EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Director-General

Brussels,
SANTE/D6/DB/ia
Ares(2015).....

Dear Professor Rasi,

Subject: **Request for an update of the 2013 advice on the impact on public health and animal health of the use of antibiotics in animals (colistin)**

I would like to submit a formal request to the EMA for an update of its 2013 advice on the impact on public health and animal health of the use of antibiotics in animals.

In the 2013 advice, the EMA made recommendations for the use of colistin in animals within the EU, based on the evidence available at that time. The advice also provided that the recommendations should be reviewed if there were a substantial increase of colistin resistance in animal bacteria and other new relevant information for public health.

A recent scientific publication reported on the emergence of a plasmid-mediated colistin (polymixins) resistance mechanism (gene *mcr-1*) in animals and humans in China. This gene has now been found also in Europe.

Therefore I would like to request the EMA to update its advice on colistin, 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 Safety Authority (EFSA) , given their shared competences on AMR.

In view of the importance of this topic, I would request EMA to finalise its opinion **by 30.06.2016 at the latest**.

Prof Guido Rasi
Executive Director
European Medicines Agency
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Canary Wharf
London E14 5EU
United Kingdom

My colleagues are at the disposal of EMA for further information on this matter. [redacted] is responsible for this dossier, [redacted] is responsible for the coordination of AMR-related issues and [redacted] is the relevant contact point in the Unit in charge of relations with agencies and advisory groups. Their contact details are indicated below.

Yours sincerely,

For the Director General absent,
Martin SEYCHELL
Deputy Director General

Xavier Prats Monné

Annex: Background and Terms of reference

Contacts:

[redacted]

Annex

Request for an update of the 2013 advice on the impact on public health and animal health of the use of antibiotics in animals (colistin)

Background

The European Commission requested in April 2013 a scientific advice from the 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. This was in accordance with the Commission "Action plan against the rising threats from AMR" adopted in November 2011.

The 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.

The advice published in 2013 dealt with the first part of the Commission request: old antibiotics/classes of antibiotics used to treat infections with multi-resistant bacteria in humans, in particular colistin and tigecycline. This advice indicated that, from the information available, transfer of resistance to colistin products encoded by mobile genetic elements (e.g. plasmids) between bacteria or from animals to humans has not been demonstrated. Based on the evidence at the time, it was considered appropriate to maintain the use of colistin in veterinary medicine but with restrictions (indications only for therapy and metaphylaxis but not for prophylaxis) in order to minimize any potential risk associated with a broader use.

The EMA advice of 2013 provided recommendations for colistin use in animals within the EU and indicated that they should be reviewed if there is a substantial increase of colistin resistance in animal bacteria and other new relevant information for public health. More specifically, in the abstract of this advice it is stated: "*For colistin use in particular, detailed monitoring of colistin resistant bacteria is required to confirm horizontal gene transfer is not involved and overall prevalence remains low. As soon as colistin resistance determinants are found on mobile genetic elements in the bacteria of concern as well as from human or animal origin, or a clonal explosion of virulent bacteria takes place, a new risk assessment would be required.*".

A recent scientific publication[1] indicated that in bacteria (*Enterobacteriaceae*) from pigs, retail raw meat (pork and chicken) and human patients in China a gene (*mcr-1*) has been found which enables horizontal (plasmid-mediated) transfer of resistance to colistin (polymyxins) between bacteria. This gene has now been found also in bacteria in Europe[2].

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[1] Liu Y-Y, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis 2015* (Published online November 18, 2015: http://dx.doi.org/10.1016/S1473-3099(15)00424-7)

[2] http://www.food.dtu.dk/english/News/Nyhed?id=FF5EA50D-7C33-44A4-8BE8-7CC52417DEAF

The Commission has been informed by the EMA on 10.12.2015 (letter ref. EMA/830805/2015), that the Committee for Medicinal Products for Veterinary Use (CVMP) considered the above publications during its December 2015 plenary meeting, took into account the recommendations of its Antimicrobials Working Party, and recommended the EMA to reinstate the AMEG group in order to update the previous advice on colistin. Following this recommendation, the EMA asked the Commission to be given a mandate to update this advice.

Terms of reference

In view of the above, and in accordance with the Article 57(1)(p) of Regulation (EC) 726/2004, the Commission asks EMA:

1. To update the 2013 advice on colistin by taking into account the recently published information on horizontally transferable resistance to colistin (polymyxins). The EMA should re-assess:

a) possible links between the use of colistin (polymyxins) in animals (where relevant) and resistance in bacteria of animal origin;

b) the impact of use of colistin (polymyxins) in animals on human health and whether restricting its use in animals would have an impact on the development of resistance in bacteria causing infections in humans.

In particular, consideration should be given to whether the conclusions and recommendations made in 2013 remain valid. If the updated advice recommends a ban of colistin (polymyxins) use in animals, it would be essential to clearly demonstrate that the risks for public health outweigh the benefits for animal health and welfare.