA to update its advice regarding the categorisation of antimicrobials and the early hazard characterisation, in line with the terms of reference annexed and, where relevant, to closely collaborate on this matter with the European Centre for Disease Prevention and Control (ECDC) and the European Food

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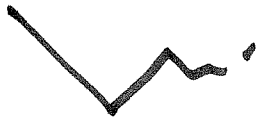
Safety Authority (EFSA), given their shared competences on antimicrobial resistance (AMR).

I would request the EMA to finalise its advice by 31.12.2018.

My services remain at your disposal for further information on this matter. You can contact Dean Bosnjak who is responsible for this dossier and Martial Plantady who is responsible for the coordination of AMR-related issues. Their respective phone numbers and e-mail addresses are indicated below.

Yours sincerely,



Xavier Prats Monne

Encl.: Terms of reference

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D. Mackay, J. Torren, Z. Kunsagi, M. Cavaleri, H. Boone (EMA)

B. Url (EFSA)

A. Ammon (ECDC)

## Annex: Terms of reference

## Request for an update of the advice on the impact on public health and animal health of the use of antibiotics in animals (categorisation of antimicrobials and early hazard characterisation)

### I. Background

The European Commission (EC) requested in April 2013 a scientific advice from the European Medicines Agency (EMA) on the impact of the use of antibiotics in animals on public health and animal health and measures to manage the possible risk to humans.[1]

The scientific advice was prepared by the Antimicrobial Advice Ad Hoc Expert Group (AMEG) and the responses were published in two sets by the EMA in July 2013 and December 2014.[2]

The EC request for advice was divided in four parts. The response published in 2013 dealt with the first request (colistin and tigecycline) while the responses published in 2014 covered the other three requests (ranking of antibiotics; new antibiotics; risk mitigation options). In response to the second request, EMA proposed to classify into three different categories the critically important antimicrobials from the World Health Organisation (WHO) list, based on their degree of risk for public health due to resistance development following use in animals, as assessed by the AMEG. However, for aminoglycosides and certain penicillins no risk profiling was available at the time; EMA recommended this profiling to be done and indicated that future assessments could result in a change of categorisation.

The updated advice on colistin, published by the EMA in 2016[3], resulted in a re-classification of this substance.

The EMA response to the third EC request indicated that the risk assessment of new antimicrobial substances for use in food-producing species should be reinforced, and that "*One of the possible options would be to introduce an early hazard characterisation, addressing the risk to public health from antimicrobial resistance (AMR), to be assessed prior to the submission of a MAA*[4]." The response further indicated, amongst other, that this characterisation could enable decisions on whether the substance should be restricted/banned from the "cascade" use in food-producing species, and that it could also give an indication to marketing authorisation applicants of the potential AMR risk to public health for proposed veterinary medicinal products and the need for risk management measures.

The participants of the EC Workshop on analysis of the EMA advice on the impact on public and animal health of the use of antibiotics in animals, held in Brussels on

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[1] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000639.jsp

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211080.pdf

[4] MAA = Marketing Authorisation Application

26.11.2015, considered an early hazard characterisation assessment as an incentive to the development of new antimicrobials and it was largely supported[5].

The EMA has recently informed the EC about the need to revise the AMEG categorisation of antimicrobials and to further elaborate on the proposed early hazard characterisation, indicating the need to revise the EMA advice of 2014 accordingly. In particular, the problem statement by the Committee for Medicinal Products for Veterinary Use (CVMP) and the Committee for Medicinal Products for Human Use (CHMP), adopted by the EMA on 23.02.2017, in its scientific reasoning indicates, amongst other, that:

- the CVMP, with the scientific input of its Antimicrobials Working Party, is in the process of finalising its considerations on aminoglycosides and penicillins,

- the experience gained indicates that further refinement should be taken into account during the consideration of the categorisation of antimicrobials (e.g. route of administration),

- the AMEG recommendation on reinforced risk assessment/early hazard characterisation for new antimicrobials needs further consideration, especially regarding how such procedure could be implemented within the current regulatory framework, and the specific information that should be submitted if the option is deemed appropriate,

- the preparation of a list of antimicrobial substances which should be reserved for human infections only, if requested by the EC, would require a similar methodology for hazard characterisation.

The CVMP/CHMP problem statement provides further details on the points of the previous EMA advice relating to categorisation and early hazard characterisation which need to be addressed at this stage; these points are reflected in the section II. ("Terms of reference") below.

With regard to the anticipated impact assessment, this problem statement indicates that:

- the revised categorisation may have a significant impact on the selection and use by veterinarians of antimicrobial medicinal products, on national treatment guidelines, ESVAC[6] and JIACRA[7],

- the early hazard characterisation may have an impact on the development and authorisation of new antimicrobials for veterinary use and on the revision of the draft CVMP guideline on assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals.

[5] https://ec.europa.eu/health/amr/sites/amr/files/ev_20151126_workshop-sum.pdf

[6] European Surveillance of Veterinary Antimicrobial Consumption

[7] Joint Interagency Antimicrobial Consumption and Resistance Analysis

## II. Terms of reference

In view of the above, and in accordance with the Article 57(1)(h) and (p) of Regulation (EC) 726/2004, the European Commission asks the EMA to update its 2014 advice on the impact of the use of antibiotics in animals on public health and animal health.

The EMA should address the following points:

1. Categorisation of antimicrobials

- Categorisation of aminoglycosides and penicillins,
- Further refinements of the criteria for the categorisation (e.g. including route of administration),
- Improved communication of the categorisation,
- Consideration of additional categorisation for antimicrobials categorised by the WHO[8] as highly important and important (in addition to the critically important antimicrobials),
- Consideration of other recent work of the WHO on classification of antimicrobials and pathogens (e.g. the 20th edition of the WHO Model List of Essential Medicines and the WHO Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics),
- Consideration of any other relevant work in this area (e.g. OIE list of antimicrobial agents of veterinary importance).

2. Early hazard characterisation

- Detailed analysis of the benefits and risks of an early hazard characterisation; if the analysis would merit continuing with the proposal:
    - Further details on the procedure of the early hazard characterisation,
    - Technical requirements of the early hazard characterisation.

[8] 5th revision of the WHO list of critically important antimicrobials for human medicine: http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/