参考資料6

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMA/381884/2014
Veterinary Medicines Division/CVMP/CHMP

Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals

Answer to the second request from the EC (ranking of antibiotics)

Answer to the third request from the EC (new antibiotics)

Answer to the fourth request from the EC (risk mitigation options)

Agreed by the Antimicrobial Advice ad hoc Expert Group (AMEG)	24 June 2014
Adopted by the CVMP for release for consultation	10 July 2014
Adopted by the CHMP for release for consultation	24 July 2014
Start of public consultation	1 August 2014
End of consultation (deadline for comments)	30 September 2014
Agreed by the Antimicrobial Advice ad hoc Expert Group (AMEG)	24 November 2014
Adopted by the CVMP	*11 December 2014*
Adopted by the CHMP	*18 December 2014*

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of Contents

Introduction

Background

In April 2013, the European Commission (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[1]. This forms part of the EC Action plan against the rising threats from Antimicrobial Resistance[2].

The request was divided in four questions:

Question 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."

The response was published in July 2013 and includes advice from the Agency on the use of colistin and tigecycline in animals[3].

The draft answers to Question 2 (ranking of antibiotics), Question 3 (new antimicrobials) and Question 4 (risk mitigation options) are provided below.

Question 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 multidrug-resistant infections in humans in the EU. The Agency should take into account the existing work of the WHO on critical antibiotics and consider the need, advantages, disadvantages and feasibility of categorising antibiotics as for example first line, second line or last resort antibiotics."[4]

Question 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)."

[1] See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf
[2] See http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf
[3] See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/07/WC500146812.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146813.pdf and http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146814.pdf
[4] See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf

Question 4:

The EC has requested the European Medicines Agency to provide: "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 critically-important in human medicine and are currently authorised as veterinary medicinal products."

Preparation of the answers

The answers were prepared by the Antimicrobial Advice ad hoc Expert Group (AMEG). The AMEG is composed of representatives and experts from the European Medicines Agency (EMA) and its Committee for Medicinal Products for Veterinary Use and Antimicrobials Working Party (CVMP/AWP) and its Committee for Medicinal Products for Human Use and Infectious Disease Working Party (CHMP/IDWP), the European Food Safety Authority (EFSA), the European Centre for Disease Prevention and Control (ECDC) and the Joint Interagency Antimicrobial Consumption and Resistance Analysis Report (JIACRA).

A stakeholders meeting was organised on 28 February 2014 and a public consultation launched with a deadline for answer on 1st April 2014. The answers received to Questions 3 and 4 were taken into account for the preparation of the draft answers.

The final answers were endorsed during the CVMP meeting of 8-10 July 2014 and CHMP 21-24 July 2014 plenary meeting.

Following the public consultation period the comments received from Stakeholders were taken into account for the revisions of the opinion. The overview of the comments received have been published[5].

Throughout the document the term 'antimicrobial' has been used in place of 'antibiotic' or 'antibacterial'.

I. Summary assessment and recommendations

Summary answer to the second request from the EC (ranking of antibiotics)

A categorisation of the WHO critically important antimicrobials[6] (CIAs) was prepared based on their degree of risk to man due to resistance development following use in animals, as assessed by the AMEG.

The AMEG proposes to classify antimicrobials from the WHO CIA list in three different categories:

- Category 1 as antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited,
- Category 2 as antimicrobials used in veterinary medicine where the risk for public health is estimated higher and
- Category 3 as antimicrobials not approved for use in veterinary medicine.

Category 1 includes some classes of antimicrobials that are listed as CIAs by WHO according to its criteria and for which use in veterinary medicine is extensive, but that nevertheless were considered to

[5] Overview of comments received on 'Answers to the request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals' (EMA/381884/2014), document reference EMA/598105/2014.
[6] For this document "antimicrobials" is defined as "active substance of synthetic or natural origin which destroys microorganisms, suppresses their growth or their ability to reproduce in animals or humans". In this context, antivirals, antiparasitics and disinfectants are excluded from the definition.

belong in this lower risk category. These classes include certain penicillins, macrolides, tetracyclines and polymyxins. There are no recommendations to avoid use of Category 1 compounds. Nevertheless, these antimicrobials are not devoid of negative impact on resistance development and spread. To keep the risk from use of these classes within Category 1 as low as possible the current principles of responsible use in everyday practice should be adhered to. Non-responsible use, including unnecessary use and unnecessarily long treatment periods, should be avoided and group treatment restricted to situations where individual treatment is not feasible.

Category 2 includes those antimicrobial classes listed as CIAs by WHO for which the risk to public health from veterinary use is only considered acceptable provided that specific restrictions are placed on their use (i.e. fluoroquinolones and systemically administered (parenteral and oral), 3rd- and 4th-generation cephalosporins). These reserved antimicrobials should be used only when there are no alternative antimicrobials authorized for the respective target species and indication.

Pending risk assessment, two other classes of antimicrobials have been included in Category 2, namely penicillins and aminoglycosides, as follows: Penicillins form a diverse class that has been divided into subclasses for the task presented. Some of these subclasses have efficacy against Enterobacteriaceae and have a high risk for transfer of resistance. Further risk profiling is needed to decide if these particular penicillins are to be regarded in the same way as 3rd- and 4th-generation cephalosporins. For the aminoglycosides, there might be a resistance risk associated with the use of this class which has as yet not been addressed.

Category 3 includes a number of the classes/compounds that are not approved in veterinary medicine and are listed separately in Table 2. The extent of use of these classes would be low, provided the restrictions detailed in Art 10 and 11 of Directive 2001/82/EC are complied with. According to these restrictions these substances may only be used by way of exception and only in companion animals (including horses that are not intended for food consumption) as MRLs have not been established to allow their use in food producing species.

This categorisation may be considered as one element when deciding on when/whether to use a certain class/compound in veterinary medicine but may not be used as the sole base when creating treatment guidelines or when deciding on risk mitigation activities. This categorisation does not directly translate into a treatment guideline for veterinary medicine.

When writing treatment guidelines, decisions on appropriate risk management measures have to be made at the class, substance or even at the indication level and consider also the route of administration. In veterinary medicine, the number of species, the wide differences in routes of administration and indications (from intramammary treatment of individual cows to treatment of thousands of fish by in-feed medication) make generalisations on antimicrobial categorisation and risk management not possible. Consequently no recommendation on treatment guidelines (i.e. if a certain compound should be first line, second line, etc., for a certain species and indication) can be given. The categorisation may be considered as one element when developing such guidelines but a number of other factors need to be considered, some of them on a regional basis, and therefore treatment guidelines need to be locally developed and implemented rather than at EU level.

Development and implementation of evidence-based national and regional treatment guidelines is encouraged.

A summary table specifying the classification for each class of antimicrobial is provided on page 11.

Summary of answer to the third request from the EC (new antimicrobials)

A specific risk assessment for each new substance or new class of antimicrobial is needed to assess the importance of the substance to human health and the risk of transfer of resistance of relevance for public health from treated animals to humans. Therefore, general conclusions cannot be drawn on the risk from substances not currently authorised for use in veterinary medicine. Recommendations can only be made on the need for and when to assess the risk from the possible authorisation of these new substances.

The authorisation of completely new classes of antimicrobials for use in animals might decrease animal and public health risk related to antimicrobial resistance provided co-selection by earlier authorised products is not implicated. To obtain a marketing authorisation (MA) for an antimicrobial, a benefit risk assessment concluding that there is an acceptable level of risk relating to resistance in bacteria (or resistance determinants) of relevance for public health in relation to the benefit for animal health and welfare is required. For new antimicrobials this risk assessment (RA) should be reinforced by introducing e.g. an early hazard characterisation only assessment prior to the submission of a marketing authorisation application (MAA).

Some substances not authorised in veterinary medicine are used off-label in animals; such use can be an indicator of the needs for new substances for animals. For the discussions of the response to Question 3, the focus has been on medicinal products only authorised in human medicine. Precise information on such use in animals is lacking and therefore the risk for public and animal health from use of those antimicrobials cannot be quantified.

A list of veterinary diseases for which human-only antimicrobials are known to be used off label was collected from individual case reports and complemented with information provided by Stakeholders. To help assess the risk of antimicrobial resistance due to off label use in animals of antimicrobials only authorised for use in man, a declaration system of this off label use could be implemented.

The main recommendations from the answer to Question 3 are:

- The risk assessment of new antimicrobial substances for use in food producing species should be reinforced. 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. Until this assessment is completed, any new antimicrobial substance (including human-only authorised) would be prohibited from use in food-producing species.
- At the time of first approval for new antimicrobial substances / a new class of antimicrobials in veterinary medicine, marketing authorisation holders (MAHs) should have plans in place to monitor susceptibility in zoonotic and indicator bacteria through approved programmes; these data should be provided by the MAH to the regulatory authorities and be comparable with human AMR surveillance data.
- Based on the outcome of antimicrobial resistance surveillance and monitoring of usage, a new risk assessment could be required for all products of a specific antimicrobial class, encompassing both generic and reference products.
- A declaration system should be put in place in order to assess the extent and evolution of off label use of human-only authorised antimicrobials.
- Flexible tools to allow banning or limitation of off label use in animals of certain antimicrobials/classes authorised only in human medicine following an unfavourable hazard characterization or benefit-risk assessment should be included in future legislation.

The detailed recommendations on Question 3 can be found on page 40 onwards.

Summary answer to the fourth request from the EC (risk mitigation options)

International organizations such as Codex Alimentarius, the WHO and the OIE have produced a number of standards, guidelines and recommendations for possible risk management options, both in general and specifically for certain antimicrobials where resistance is considered to be of higher risk to public health. Such guidelines and recommendations range from prioritization in the use of certain antimicrobials in food animals to substantiate restrictions in their use, particularly in relation to 3rd- and 4th-generation cephalosporins, and to revision of responsible use guidelines. Because of the importance ascribed to co-resistance in the horizontal transmission of resistance, decreasing the frequency of use of antimicrobials in animal production in the EU in accordance with responsible use guidelines has been afforded high priority, particularly in relation to resistance to 3rd– and 4th-generation cephalosporins and carbapenems.

In addition to actions performed at the EU level, a range of measures are in place in individual countries, ranging from voluntary restrictions on the use of certain CIAs, to bans on their first-line use in certain animal species if sensitivity tests have not been undertaken. Many of the restrictions have been applied particularly in Scandinavian countries, although more recently voluntary controls on the use of 3rd- and 4th-generation cephalosporins are being introduced in other Member States (MSs). Difficulties in estimating the impact of risk management measures have been acknowledged. Such difficulties include (a) the complexity in linking antimicrobial usage in food production animals to resistance in bacteria from human samples in EU MSs, (b) problems in identifying the effects of a single action when several actions may be implemented simultaneously, (c) difference in assessing the risk(s) associated with the use of the same antimicrobial in different animal species, and (d) the effects of cross- and co-resistance. Finally what may be regarded as the key 'measurements of success' and desired outcomes for an effective policy, and how they will be measured are stated.

Overall, the strongest evidence for potential beneficial effects to human health of risk mitigation measures involving reductions in the use of CIAs, and particularly 3rd- and 4th-generation cephalosporins and fluoroquinolones, are reductions in the occurrence of resistance to such antimicrobials in *E. coli* from broilers, poultry meat and pigs in countries where such policies have been actively implemented. Most evidence for this has come from studies in Scandinavian countries and the Netherlands but as yet the effects of voluntary or compulsory withdrawal of cephalosporins for use in food animals in several EU MSs have not been assessed.

The potential for a negative impact on animal health when risk management measures are implemented must be considered. Therefore close attention may need to be paid to husbandry conditions when measures to reduce antimicrobial consumption are implemented. Examples of existing positive and negative aspects of various risk management measures undertaken by individual MSs have been considered, together with details of costs, both real and estimated, that have been attributed to the control of antimicrobials in food animals. Possible further regulatory and non-regulatory risk management measures, together with their pros and cons that may be considered have also been provided.

The expiry of marketing protection often, but not always, results in the entry of generics in the market and a consequent decrease in price of concerned medicines. The increased availability of generics appears to have contributed to large increases in usage levels of certain CIAs because of a lowering of costs and increase of marketing activities. Off label use of antimicrobials authorised in veterinary medicine covers many different situations. Examples in the context of this question include the use of

an approved veterinary product for a non-approved indication or in a non-approved species. Information provided by stakeholders documents a number of relevant indications where there is a lack of authorised antimicrobial products for major species. More information is needed on off label use, especially on off label use of CIAs, before an assessment can be made of any risk this may have for AMR development.

Assessment of the EU-wide impact of new risk management measures requires the development of internationally-agreed systems that are capable of measuring their success or failure through adequate monitoring systems of antimicrobial sales/use and resistance. Such monitoring systems may include:

- Monitoring by ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) of changes in antimicrobial consumption, in particular of fluoroquinolones and cephalosporins as a means to measure impact of actions implemented.
- More precise data by animal species/livestock production categories in future ESVAC reports, including e.g. the use of DDDA (Defined Daily Dose Animals) and DCDA (Defined Cure Dose Animals).
- Prescribers should keep records of off-label use to be provided at the request of the Authorities.
- Authorities should be encouraged to collect data on off label use.
- Regular joint analyses of the evolution of antimicrobial resistance and consumption by the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) EU expert group are recommended.

In addition the following activities should be implemented:

- Reduction of overall antimicrobial consumption. In light of the importance ascribed to co-resistance, high priority should be given to decreasing the total antimicrobial use in animal production in the EU.
- Promotion of good farming practices and animal husbandry.
- Further research is recommended into:
    - The off label use of antimicrobials in animals;
    - The extent of metaphylactic use of orally administered AMs and the impact of this practice on the development and persistence of resistance in the gut microflora of the animals;
    - Pathways of dissemination of antimicrobial-resistant bacteria from animals to food;
    - Methods for the quantification of the spread of resistance genes from commensals to pathogens in foods and the environment;
    - Methodologies to evaluate the potential economic consequences and impact on both human and animal health and welfare that would result from the introduction of new risk management measures;
- Appropriate strengths and pharmaceutical forms of those antimicrobials identified with a lower risk should be available and authorised for veterinary use in all EU countries. Antimicrobials should be marketed with the adequate pack size, according to the required posology for animal treatment.

Legal tools should be provided to allow restrictions to be placed on the use of the “cascade” depending on the outcome of an AMR risk assessment conducted within the framework of the medicines authorisation procedure. Should future legislation on antimicrobial usage be considered necessary following such risk assessments, then flexible tools should be in place to enable restriction of use.

Adherence to the latest guidelines and recommendations from international bodies, regulatory authorities and professional associations on responsible use is considered to be of primary importance, particularly in relation to the use of antimicrobials regarded as of critical importance for human health.

The overall conclusions on Question 4 can be found on page 61 onwards.

Data summary table

The antimicrobial classes have been classified as Category 1, 2 or 3 according to the risk to public health resulting from development of antimicrobial resistance.

Table 1: Summary table

Antimicrobial class **Category 1** Antimicrobials used in veterinary medicine where the risk for public health is currently estimated low or limited	**Hazard of zoonotic relevance (as detailed in Q2, Table 1)**	**Probability of resistance transfer (as detailed in Q2, Table 2)**	**Use in veterinary medicine (EMA/ESVAC, 2013) and information from Member States Marketing Authorisations**	**Concluding remarks**
Macrolides (including ketolides)	*Campylobacter* spp. *Salmonella* spp.	High	Approved (including group medication)	Compliance with responsible use principles is necessary to reduce the risk Measures to reinforce responsible use principles are needed
Penicillins, Natural	None specific	High	Approved (including group medication)	Compliance with responsible use principles is necessary to reduce the risk for co-resistance
Penicillins: Narrow-spectrum, β-lactamase-resistant penicillins	None specific	High	Approved (predominately intramammary formulations)	Compliance with responsible use principles is necessary to reduce the risk responsible use principles are needed due to risk for co-resistance
Polymyxins (e.g. colistin)	Enterobacteriaceae	Low	Approved (including group medication)	See response to Question 1
Rifamycins	None specific	High	Approved (limited use predominantly in horses and intramammary formulations)	Compliance with responsible use principles is necessary to reduce the risk for co-resistance

Antimicrobial class **Category 1** Antimicrobials used in veterinary medicine where the risk for public health is currently estimated low or limited	**Hazard of zoonotic relevance (as detailed in Q2, Table 1)**	**Probability of resistance transfer (as detailed in Q2, Table 2)**	**Use in veterinary medicine (EMA/ESVAC, 2013) and information from Member States Marketing Authorisations**	**Concluding remarks**
Tetracyclines	*Brucella* spp.	High	Approved (including group medication)	Compliance with responsible use principles is necessary to reduce the risk for co-resistance

Category 2 Antimicrobials used in veterinary medicine where the risk for public health is currently estimated higher	**Hazard of zoonotic relevance**	**Probability of resistance transfer**	**Use in veterinary medicine**	**Concluding remark**
Cephalosporins, 3rd- and 4th-generation	Enterobacteriaceae	High	Approved (restrictions apply)	Compliance with existing restrictions is needed (see Question 4)
Fluoroquinolones and other quinolones	*Campylobacter* spp. Enterobacteriaceae	High	Approved (including group medication, restrictions apply)	Compliance with existing restrictions is needed
Class of antimicrobials for which a risk profiling is required before a final decision on its category can be made:				
Aminoglycosides	Enterobacteriaceae *Enterococcus* spp.	High	Approved (including group medication)	Further risk profiling needed due to importance in vet med
Penicillins: Aminopenicillins including β-	Enterobacteriaceae *Enterococcus* spp.	High	Approved	Further risk profiling needed due to importance

Category 2 Antimicrobials used in veterinary medicine where the risk for public health is currently estimated higher	**Hazard of zoonotic relevance**	**Probability of resistance transfer**	**Use in veterinary medicine**	**Concluding remark**
lactamase inhibitors combinations (e.g. co-amoxiclav)				in vet med

Antimicrobial class **Category 3** Antimicrobials currently not approved for use in veterinary medicine	**Hazard of zoonotic relevance**	**Probability of resistance transfer**	**Use in veterinary medicine**	**Concluding remark**
Carbapenems and other penems	Enterobacteriaceae	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance. As co-resistance is an important issue, it is of high priority to decrease the total antimicrobial use in animal production in the EU
Ceftaroline and ceftobiprole	MRSA (Methicillin-resistant *Staphylococcus aureus)*	Low	Not approved	No specific concern identified yet
Cyclic esters (e.g. fosfomycin)	Enterobacteriaceae	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
Glycopeptides	*Enterococcus spp.* MRSA	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk

Antimicrobial class **Category 3** Antimicrobials currently not approved for use in veterinary medicine	**Hazard of zoonotic relevance**	**Probability of resistance transfer**	**Use in veterinary medicine**	**Concluding remark**
				for spread of resistance
Glycylcyclines	Enterobacteriaceae MRSA	Low	Not approved	See response to Question 1
Lipopeptides	*Enterococcus* spp. MRSA	Low	Not approved	No specific concern identified yet
Monobactams	Enterobacteriaceae	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
Oxazolidinones	*Enterococcus* spp. MRSA	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
Penicillins: carboxy-penicillins and ureido-penicillins including β-lactamase inhibitors combinations	*Enterobacteriaceae* *Enterococcus* spp.	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
Riminofenazines	None specific	Low	Not approved	No specific concern identified yet
Sulfones	None specific	Low	Not approved	No specific concern identified yet
Drugs used solely to treat tuberculosis or other mycobacterial diseases	None specific	High	Not approved	No specific concern identified yet

II. Answer to the second request from the EC (ranking of antibiotics)

1. Summary assessment and recommendations

A categorisation of the WHO critically important antimicrobials[7] (CIAs) was prepared based on their degree of risk to man due to resistance development following use in animals, as assessed by the AMEG.

The AMEG proposes to classify antimicrobials from the WHO CIA list in three different categories:

- Category 1 as antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited,
- Category 2 as antimicrobials used in veterinary medicine where the risk for public health is estimated higher and
- Category 3 as antimicrobials not approved for use in veterinary medicine.

Category 1 includes some classes of antimicrobials that are listed as CIAs by WHO according to their criteria and where use in veterinary medicine is extensive, but that nevertheless were considered to belong in this lower risk category. These classes include certain penicillins, macrolides, tetracyclines and polymyxins. There are no recommendations to avoid use of Category 1 compounds. Nevertheless, these antimicrobials are not devoid of negative impact on resistance development and spread. To keep the risk from use of these classes within Category 1 as low as possible the current responsible use principles in everyday practice should be adhered to. Non-responsible use, including unnecessary use and unnecessarily long treatment periods, should be avoided and group treatment restricted to situations where individual treatment is not feasible.

Category 2 includes those antimicrobial classes listed as CIAs by WHO for which the risk to public health from veterinary use is considered only acceptable provided that specific restrictions are placed on their use (i.e. fluoroquinolones and systemically administered (parenteral and oral), 3rd- and 4th-generation cephalosporins). These reserved antimicrobials should be used only when there are no alternative antimicrobials authorized for the respective target species and indication.

Pending risk assessment two other classes of antimicrobials have been included in Category 2, namely penicillins and aminoglycosides, as follows: Penicillins form a diverse class that has been divided into subclasses for the task presented. Some of these subclasses have efficacy against *Enterobacteriaceae* and have a high risk for transfer of resistance. Further risk profiling is needed to decide if these particular penicillins are to be regarded in the same way as 3rd- and 4th-generation cephalosporins. For the aminoglycosides, there might be a resistance risk associated with the use of this class which has as yet not been addressed.

A number of the classes/compounds listed in Table 2 are not approved in veterinary medicine and are presented separately as Category 3. The extent of use of these classes would be low, provided the restrictions detailed in Art 10 and 11 of Directive 2001/82/EC are complied with. According to these restrictions these substances may only be used by way of exception and only in companion animals

[7] For this document “antimicrobials” is defined as “active substance of synthetic or natural origin which destroys microorganisms, suppresses their growth or their ability to reproduce in animals or humans”. In this context, antivirals, antiparasitics and disinfectants are excluded from the definition.

(including horses that are not intended for food consumption) as MRLs have not been established to allow their use in food-producing species.

This categorisation may be considered as one element when deciding on when/whether to use a certain class/compound in veterinary medicine but may not be used as the sole base when creating treatment guidelines or when deciding on risk mitigation activities. This categorisation does not directly translate into a treatment guideline for veterinary medicine.

When writing treatment guidelines, decisions on appropriate risk management measures have to be made at the class, substance or even at the indication level and consider also the route of administration. In veterinary medicine, the number of species, the wide difference in routes of administration and indications (from intramammary treatment of individual cows to treatment of thousands of fish by in-feed medication) makes generalisations on antimicrobial categorisation and risk management not possible. Consequently no recommendations on treatment guidelines (i.e. if a certain compound should be first line, second line, etc., for a certain species and indication) can be given. The categorisation may be considered as one element when developing treatment guidelines but a number of other factors need to be considered, some of them on a regional basis, and therefore treatment guidelines need to be locally developed and implemented rather than at EU level.

Development and implementation of evidence-based national and regional treatment guidelines is encouraged.

A summary table specifying the classification for each class of antimicrobial is provided on page 11.

2. Introduction

2.1. Background

The EC has requested the European Medicines Agency to provide: *"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 multidrug-resistant infections in humans in the EU. The Agency should take into account the existing work of the WHO on critical antibiotics and consider the need, advantages, disadvantages and feasibility of categorising antibiotics as for example first line, second line or last resort antibiotics."*[8]

2.2. Scope of the response

The EMA/CVMP/CHMP/AMEG is asked to rank antimicrobial agents for their importance in human medicine and further to consider their possible categorisation as "first line", "second line" or "last line" treatment. It is understood that the request for further categorisation refers to the use of the substances in veterinary medicine. Advice is requested on the possibility/need to limit the use of certain antimicrobial agents in veterinary medicine in order to mitigate risks to human health.

3. Considerations for the response

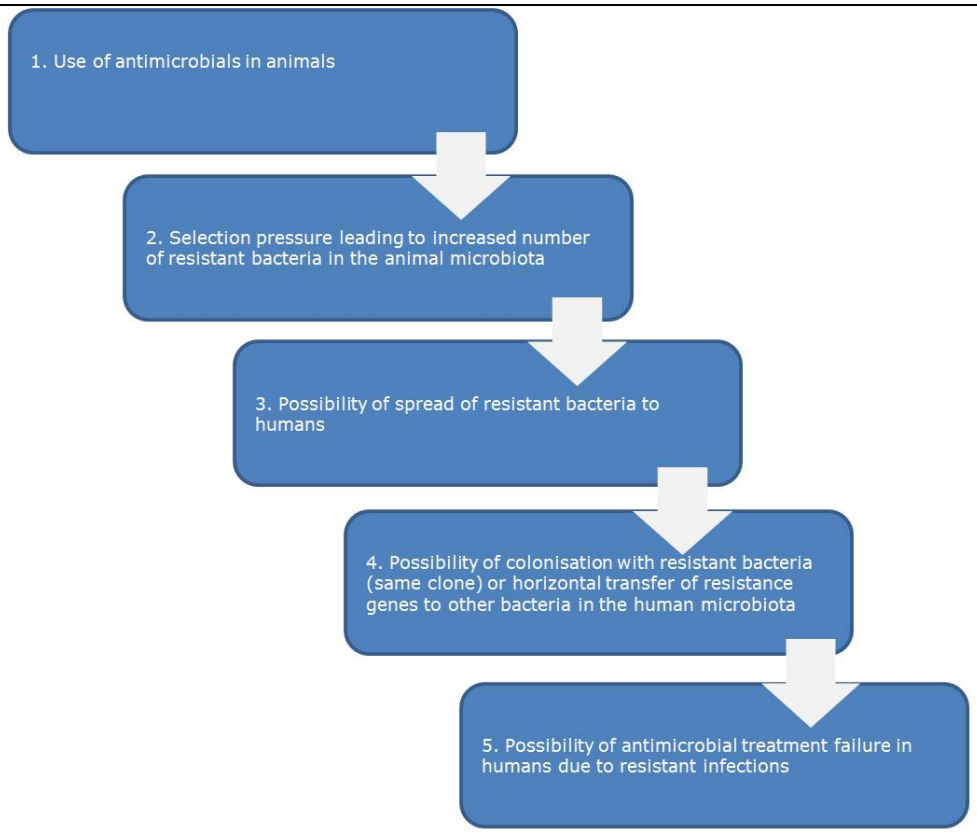
3.1. Risk to public health

The risk to public health from the development, emergence and spread of resistance consequent to use of antimicrobials in veterinary medicine is dependent on multiple risk factors (Graveland et al., 2010;

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

Persoons et al., 2011). The figure below summarises the chain of events that may lead from use of antimicrobials in animals to a compromised antimicrobial treatment in humans.

Figure 1: Chain of events



Schematic figure presenting the chain of events. Use of antimicrobial agents in animals (1) will lead to an increased selection pressure which may be influenced by factors such as the dose rate, duration of treatment, route of administration, etc.(2). Whether resistant bacteria will spread to humans in significant amounts depends on their number and viability which will vary dependent on bacterial clones, including mode of resistance. For foodborne risks, postharvest factors such as procedures and handling at the slaughterhouse, during processing and retail and in the domestic environment also have an impact (3). The likelihood of consequent colonisation/infection in humans (4) will depend on the bacteria in question but also on various factors such as previous health status and concomitant use of antimicrobial agents in humans. The presence of drug-resistant bacteria is only of consequence to humans if such resistance contributes to an increase in the virulence of an infection or a bacterial infection requires treatment with an antimicrobial to which resistance has developed (5).

A categorisation according to antimicrobial resistance known to be associated with certain classes may be a useful tool for risk assessment; however, it also has limitations due to co-selection between similar and also highly different classes. As an example, co-selection exists between similar substances like amoxicillin and third-generation cephalosporins (Persoons et al., 2012). In other words, restrictions on one class alone might not have the desired impact because of co-selection of AMR.

3.2. Discussion of the WHO list of critically / highly important antimicrobial agents

WHO has published a list of critically/highly important antimicrobial agents for human use (AGISAR, 2009; WHO, 2011) below abbreviated as “CIAs and HIAs”. The list of CIAs and HIAs is intended to be used as a reference to help formulate and prioritize risk assessment and risk management strategies

for the responsible use of antimicrobials in man and also for containing AMR due to non-human antimicrobial use. It is not intended to be used as the sole source of information for developing risk management strategies.

3.2.1. The WHO list is built on two criteria:

- **Criterion 1**. Antimicrobial agents used as sole therapy or one of few alternatives to treat serious human disease;

- **Criterion 2**. Antimicrobial agents used to treat diseases caused by either: (1) organisms that may be transmitted *via* non-human sources or (2) diseases caused by organisms that may acquire resistance genes from non-human sources.

If both these criteria are fulfilled the substance or class is regarded as a CIA.

The list of CIAs and HIAs, which meet WHO Criterion 1, is presented with comments specific to the EU in Table 2.

The list of substances and definition for the WHO criterion 1 is applicable for the EU, as due to extensive movement of people between countries the nature of the need for antimicrobials to treat multidrug-resistant infections is similar across them, although the extent of need may vary between countries and regions within the EU. Some comments are added in the table, addressing the EU-specific concerns, but overall the WHO list is applicable as part of the answer.

Criterion 2 is equally applicable in principle but the EMA/CVMP/CHMP/AMEG finds this criterion insufficiently detailed for the purpose of responding to this request for scientific advice. Furthermore, criterion 2 has never been revised and might need updating to take into account recently gained knowledge. For this reason, transfer of resistance is discussed using a score system built on several criteria. The score system contains the same information as WHO Criterion 2 but with a higher level of detail (see Section 2.3).

Table 2 presents an amended version of the WHO list of CIAs and HIAs modified to consider EU particulars. To reduce the number of items in the list, the antimicrobials are mainly presented as classes although some unique characteristics for individual substances are presented as appropriate. The list is not exhaustive as some classes/substances on the WHO list but of less importance for human medicine in EU are omitted. For each class/substance, examples among the most important infective agents are listed. These agents are bacteria causing infections against which there are few treatment alternatives. Dependent on resistance pattern, a listed substance may be the sole available treatment. Some of these bacteria (or their resistance genes) could have an animal reservoir and thus in a sense be zoonotic. In some cases resistance has shown to spread between animals and humans, in other cases such transfer remains a theoretical possibility. Hazards (“bug/drug combinations”, i.e. the bacteria when resistant against the antimicrobial in question) that might in theory have such a zoonotic potential are listed in a separate column.

Table 2: Antimicrobials that fulfil WHO criterion 1 with comments addressing EU concerns

Antimicrobial class	Bacterial targets in human medicine (for which availability of class/substance is critically important due to few alternatives)	Hazard of potential zoonotic relevance
Aminoglycosides	• Enterococcal endocarditis • Multidrug-resistant (MDR) Gram-negative bacteria (particularly Enterobacteriaceae and *Pseudomonas* spp.) • (MDR) tuberculosis	*Enterobacteriaceae* *Enterococcus* spp.
Carbapenems and other penems	• Multidrug-resistant (MDR) Gram-negative bacteria (e.g. Enterobacteriaceae)	Enterobacteriaceae
Cephalosporins, 3rd- and 4th-generation	• Acute bacterial meningitis and disease due to *Salmonella* spp. in children • Gonococcal infections	Enterobacteriaceae
Ceftaroline and ceftobiprole	• MDR staphylococci (e.g. MRSA) • Penicillin non-susceptible *Streptococcus pneumoniae* (PNSP)	MRSA
Cyclic esters (e.g. fosfomycin)	• ESBL (extended-spectrum beta-lactamases)-producing *E. coli* causing UTI • MDR Gram-negative bacteria (IV formulation)	Enterobacteriaceae
Fluoroquinolones and other quinolones	• *Campylobacter* spp. • Invasive *Salmonella* spp. infection • MDR *Shigella* spp. • *Pseudomonas aeruginosa,* PNSP and MDR TB (tuberculosis) (intravenous/oral)	*Campylobacter* spp. Enterobacteriaceae
Glycopeptides	• MDR staphylococci (e.g. MRSA), • MDR *Enterococcus* spp. • PNSP	*Enterococcus* spp. MRSA
Glycylcyclines	• MDR Gram-negative bacteria • MDR staphylococci (e.g. MRSA)	MRSA Enterobacteriaceae
Lipopeptides	• MDR staphylococci (e.g. MRSA) • MDR *Enterococcus* spp. • PNSP	*Enterococcus* spp. MRSA
Macrolides (including ketolides)	• *Legionella* spp. • *Campylobacter* spp. • Invasive MDR *Salmonella* spp. and *Shigella* spp. infections	*Campylobacter* spp. Invasive *Salmonella* spp.
Monobactams	• MDR Gram-negative bacteria, especially those producing metallo-beta-lactamases (MBL)	Enterobacteriaceae

Oxazolidinones	• MDR staphylococci (e.g. MRSA) • MDR *Enterococcus* spp. (e.g. VRE) • MDR TB • PNSP	*Enterococcus* spp. MRSA
Penicillins, Natural	• Syphilis	None specific
Penicillins: Aminopenicillins including β-lactamase inhibitors combinations (e.g. amoxicillin + clavulanic acid)	• *Listeria* spp. • *Enterococcus* spp.	*Enterococcus* spp. Enterobacteriaceae
Penicillins: Carboxy-penicillins and ureido-penicillins	• MDR *Pseudomonas* spp. • MDR Enterobacteriaceae (temocillin)	Enterobacteriaceae
Polymyxins	• MDR Enterobacteriaceae	Enterobacteriaceae
Rifamycins	• Mycobacterial diseases including tuberculosis	None specific
Riminofenazines	• Leprosy • MDR TB	None specific
Sulfones	• Leprosy	None specific
Tetracyclines	• *Brucella* spp.	*Brucella* spp.
Drugs used solely to treat tuberculosis or other mycobacterial diseases (in particular, isoniazid, pyrazinamide, ethambutol and capreomycin)	Tuberculosis and other *Mycobacterium* spp. diseases	None specific

3.3. Transmission of resistance and determinants from animals to man

The likelihood of spread of antimicrobial resistance from animals to humans depends on a number of factors that, influence either the spread of organisms exhibiting such resistance or the spread of resistance genes per se. Four different criteria defining the risk for spread are discussed below. The resistance to a particular substance/class has highest risk for spread if all four criteria are fulfilled. It must be stressed that this ranking is not equal to a classification for a full risk assessment as it contains information about only one of several relevant factors to consider. The likelihood of spread varies over time and depends on the "bug-drug" combination. Whether it is ever detected also depends on the methodology by which it is searched for, including origin of strains sampled. Whether the criteria are fulfilled for a certain substance/class may therefore need to be modified if new data become available from studies conducted under different conditions, or in the event that the concerned resistance mechanisms of the bacteria are proven to have evolved and reorganised over time.

Exposure to antimicrobials amplifies resistance (Levy, 2002; MacKenzie et al., 2007). In general when there is a decrease in the exposure of animals to antimicrobials a decrease in resistance is observed. Nevertheless resistance can persist in the absence of antimicrobial use (Enne et al., 2001). If this is the case (or in case of co-resistance), reduction of the consumption, in veterinary medicine, of a certain substance will not necessarily lead to consequent reduction in resistance.

The aspects of evolution and organisation of the resistance mechanisms are presented here according to four criteria to describe the likelihood of spread:

1) The presence of a chromosomal mutation contributing to the development of resistance to a clinically-relevant antimicrobial. Such mutations may occur randomly, and may give rise to high level resistance. Alternatively a series of stepwise mutations may be required before resistance reaches a level regarded as of therapeutic importance. Stability of the mutation(s) in the chromosome is also required for a critical level of spread of organisms exhibiting such resistance, whereby mutational resistance passes from the parent to the daughter bacterial colonies (clonal spread). A single mutational event giving rise to resistance to a particular antimicrobial might result in resistance to several substances within related classes of antimicrobial agents.

2) Organisation of non-chromosomal resistance genes into horizontally-transferable elements (Carattoli, 2009), enabling localisation on DNA outside the bacterial chromosome (e.g. conjugative or mobilisable plasmids, transposons, integron-gene cassettes). The likelihood of further spread is variable, dependent on the plasmid, the presence or absence of genes mediating plasmid transfer, whether horizontal plasmid/gene transfer is limited to one type of organism or if it crosses borders between related or distinct bacterial species.

3) Other factors such as: (a) the incorporation of plasmid- or transposon/integron-mediated resistance into the bacterial chromosome in discrete ‘resistance islands’, which may require mobilisation by other plasmids or by bacteriophages for horizontal transfer either within or between bacterial species; (b) presence of plasmid addiction systems. Such systems involve plasmid-mediated genes encoding toxin-antitoxin proteins where they serve to stabilise the plasmid within a bacterial population and, in the case of plasmids which code for resistance to a range of antimicrobials, lessen their chances of loss when antibiotic selection pressure is withdrawn. Such systems are becoming increasingly identified in plasmids belonging to a wide range of incompatibility groups, and may have an important role in the maintenance of such plasmids in host bacteria.

4) The presence of a cluster of resistance genes will enable more efficient spread by co-selection. This process allows resistance spread for substance A while the unrelated substance B is used, because of linkage of resistance genes.

In addition to the factors above, that for the most part relate only to genetic mechanisms, there are many other factors that may affect the probability of transfer of resistant bacteria or its determinants from animals to humans which reflect the conditions of use of the antimicrobial substance, e.g. dosing route and regimen, volume of usage, animal husbandry conditions. These must be taken into consideration for a full public health risk assessment (Codex Alimentarius, 2009; Codex Alimentarius, 2011).

For bacteria that may be foodborne there are a number of additional factors to consider such as consumption habits, environmental factors and the processes between slaughter and intake of food (Codex Alimentarius, 2009; Codex Alimentarius, 2011).

The table below lists the same classes/substances as those discussed above, but adding information on the likelihood of spread of resistance. Based on the different criteria a score system is applied and transferred into an estimation of the probability of resistance transfer.

Table 3 Classification of antimicrobial classes according to their probability of transfer of resistance genes and resistant bacteria

Antimicrobial class	Vertical transmission of resistance gene(s)[a]	Mobile genetic element-mediated transfer of resistance[b]	Co-selection of resistance[c]	Potential for transmission of resistance through zoonotic and commensal food-borne bacteria[d]	Evidence of similarity of resistance: genes / mobile genetic elements / resistant bacteria[e]	Overall probability of resistance transfer	References
Classes of antimicrobials for which there are substances authorised for use in veterinary medicine							
Aminoglycosides	2	3	2	3	3	**High**	(Gonzalez-Zorn et al., 2005) (Chen et al., 2007) (Liu et al., 2008) (Du et al., 2009) (Davis et al., 2010) (Hopkins et al., 2010) (Deng et al., 2011)
Cephalosporins: 3rd-and 4th-generation	3	3	3	3	4	**High**	(Liebana et al., 2013) (EFSA, 2011) (Catry et al., 2010) (EMA, 2012) (EMA/CVMP/SAGAM, 2009b) (Kluytmans et al., 2013)
Fluoroquinolones and other quinolones, without *qnr* gene	2	1	1	3	2	**High**	(EMA, 2010) (EMA/CVMP/SAGAM, 2007) (Aldred et al., 2014) (Poirel et al., 2008)
Fluoroquinolones and other quinolones, counting *qac* and *qnr* genes	3	3	2	3	2	**High**	(EMA, 2010) (EMA/CVMP/SAGAM, 2007) (Aldred et al., 2014) (Poirel et al., 2008)

Antimicrobial class	Vertical transmission of resistance gene(s)[a]	Mobile genetic element-mediated transfer of resistance[b]	Co-selection of resistance[c]	Potential for transmission of resistance through zoonotic and commensal food-borne bacteria[d]	Evidence of similarity of resistance: genes / mobile genetic elements / resistant bacteria[e]	Overall probability of resistance transfer	References
Macrolides (including ketolides)	3	3	3	3	2	**High**	(Pyorala et al., 2014) (EMA/CVMP/SAGAM, 2011) (Roberts, 2008) (Roberts, 2011)
Penicillins: natural, aminopenicillins, carboxypenicillins and ureidopenicillins, including β-lactamase inhibitors combinations	3	1	2	2	2	**High**	(Bush and Jacoby, 2010)
Polymyxins (e.g. colistin)	1	1	2	1	1	**Low**	(EMA, 2013b) (Halaby et al., 2013) (Monaco et al., 2014)
Rifamycins	2	3	2	2	2	**High**	(Tupin et al., 2010) (Floss and Yu, 2005) (Arlet et al., 2001)
Tetracyclines	3	3	3	3	4	**High**	(Chopra and Roberts, 2001) (Butaye et al., 2003) (Butaye et al., 2006)
Antimicrobials not authorised for use in veterinary medicine in the EU							
Carbapenems and other penems	3	3	3	2	2	**High**	(Le Hello et al., 2013) (EFSA, 2013) (Dortet et al., 2014)
Ceftaroline and ceftobiprole	1	1	1	1	1	**Low**	(Casapao et al., 2012) (Curcio, 2014) (Duplessis and Crum-Cianflone, 2011) (Pillar et al., 2008)

Antimicrobial class	Vertical transmission of resistance gene(s)[a]	Mobile genetic element-mediated transfer of resistance[b]	Co-selection of resistance[c]	Potential for transmission of resistance through zoonotic and commensal food-borne bacteria[d]	Evidence of similarity of resistance: genes / mobile genetic elements / resistant bacteria[e]	Overall probability of resistance transfer	References
Cyclic esters (e.g. fosfomycin)	3	3	2	1	1	**High**	(Wachino et al., 2010) (Oteo et al., 2009) (Karageorgopoulos et al., 2012) (Pérez, 2014)
Glycopeptides	2	2	2	2	2	**High**	(Rice, 2012) (Braga et al., 2013) (Silveira et al., 2014)
Glycylcyclines	2	1	2	1	1	**Low**	(EMA, 2013c)
Lipopeptides	1	1	1	1	1	**Low**	(Kelesidis, 2013) (Kelesidis and Chow, 2014) (Bayer et al., 2013)
Monobactams	3	3	3	3	2	**High**	(Liebana et al., 2013) (EFSA, 2011) (Catry et al., 2010) (EMA, 2012) (EMA/CVMP/SAGAM, 2009b) (Kluytmans et al., 2013)
Oxazolidinones	3	3	2	1	2	**High**	(Diaz et al., 2012) (Endimiani et al., 2011) (Gu et al., 2013) (Sanchez Garcia et al., 2010) (Bonilla et al., 2010) (Liu et al., 2013) (Mendes et al., 2014)
Riminofenazines	1	1	1	1	1	**Low**	(Hartkoorn et al., 2014) (Grosset et al., 2012)

Antimicrobial class	Vertical transmission of resistance gene(s)[a]	Mobile genetic element-mediated transfer of resistance[b]	Co-selection of resistance[c]	Potential for transmission of resistance through zoonotic and commensal food-borne bacteria[d]	Evidence of similarity of resistance: genes / mobile genetic elements / resistant bacteria[e]	Overall probability of resistance transfer	References
Sulfones	1	1	1	1	1	**Low**	(Veziris et al., 2013)
Drugs used solely to treat tuberculosis or other mycobacterial diseases (e.g. isoniazid)	2	2	2	2	2	**High**	(Ando et al., 2014) (Bernardes-Genisson et al., 2013) (Gagneux, 2012)

[a]Vertical transmission of resistance gene. Defined as the vertical transfer of a resistance gene through the parent to the daughter bacteria in a successful, highly disseminated resistant clone of bacteria through a bacterial population, e.g. *E. coli* ST131 clone, MRSP CC(71) clone, MRSA ST398 clone. Probability (1 to 3): 1, no vertical transmission of gene described as associated with in a particular successful resistant clone; 2, gene is exclusively on the core bacterial chromosome in a particular successful resistant clone; 3, gene is on a mobile genetic element, e.g. plasmid, in a particular successful resistant clone.

[b]Mobile genetic element-mediated transfer of resistance. Defined as a resistance gene that is transmitted by means of mobile genetic elements (horizontal transmission of the gene occurs). Probability (1 to 3): 1, no gene mobilization described; 2, gene is exclusively on the core bacterial chromosome; 3, gene is on a mobile genetic element, e.g. plasmid.

[c]Co-selection of resistance. Defined as selection of resistance which simultaneously selects for resistance to another antimicrobial. Probability (1 to 3): 1, no co-mobilization of the gene or risk factor described; 2, gene is either co-mobilized or a risk factor has been described; 3, gene is co-mobilized and a risk factor has been described.

[d]Transmission of resistance through zoonotic and commensal food-borne bacteria. Defined as transmission of resistance through food-borne zoonotic pathogens (e.g. *Salmonella* spp., *Campylobacter* spp., *Listeria* spp., *E. coli* (VTEC/STEC) or transmission of resistance through commensal food-borne bacteria (e.g. *E. coli*, *Enterococcus* spp.). Probability (1 to 3): 1, no transmission of resistance through food-borne zoonotic pathogens or commensal food-borne bacteria; 2, transmission of resistance through food-borne zoonotic pathogens or commensal food-borne bacteria; 3, transmission of resistance through food-borne zoonotic pathogens and commensal food-borne bacteria.

[e]Evidence of similarity of resistance: genes/mobile genetic elements/resistant bacteria. Genes - Defined as similar resistance gene detected in bacterial isolates of animal and human origin; Mobile genetic elements - Defined as a similar resistance mobile genetic element detected in bacterial isolates of animal and human origin; Resistant bacteria - Defined as a similar bacterium harboring a resistance gene (either chromosomally or mobile genetic element-encoded) of animal and human origin. Probability (1 to 3): 1,

unknown resistance similarity; 2, genes or mobile genetic elements or resistant bacteria similar between animals and humans; 3, genes and mobile genetic elements similar between animals and humans; 4, genes and mobile genetic elements and resistant bacteria similar between animals and humans.

The scoring of the table above is based on the expert opinion of the members of the Working Group and on the references included in the table.

3.4. Treatment guidelines for use of antimicrobial agents in animals

The factors discussed above (importance of the antimicrobial agent in human medicine as presented in Table 1 and the probability of resistance transfer as presented in Table 2) are only two of a number of factors to consider when creating treatment guidelines for veterinary use. These two factors are relevant for the entire EU whereas most other factors to consider are dependent on the local situation.

There are several examples from different member states where official bodies and/or prescribers' organisations have published treatment guidelines listing antimicrobial agents and classifying them as "first line", "second line" and "last line"(Danish Veterinary and Food Administration, 2013; French Directorate-General for Food, 2013; MARAN, 2013). These guidelines target certain animal species and subspecies (e.g. age groups) and infections and take into consideration, amongst other factors, the local resistance situation. To be effective they need to be locally implemented and effort needs to be made to ensure understanding and acceptance, including training of prescribers of AMs. Thus, treatment guidelines will differ between countries and regions. What is recommended for a certain disease in one country/region where the resistance situation is favourable might be ineffective in another country. On the contrary, use of an antimicrobial agent recommended in a local situation where the resistance situation is less favourable might be regarded as non-responsible if used in other countries/regions. Therefore, treatment guidelines cannot be established on an EU-wide level. Efforts to create EU-wide guidelines might even be counter-productive as they cannot be applicable for the entire EU without contradicting some adequately working existing local guidelines. In addition, guidelines will need to be updated as the antimicrobial resistance situation and availability of products evolves over time.

For this reason, the EMA/CVMP/CHMP/AMEG cannot recommend the EC to create detailed guidelines on what substance to use as "first line", "second line" or "last line" medication for certain animal infections in the EU. EU Member States (MSs) could be encouraged to develop such detailed guidelines taking into account among other information the general categorisation presented in this document.

The Draft Commission Staff Working Document on Guidelines for prudent use of antimicrobials in veterinary medicine is welcomed as an overarching framework for those guidelines (draft to be published in the near future).

Ideally, the criticality of use in veterinary medicine should be directly considered when creating treatment guidelines. For instance, there are situations where a substance could be approved and recommended as the first line treatment for a certain condition in a certain species where there are no effective alternatives even if the substance as such belongs to a category where the risk to public health is considered high. When risk to public health is considered in a benefit/risk perspective it could be that a higher risk level is found acceptable in case of a certain disease/species to be treated. Nevertheless, this reasoning has not been applied in this scientific advice due to lack of data on resistance in target animal pathogens.

For information, a brief summary of current usage patterns is included in Annex I. This summary is to be regarded as information important to get a full picture of the class in question but should not be seen as a recommendation for future use. Some risk management measures that are applied to restrict use are also listed. Data provided from ESVAC indicate that the extent of use of antimicrobials differs considerably between MSs. Thus there appears to be room for reconsideration of treatment practice at least in some MSs and for some livestock production systems. For the future it is critical for all MSs to continue working to minimize the need for unnecessary use of any antimicrobial in both human and veterinary medicine.

The use in veterinary medicine of a certain substance/class has been considered by the AMEG only as the basis to distinguish between substances to be addressed in response to Question 3 and Question 4 respectively of this scientific advice. Classes/substances included in Table 1 and Table 2 which are not listed in the Table 8 in the Annex are not approved for use in veterinary medicine in the EU.

4. Categorisation

As requested by the EC, a categorisation of antimicrobials is presented below and in Summary Table 1. For categories 1 and 2, the categorisation is based on:

- Their need in human medicine (as presented in Table 2),
- And the risk for spread of resistance from animals to humans (as presented in Table 3).

These two factors are product-independent and apply over the whole of the EU independently of the animal health situation, and of the availability of antimicrobial products for animals in individual Member States.

Category 3 includes antimicrobials not yet authorised in veterinary medicine.

This categorisation may be considered as one element when deciding on when/whether to use a certain class/substance in veterinary medicine but it may not be used as the sole base when creating treatment guidelines or else when deciding on risk mitigation activities. It should not be interpreted as a recommendation for treatment guidelines.

The categorisation could also be taken into account when considering hazard characterization for the risk assessment in applications for Marketing Authorisations for VMPs (Veterinary Medicinal Products).

Development and implementation of evidence-based national and regional treatment guidelines is encouraged.

4.1. Category 1: Antimicrobials used in veterinary medicine where the risk for public health is currently estimated as low or limited

Category 1 includes some classes of antimicrobial that have widespread use in veterinary medicine (EMA/ESVAC, 2013), and also include substances which are regarded as first choice in many treatment guidelines. These are **certain penicillins**, **tetracyclines**, **macrolides** and **polymyxins**. In addition there is some limited use of rifampicin (a rifamycin) in veterinary medicine.

Penicillins with narrow spectrum of activity (e.g. penicillin G and penicillin V) belong together with tetracyclines to a category where the risk to public health is estimated as low. This is because there are no specific associated hazards identified to which people could be exposed from animals in the EU. For tetracyclines, *Brucella* is listed but this pathogen has a much lower prevalence in EU compared to other regions.

More information on macrolides is available in a reflection paper (EMA/CVMP/SAGAM, 2011). In human medicine, certain macrolides (e.g. azithromycin) are becoming increasingly used in developing countries to treat invasive *Salmonella* spp. and *Shigella* spp. infections in man, such as those caused by typhoidal *Salmonellae* (e.g., *S.* Typhi) or by *Sh. dysenteriae* type 1 (Shiga's bacillus), when patients fail to respond to treatment with more conventional antimicrobials such as the fluoroquinolones. So far use of these antimicrobials is limited in the EU and *S. Typhi*, *S. Paratatyphi* and *Sh. dysenteriae* 1 are not zoonotic hazards, but there is a need for awareness as in the future macrolide-resistant *Salmonella* spp. other than typhoidal serovars may become a concern.

For more information on the most extensively used polymyxin in veterinary medicine, i.e. **colistin**, see the response to the 1st request from the EC (EMA, 2013a). The EU has recently launched an article 35 referral on products containing colistin for oral use in food producing animals which will align the SPCs for these products with responsible use principles.

Currently there are no recommendations to avoid use of Category 1 substances beyond what is stated by general responsible use principles. Nevertheless, these antimicrobials are not devoid of negative impact on resistance development and spread, and even if extensive use in veterinary medicine is to be expected, it is also of importance to ensure that any use is responsible. Category 1 substances might be of concern e.g. if they facilitate spread of multidrug-resistant (MDR) strains due to co-resistance. This is a known problem for e.g. MRSA[9] where many antimicrobials could facilitate spread.

4.2. Category 2: Antimicrobials used in veterinary medicine where the risk for public health is currently estimated as higher

The classes/substances discussed under this category are considered by EMA/CVMP/CHMP/AMEG in response to Question 4 as "*certain classes of antibiotics or antibiotic substances that are critically important in human medicine and are currently authorised as veterinary medicinal products"*. For more details on each class, please see the response to Question 4 from the EC.

Fluoroquinolones and **3rd- and 4th-generation cephalosporins** are of special concern. These antimicrobials have been used in some countries as first-line treatment for a variety of infections in veterinary medicine. The EMA/CVMP Scientific Advisory Group on Antimicrobials (SAGAM) has provided risk profiles for fluoroquinolones and 3rd and 4th generation cephalosporins (EMA/CVMP/SAGAM, 2007; EMA/CVMP/SAGAM, 2009b) and considering these risk profiles the CVMP concluded, amongst other recommendations, that an appropriate level of risk mitigation would be to reserve them for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other antimicrobials. This recommendation is applicable in all EU MSs and has been implemented in legislation in some. Product information for concerned products has been updated to include the recommendation. It should be noted that 3rd- and 4th-generation cephalosporins in formulations to be administered locally were outside the scope of the referral.

These reserved antimicrobials should be included in treatment guidelines only when there are no alternatives that could be used. In some MSs these Category 2 substances are the only available choices approved for certain species and infections. In such cases, all efforts should be made to reduce the need for their use and to convince companies to seek marketing authorisations for alternative substances (including non-antimicrobial agents) presenting a lesser risk for public health.

The recommendations with regards to these Category 2 substances as reserved antimicrobials have been implemented in all SPCs for VMPs for food-producing species. For fluoroquinolones a community referral was launched in April 2009 (EMA) and a corresponding referral for systemically active (parenteral and oral) 3rd- and 4th-generation cephalosporins was launched in March 2011 (EMA, 2012). These referrals have resulted in the harmonisation of relevant parts of the SPCs. Responsible use and other relevant recommendations have been included to mitigate the emergence and spread of antimicrobial resistance in pathogens relevant to public and animal health.

Aminoglycosides and **certain penicillins** are classes of antimicrobials for which **no risk profiling has yet been made** by the EMA/CVMP. These classes have been added to Category 2 based on the information available on criticality of use in human medicine and probability of spread of resistance

[9] For more detailed information, please see the reflection paper *MRSA in food-producing and companion animals in the EU: Epidemiology and control options for human and animal health* (EMEA/CVMP/SAGAM/68290/2009)

from animals to humans as defined in this document. EMA/CVMP/CHMP/AMEG recommends profiling the risk to public health related to use of these classes in veterinary medicine. Future assessments could result in a change of the categorisation.

Aminoglycosides are used extensively in veterinary medicine and also given as oral group/flock medication; no restrictions of use apply for this class. As they may be effective against MDR Enterobacteriaceae in humans and as the risk for spread of resistance from animals to humans is ranked “high”, there might be a concern with the use of this class which is currently not addressed. To further elaborate on possible risks from aminoglycoside use in animals a more detailed risk profile would be needed.

Penicillins are a diverse class including substances like penicillin G and V with no activity against Enterobacteriacea and substances with extended spectrum. Those with extended spectrum could be of concern if their ability to facilitate spread of ESBLs is similar to 3rd- and 4th-generation cephalosporins. Therefore, a more detailed risk profile on penicillins with activity against Enterobacteriaceae is recommended. It is recommended to consider the diversity of the penicillin class when discussing risk to public health in a veterinary treatment guideline perspective.

4.3. Category 3: Antimicrobials currently not approved for use in veterinary medicine

A number of the classes/substances listed are not currently approved in veterinary medicine and these are presented separately as Category 3. The extent of use of these classes would be low provided the restrictions detailed in Art 10 and 11 of Directive 2001/82/EC, as amended (Official Journal of the European Communities, 2001) are complied with. According to these restrictions they may only be used by way of exception and only in companion animals (non-food producing species) as maximum residue limits (MRLs) have not been established to allow their use in food producing animals. For more information about these classes, please see the response to Question 3.

4.4. Conclusions on Question 2

See Table 1: **Summary table** concluding remarks for a summary of the analysis of the data.