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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for the development of a reflection paper on the use of extended-spectrum penicillins in animals in the European Union: development of resistance and impact on human and animal health

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Keywords	Extended-spectrum penicillins, animals, veterinary medicine, aminopenicillins, antimicrobial resistance.

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1. Introduction

As part of the European Commission (EC) Action plan against antimicrobial resistance (European Commission, 2011), the EC requested advice from the European Medicines Agency (EMA) on the impact of the use of antibiotics in animals on public and animal health and measures to manage the possible risk to humans. Within this advice, it was noted that extended-spectrum penicillins with activity against *Enterobacteriaceae* might have the ability to facilitate the spread of bacterial isolates resistant to extended-spectrum beta-lactams, similarly to 3rd- and 4th-generation cephalosporins, and therefore further risk profiling was recommended (EMA, 2014).

This concept paper will focus on authorised veterinary medicinal products containing extended-spectrum penicillins[1] (aminopenicillins, including their combinations with beta-lactamase inhibitors) which are currently classified as Category 2[2] by EMA/AMEG[3], pending risk profiling before a final decision on the category. Aspects regarding the use of these substances in veterinary medicine and their potential public health risks are discussed.

2. Problem statement

Bacterial resistance to extended-spectrum beta-lactams has evolved rapidly in recent years especially in *Enterobacteriaceae* (Liebana et al., 2013). These bacteria carry beta-lactamases (such as ESBL-, AmpC cephalosporinases or carbapenemases) capable of hydrolysing many critically important beta-lactam antimicrobials. Bacterial isolates resistant to extended-spectrum beta-lactams are also often resistant to several other antimicrobial classes, limiting the treatment options. Similar resistance development has been observed in several human and animal pathogens (Abraham et al., 2014; ECDC/EMA, 2009; Seiffert et al., 2013). Resistant bacteria and their resistance determinants can be transferred between animals and humans (EMA/CVMP, 2015). These bacteria often colonise food animal species and the same bacteria are also found in food of animal origin, although the occurrence in food is usually lower than in animals (Doyle, 2015; Economou and Gousia, 2015). This has raised a concern that veterinary use of antimicrobials may present a public health risk to humans. Decrease in the use of antimicrobials in animal production in the EU as well as promotion of responsible use of antimicrobials has a high priority (European Commission, 2011).

The veterinary use of 3rd- and 4th-generation cephalosporins is linked to emergence of resistance to extended-spectrum beta-lactams in food animal species. It has been assessed by the EMA that veterinary use of these substances may present a risk for public health similarly to fluoroquinolones (EMA, 2014). These agents were classified as Category 2 antimicrobials by the EMA (EMA, 2014). Category 2 agents are considered critically important antimicrobials (CIAs) for which the risk to public health from veterinary use is only considered acceptable provided that specific restrictions are applied. These antimicrobials should be used only when there are no alternative antimicrobials authorized for the respective target animal species and indication.

Extended spectrum penicillins, especially those with beta-lactamase inhibitors, have a spectrum of activity similar to 2nd- and 3rd-generation cephalosporins. Extended-spectrum penicillins include 1) aminobenzylpenicillins (later: aminopenicillins), 2) amidopenicillins, 3) carboxypenicillins, 4) ureidopenicillins, and 5) beta-lactamase resistant penicillins. Extended-spectrum penicillins are often combined with beta-lactamase inhibitors (such as clavulanic acid) to enhance their activity against

[1] In this paper extended spectrum penicillins refer to amoxicillin and ampicillin which are included within the ATCvet code QJ01CA, classified as extended spectrum penicillins. According to the ATCvet classification, combinations of penicillins, including beta-lactamase inhibitors, are included under the code QJ01CR.
[2] Antimicrobials used in veterinary medicine where the risk for public health is currently estimated as higher
[3] AMEG: Antimicrobial Advice ad hoc Expert Group

beta-lactamase producing bacteria. Depending on the substance, their spectrum covers *Enterobacteriaceae*, or even *Pseudomonaceae* (Giguère et al., 2013). Group 1 substances (ampicillin, amoxicillin, and their combinations with clavulanic acid) are authorised in veterinary medicine and have been widely used for decades for the treatment and prevention of infections in many food and companion animal species. Substances belonging to other groups have marketing authorisations only for humans. The use of these substances is limited to individual companion animals as off-label use and is thus beyond the scope of this document.

Veterinary authorised extended-spectrum aminopenicillins and their combinations with beta-lactamase inhibitors are classified as Category 2[4] by EMA/AMEG pending a final decision on the category. Veterinary use of aminopenicillins might have the ability to facilitate the spread of antimicrobial resistance similarly to 3rd- and 4th-generation cephalosporins, and therefore further risk profiling is needed (EMA, 2014).

3. Discussion

It is evident after seven decades of antimicrobial use, that the use of antimicrobials is a cause of antimicrobial resistance. Many studies have reasserted the link between use and resistance: the higher the use and thus the selection pressure – the higher the resistance (ECDC/EFSA/EMA, 2015; ECDC/EFSA/EMA/SCENIHR, 2009). Aminopenicillins are widely used both in animals and humans. Penicillins were the second largest antimicrobial class used in food animal species, including horses, in the EU in 2012 (EMA/ESVAC, 2014). Extended-spectrum penicillins contributed a remarkable proportion of total penicillin use, although there is wide variation between the member states. In food producing animal species, the treatment indications of aminopenicillins include respiratory infections, mastitis, metritis, and enteric infections in major livestock animal species (pigs, cattle and poultry). Aminopenicillin formulations include oral powder and solution, and injectables either alone or in combination with other antimicrobial classes. Aminopenicillins with or without beta-lactamase inhibitors are also widely used for the treatment of dogs and cats (Rantala et al., 2004; Thomson et al., 2009) and to lesser extent in horses (Dallap Schaer et al., 2012; Dunkel and Johns, 2015).

Due to decades of widespread use of aminopenicillins, resistance to these substances is very frequent in zoonotic and indicator bacteria from humans, animals and food of animal origin (EFSA/ECDC, 2014) as well as in animal pathogens (Nedbalcova et al., 2014; Swedres-Svarm, 2013) and the nature of this resistance has developed in recent years. Resistance in these bacteria to 3rd-generation cephalosporins is still at a low level, although evidence indicates an increase in resistance (EFSA/ECDC, 2014). Several studies have reported high occurrence of 3rd-generation cephalosporin resistance among *Enterobacteriaceae* of livestock and food from livestock origin (Doyle, 2015; Economou and Gousia, 2015). Verkade and Kluytmans (2014) report about emerging methicillin resistant *Staphylococcus aureus (*MRSA) especially in pigs, which has raised concerns about antimicrobial use in animals and its potential consequences to human health. Resistance determinants coding resistance to aminopenicillins and cephalosporins are often located in transmissible gene elements to which different types of resistance genes cluster (Jackson et al., 2015). Therefore the use of aminopenicillins may also select resistance to other antimicrobial classes in addition to beta-lactams. Likewise, the use of other antimicrobial classes may select co-resistance to extended-spectrum penicillins.

Despite a high occurrence of aminopenicillin resistance, aminopenicillins remain important agents in veterinary medicine. They are still effective against streptococci and many respiratory pathogens such as *Pasteurellaceae.* In companion animal species these drugs are important in treating bite wound infections, urinary tract infections and respiratory infections. Ensuring the availability of these

[4] Antimicrobials used in veterinary medicines where the risk for public health is currently estimated as higher

important drugs in veterinary medicine may also decrease the need to use other agents in animal husbandry. When combined with clavulanic acid, these substances can be used for treating infections caused by *Enterobacteriaceae* provided that a pathogen is susceptible to the drug, and that sufficient dosages are used, since MICs (minimal inhibitory concentrations) of the wild type *Enterobacteriaceae* for aminopenicillins are relatively high (Giguère et al., 2013). The importance of proper diagnosis and bacteriological culture, and excluding other infectious agents, cannot be overemphasised since the use of inefficient drugs or too low dosages may further select resistant isolates.

To conclude, aminopenicillins are widely used drugs and resistance to them is common both in humans and in animals. Regardless of this, their use still offers many benefits. Aminopenicillins have a wide margin of safety and many important pathogens are still susceptible to these drugs. For many conditions aminopenicillins can be considered as a primary treatment option in many animal species. However, because these agents are also listed as CIAs for humans and the AMEG advice, further risk profiling is needed to decide if these are to be regarded in the same way as 3rd- and 4th-generation cephalosporins (EMA, 2014).

4. Recommendation

The CVMP recommends drafting a reflection paper to decide if veterinary authorised aminopenicillins, including their beta-lactamase inhibitor combinations, are to be included in Category 2, i.e. regarded in the same way as 3rd- and 4th-generation cephalosporins and fluoroquinolones with restrictions placed on their use.

The reflection paper should critically review recent information on use of those substances in food producing and companion animals in the EU, their effect on development of resistance to these substances in bacterial species that are of importance for human and animal health, and the potential impact on animal and human health.

The reflection paper should include information on:

- Their use in veterinary medicine;
- Their use in human medicine;
- Mechanisms and spread of resistance in relevant bacteria;
- Occurrence of resistance in bacteria from food producing and companion animals;
- Possible links between the use of these substances in animals and resistance in bacteria of animal origin;
- Impact on animal health;
- Impact on human health.

5. Proposed timetable

The end of consultation of the concept paper is 31 October 2015; the reflection paper is expected to be released for consultation by the second quarter of 2016.

6. Resource requirements for preparation

The development of the reflection paper will require the appointment of one Antimicrobials Working Party (AWP) rapporteur, and physical and virtual meetings of the AWP rapporteur and experts.

7. Impact assessment (anticipated)

The reflection paper will provide information on the development of antimicrobial resistance to these substances and provide further clarification on the need and priority of risk management measures. In addition, the reflection paper may detect gaps in our knowledge and identify subjects for further research.

8. Interested parties

Veterinarians, veterinary pharmaceutical industry, human healthcare professionals, public health professionals, farmers, consumers and regulators.

9. References to literature, guidelines, etc.

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