EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Director General

Brussels,
SANCO/MN/sl/ddg1.d.6(2012)8317

Dear Professor G. Rasi,

Subject: Request for advice on the impact on public health and animal health of the use of antibiotics in animals

The Commission considers antimicrobial resistance to be a public health threat which is of particular importance and to which it attaches high priority. The aims of the Communication from the Commission to the European Parliament and the Council on the 'Action Plan against the rising threats from Antimicrobial Resistance (AMR)' are to strengthen the prevention and control of antimicrobial resistance across all sectors and to secure the availability of new antibiotics.

I would like to stress, with reference to the resolutions of the European Parliament and the Council conclusions and recommendations on this subject, that the European Parliament and the Council also consider antimicrobial resistance to be a public health threat and issued a call for action.

The three agencies ECDC, EFSA and EMA are intensively involved in carrying out the Commission action plan on antimicrobial resistance. However, additional scientific advice is needed. In particular Action 7 sets out a request for scientific advice on whether the development of new classes of veterinary antibiotics could contribute to reducing antimicrobial resistance and whether these new classes could be used in the veterinary sector or should be set aside for human use.

Therefore, I would like to request EMA to provide scientific advice in accordance with the terms of reference as included in the Annex to this letter. The request is subdivided in four parts with different timelines. This approach should help the Agency to manage the workload and structure effectively the advice process. The suggested dates foreseen for the requested scientific advice on the first, second, third and fourth part are June 2013, June 2014, December 2014 and December 2014, respectively.

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It is specifically important that all relevant scientific committees of EMA (e.g. CVMP and CHMP) are involved, in order to ensure a comprehensive and multifaceted approach. Moreover, the involvement of EFSA and ECDC at an early stage in establishing this advice is important given their shared competences in the area of antimicrobial resistance. This is also in line with Article 59 of Regulation (EC) No 726/2004 and the cooperation agreement between these three agencies on the integrated use and reporting of data on consumption of, and resistance to, antimicrobial agents in humans, animals and food in the European Union.

Yours sincerely,

Paola Testori-Coggi

Annexe: Terms of reference

Enclosure: Mr Marc Sprenger, Executive Director ECDC
Ms Catherine Geslain-Lanéelle, Executive Director EFSA
Ms Hilde Boone, Mr Emer Cooke, Mr David Mackay (EMA)

Annex: Terms of reference for advice on the impact on public health and animal health of the use of antibiotics in animals

The continued availability of effective antibiotics is important for combatting infectious diseases in both humans and animals. Resistance from the use of antibiotics is a recognised and growing concern in the use of both human and veterinary antibiotic medicines.

The concern over the use of antibiotics in animals has led to the publication of a number of reports in Europe[1] and other regions of the world. Some reports emphasise the need for greater control over the use of antibiotics in animals because of the (potential) public health impact, but there are also reports suggesting that there is insufficient evidence to support the link between the use of antibiotics in animals and the occurrence of resistant bacteria in humans. However, there is mounting evidence that antibiotic use in animals contributes to the development of resistance in bacteria for humans for at least some organisms and some antibiotics. In November 2009 EFSA, ECDC and EMA issued a joint report on AMR[2] which focussed on zoonotic infections. This report specified the classes of antibiotics of high concern to public health and ranked four combinations of organism/antibiotics as most relevant for public health in the EU.

Following the publication of the above mentioned joint report of EFSA, ECDC and EMA on AMR a new issue emerged: the role of 'old' antibiotics or new antibiotics belonging to 'old' classes of antibiotics that have been re-introduced or have a new use to treat multi-resistant bacteria in humans. It appears that some of these antibiotics have become life-saving treatments for human patients, such as for example the antibiotics colistin and tigecycline. However, because these antibiotics or other related antibiotics are also being used in animals, this use may affect the efficacy of such antibiotics for treatment of human infections. When these antibiotics were granted marketing authorisations for veterinary use, the importance of these antibiotics for human health was not known or was not of concern. Therefore this aspect could not be considered in the marketing authorisation procedure. It is pointed out that some of these antibiotics may not be authorised for veterinary use, for example tigecycline. However, in such case the potential for a concern from the use of veterinary antibiotics falling within the same class needs to be assessed.

Innovation in veterinary pharmaceuticals is required in order to ensure the future availability of antibiotics to protect animal health and welfare. The animal health industry needs a predictable and consistent regulatory system to enable them to plan their investments. Clarification will be needed as to whether new types of veterinary antibiotics could receive a marketing authorisation or not. The advice should be the scientific base for establishing regulatory requirements for veterinary antibiotics in the future. Moreover, based on the advice the Commission will decide whether the development of veterinary antibiotics should be encouraged.

The requested advice is divided in four parts with specific timelines. This approach should help the Agency to structure effectively the process. EMA is requested to collaborate with EFSA and ECDC, where relevant, given their shared competences on AMR. With these points in mind and in the context of the Action plan against the rising threat from AMR, the

[1] For example report of European Parliament on the Microbial Challenge-Rising threats from Antimicrobial Resistance; Council conclusions of 22 June 2012 on 'The impact of antimicrobial resistance in the human health sector and in the veterinary sector – a 'One Health' perspective';

[2] Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant *Staphylococcus aureus* (MRSA) in livestock, companion animals and food (link: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500004306.pdf) .

following scientific advice is requested.

1. Advice on 'old' antibiotics or new antibiotics belonging to 'old' classes of antibiotics that have been re-introduced or have a new use to treat multi-resistant bacteria in humans, in particular colistin and tigecycline. EMA should consider in particular:

a) Possible links between the use of those substances in animals (where relevant) and resistance in bacteria of animal origin;

b) The impact of use of those substances or other related antibiotics in animals on human health and whether restricting or not their use as veterinary medicines would have an impact on the development of resistance in bacteria causing infections in humans.

2. Advice on classes or groups of antibiotics ranked according to their relative importance for their use in human medicine, in particular considering whether these antibiotics are essential to treat multi-resistant infections in humans in the EU. The Agency should take into account the existing work of the WHO on critical antimicrobials and consider the need, advantages, disadvantages and feasibility of categorising antibiotics as for example first line, second line or last resort antibiotics.

3. Advice what the possible impact could be on the treatment of resistant bacteria in humans of granting marketing authorisations for new classes of veterinary antibiotics, and whether there is a need to restrict or ban the use in animals of certain new classes of antimicrobials or antibiotic substances (especially those that are important in human medicine) that are currently not authorised. It is stressed that the advice could discuss a positive impact (for example, better management of resistance in animals) or a negative impact (for example, increased risk of development of resistance in humans).

4. Advice on the risk mitigation options [alternatives], including an assessment of costs and benefits, related with the use of certain classes of antibiotics or antibiotic substances that are of critical important in human medicine and are currently authorised as veterinary medicinal products.

The above requested advice should point out whether or not there is any evidence - direct or indirect - on the transfer of resistance from animals to human bacteria. Advice on possible measures to restrict the use of veterinary antimicrobials could also cover off-label use. If the advice were to propose a ban on certain uses of antimicrobials, it would be essential to clearly lay down the criteria for this ban in terms of risks that would be considered unacceptable, irrespective of the benefits to animal health and welfare of the medicine concerned.

For any questions regarding this request please contact Martinus Nagtzaam (SANCO D6).