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## 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)

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## 1.

# 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<sup>1</sup>. This forms part of the EC Action plan against the rising threats from Antimicrobial Resistance<sup>2</sup>.

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<sup>3</sup>.

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.”<sup>4</sup>*

### 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).”*

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<sup>1</sup> See [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/04/WC500142070.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf)

<sup>2</sup> See [http://ec.europa.eu/dgs/health\\_consumer/docs/communication\\_amr\\_2011\\_748\\_en.pdf](http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf)

<sup>3</sup> 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/Other/2013/07/WC500146812.pdf), [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/07/WC500146813.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](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146814.pdf)

<sup>4</sup> See [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/04/WC500142070.pdf](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 1<sup>st</sup> 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<sup>5</sup>.

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<sup>6</sup> (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

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<sup>5</sup> 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.

<sup>6</sup> 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), 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-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	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
<b>Category 1</b> Antimicrobials used in veterinary medicine where the risk for public health is currently estimated low or limited				
<b>Macrolides (including ketolides)</b>	<i>Campylobacter</i> spp. <i>Salmonella</i> 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
<b>Penicillins, Natural</b>	None specific	High	Approved (including group medication)	Compliance with responsible use principles is necessary to reduce the risk for co-resistance
<b>Penicillins: Narrow-spectrum, <math>\beta</math>-lactamase-resistant penicillins</b>	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
<b>Polymyxins (e.g. colistin)</b>	Enterobacteriaceae	Low	Approved (including group medication)	See response to Question 1
<b>Rifamycins</b>	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

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

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

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

<b>Antimicrobial class</b> <b>Category 3</b> Antimicrobials currently not approved for use in veterinary medicine	<b>Hazard of zoonotic relevance</b>	<b>Probability of resistance transfer</b>	<b>Use in veterinary medicine</b>	<b>Concluding remark</b>
<b>Carbapenems and other penems</b>	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
<b>Ceftaroline and ceftobiprole</b>	MRSA (Methicillin-resistant <i>Staphylococcus aureus</i> )	Low	Not approved	No specific concern identified yet
<b>Cyclic esters (e.g. fosfomycin)</b>	Enterobacteriaceae	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
<b>Glycopeptides</b>	<i>Enterococcus spp.</i> MRSA	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk

<b>Antimicrobial class</b>	<b>Hazard of zoonotic relevance</b>	<b>Probability of resistance transfer</b>	<b>Use in veterinary medicine</b>	<b>Concluding remark</b>
<b>Category 3</b> Antimicrobials currently not approved for use in veterinary medicine				
				for spread of resistance
<b>Glycylcyclines</b>	Enterobacteriaceae MRSA	Low	Not approved	See response to Question 1
<b>Lipopeptides</b>	<i>Enterococcus</i> spp. MRSA	Low	Not approved	No specific concern identified yet
<b>Monobactams</b>	Enterobacteriaceae	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
<b>Oxazolidinones</b>	<i>Enterococcus</i> spp. MRSA	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
<b>Penicillins: carboxy-penicillins and ureido-penicillins including <math>\beta</math>-lactamase inhibitors combinations</b>	<i>Enterobacteriaceae</i> <i>Enterococcus</i> spp.	High	Not approved	Use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance
<b>Rimino-fenazines</b>	None specific	Low	Not approved	No specific concern identified yet
<b>Sulfones</b>	None specific	Low	Not approved	No specific concern identified yet
<b>Drugs used solely to treat tuberculosis or other mycobacterial diseases</b>	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<sup>7</sup> (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), 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-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

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<sup>7</sup> 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.”*<sup>8</sup>

### **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;

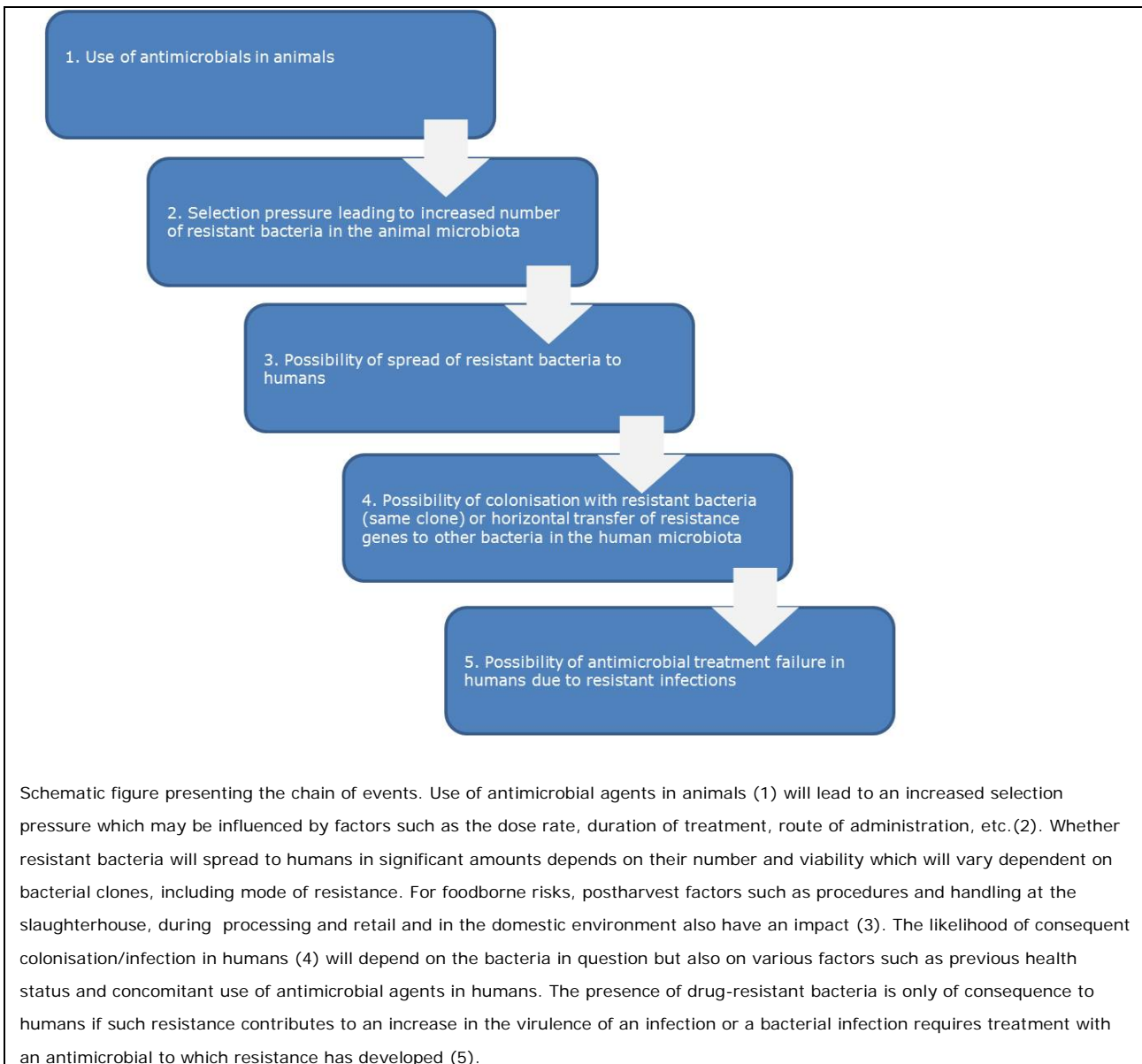
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<sup>8</sup> See [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/04/WC500142070.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf)



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



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
<b>Aminoglycosides</b>	<ul style="list-style-type: none"> <li>• Enterococcal endocarditis</li> <li>• Multidrug-resistant (MDR) Gram-negative bacteria (particularly Enterobacteriaceae and <i>Pseudomonas</i> spp.)</li> <li>• (MDR) tuberculosis</li> </ul>	<i>Enterobacteriaceae</i> <i>Enterococcus</i> spp.
<b>Carbapenems and other penems</b>	<ul style="list-style-type: none"> <li>• Multidrug-resistant (MDR) Gram-negative bacteria (e.g. Enterobacteriaceae)</li> </ul>	Enterobacteriaceae
<b>Cephalosporins, 3<sup>rd</sup>- and 4<sup>th</sup>-generation</b>	<ul style="list-style-type: none"> <li>• Acute bacterial meningitis and disease due to <i>Salmonella</i> spp. in children</li> <li>• Gonococcal infections</li> </ul>	Enterobacteriaceae
<b>Ceftaroline and ceftobiprole</b>	<ul style="list-style-type: none"> <li>• MDR staphylococci (e.g. MRSA)</li> <li>• Penicillin non-susceptible <i>Streptococcus pneumoniae</i> (PNSP)</li> </ul>	MRSA
<b>Cyclic esters (e.g. fosfomycin)</b>	<ul style="list-style-type: none"> <li>• ESBL (extended-spectrum beta-lactamases)-producing <i>E. coli</i> causing UTI</li> <li>• MDR Gram-negative bacteria (IV formulation)</li> </ul>	Enterobacteriaceae
<b>Fluoroquinolones and other quinolones</b>	<ul style="list-style-type: none"> <li>• <i>Campylobacter</i> spp.</li> <li>• Invasive <i>Salmonella</i> spp. infection</li> <li>• MDR <i>Shigella</i> spp.</li> <li>• <i>Pseudomonas aeruginosa</i>, PNSP and MDR TB (tuberculosis) (intravenous/oral)</li> </ul>	<i>Campylobacter</i> spp. Enterobacteriaceae
<b>Glycopeptides</b>	<ul style="list-style-type: none"> <li>• MDR staphylococci (e.g. MRSA),</li> <li>• MDR <i>Enterococcus</i> spp.</li> <li>• PNSP</li> </ul>	<i>Enterococcus</i> spp. MRSA
<b>Glycylcyclines</b>	<ul style="list-style-type: none"> <li>• MDR Gram-negative bacteria</li> <li>• MDR staphylococci (e.g. MRSA)</li> </ul>	MRSA Enterobacteriaceae
<b>Lipopeptides</b>	<ul style="list-style-type: none"> <li>• MDR staphylococci (e.g. MRSA)</li> <li>• MDR <i>Enterococcus</i> spp.</li> <li>• PNSP</li> </ul>	<i>Enterococcus</i> spp. MRSA
<b>Macrolides (including ketolides)</b>	<ul style="list-style-type: none"> <li>• <i>Legionella</i> spp.</li> <li>• <i>Campylobacter</i> spp.</li> <li>• Invasive MDR <i>Salmonella</i> spp. and <i>Shigella</i> spp. infections</li> </ul>	<i>Campylobacter</i> spp. Invasive <i>Salmonella</i> spp.
<b>Monobactams</b>	<ul style="list-style-type: none"> <li>• MDR Gram-negative bacteria, especially those producing metallo-beta-lactamases (MBL)</li> </ul>	Enterobacteriaceae

<b>Oxazolidinones</b>	<ul style="list-style-type: none"> <li>• MDR staphylococci (e.g. MRSA)</li> <li>• MDR <i>Enterococcus</i> spp. (e.g. VRE)</li> <li>• MDR TB</li> <li>• PNSP</li> </ul>	<i>Enterococcus</i> spp. MRSA
<b>Penicillins, Natural</b>	<ul style="list-style-type: none"> <li>• Syphilis</li> </ul>	None specific
<b>Penicillins: Aminopenicillins including <math>\beta</math>-lactamase inhibitors combinations (e.g. amoxicillin + clavulanic acid)</b>	<ul style="list-style-type: none"> <li>• <i>Listeria</i> spp.</li> <li>• <i>Enterococcus</i> spp.</li> </ul>	<i>Enterococcus</i> spp. Enterobacteriaceae
<b>Penicillins: Carboxy-penicillins and ureido-penicillins</b>	<ul style="list-style-type: none"> <li>• MDR <i>Pseudomonas</i> spp.</li> <li>• MDR Enterobacteriaceae (temocillin)</li> </ul>	Enterobacteriaceae
<b>Polymyxins</b>	<ul style="list-style-type: none"> <li>• MDR Enterobacteriaceae</li> </ul>	Enterobacteriaceae
<b>Rifamycins</b>	<ul style="list-style-type: none"> <li>• Mycobacterial diseases including tuberculosis</li> </ul>	None specific
<b>Riminofenazines</b>	<ul style="list-style-type: none"> <li>• Leprosy</li> <li>• MDR TB</li> </ul>	None specific
<b>Sulfones</b>	<ul style="list-style-type: none"> <li>• Leprosy</li> </ul>	None specific
<b>Tetracyclines</b>	<ul style="list-style-type: none"> <li>• <i>Brucella</i> spp.</li> </ul>	<i>Brucella</i> spp.
<b>Drugs used solely to treat tuberculosis or other mycobacterial diseases</b> (in particular, isoniazid, pyrazinamide, ethambutol and capreomycin)	Tuberculosis and other <i>Mycobacterium</i> 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) <sup>a</sup>	Mobile genetic element-mediated transfer of resistance <sup>b</sup>	Co-selection of resistance <sup>c</sup>	Potential for transmission of resistance through zoonotic and commensal food-borne bacteria <sup>d</sup>	Evidence of similarity of resistance: genes / mobile genetic elements / resistant bacteria <sup>e</sup>	Overall probability of resistance transfer	References
<b>Classes of antimicrobials for which there are substances authorised for use in veterinary medicine</b>							
Aminoglycosides	2	3	2	3	3	<b>High</b>	(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: 3 <sup>rd</sup> -and 4 <sup>th</sup> -generation	3	3	3	3	4	<b>High</b>	(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 <i>qnr</i> gene	2	1	1	3	2	<b>High</b>	(EMA, 2010) (EMA/CVMP/SAGAM, 2007) (Aldred et al., 2014) (Poirel et al., 2008)
Fluoroquinolones and other quinolones, counting <i>qac</i> and <i>qnr</i> genes	3	3	2	3	2	<b>High</b>	(EMA, 2010) (EMA/CVMP/SAGAM, 2007) (Aldred et al., 2014) (Poirel et al., 2008)

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



Antimicrobial class	Vertical transmission of resistance gene(s) <sup>a</sup>	Mobile genetic element-mediated transfer of resistance <sup>b</sup>	Co-selection of resistance <sup>c</sup>	Potential for transmission of resistance through zoonotic and commensal food-borne bacteria <sup>d</sup>	Evidence of similarity of resistance: genes / mobile genetic elements / resistant bacteria <sup>e</sup>	Overall probability of resistance transfer	References
Cyclic esters (e.g. fosfomycin)	3	3	2	1	1	<b>High</b>	(Wachino et al., 2010) (Oteo et al., 2009) (Karageorgopoulos et al., 2012) (Pérez, 2014)
Glycopeptides	2	2	2	2	2	<b>High</b>	(Rice, 2012) (Braga et al., 2013) (Silveira et al., 2014)
Glycylcyclines	2	1	2	1	1	<b>Low</b>	(EMA, 2013c)
Lipopeptides	1	1	1	1	1	<b>Low</b>	(Kelesidis, 2013) (Kelesidis and Chow, 2014) (Bayer et al., 2013)
Monobactams	3	3	3	3	2	<b>High</b>	(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	<b>High</b>	(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	<b>Low</b>	(Hartkoorn et al., 2014) (Grosset et al., 2012)

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

<sup>a</sup>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.

<sup>b</sup>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.

<sup>c</sup>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.

<sup>d</sup>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.

<sup>e</sup>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. Paratyphi* 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<sup>9</sup> 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 **3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup> and 4<sup>th</sup> 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 3<sup>rd</sup>- and 4<sup>th</sup>-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) 3<sup>rd</sup>- and 4<sup>th</sup>-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

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<sup>9</sup> 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* (EMA/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 Enterobacteriaceae and substances with extended spectrum. Those with extended spectrum could be of concern if their ability to facilitate spread of ESBLs is similar to 3<sup>rd</sup>- and 4<sup>th</sup>-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.

### **III. Answer to the third request from the EC (new antibiotics)**

#### **1. Summary answer**

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 no general conclusions can be drawn on the risk from substances not currently authorised for use in veterinary medicine. Recommendations can only be made on how 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 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 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 such off label use could be implemented.



## 2. Introduction

The third request of the EC on the impact on public health and animal health of the use of antibiotics in animals is as follows:

*“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).”*

Similar classes of antimicrobials are authorised for use in humans and animals (see for details the answer to Question 2). Only a few classes of antimicrobials are authorised for use only in human medicine.

There is a lack of new antimicrobials for human and veterinary medicine.

The need for new antimicrobials for use in animals, the requirements for Marketing Authorisations for new antimicrobials for use in animals, as well as the off label use in animals of antimicrobials currently authorised for human use only will be addressed.

The European legislation (Articles 10 and 11 of the Directive 2001/82/EC)<sup>10</sup> allows for administration under certain conditions of products that are not authorised in veterinary medicine. These provisions intend to take into account the small market for certain species of animals and for indications of minor use. In summary the provisions (the so called “cascade”) can only be used by way of exception, under the direct responsibility of a veterinarian, and in particular to avoid causing unacceptable suffering to animals. Such administration is called off label use.

Before a veterinary medicinal product intended for food-producing animals can be authorised in the EU, the safety of its pharmacologically active substances and their residues must first be evaluated and included in a specific list (Table 1, allowed substances) of the Annex to Commission Regulation (EU) No 37/2010 (Official Journal of the European Communities, 2010), which details the so called “Maximum Residue Limits” (MRLs). Therefore antimicrobials without MRLs cannot be legally used in food producing animals. This restriction does not apply to companion animals (non-food producing animals).

Further details on the Marketing Authorisation of antimicrobials and on the off label use are provided in Annex III – Summary of regulation of medicinal products for use in animals in the EU - Maximum residue limits (MRLs) and marketing authorisations.

Risk for transfer of resistance in bacteria of public health relevance is only one factor of several that it is the veterinarian’s responsibility to consider when deciding on what is appropriate treatment for a certain infection.

## 3. International recommendations

International organisations have published a number of standards and guidelines relating to the authorisation and use of antimicrobials in animals. These recommendations indicate that the

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<sup>10</sup> According to the European Directive 2001/21/EC, as amended, ‘off label’ use is defined as: “The use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics (SPC), including the misuse and serious abuse of the product.”

authorisation of antimicrobials should address the potential impact on human health of the authorisation of such products (Codex Alimentarius, OIE).

### **3.1. WHO recommendations**

When a new class of antimicrobials comes on the market, it should be considered “critically important” from the outset unless strong evidence suggests otherwise.

Existing drugs that are already classified as “critically important” antimicrobials but which are not currently used in food production such as carbapenems, oxazolidinones (linezolid) and lipopeptides (daptomycin) should not be used in the future in food animal production”.

### **3.2. OIE recommendations**

Antimicrobial classes/sub classes used only in human medicine are not included in [this] OIE list. Recognising the need to preserve the effectiveness of the antimicrobial agents in human medicine, careful consideration should be given regarding their potential use (including extra-label/off label use) / authorisation in animals.”

The above recommendations have been taken into account for the preparation of this answer (and Question 2) for the EC.

## **4. The need for new antimicrobials in veterinary medicine**

### **4.1. Considerations on marketing authorisations (MAs) of antimicrobials for animals**

Antimicrobials are essential for the treatment of many microbial infections in humans and animals. The lack of a clear policy on the development of new antimicrobials is a burden for the veterinary pharmaceutical industry as it leads to uncertainty and hampers development of new antimicrobials that are required for animal health. Completely new veterinary-only classes of antimicrobials have the potential to decrease animal and public health risk. To achieve minimal negative impact on public health, veterinary antimicrobials should not be identical to or favour resistance determinants that give cross-resistance with antimicrobials that are structural analogues of those used in human medicine. Nor should they produce co-selection by facilitating the dissemination of resistance genes. According to various stakeholders, the research and development costs of new antimicrobials that fulfil these conditions are considered undesirable high.

During past years, the following new antimicrobial active substances have been authorised for use in veterinary medicine using the centrally authorised procedure: difloxacin (belonging to the class fluoroquinolones, first authorised in 1998), valnemulin (a pleuromutilin, 1999), pirlimycin (a lincosamide, 2001), tulathromycin (a macrolide, 2003), tylvalosin (a macrolide, 2004), ceftiofur (a 3<sup>rd</sup> generation cephalosporin, 2005), cefovecin (a 3<sup>rd</sup> generation cephalosporin, 2006), gamithromycin (a macrolide, 2008), pradofloxacin (a fluoroquinolone, 2011) and tildipirosin (a macrolide, 2011). None of these antimicrobials belongs to a new class of antimicrobials. Further information on these substances can be found in Annex II, of this document. It should be noted that other antimicrobials may have been authorised using routes other than the Centralised Procedure. In addition, agents with anti-infective activity can be authorised for non-infectious indications (e.g. monensin for ketosis) and administration of these substances will also exert an antimicrobial selection pressure.

Also of note is that antimicrobial classes that have been authorised for decades in animals may later become of interest for treatment of human infections; for example the classes of pleuromutilins and polymyxins have only recently received authorisation in human medicine or have been authorised for new indications.

#### **4.2. Indications for which new antimicrobials are needed**

Stakeholders were asked to provide specific examples of indications for which there is a lack of antimicrobial veterinary products. A primary area of concern is Minor Species such as rabbits, pheasants, ducks, exotics, bees, fish (other than Salmon), etc. The need for antimicrobials to cover minor species could most often be met by expanding the indications for existing veterinary medicinal products or by developing new products containing substances/classes previously approved in VMPs. From the information received from stakeholders no specific concerns were raised indicating a need for new classes (not previously used in veterinary medicine) for minor species.

A second area of concern affecting both food producing and companion animals is the indication for colibacillosis and diseases with involvement of coliforms, such as neonatal diarrhoea, sepsis and mastitis. Additional specific indications highlighted by the stakeholders were *Brachyspira hyodysenteria* in swine (MDR), *Rhodococcus equi* and anaerobe infections (*Clostridium*) in the horse, enterococci and respiratory *Mycoplasma* infections in poultry, bovine respiratory disease (*Pasteurellaceae* & *Mycoplasma*), and bovine interdigital dermatitis.

Thirdly, specific bacteria of concern have been highlighted: extended spectrum betalactamase (ESBL)-producing *E. coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), for which additional information and recommendations have been made earlier by EMA/CVMP (EMA/CVMP/SAGAM, 2009b).

Research should also be encouraged into development and testing of novel antimicrobial therapies that ideally are not susceptible to development of microbial resistance.

#### **4.3. Benefit of marketing authorisation for new substances**

Section 4.2. outlines indications for which there is a need for new antimicrobial products in veterinary medicine. The authorisation of completely new classes of antimicrobials for use in animals only might decrease animal and public health risk by reducing the selection pressure on existing classes provided there is no co-selection by already authorised products.

Should a need for a veterinary medicinal product containing a Category 3 substance be identified, authorisations could only be considered on the basis of a positive benefit-risk assessment where the risk for transfer of resistance to humans is included in the assessment. CVMP is working on further guidance on the conduct of risk assessment for antimicrobials where the focus is on the risk to public health.

Category 3 contains numerous products with different uses in human medicine and any potential benefits to animal health as well as their AMR risk profile if used in veterinary medicine are likely diverse. Thus whether the benefit-risk balance for Category 3 containing products for veterinary use would be found positive cannot be foreseen.

#### **4.4. Risk of marketing authorisations for new substances**

It is not possible to accurately predict and quantify the risk to public health that could result following authorisation of human only antimicrobial substances into veterinary medicine.

Many of the risk factors related to development and transfer of antimicrobial resistance are known: amount of use of the antimicrobial; intensity of use (interval, duration, route of administration); mutation and resistance transfer capacities of bug-drugs combinations; impact of housing conditions on presence and transfer of commensal and zoonotic bacteria; factors affecting foodborne transmission such as food processing and storage, and end user hygiene. To accurately forecast the exact final impact of each factor is currently not possible; however, prior to product approval an assessment should be made of the potential risk to public health based on the available knowledge at the time.

Every antimicrobial use will instantly result in a Darwinian selection pressure that leads to mutations conferring resistance that can spread to daughter colonies (vertical spread). Once stably present in the genome, resistance determinants can further be spread by mobile genetic elements (horizontal gene transfer) to commensal and pathogen bacteria that will end up in the environment or food of the vulnerable human patient. By linking of new resistance mechanisms with earlier evolved resistance genes, the use of even non-structural analogue substances can then result in an efficient spread in the body and environment. Resistance to carbapenems for instance, for which no authorisation is present in veterinary medicine, has already been documented in animals and simultaneous resistance to older substances was present (Abraham et al., 2014; Liebana et al., 2013).

As the evolution of resistance development is complex and cannot be precisely forecast prior to use of a new substance, it is recommended that at the time of first approval for new antimicrobial substances/a new class of antimicrobial in veterinary medicine, marketing authorisation holders (MAHs) should have plans in place to monitor evolution of susceptibility in zoonotic and indicator bacteria through approved programmes.

#### ***4.5. The current off label use of substances authorised for use only in human medicine***

As detailed above and in the Annex, the "cascade" system allows use of substances in animals that currently have been authorised for human medicine only. Examples of antimicrobials authorised for use in human medicine which have been used in veterinary medicine, have been compiled based upon answers of different stakeholders (Table 4.)

**Table 4:** Examples of specific antimicrobials and indications for which human only authorised antimicrobial classes have been used off label in animals

The first part of the table includes substances that are not authorised in veterinary medicine. The second part of the table lists antimicrobials for which analogue substances are authorised in veterinary medicine.

Substance/class only authorised in human medicine	Target animal species	Indication/target pathogen
Carbapenems	Companion animals	Undefined (declining), and <i>E. coli</i> (Han et al., 2010; Pomba et al., 2014; Shaheen et al., 2013)
Mupirocin	Companion animals	MRSA
Nitrofurantoin	Cats	UTI
Rifampicin*	Horses	<i>Rhodococcus equi</i> (respiratory infections)
	Dogs	MRSP
Ticarcillin	Horse	<i>Klebsiella</i> spp. infections
Vancomycin	Companion animals	MRSA
	Horses	Infections caused by MRSA and enterococci

Human authorised substance with structural analogues in veterinary medicine	Target animal species	Indication/target pathogen
Amikacin#	Horse	Septic arthritis
	Dogs	Superficial bacterial folliculitis
Azithromycin#, *	Horse (non-food producing)	<i>Rhodococcus equi</i> (respiratory infections)
	Birds	Psittacosis
	Cats	<i>Chlamydophila felis</i>
Cefazolin	Dogs and cats	Respiratory tract, joint, and bone infections
Ciprofloxacin	Dogs and cats	Pyoderma/UTI
Ofloxacin#	Horse	Treatment of eye infections resistant to commonly used ophthalmic antimicrobial treatments
Clarithromycin	Fowl, horses and pets	Various, including respiratory infections, (e.g. combination therapy for <i>Mycobacterium</i> spp.), <i>Nocardia</i> , <i>Actinomyces</i> spp.

UTI: urinary tract infections, MRSA: methicillin resistant *Staphylococcus aureus*, MRSP: methicillin resistant *Staphylococcus pseudintermedius*, \* macrolide (azithromycin) and rifampicin are used in combination for the treatment of *R. equi* infections, #Commission Regulation (EC) No 1950/2006 (Official Journal of the European Union, 2006), as amended by Commission Regulation (EU) No

122/2013 of 12 February 2013 (Official Journal of the European Union, 2013), list of substances essential for the treatment of *Equidae* which may be administered to horses intended for slaughter for human consumption subject to a withdrawal period of not less than 6 months.

No quantitative data are available on the extent of use of these substances.

Most of the information about off-label use of antimicrobials authorised for human use relates to use in companion animals (including horses).

#### **4.6. Benefits of off label use**

Table 4 highlights the need for “cascade” use and gives examples of human only antimicrobials that are used in veterinary medicine.

Many of the indications included in the table would not be treatable without the use of human only authorised antimicrobials. This has implications for animal welfare.

As no monitoring system of off label use is available, it is not possible to assess all the current off label uses of antimicrobials only authorised in humans.

#### **4.7. Risk linked to off-label use of antimicrobials authorised on the human side**

The extent of off-label use has so far not been evaluated at the EU level and detailed investigations at country level are scarce.

Although care should be applied in making inferences as ESVAC does not yet collect data according to use in species or production systems, data adjusted by population correction unit (PCU) show high differences in antimicrobial use between countries which suggests that there could be potential to reduce antimicrobial consumption. In answering this question, use of classes/substances which are not approved for use in veterinary medicine was considered. The level of risk to public health is not known as no risk assessments have been performed. Example: Use of carbapenems to treat ESBL-producing bacteria in dogs.

Monitoring of use of these products would be of value as it would allow for estimation of the current and future need for new veterinary medicinal products. Collecting these data would allow for an assessment of the exposure in animals to human only authorised antimicrobials and a better estimate of the risk to public health from such use.

The current MRLs legislation is intended to manage the public health risk due to residues in meat, eggs, milk and other food products related to the administration of veterinary products. As indicated above and detailed in the Annex III, MRLs need to have been established in order to use these substances according to the “cascade” in food-producing animals.

A particular situation might arise when an MRL is established for a substance, but when no product is currently marketed for food producing animals. This would potentially allow use of human-only authorised antimicrobials in food producing species under the “cascade”. The main purpose of MRL legislation is not to safeguard humans against the transfer of antimicrobial resistance from animals (although development of AMR in human gut flora due to antimicrobial residues is addressed) and therefore it is not considered appropriate to use this as an indirect means to restrict off-label use of antimicrobials in food producing species.

In order to address as early as possible the risk of AMR, and to avoid the aforementioned situation, it might be considered that further to the MRL legislation, alongside antibiotic residue concerns the

hazard analyses related to antimicrobial resistance are also considered, this might provide an early signal to applicants about the risks linked to AMR. This could be achieved by including this part of the risk assessment simultaneously with or prior to the MRL assignment. The complexities of such an early assessment should be further discussed.

Illegal import of antimicrobials is not within the definition of off label use<sup>11</sup> and is outside the scope of this report, but when preparing the answer to this request it was noted that there are some indications of import of illegal antimicrobials from outside Europe. Illegal use of antimicrobials should be prosecuted, especially taking into account the possible implications for human and animal health.

#### **4.8. Benefit-risk of off label use**

In the preparation of this document, different stakeholders stated that certain medical antimicrobials, including carbapenems, tigecycline, daptomycin, oxazolidinones, vancomycin and mupirocin should be banned from use in all veterinary medicine.

In the EMA reflection paper on glycyclus (tigecycline, Question 1), it is stated that 'Should, in the future, a need for such medicinal products for animals be identified, authorisations could be considered on the basis of a positive benefit-risk assessment where the risk for transfer of resistance to humans is included in the assessment.' (EMA/CVMP/CHMP/AMEG, 2013).

Two classes of antimicrobials currently approved in human medicine only are at present internationally regarded as of special concern; carbapenems and glycopeptides. In the answer to Question 2, the AMEG's recommendation for carbapenems and glycopeptides is that their use in veterinary medicine should be kept to an absolute minimum due to the high risk for spread of resistance.

Carbapenems are of highest concern from a risk assessment perspective as they target MDR Gram-negative infections for which there are few alternatives in human medicine.

EFSA has recently produced a Scientific Opinion on carbapenem resistance in food animal ecosystems (EFSA, 2013). The EFSA opinion is the result of the finding of carbapenem resistance in food producing animals, and is not linked to any submission of a Marketing Authorisation Application for those substances. The fact that carbapenems are not authorised in animals but resistance has been found in different animal species highlights the complexity of the relationship between antimicrobial use in animals and resistance.

In this opinion EFSA recommends:

"As carbapenems are not licensed for use in food-producing animals in the EU and other parts of the world, one simple and effective control option to minimise the further emergence and possible spread of such strains transmitted via the food chain would be to continue to prohibit the use of carbapenems in food-producing animals. " (Please note that carbapenems are not specifically prohibited, but are not authorised for use in animals and do not have MRLs established).

Based on this opinion, and as the need to use carbapenems in animals seems very low, the EC might consider:

- To formally prohibit the off label use of carbapenems in food producing animals;
- To prohibit the use of carbapenems in all animal species;
- To limit the use in non-food-producing animals:

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<sup>11</sup> According to Article 16 of Directive 2001/82/EC off label use is defined as "The use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics (SPC), including the misuse and serious abuse of the product."

For this last case possible risk management options include:

- Establish a list of diseases where such use is possible;
- Official declaration of use of carbapenems to the relevant authority.

More generally for antimicrobial classes of Category 3, to mitigate the risk from their off label use it is critical that the conditions outlined in Articles 10 and 11 of the Directive 2001/82/EC, as amended (Official Journal of the European Communities, 2001) are strictly applied, i.e. that the products are only to be used by way of exception, under direct responsibility of a veterinarian and in particular to avoid causing unacceptable suffering to the animals. Monitoring of use would indirectly allow also for monitoring of the need for these substances in veterinary medicine.

In addition, in accordance with Commission Regulation 504/2008 (Official Journal of the European Union, 2008), horses can be declared as either intended for human consumption (food producing horse) or not intended for human consumption (non-food producing horse) in which case they would require a horse passport. For those horses not intended for human consumption a list of “essential substances” has been established according to Commission Regulation (EU) No 122/2013 (Official Journal of the European Union, 2013). On this list 4 antimicrobials (ticarcillin, azithromycin, rifampicin and amikacin), authorised in human medicine, have been included for use in the specific cases detailed by the legislation (Annex of the regulation). No data on the use of these substances under the mentioned regulation was available so it is not possible to estimate the overall risk of use of those substances under these conditions.

At the EU/EEA, the ESVAC project has proposed a detailed monitoring system to estimate antimicrobial consumption (EMA/ESVAC, 2012b). The ESVAC project cannot capture information relating to off label use as the data are not collected according to indication of use in animal species and, more importantly, the data collected refer to authorised preparations for use in animals. Illegal use (i.e. use not in line with the Marketing Authorisation (MA) or the “cascade”) would also not be necessarily collected in the ESVAC project. In the future the intended ESVAC collection of data at farm level might provide some relevant information on the use of antimicrobials at farm level and identify some of the off-label use. Such data collection should be promoted, but collecting automated or prescription data is more resource-demanding than the collection of overall sales of antimicrobials.

To estimate the risk of off label use the need to use certain antimicrobials only used in humans has to be considered. Precise information is lacking and the risk cannot be quantified. For instance methicillin-resistant *S. pseudintermedius* (MRSP) in skin infections in dogs are a great concern based upon individual case reports, but the overall burden at regional or European level cannot be judged.

#### **4.9. Discussion and recommendations (including possible risk management options) for Question 3**

To minimise the public health risk related to antimicrobial resistance derived from animal husbandry, new antimicrobials should preferably belong to classes not used in human medicine. A specific risk assessment for each new substance or new class of antimicrobial is needed to assess the risk of transfer of resistance of relevance for public health from treated animals. Furthermore a specific risk assessment is required not only for each substance but for each product taking into consideration the condition of its use (e.g. species, dose regimen and route of administration).

Some recommendations can be made on how and when to estimate the risk from the possible authorisation of new substances.

The following recommendations are made:



- Currently, if MRLs were to be approved for a human-only authorised antimicrobial substance, the substance could be used legally to treat food-producing species without consideration of the AMR-related risk to public health. 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.

Based on the outcome of this substance-related assessment, a decision could then be made as to whether the antimicrobial should be restricted/banned from use in food-producing species under the “cascade”.

This hazard characterisation could also give an indication to MA applicants of the potential AMR risk to public health for proposed VMPs and the need for risk management measures. A full, tailored product-related AMR risk assessment would still be required as part of an MA application and taken into consideration for the benefit-risk assessment for the product, which also takes into account aspects of animal health and welfare.

The foodborne route of resistance transfer is considered to be of importance due to the high level of potential human exposure; however, if there is industry interest, the option of early hazard characterisation could also be extended to substances intended for products for companion animals where there is concern regarding transfer of resistance to humans through direct contact.

- 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.

These regularly updated databases preferably should also be accessible to veterinary practitioners so that the information can be taken into account for prescribing and when considering the approach to unexpected relapse.

- 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.
- Put in place a declaration system in order to assess the extent and evolution of off label use of human only authorised antimicrobials.

Information on the off-label use in animals of antimicrobials authorised in human medicine only is lacking. Monitoring of off label use needs to be facilitated. When collecting data on consumption of off label use of antimicrobials in animals the animal species (body weight), product, indication, regimen (dose, duration, treatment interval, route of administration/formulation) are important to assess.

Information collected from stakeholders provides a limited but very relevant number of indications where there is a lack of authorised antimicrobials in veterinary medicine for major species. Here, ESBL (extended-spectrum beta-lactamases) producing *E. coli*, MRSA, MRSP, *Brachyspira* and *Rhodococcus* are clearly demonstrated indications of concern. For minor species, there is a clear lack of authorised veterinary antimicrobials.

Although the use of veterinary antimicrobials authorised in other species may address the some of the quoted gaps, limited information is available to the veterinarian when deciding on the treatment for those species and indications.

Conditions for Marketing Authorisations of antimicrobials for the above indications and for minor species and minor uses should be facilitated without compromising public health. This could be done in the form of scientific advice, extending protection periods, etc.

- Include in future legislation 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.

Some MSs have already such a (pre)approval notification system in place, e.g. in Sweden use of some substances is prohibited unless permission is given by the Board of Agriculture. At the European level, information relating to the use under the “cascade” of human only authorized antimicrobials is lacking.

If high levels of off label use, including misuse and serious abuse, are predicted, or if after a Marketing Authorisation approval - detected or reported - Marketing Authorisation Holders should be requested to take adequate risk management measures to mitigate the consequences of such use.

Those measures from regulators should include the option of banning of off-label use.

This recommendation is also applicable for substances already authorised (see answer to Question 4).

#### **4.10. Remarks on classes of antimicrobials**

During the preparation of the answer to Question 2, the classes of critically important antimicrobials that are authorised for use in human medicine but not in veterinary medicine (Category 3) were analysed in detail. The resulting recommendations were as follows:

- Carbapenems and other penems; use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance. EFSA recently has made a risk assessment for carbapenems, a class of antimicrobials of increasing human importance, and it concluded that carbapenems should not be used for food producing animals, it also concluded that “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: No specific concern identified yet.
- Cyclic esters (e.g. fosfomycin); use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance.
- Glycopeptides; use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance.
- Glycylcyclines; see response to Question 1<sup>12</sup>.
- Lipopeptides; No specific concern identified yet.

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<sup>12</sup> 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/Other/2013/07/WC500146812.pdf) and [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/07/WC500146814.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146814.pdf)

- Monobactams; use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance.
- Oxazolidinones; 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  $\beta$ -lactamase inhibitors combinations; use in veterinary medicine should be kept at an absolute minimum due to high risk for spread of resistance.
- Riminofenazines; No specific concern identified yet.
- Sulfones; No specific concern identified yet.
- Drugs used solely to treat tuberculosis or other mycobacterial diseases; No specific concern identified yet.

Before considering applying for any marketing authorisation for products containing antimicrobials belonging to any of the above mentioned classes, the above concluding remarks should be taken into account.

Please note that the above list is not inclusive of all antimicrobials authorised in human medicine.

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

### 1. Summary answer

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 substantive restrictions in their use, particularly in relation to 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-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 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins are being introduced in other MSs. Difficulties in estimating the impact of risk management measures have been acknowledged. Such difficulties include the complexity in linking antimicrobial usage in food production animals to resistance in man in EU countries, problems in identifying the effects of a single action when several actions may be implemented simultaneously, difference in assessing the risk(s) associated with the use of the same antimicrobial in different animal species, 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 3<sup>rd</sup>- and 4<sup>th</sup>-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 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.
- 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.

In addition the following activities should be implemented:

- Reduction of overall antimicrobial consumption.
- Promotion of good farming practices and animal husbandry.
- Further research into: the off-label use of antimicrobials in animals; actions could be derived from the result of research findings; pathways of dissemination of AMR 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-based measure; 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 animal have been recommended.

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.

Also, 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.

## 2. Introduction

### 2.1. Background

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.”*

### 2.2. Scope of the response

The answer addresses all critically important antimicrobials, focussing on those under the category of higher risk to public health. Of these, risk profiles for fluoroquinolones and cephalosporins have been produced by the EMA/CVMP, which have resulted in certain risk management measures being applied.

The answer primarily focuses on the use of such antimicrobials in food producing animals. Measures put in place with regard to food producing animals may not be automatically applied to companion animals. Furthermore practices such as the movement of animals, the mixing of animals, biosecurity aspects of animal husbandry, and the import of animals and animal feed from countries out with the EU, all of which may impinge on AMR, are considered to be outside the remit of the answer.

## 3. Considerations for the response

To assist stakeholders in responding to this request, the AMEG subdivided the overarching request into a series of sub-questions<sup>13</sup>, as follows:

- Are there examples of animal diseases for which the use of Critically-Important Antimicrobials (CIAs) for human use (see WHO list of CIAs) is essential? (Stakeholders were particularly asked to concentrate on fluoroquinolones and 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins; other CIAs could be included if considered appropriate)?
- Are there examples of situations where risk mitigation measures on use of antimicrobials in animals have led to a positive or negative impact on animal health and welfare, an economic impact or a practical impact on animal husbandry?
- Stakeholders were further asked if they could indicate, if known, whether such measures were voluntary or compulsory, and to provide details of the duration over which the measures had been in place and difficulty and timing of implementation.
- Input was requested on the possible need of further future risk mitigation measures in relation to the use of certain classes of antibiotics or antibiotic substances that are currently authorised as veterinary medicinal products. It was requested that, if possible, this should include an estimate of the cost and benefits of such measures.

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<sup>13</sup> See the “Overview of preliminary comments received on public consultation on the request to the European Medicines Agency from the European Commission for scientific advice on the impact on public health and animal health of the use of antibiotics in animals” (EMA/393557/2014) for further information. Available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/07/WC500170255.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170255.pdf)

- To allow the assessment of measures to promote responsible use of CIAs in animals, data were requested on the impact of expiry of marketing exclusivity of CIAs used in animals on sales and usage patterns.

The exemplar antimicrobials chosen to assist in answering Question 4 were fluoroquinolones and 3<sup>rd</sup> - and 4<sup>th</sup>-generation cephalosporins, although it was emphasised that any other antimicrobials listed as 'critically-important' by WHO could be considered. The document has concentrated on the use of such antimicrobials that relate to animal husbandry. Other risk management options, for example those involving the movement and mixing of animals, and biosecurity aspects of animal husbandry which may impact on AMR have not been considered in this document (see above).

### **3.1. Background: Existing international recommendations:**

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. Examples follow below.

#### **3.1.1. Codex Alimentarius**

The Codex provides guidelines for risk analysis of foodborne antimicrobial resistance in CAC/GL77 – 2011 (Codex Alimentarius, 2011). These risk management options cover a number of possible actions to reduce the risk of contamination of food and to reduce the risk related to the selection and dissemination of AMR microorganisms and/or determinants.

#### **3.1.2. WHO and OIE**

WHO and OIE have produced lists of CIAs and have provided recommendations as follows.

##### **3.1.2.1. WHO**

WHO have prioritized among the Critically-Important Antimicrobials the following classes to be considered of highest priority for risk management: Fluoroquinolones, 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins, macrolides and glycopeptides.

##### **3.1.2.2. OIE**

OIE have adopted recommendations on fluoroquinolones and 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins. Among the VCIA (Veterinary Critically Important Antimicrobials) in the OIE list, some antimicrobials are considered to be critically important both for human and animal health. This is the case for fluoroquinolones and for 3<sup>rd</sup>- and 4<sup>th</sup>-generation of cephalosporins. Therefore these two classes should be used according to the following recommendations:

- Not to be used as preventive treatment applied by feed or water in the absence of clinical signs in the animal(s) to be treated.
- Not to be used as a first-line treatment unless justified. When used as a second line treatment, usage should ideally be based on the results of bacteriological tests.
- Extra-label/off label use should be limited and reserved for instances where no alternatives are available. Such use should be in agreement with the national legislation in force.

### **3.2. Difficulties in responding to the request**

The following difficulties in responding to the request were acknowledged.

Firstly, the complexity in linking antimicrobial usage in food production animals to resistance in man. For example, the clonal spread of AMR strains in food animals and the community, which is common in *Salmonella* spp. and ESBL-producing *E. coli*, can profoundly affect conclusions about antimicrobial consumption in animals and development of resistance in organisms causing infections in humans.

Antimicrobial usage in either the human or veterinary sectors in the EU is undoubtedly linked to the emergence and dissemination of many antimicrobial-resistant strains in both humans and food animals. In some cases resistance might also be linked to bacterial clonal spread. For example, a clone of *Salmonella* Typhimurium definitive phage type (DT) 104 resistant to five unrelated antimicrobials emerged simultaneously into bovine animals in the UK and into North America following its introduction from countries in Southeast Asia.

Secondly, several management actions may be implemented simultaneously and there may be difficulties in identifying the effect of each individual action. For example, there are undoubtedly difficulties in evaluating the consequence of a specific action, such as the replacement of one antimicrobial class by other antimicrobials, especially if this is done in conjunction with other practices which may impact on resistance.

Thirdly, the use and consequently the associated risk(s) of the same antimicrobial in different animal species may be different.

Fourthly, since numerous antimicrobial resistance genes code for resistance mechanisms affecting several substances of a specific antimicrobial class, (defined as 'cross-resistance'), the impact of resistance to a specific antimicrobial within a class may be difficult to determine. The importance of 'cross- or co-resistance', defined as the simultaneous presence in a bacterium of different genes giving resistance to several different antimicrobial classes is also important since antimicrobial treatment with one substance of one of these antimicrobial classes will select this type of multidrug-resistant clone and co-select resistance in the different families, as has been demonstrated with tetracyclines and tetracycline derivatives (Catry and Threlfall, 2009; Kanwar et al., 2013). The importance of co-resistance also has been acknowledged by EFSA, who have stated that 'as co-resistance is an important issue, it is also of high priority to decrease the total antimicrobial use in animal production in the EU' – see above (EFSA, 2011). The EMA/CVMP has also recommended to reduce total antimicrobial use, e.g. for MRSA: *"Due to the multiresistant character of MRSA, there are several antimicrobial classes that may increase the risk of spread of MRSA. Therefore, to be effective to control the emergence of MRSA, measures to reduce the use of antimicrobials cannot be limited to any specific class but routine use of antimicrobials is to be regarded as a risk factor. Any measures to be taken should consider all antimicrobials with the aim to eliminate unnecessary use or replace use with other strategies."* (EMA/CVMP/SAGAM, 2009a), and for MRSP: *"Routine use of antimicrobials is a risk factor for spread of MRSP. There are several antimicrobial classes that may increase the risk. Therefore it would be beneficial to reduce total antimicrobial usage."*(EMA/CVMP/SAGAM, 2011)

Finally, there is an absolute need to define what are regarded as the key 'measurements of success' and desired outcomes for an effective risk management policy, and how they will be measured.



### **3.3. Risk mitigation measures implemented at the EU and national level**

#### **3.3.1. Responsible use guidelines**

A range of responsible use guidelines at the EU level are currently under revision, and include details of policies implemented by individual MSs. The guidelines include a list of general considerations to be taken into account before antimicrobials are used, and also special considerations before using antimicrobials considered critical for preventing or treating life-threatening infections in humans. These guidelines are summarised below.

##### **3.3.1.1. Guidelines for the use of antimicrobials considered critical for preventing or treating life-threatening infections in humans**

General guidelines for the use of CIAs are as follows:

- Such antimicrobials should only be used where a veterinarian has assessed, based on antimicrobial susceptibility testing and/or justified by relevant epidemiological data, that there is no other effective non critically-important antimicrobial available.
- In the case that exceptional use under the so-called “cascade”/off label use is unavoidable and legally possible, prescription and final use should be sufficiently justified and recorded. Such use based on clinical grounds considered by the prescribing veterinarian in order to avoid suffering of diseased animals, and considering ethical and public health concerns, should be at the same time limited to those cases where there is no other alternative available.

Specific guidelines for the use of critically-important antimicrobials:

- The CVMP produced a 5 year strategy on antimicrobials, the 2011-2015 strategy (EMA/CVMP 2011) which indicates that special emphasis should be put on the need to reserve the use of fluoroquinolones and 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins for conditions that have responded poorly or are likely to respond poorly to other classes of antimicrobials, and to avoid use for general prophylaxis. The recommendations also indicate that group treatments must be justified in relation to the severity and contagiousness of the disease.
- Recommendations for the use of fluoroquinolones, 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins and macrolides have been produced by EMA (EMA/CVMP/SAGAM, 2009b; EMA/CVMP/SAGAM, 2011; EMEA/CVMP, 2006). Safety assessments for tigecycline and colistin have been provided in the answer to Question 1. The CVMP has also addressed many referrals for antimicrobial veterinary medicinal products with the aim to promote their responsible use<sup>14</sup>.

### **3.4. EFSA**

For cephalosporins, EFSA have made the following recommendation (EFSA, 2011):

- ‘A highly effective control option would be to stop all uses of cephalosporins/systemically active 3rd/4th-generation cephalosporins, or to restrict their use (use only allowed under specific circumstances)’.

For carbapenems, EFSA have made the following recommendation (EFSA, 2013):

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<sup>14</sup> See

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet\\_referral\\_search.jsp&mid=WC0b01ac05805c5170](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_referral_search.jsp&mid=WC0b01ac05805c5170)

- ‘At present, carbapenems are not licensed for use in food-producing animals in the EU and other parts of the world, and therefore one simple and effective control option to minimise the further emergence and possible spread of such strains transmitted via the food chain would be to continue to prohibit the use of carbapenems in food-producing animals’.

Because of the importance ascribed to co-resistance (see below), in both the above Opinions decreasing the frequency of use of antimicrobials in animal production in the EU in accordance with responsible use guidelines has also been afforded high priority. In particular, in the cephalosporin Opinion (EFSA, 2011), it was stated that as co-resistance is an important issue, it is also of high priority to decrease the total antimicrobial use in animal production in the EU.

### ***3.5. Policies for individual Member States for the use of critically-important antimicrobials***

These include:

#### Belgium:

Formulariae on the responsible use of antimicrobials for pigs, poultry and bovines have been published by AMCRA (Antimicrobial Consumption and Resistance in Animals) and are used on a voluntary basis. A colour code is used to determine the conditions of use for each molecule, based on the importance of the molecule for animal and human health and classification of the molecules by the WHO and OIE. ‘Red’ molecules can only be used when the diagnosis is based on laboratory testing and the pathogen is resistant to first, second or third choice antimicrobials with yellow or orange colour code. The quinolones and the 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins are red-coded molecules. They may only be present on the farm for a 5-day therapy and do not belong in the stock of medicines a farmer is allowed to have when there is an agreement with the veterinarian. Aside from this, a general reduction of antimicrobial consumption in animal husbandry together with target indicators is scheduled.

#### Czech Republic:

Legal provision – Decree No 344/2008; §3 / 2 - stipulated conditions for prescribing and handling antimicrobials under a “prudent use” regimen, including possible fines when the law is not followed. The aim of this legal rule is to strengthen adherence to the recommendations given in the SPCs of certain VMPs (containing (fluoro) quinolones, 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins, ansamycins (rifaximin) and aminoglycosides of higher generations (e.g. gentamicin, kanamycin).

#### Denmark:

Restrictions on the use of fluoroquinolones have been in operation since 2002. The restriction means that before prescribing, the veterinarian should perform microbiological examination and susceptibility testing to ensure that no other class of antimicrobials will be effective. Additionally the swine industry voluntarily forbade the use of 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins in 2010.

#### Finland:

Following the implementation of the 2006 EU regulations on growth promoters, off label use of the following antimicrobials in all animal species has been banned: avoparcin, vancomycin, teicoplanin, virginiamycin, 3<sup>rd</sup>- and 4<sup>th</sup>- generation cephalosporins, rifampicin, rifabutin, moxifloxacin, ofloxacin, levofloxacin, gatifloxacin, tigecycline, mupirocin, telithromycin, daptomycin, linezolid, quinupristin-dalphopristin, carbapenems and monobactams.

#### France:

The pig sector introduced a voluntary restriction of the use of 3<sup>rd</sup>- and 4<sup>th</sup>- generation cephalosporins in pig production in 2010. This led to a decrease of 62% in the number of animals treated with these substances in 2012 compared to 2010.

#### Germany:

Goals to reduce overall use of antimicrobials by benchmarking of farms against one another are being implemented.

#### The Netherlands:

According to national veterinary drugs legislation, prescribing and use the most critical antimicrobials for human healthcare, 3<sup>rd</sup>- and 4<sup>th</sup>- generation cephalosporins and fluoroquinolones, is allowed only after susceptibility testing of the pathogen for first and second choice antimicrobials.. For pork production there are voluntary restrictions on the use of 3<sup>rd</sup>-and 4<sup>th</sup>-generation cephalosporins and fluoroquinolones. For dairy cattle there are similar voluntary restrictions on the use of 3<sup>rd</sup>-and 4<sup>th</sup>- generation cephalosporins in dry cow treatment.

#### Sweden:

From 1 January 2013 a regulation has been in force that restricts the use of 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins and fluoroquinolones in animals. The restriction means that before prescribing, the veterinarian should do microbiological examination and susceptibility testing to ensure that no other type of antimicrobials will be effective.

#### United Kingdom:

The British Poultry Council introduced a voluntary ban on the use of fluoroquinolones in day-old chicks and 3<sup>rd</sup>- and 4<sup>th</sup>- generation cephalosporins in poultry production from January 2012.

### **3.6. Examples of risk management measures that have led to a positive or negative impact**

Details of various risk management measures that have been undertaken in the EU to date, together with positive and negative aspects, are summarised in Table 5 below.

**Table 5:** Risk management measures: positive and negative aspects

Risk management measures	Positive aspects	Negative aspects
Withdrawal of growth promoters in several European countries prior to the EU-wide ban on antibiotic growth promoters in 2006	Major reductions in vancomycin-resistant <i>E. faecium</i> from broilers and pigs in Denmark following decreased use of avoparcin  Reduction in macrolide resistance (tylosin) in <i>E. faecium</i> among broilers	Following the withdrawal of growth promoters in Denmark in 2008/2009, there was a substantive increase in the following two years in the use of certain therapeutic antimicrobials in animals, particularly tetracyclines in pigs
EU-wide ban on antibiotic growth promoters in 2006	Overall reduction in resistance to antimicrobials previously used in growth promoters in farm animals and in humans in various EU countries	Withdrawal associated with a deterioration in overall animal health, including increased diarrhoea, weight loss and mortality due to <i>E. coli</i> and <i>Lawsonia intracellularis</i> in early

Risk management measures	Positive aspects	Negative aspects
		post-weaning pigs, and clostridial necrotic enteritis in broilers
Danish 'Yellow Card' system.	20% drop in antimicrobial usage since its introduction in July 2010	Reports of increases in the occurrence of enteritis and peritonitis in slaughter pigs and of weaning piglets with oedema disease.'
Ban on fluoroquinolone usage in poultry in Finland since 1993.	Occurrence of fluoroquinolone resistance in <i>Campylobacter</i> from cases of infection in persons infected in Finland ca. 20-30 times lower than in Finnish persons infected in Spain	No adverse aspects reported
Voluntary ban on use of fluoroquinolones in poultry in the Netherlands from 2009	Reduction of resistance to fluoroquinolones in <i>E. coli</i> from broilers and poultry meat from ca. 57-50 % in 2009 to 50-41% in 2012	No adverse aspects reported
Self-ban of third-generation cephalosporin usage in Danish pig production in July 2011	Reduction of ESBL-producing organisms in slaughter pigs	No adverse aspects reported
Voluntary ban on use of 3 <sup>rd</sup> -generation cephalosporins in Danish poultry from 2009	Substantive reduction of resistance to cephalosporins in <i>E. coli</i> from broilers and poultry meat	No adverse aspects reported
Advice to government from the Dutch Health Council in 2011 to limit the use of antimicrobials that are of public health concern in food-producing animals.	Significant falls in resistance levels in farm animals, including in ESBL-producing <i>E. coli</i> in poultry and pigs	The Dutch Animal Health Service GD reported many more <i>E. coli</i> infections over 2012 and a strong increase in the number of dead animals submitted for pathological investigation
Voluntary ban by the British Poultry Council from 2012 on the use of all cephalosporins in the poultry meat production chain from 1 January, 2012, as well prophylactic use of all quinolones for day-old chicks	Information not yet available	Information not yet available

In other countries voluntary suspension of use of ceftiofur in hatcheries (e.g. in Quebec, Canada, from 2005 to 2006) resulted in a substantive fall in cephalosporin resistance in *Salmonella* spp. from cases of human infection. Resistance to cephalosporins increased again as the ban ended (Dutil et al., 2010; Webster, 2009).

### **3.6.1.1. Positive impact**

#### **3.6.1.1.1. Antimicrobial growth promoters**

##### Prior to 2006

Several positive results have been documented in various EU countries following the reduction in use of specific antimicrobial growth promoters prior to the EU ban on the use of these substances in 2006. For example, from 1996 –2008, there were major reductions in vancomycin-resistant *Enterococcus faecium* from broilers and pigs in Denmark following decreased use of avoparcin (DANMAP, 2006). The reduction in usage of avoparcin was therefore considered not only to dramatically reduce the food animal reservoir of enterococci resistant to these growth promoters, but also to reduce the reservoir of resistance genes that encode resistance to several clinically-important antimicrobial agents in humans. However, one publication (Heuer et al., 2002) indicates that such reduction might reflect differences in isolation procedures.

Similarly, macrolide resistance, (specifically to tylosin, which is used for therapy as well as having been used as an antimicrobial growth promoter) and also resistance to avilomycin were reduced in *E. faecium* among broilers (WHO, 2003). This resulted in a concomitant overall reduction in resistance to other antimicrobial growth promoters in farm animals and resistance to these substances in bacteria in humans in various countries. For example, in Sweden a ban on growth promoters in the 1980s resulted in an increase in post-weaning diarrhoea in piglets; to avoid post-weaning diarrhoea in piglets and necrotic enteritis in poultry, dietary levels of protein were reduced and dietary fibre increased, resulting in improved animal health (Report from the Commission on Antimicrobial Feed Additives, Stockholm, 1997).

##### Post 2006

Following the EU ban on antibiotic growth promoters in 2006, an overall reduction in resistance to antibiotic substances previously used in growth promoters in farm animals and in humans has been reported in some Scandinavian countries – e.g., Denmark and Sweden (DANMAP, 2008; DANMAP, 2009; DANMAP, 2010; Grave et al., 2006; SVARM, 2008; SVARM, 2009; SVARM, 2010).

#### **3.6.1.1.2. General antimicrobial usage**

A yellow card system enabling Danish vets to identify pig farms with continual health problems was introduced in Denmark in 2010. The Danish Veterinary and Food Administration (DVFA) now sets threshold levels of medication for three categories of pigs and producers are required to bring antimicrobial use down to required levels within nine months, with additional veterinary supervision. As a result of this system, since its introduction in July 2010, a 20% drop in antimicrobial usage has been reported (DANMAP, 2012).

#### **3.6.1.1.3. Specific antimicrobials - fluoroquinolones**

In Finland, fluoroquinolones have not been used for the treatment of salmonellosis in poultry since 1993. A consequence of this voluntary withdrawal has been observed in a 2003 study of resistance to this class of antimicrobials in *Campylobacter* from Finnish patients, in which resistance in patients who had not recently travelled abroad was shown to be 2-3%, whereas 61% of *Campylobacter* spp. from patients who had recently travelled to Spain were fluoroquinolone-resistant (Rautelin et al., 2003). In the Netherlands a voluntary ban on fluoroquinolones from 2009 resulted in a reduction of resistance to fluoroquinolones in *E. coli* from broilers and poultry meat from ca. 57-50 % in 2009 to 50-41% in 2012 (MARAN, 2009; MARAN, 2012).

#### **3.6.1.1.4. Specific antimicrobials - cephalosporins**

In Quebec, Canada, poultry farmers agreed to voluntarily suspend use of ceftiofur in hatcheries in 2005-2006, but began using the antimicrobial again in late 2007. The result was that during the voluntary ban, cephalosporin resistance in *Salmonella* from cases of human infection fell sharply, but they began rising again as the ban ended (Dutil et al., 2010; Webster, 2009). In Denmark, a self-ban of 3<sup>rd</sup> generation cephalosporins in Danish pig production in July 2011 has resulted in a reduction of ESBL-producing organisms in slaughter pigs (Agerso and Aarestrup, 2013). In the Netherlands a voluntary ban on 3<sup>rd</sup> generation cephalosporins from 2009 resulted in a reduction of resistance to this class of antimicrobial in *E. coli* from broilers and poultry meat from ca. 17 to 20% in 2009 to 6 to 8% in 2012 (MARAN, 2009; MARAN, 2012). As with fluoroquinolone resistance (see above) it was considered that such reductions may reduce potential transmission to man but no supportive evidence has been provided.

More recently, in 2011 the Dutch Health Council advised the government to limit the use in food-producing animals of antimicrobials that are of public health concern. This advice was mainly based on the ESBL threat, and included advice to restrict the use of beta-lactams, fluoroquinolones and aminoglycosides in animals. A result of this recommendation has been significant recent falls in resistance levels in farm animals, including in ESBL-producing *E. coli* in poultry and pigs (Mevius and Heederik, 2014). In the UK, in 2012 the British Poultry Council announced a voluntary ban on use of all cephalosporins in the poultry meat production chain from 1 January, 2012, as well prophylactic use of all quinolones for day-old chicks. Information on the results of this initiative has not yet been published.

In addition to the risk management activities presented above for fluoroquinolones and cephalosporins, countries such as Finland and Sweden have brought in legislation to encompass recommendations not to use these classes as first line treatment. Furthermore, off label use of cephalosporins is now banned in Finland (Act No. 847/2008. Available at: <http://www.finlex.fi/sv/laki/alkup/2008/20080847>)

#### **3.6.1.2. Negative impact**

##### **3.6.1.2.1. General considerations**

In 2003, Casewell *et al* considered that, following the ban of all food animal growth-promoting antimicrobials by Sweden in 1986 and the EU ban on avoparcin in 1997 and bacitracin, spiramycin, tylosin and virginiamycin in 1999, the only attributable effect in humans some three years later was a diminution in acquired resistance in enterococci from human faecal carriers (Casewell *et al.*, 2003). They noted that there had been an increase in human infection from vancomycin-resistant enterococci in Europe, which they concluded was probably related to the increased in usage of vancomycin for the treatment of methicillin-resistant staphylococci. They also concluded that the ban of growth promoters revealed that these agents had important prophylactic activity and their withdrawal was associated with a deterioration in animal health, including increased diarrhoea, weight loss and mortality due to *E. coli* and *Lawsonia intracellularis* in early post-weaning pigs, and clostridial necrotic enteritis in broilers.

##### **3.6.1.2.2. Specific considerations**

Following the withdrawal of antimicrobial growth promoters for use in cattle, broilers and finisher pigs in Denmark in February 1998 and in weaner pigs in 1999, there was a substantive increase in the use of certain therapeutic antimicrobials in these animals, particularly tetracyclines in pigs, in the following two years (DANMAP, 1999; DANMAP, 2000; DANMAP, 2001; DANMAP, 2002; WHO, 2003). More recently the Danish yellow card system is reported to have resulted in an overall reduction in

antimicrobial use in food animals in that country, particularly pigs, but there has been a concomitant increase in the incidence of enteritis and peritonitis in slaughter pigs, including increases in meat inspection lesions. Specifically, the prevalence of chronic peritonitis, umbilical hernia and chronic enteritis was statistically higher in 2011 than in 2010, whereas the prevalence was lower for tail bite infection, chronic pericarditis, and chronic pneumonia (odd's ratio (OR) = 0.7) ( $P < 0.001$ ) (Alban et al., 2013). In the Netherlands, following limitations in use of beta-lactams, fluoroquinolones and aminoglycosides in animals in April 2013, the Dutch Animal Health Service GD reported many more *E. coli* infections over 2012 and a strong increase in the number of dead animals submitted for pathological investigation. Precise figures are not available, but in non-weaned pigs, *E. coli* would normally be around 7% of the total samples seen, and has risen to above 20%. In the last quarter of 2012, the percentages of weaned piglets diagnosed with diarrhoea increased from a general average of 7% to 12%, and the percentage of weaners with oedema disease increased from 5% to 14%. These increases were partly explained by changes in feed composition but also the strong reduction in antimicrobial use in pigs in the Netherlands.

A further consideration put forward by some stakeholders was that if there is a delay in treatment of pigs when the herd is known to be infected with *Streptococcus suis*, this will cause significant mortality of weaned piglets. Similarly, if rabbits have to wait until clinical disease of epizootic rabbit enteropathy develops before treatment can be given, mortality increases significantly.

The use of antimicrobials for routine or systematic prevention of disease is of concern. Although there was a ban of antimicrobial growth promotion in 2006, systematic preventive use of antimicrobials is routinely practised in some intensively reared livestock in some countries. The majority of preventive treatments are still given by oral group treatment, and a recent systematic review in swine (Burow et al., 2014) and experimental studies (Zhang et al., 2013) have shown that in particular the oral administration route leads to a dramatic increase of resistance in commensal bacteria, which in the end will be detrimental to the health of both animals and humans. Use of antimicrobials for growth promotion is only one form of undesirable antimicrobial selection pressure, and in-feed medication, as well as prophylactic and metaphylactic group medication by the oral route, continue today to exert a substantial selection pressure on commensal and pathogenic bacteria. The beneficial effect of the antimicrobial growth promoter ban thus may partially have been impacted by such alternative practices. Therefore these practices might need more consideration in new mitigation measures.

In addition to the risk management implemented for fluoroquinolones and cephalosporins above, other countries such as Finland and Sweden have put in legislation the recommendations not to use these classes as first line treatment. Furthermore, off label use of cephalosporins has been banned in Finland (Act No 847/2008, available at: <http://www.finlex.fi/sv/laki/alkup/2008/20080847>). No information is available on the economic impact of risk management measures (RMM) on AMR taken in non-EU countries.

### **3.7. Cost estimation of risk management measures**

#### **3.7.1. Cost estimates**

The cost ascribed to the implementation of the Danish yellow card system has been estimated as approximately € 1 million *p.a.* by (Alban et al., 2013). For the most part, the costs of mitigation measures have been provided by stakeholders only as estimates.

Costs resulting from overall restrictions in the preventative use of antimicrobials were provided for individual animal species, although again these were estimates from stakeholders. For example, for pigs in the UK, with a production level of 10 million pigs/year and with 30% of herds affected with

diseases for which antimicrobials were not permitted, an increase in mortality of 2% at €40/pig was estimated to result in costs to the producer of €2.4 million p.a. If these costs were extended to the whole of the EU, with 250 million pigs, then the costs were estimated at €60 million p.a. A similar mortality figure of 2% could be put on post-weaning mortality due to *E. coli* if left untreated with zinc oxide or colistin. A ban on preventative use could affect 95% of pig farms at an estimated cost of €190 million. Likewise for rabbits, should a country produce 10 million rabbits/ year and the mortality resulting from restrictions in the use of specific antimicrobials increased from 0% to 10% in 50% of herds at €1.5/ rabbit, then the cost for that country is estimated as €0.75 million. When extended across the EU with 450 million rabbits produced each year, then the overall cost to the EU is estimated at €33.75 million.

It should be emphasised that the above costs for pigs and rabbits were derived from personal communications and were not from published literature.

Direct and indirect costs of environmental pollution resulting from antimicrobial usage are considered to fall out with the scope of this document and have not been taken into account, nor have additional costs that might result from under-treatment of animals and the concomitant impact of infections with zoonotic bacteria on human health.

### 3.7.2. Organic versus conventional production

When considering organic versus conventional production, references were provided by Stakeholders which purported to demonstrate that organically-produced meat was either more contaminated, or at least equally contaminated, with a greater variety of bacteria than was observed in meat produced under non-organic conditions. For example Danish organic broiler meat has been shown to be more frequently contaminated with *Campylobacter* spp. than conventional broiler carcasses; furthermore, when assessing the relative risk of becoming ill following exposure to *Campylobacter* spp. from conventional or organic broiler meat the risk per serving from organic carcasses was 1.7 times higher than that of conventional carcasses (Rosenquist et al., 2013).

Co-resistance rates of ESBL-positive *E. coli* isolates from meat from organic and conventionally-reared chickens at retail was not different between conventional and organic samples (co-trimoxazole 56%, ciprofloxacin 14%, and tobramycin 2%), except for tetracycline, 73% and 46%, respectively. Six of 14 conventional meat samples harboured multi locus sequence types (MLST) types also reported in humans and 5 of 10 organic samples harboured MLST also reported in humans. In conclusion, the majority of organic chicken meat samples were also contaminated with ESBL-producing *E. coli*, and the ESBL-encoding genes and strain types were largely the same as in conventional meat samples (Cohen Stuart et al., 2012).

When investigating the occurrence of antimicrobial resistance in mastitis pathogens (*Staphylococcus aureus*, non-aureus staphylococci, *Streptococcus dysgalactiae*, *Streptococcus uberis*) from farms with organic and conventional dairy production in Switzerland, the frequency of antimicrobial resistance in organic farms, in which the use of antimicrobials is very restricted, was not different from conventional farms, which was contrary to expectation (Roesch et al., 2006).

Certain organic food production systems may be associated with lower levels of AMR. For example the above findings for organic versus conventional production were in contrast to those described in a recent systematic review involving seven studies in humans and 223 studies of nutrient and contaminant levels in foods (Smith-Spangler et al., 2012). *Escherichia coli* contamination risk did not differ between organic and conventional produce. Bacterial contamination of retail chicken and pork was common and unrelated to farming method, but the risk for isolating bacteria resistant to three or



more antimicrobials was found to be higher in conventional than in organic chicken and pork (risk difference, 33% [CI, 21% to 45%]).

### 3.8. Further possible risk management measures

The tables below contain examples of possible risk management measures to reduce the impact on public health of AMR due to use of antimicrobial veterinary medicinal products. Risk management measures should be proportionate to the potential severity of the risk and their effectiveness should be monitored and reviewed.

#### 3.8.1. Examples of possible regulatory risk management measures

The options for risk management measures (RMM) listed in Table 6 below are either already available under current EU legislation or might be considered as future legislative proposals. These options could be used after a specific benefit-risk assessment of the product and are not to be considered as general measures.

**Table 6:** Possible regulatory risk management measures

Possible options for regulatory risk management	Comments
<b>Withdrawal/suspension of existing Marketing Authorisations as a result of a referral procedure</b>	This should only be considered after an AMR risk assessment that demonstrates a serious risk to human health which cannot be mitigated by other restrictions on use and indicates that the overall benefit-risk (B/R) for the VMP is no longer positive. The availability of alternative treatment options for animals should also be taken into account in the B/R assessment.
<b>Limiting approval of new MA applications, extensions, variations</b>	Applications for products containing new substances, or extensions/variations to add new formulations, species or indications to existing products, should be subject to full AMR risk assessment that takes account of the potential impact on public health before approval. Effect on resistance of variations in route of administration, duration, dose and interval should be considered in the antimicrobial risk assessment. A refusal should be considered if the AMR risk cannot be mitigated by restrictions on use and the overall benefit-risk balance for the VMP is negative.
<b>SPC Restrictions aimed at reducing exposure to the antimicrobial:</b>	The SPC restrictions, below, can be taken into account for refinement of the AMR risk assessment submitted as part of a MA application or during a referral procedure:
- Prophylactic use	No prophylactic use
- Metaphylaxis	No metaphylactic use

Possible options for regulatory risk management	Comments
<ul style="list-style-type: none"> <li>- Herd/ flock and group treatments</li> </ul>	<ul style="list-style-type: none"> <li>- Restrictions from use as mass treatment for herds, flocks and groups of animals.</li> <li>- Treatment of individual animals only.</li> </ul>
<ul style="list-style-type: none"> <li>- Indications</li> </ul>	<ul style="list-style-type: none"> <li>- Indications for the treatment of named pathogens only, with avoidance of general indications.</li> <li>- Prohibition of indications for production enhancement (e.g. increase of feed efficiency or growth promotion).</li> <li>- Restrictions to indications where limited/no other treatment options are available.</li> </ul>
<ul style="list-style-type: none"> <li>- Species</li> </ul>	<ul style="list-style-type: none"> <li>- Restriction to use in certain species only according to need and extent of use.</li> </ul>
<ul style="list-style-type: none"> <li>- Dosing regimens, administration</li> </ul>	<ul style="list-style-type: none"> <li>- Duration of treatment limited to the time needed for cure of disease<sup>15</sup>.</li> <li>- Restriction from use as formulations that prevent accurate dosing for individual animals e.g. in feed or water.</li> </ul>
<ul style="list-style-type: none"> <li>- Responsible use warnings</li> </ul>	<p>Addition of warnings to SPC as advised in the Guideline on the SPC for Antimicrobial Products (EMA/CVMP/SAGAM/383441/2005), and included for fluoroquinolones and 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporins following referral procedures (EMA, 2010; EMA, 2012)</p> <ul style="list-style-type: none"> <li>- Use to be based on culture and sensitivity testing.</li> <li>- To be reserved for treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.</li> </ul>
<p><b>Restrictions on “cascade” use</b></p>	<ul style="list-style-type: none"> <li>- Authorised VMPs: restrictions to be placed in the SPC based on the outcome of an AMR risk assessment<sup>16</sup>.</li> <li>- Monitoring of “cascade” use (species, volumes, indications) with option to place subsequent restrictions.</li> </ul>
<p><b>Post Authorisation Surveillance</b></p>	<ul style="list-style-type: none"> <li>- Requirement for monitoring of sales and consumption through a post-approval process (“Transparency at Use”)</li> </ul>

<sup>15</sup> A restriction to a maximum treatment duration of 3 weeks was implemented in the SPCs for tylosin products administered orally to pigs as a result of a referral procedure.

<sup>16</sup> A contraindication from use in poultry was added to the SPC for 3<sup>rd</sup>- and 4<sup>th</sup>- generation cephalosporin products as a result of a referral procedure.

Possible options for regulatory risk management	Comments
<b>Restriction on distribution channels</b>	<ul style="list-style-type: none"> <li>- Restriction of antimicrobials to prescription only medicines<sup>17</sup></li> <li>- Restriction to administration only under direct supervision of the veterinarian</li> </ul>
<b>Controls on advertising</b>	<ul style="list-style-type: none"> <li>- Restriction of advertising of antimicrobials only to those professionals allowed to prescribe them</li> </ul>

### 3.8.1.1. Examples of possible non-regulatory controls

Possible non-regulatory controls that might be considered are listed in Table 7.

**Table 7:** Possible non-regulatory risk management measures

Possible non-regulatory risk management measures	Comments
Development and implementation of evidence-based national and regional treatment guidelines	See response to Question 2.
EC's Guidelines for prudent use of antimicrobials in veterinary medicine	These guidelines contain an overview of responsible use principles that have been applied in the development of national strategies against AMR. Some of the measures are adopted in legislation at a national level.
OIE Terrestrial Animal Health Code (OIE (World Organisation for Animal Health), 2014)	Chapters 6.2 to 6.10, applied indirectly through EU legislation.
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.	
Training of professionals and users on the responsible use of antimicrobials	
Voluntary bans on use of certain classes by specific livestock sectors	
Promotion of good farming practices and animal husbandry	Such practices can serve to avoid infections and lessen the spread of AMR by various routes.

<sup>17</sup> In the EU antimicrobials for animals are "prescription only".

### **3.9. Increased use of generics**

Increased availability of generics appears to have contributed to large increases in usage levels because of a lowering of costs (Chauvin, 2009; Jensen et al., 2010; Monnet et al., 2005; Toutain and Bousquet-Melou, 2013). The fluoroquinolones (enrofloxacin), 3<sup>rd</sup>-generation cephalosporins (ceftiofur), 4<sup>th</sup> generation cephalosporins (cefquinome), macrolides (tilmicosin), trimethoprim/sulfa combinations, amoxicillin, pleuromutilin (tiamulin) and oxytetracycline and chlortetracycline have all been exposed to generic competition.

As reported by a stakeholder at least six generic versions of ceftiofur came on the market in the UK following the expiration of marketing exclusivity. This led to reductions in price and to increased marketing, including advertising directly to farmers.

Expiry of marketing exclusivity period does sometimes (but not always) result in the entry of generics in the market and a consequent decrease in the price of concerned medicines. According to a survey of veterinarians in Europe conducted by the Federation of Veterinarians of Europe and published in 2013, this price erosion was perceived as not influencing the prescribing behaviour of the veterinarians (De Briyne et al., 2013).

A new AMR risk assessment is not required for generic veterinary medicines under the current legislation. It might be considered that generic products could increase exposure to certain antimicrobials, and coupled with the evolution of antimicrobial susceptibility since first authorisation of the reference product, would lead to an altered risk.

#### **3.9.1. Conclusions for generic products**

The increased availability of generics appears to have contributed to increases in usage levels of a wide range of antimicrobial substances, including CIAs because of a lowering of costs and increase in marketing activities. This applies also to fluoroquinolones and systemically administered 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins which are not recommended for first-line treatment.

The competitive environment provided by generic veterinary medicines may influence the development of new drugs and formulations with modified pharmacokinetic properties.

#### **3.9.2. Off-label use**

The term "off-label use" covers many different situations. It can be the use of an approved veterinary product for a non- approved indication or a non-approved species. It also covers the use in veterinary medicine of substances approved only in human medicine (see Question 3).

Precise information is lacking on the extent of off-label use and on the potential risk from this use.

For instance use of human only antimicrobials in MRSP in skin infections in dogs appears to be significant based upon individual case reports, but the overall burden at regional or European level cannot be assessed.

For classes/substances approved in veterinary medicine but used for a non-approved purpose, the risk to public health is likely similar to the risk from authorised use but might be higher if the extent of use off label is high.

Information collected from stakeholders documents a limited but very relevant number of indications for major species for which there is a lack of authorised antimicrobials in veterinary medicine. ESBL

producing *E. coli*, MRSA, MRSP, *Brachyspira* spp. and *Rhodococcus* spp. are particular indications of concern. For minor species, there is a clear lack of authorised veterinary antimicrobials.

More information is needed on off label use, targeting specific areas of concern. For instance, further information is needed on off label use of Category 2 antimicrobials, as action is needed to minimize all such use.

- This data collection simultaneously can be used to ascertain the frequency of off label use (equal to the need in veterinary practice) which is required for a further risk assessment, and to evaluate the effectiveness of interventions over time. Use in regards to animal species (body weight), indication, regimen (dose, duration, treatment interval, route of administration/formulation) are all required to assess if product literature (SPC) is adequately followed and to conclude if the product is used off label.
- In the EU/EEA, the ESVAC project has proposed a detailed monitoring system to estimate antimicrobial consumption (EMA/ESVAC, 2012a), since the current ESVAC overall collection of data cannot provide information on off label use as the data are not collected according to indication of use in animal species and more importantly the data only refer to preparations authorised for use in animals. The intended ESVAC collection of data at farm level might however in the future provide some relevant information to help identify some of the off label use in the major species.

### **3.10. Overall conclusions on Question 4**

The strongest evidence for potential beneficial effects to human health of risk mitigation measures involving reductions in the use of CIAs, and particularly cephalosporins and fluoroquinolones, is from reports of 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. In the EU the main evidence for such reductions in incidence comes from studies in Scandinavian countries and the Netherlands, where policies to reduce antimicrobial consumption in food animals have been in place for several years. In general, it is considered that such reductions decrease potential for transmission of resistant organisms to man, but supportive evidence is limited. In Canada there is substantive evidence for a reduction in resistance to 3<sup>rd</sup>- generation cephalosporins in *Salmonella* spp. from cases of human infection following the voluntary withdrawal of ceftiofur use in hatcheries. The effects of voluntary or compulsory withdrawal of cephalosporins for use in food animals in several EU MSs have as yet not been assessed.

Stakeholders have reported that negative effects of the withdrawal of cephalosporins in pigs include reports of increases in the occurrence of enteritis and peritonitis in slaughter pigs and of weaners with oedema disease. Banning the use of specific substances may lead to increased selection pressure on the remaining antimicrobials, and thereby speed development of AMR.

Costs of antimicrobial withdrawal policies are for the most part estimates, and range from €1 million to €60 million per annum for the EU, depending on the animal species affected.

Stakeholders have reported that there is little difference in the isolation of drug-resistant bacteria from organic or conventionally-produced meat.

An important general observation was that risk mitigation measures should be based on proper risk assessments, and that such measures must be part of an overall solution. Risk assessments have already been provided for (fluoro)quinolones and 3<sup>rd</sup>- and 4<sup>th</sup>- generation cephalosporins. As a result, more specific recommendations are that cephalosporins and fluoroquinolones should be excluded as a first drug of choice for clinical diseases both in individual animals and groups of animals, unless clinical

history or laboratory analysis indicates that they are needed. Should first line treatment fail, then bacteriological examination should be performed prior to use of cephalosporins or fluoroquinolones as an alternative. A further recommendation is that risk assessments should be undertaken for aminoglycosides and certain penicillins (see the answer to Question 2).

As foods are a vehicle for spreading AMR bacteria and resistance genes therein from food production animals to humans, identification of the pathways for dissemination of AMR organisms and resistance genes from animals to food are of fundamental importance. Further research into pathways of dissemination of AMR bacteria from animals to food are therefore recommended, and also research into methods for the quantification of the spread of resistance genes from commensals to pathogens in foods and the environment. This will improve the quality of risk modelling.

In relation to the increased use of generic products and the expiry of marketing exclusivity, the quality, safety and effectiveness of generic veterinary medicine products are considered to be equivalent to that of the originator product, but the overall opinion was that the increased availability of generics appears to have contributed to increases in usage levels because of a lowering of costs.

Many substances are given by the oral administration route for preventive purposes and metaphylaxis. Recent strong evidence (Burow et al., 2014; Zhang et al., 2013) has highlighted the risk of resistance development in commensal bacteria following administration of antimicrobials by this route, and such usage must be taken into account for further mitigation measures and for research.

### **3.11. Summary assessment and recommendations on Question 4**

A number of risk management options have already been implemented at the EU/national level. The need for further risk management measures should be based on evidence and on a dedicated risk assessment. Measuring the impact of individual risk management measures is difficult, but efforts should be made to evaluate the effectiveness of such measures by means of agreed criteria.

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 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 and DCDA.
- Prescribers should keep records of off label use to be provided at the request of the Authorities.
- Authorities should be encouraged to collect off label use data.
- Regular joint analyses of the evolution of antimicrobial resistance and consumption by the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) EU expert group.
- In addition the following activities should be carried out:
  - Reduction of overall antimicrobial consumption.
  - Promotion of good farming practices and animal husbandry.
  - Further research into the off label use of antimicrobials in animals; actions could be derived from the result of research findings.

- Further research into pathways of dissemination of AMR bacteria from animals to food and also into methods for the quantification of the spread of resistance genes from commensals to pathogens in foods and the environment.
- Further research into 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 animal
- Researching 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-based measures.
- 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. Also, 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.

### ***Acknowledgements***

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## V. Annex

### **Annex I - Antimicrobial classes used in veterinary medicine and restricted by risk management measures implemented in some countries (Question 2)**

**Table 8:** Antimicrobial class, summary of veterinary use in the EU and risk management measures implemented by some countries

Antimicrobial class	Summary of veterinary use in the EU	Risk management measures implemented by some countries
<p><b>Aminoglycosides</b></p>	<p>Extensively used in veterinary medicine (EMA/ESVAC, 2013; EMA/ESVAC, 2014).</p> <ul style="list-style-type: none"> <li>• Main Indications: septicaemias, digestive, respiratory and urinary diseases</li> <li>• Pharmaceutical Form: premix, oral powder and solution, and injectable</li> <li>• Species: cattle, pigs, sheep, goats, horses, dogs and cats</li> </ul> <p>Of the group, the most used substances are:</p> <ul style="list-style-type: none"> <li>- Gentamycin: indicated for <i>Pseudomonas aeruginosa</i> infections with few alternatives.</li> <li>- Neomycin: <i>Escherichia coli</i>.</li> </ul>	<p>Those recommended by responsible use.</p>
<p><b>Cephalosporins (3<sup>rd</sup>- and 4<sup>th</sup>- generation)</b> <i>Note: The classification of cephalosporins as generations is not considered helpful and not able to properly categorise cephalosporins according to their antimicrobial spectrum.</i></p>	<ul style="list-style-type: none"> <li>• Indications: treatment of septicaemias, respiratory infections, and mastitis</li> </ul> <p>Alternatives might be limited in case of staphylococci infections.</p> <ul style="list-style-type: none"> <li>• Pharmaceutical Form: injectable and intramammary</li> <li>• Species: cattle, pigs, horses, dogs and cats,</li> </ul>	<p><b>CVMP referrals on systemically active 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporins</b>, the following information has to be added to the SPCs of those products:</p> <ul style="list-style-type: none"> <li>- Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans. "Product name (to be completed nationally)" selects for resistant strains such as bacteria carrying extended spectrum beta-lactamases (ESBLs) and may constitute a risk to human health if these strains disseminate to humans e.g. via food. For this reason, "product name (to be completed nationally)"</li> </ul>



		<p>should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment. Official, national and regional antimicrobial policies should be taken into account when the product is used. Increased use, including use of the product deviating from the instructions given in the SPC, may increase the prevalence of such resistance. Whenever possible, "product name (to be completed nationally)" should only be used based on susceptibility testing.</p> <p>To be added to all products indicated for bovine metritis: "Do not use as prophylaxis in case of retained placenta."</p> <p><b>Measures taken at national level<sup>18</sup></b></p> <p>NL: Pork production quality systems refrained voluntarily from their use. Dairy production quality system banned them in dry cow treatment</p> <p>FR: Pig sector took the initiative to limit their use at the end of 2010.</p> <p>UK: British Poultry Council introduced a voluntary ban in 2012 on their use in parts of the production system</p> <p>DK: Swine industry voluntarily forbid their use in 2010</p> <p>SE: Regulation introduced in 2013 that restricts their use by veterinarians</p> <p>FI: No products are approved nationally. Off label use is banned</p>
<p><b>Fluoro- and other quinolones</b></p>	<ul style="list-style-type: none"> <li>• Indications: septicaemias and infections such as colibacillosis.</li> <li>• Pharmaceutical Form: premix, oral powder and solution, and injectable</li> <li>• Species: cattle, pigs, chickens, turkeys, rabbit, dogs and cats.</li> <li>• Extent of use varies considerably between countries in EU.</li> </ul>	<p><b>CVMP referral on fluoro- and other quinolones</b>, the following information has to be added to the SPC of fluoroquinolones:</p> <p>"Official and local antimicrobial policies should be taken into account when the product is used."</p> <p>"Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials."</p> <p>"Whenever possible, fluoroquinolones should only be used based on susceptibility testing."</p>

<sup>18</sup> From EC draft guidance on prudent use.

		<p>“Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance.”  For quinolones, excluding fluoroquinolones, similar measures have been recommended:  “Official and local antimicrobial policies should be taken into account when the product is used.”  “Whenever possible, quinolones should only be used based on susceptibility testing.”  “Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the quinolones and may decrease the effectiveness of treatment with other (fluoro) quinolones due to the potential for cross resistance.”</p> <p><b>Measures taken at national level</b>  NL: Pork production quality systems refrained voluntarily from their use.  UK: British Poultry Council introduced a voluntary ban in 2012 on their use in part of the production system.  DK: Government put an order into force in 2002 allowing their use in food production animals only if laboratory test shows no other antimicrobial is effective  SE: Regulation introduced from 2013 that restricts their use by veterinarians</p>
<p><b>Macrolides (including ketolides)</b></p>	<ul style="list-style-type: none"> <li>• Indications: To treat Mycoplasma infections, haemorrhagic digestive disease and proliferative enteropathies (ileitis) associated with <i>Lawsonia intracellularis</i> in pig. Mycoplasma infections in poultry. Respiratory infections in cattle and sheep and liver abscesses in cattle.</li> <li>• Pharmaceutical Form: premix, oral powder and solution, and injectable.</li> </ul>	<p>In November 2013 the CVMP started a procedure for all veterinary medicinal products containing tylosin to be administered orally via feed or the drinking water to pigs to review the treatment durations in pigs and the indication for swine dysentery (caused by <i>Brachyspira hyodysenteriae</i>).</p> <p>CVMP recommendations on macrolides: Responsible use of antimicrobials should be strongly promoted. It is acknowledged that macrolides are first line treatment against a number of animal diseases but still there is a need to avoid overuse, for e.g. general prophylaxis where no specific diagnose is evident or</p>

	<ul style="list-style-type: none"> <li>• Species: cattle, sheep, pigs, and poultry.</li> <li>• Extensive use mostly in oral forms and as premix</li> <li>• Newer injectable long acting formulations have been authorised during the last years; gamithromycin, tulathromycin and tildipirosin (EMA/CVMP, 2003; EMA/CVMP, 2010; EMA/CVMP, 2013 )</li> </ul>	<p>where the disease in question would self-cure without antimicrobial . Duration of treatment should be limited to the minimum required time for cure of diseases. There might be a need to review certain SPCs to reduce the approved treatment duration in cases where it is found unnecessarily long in relation to the severity of the disease.</p> <p>Doses should preferably be selected considering AMR related risks. In case of old products where data on dose selection are sparse doses should anyway be reviewed and in case they are obviously too low (e.g. compared to other products containing the same active substance) this should be addressed. Notably there are often several different doses approved for different indications and thus there is an option to increase doses where relevant without asking for new tolerance or safety data.</p> <p>Indications for use should preferably be restricted to those for which efficacy has been proven and general indications without a solid clinical basis should be avoided. In case of old products where data are sparse indications should be reviewed and revised where appropriate to be as accurate as possible. In particular, combination products are of concern as there seems to be products on the market for which the choice of included active components is questionable. The use of combinations in situations where products with a single active substance would be enough unnecessarily increases selection pressure for antibiotic resistance. (EMA/CVMP/SAGAM, 2011)</p>
<p><b>Penicillins Natural -Lactamase-sensitive</b></p>	<ul style="list-style-type: none"> <li>• <u>Indications:</u> Treatment of septicaemias, respiratory infections, and mastitis.</li> <li>• <u>Pharmaceutical Form:</u> premix, oral power and injectable.</li> <li>• <u>Species:</u> cattle,</li> </ul>	<p><b>Measures taken at national level</b> DK: only simple penicillins are allowed for the treatment of mastitis unless a laboratory test shows this will not be effective</p>

	sheep, pigs, poultry, horses dogs and cats	
<b>Penicillins, Broad spectrum <math>\beta</math>-lactamase-sensitive - Aminopenicillins</b>	<ul style="list-style-type: none"> <li>• <u>Indications:</u> To treat number of infections including pasteurellosis and colibacillosis in poultry and <i>Streptococcus suis</i> in pigs. Respiratory infections in cattle and pigs.</li> <li>• <u>Pharmaceutical Form:</u> Oral powder and solution, injectable and intramammary</li> <li>• <u>Species:</u> cattle, sheep, pigs, poultry and dogs.</li> </ul>	
<b>Penicillins, Narrow spectrum <math>\beta</math>-Lactamase-resistant</b>	<ul style="list-style-type: none"> <li>• <u>Indications:</u> Metritis and mastitis.</li> <li>• <u>Pharmaceutical Form:</u> intramammary</li> <li>• <u>Species:</u> cattle and sheep.</li> </ul>	
<b>Penicillins, <math>\beta</math>-lactamase protected Broad-spectrum Co-amoxiclav (amoxicillin &amp; clavulanic acid)</b>	<ul style="list-style-type: none"> <li>• <u>Indications:</u> To treat number of infections including respiratory infections, mastitis, metritis and colibacillosis in cattle and pigs.</li> <li>• <u>Pharmaceutical Form:</u> oral powder and solution, and injectable.</li> <li>• <u>Species:</u> cattle, pigs, dogs and cats.</li> </ul>	
<b>Polymyxins</b>	<ul style="list-style-type: none"> <li>• <u>Indications:</u> Septicaemias, colibacillosis, and urinary infections. Cyclic polypeptides are widely used against Gram-negative digestive infections.</li> <li>• <u>Pharmaceutical Form:</u> oral powder and</li> </ul>	<p>The EC has launched a referral on oral forms of colistin.</p> <p>The EMA/CVMP/CHMP/AMEG have produced lengthy recommendations on the use of colistin (EMA, 2013b) and indicated the need to revise the Marketing Authorisations for products containing colistin:</p> <p>“The SPCs for currently authorised products should be reviewed to</p>

	<p>solution.</p> <ul style="list-style-type: none"> <li>• <u>Species:</u> cattle, sheep, pigs and poultry.</li> <li>• Otis in companion animals (local treatment)</li> </ul>	<p>ensure consistency for measures to ensure responsible use in regards to protecting animal health and limiting the possibility of future risk to public health. Based on the current evidence, it is considered appropriate to maintain the use of colistin in veterinary medicine, but to restrict indications to therapy or metaphylaxis, and to remove all indications for prophylactic use in order to minimise any potential risk associated with a broader use. Reduction-of-use is expected to follow from elimination of prophylactic-use and other measures to implement responsible-use. This recommendation is made on the basis that it is prudent to minimise the possibility of resistance to colistin developing as a result of its use in animals and thereby also reduce the possibility that any resistance that does develop will be transferred to man.”</p>
<b>Rifamycins</b>	<p>Limited use in veterinary medicine.</p> <ul style="list-style-type: none"> <li>• <u>Indications:</u> Rifamixin is the only substance of the group authorised for use in food producing species with indications limited to intramammary or intrauterine use</li> <li>• <u>Pharmaceutical Form:</u> intramammary</li> <li>• <u>Species:</u> cattle.</li> </ul> <p>Comment: Rifampicin is included in the list of essential substances for horses for the treatment of <i>Rhodococcus equi</i> infections in equines.</p>	<p>Those recommended by responsible use.</p>
<b>Tetracyclines</b>	<ul style="list-style-type: none"> <li>• <u>Indications:</u> Respiratory diseases bacterial enteritis, urinary tract infections, metritis, mastitis, and pyodermatitis. Specific conditions keratoconjunctivitis in cattle, chlamydiosis, heartwater, anaplasmosis, actinomycosis,</li> </ul>	<p>Those recommended by responsible use.</p>

actinobacillosis, ehrlichiosis (especially doxycycline), doxycycline are often effective to a somewhat lesser degree against resistant strains of *Staphylococcus aureus*

- Pharmaceutical Form: premix, oral powder and solution, injectable and intramammary
- Species: cattle, sheep, goats, pigs, horses and poultry.

## **Annex II - List of centrally authorised veterinary antimicrobial substances (Question 3)**

**Difloxacin** is a fluoroquinolone first authorised for use in 1998. In cattle it is authorised for the treatment of bovine respiratory disease (shipping fever, calf pneumonia) caused by single or mixed infections with *Pasteurella haemolytica*, *Pasteurella multocida*, and/or *Mycoplasma* spp. In chickens and turkeys it is indicated for the treatment of chronic respiratory infections caused by sensitive strains of *Escherichia coli* and *Mycoplasma gallisepticum*. In turkeys it is indicated for the treatment of infections caused by *Pasteurella multocida*. In dogs it is indicated for the treatment of acute uncomplicated urinary tract infections caused by *Escherichia coli* or *Staphylococcus* spp. and superficial pyoderma caused by *Staphylococcus intermedius*.

**Valnemulin** is a pleuromutilin first authorised for use in 1999. In pigs it is authorised for the treatment of swine enzootic pneumonia and swine dysentery, porcine proliferative enteropathy or porcine colonic spirochaetosis and in rabbits for epizootic rabbit enteropathy.

**Pirlimycin** is a lincosamide first authorised in 2001. Presented as an intramammary solution for the treatment of subclinical mastitis in lactating cows due to Gram-positive cocci susceptible to pirlimycin including staphylococcal organisms such as *Staphylococcus aureus*, both penicillinase positive and penicillinase-negative, and coagulase-negative staphylococci; streptococcal organisms including *Streptococcus agalactiae*, *Streptococcus dysgalactiae* and *Streptococcus uberis*.

**Tulathromycin** is a macrolide first authorised for use in 2003. In cattle it is authorised for treatment and prevention of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* and treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*. In pigs it is authorised for the treatment and prevention of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae* and *Haemophilus parasuis* sensitive to tulathromycin.

**Tylvalosin** is a macrolide first authorised for use in 2004. In pigs it is authorised for treatment and prevention of swine enzootic pneumonia caused by susceptible strains of *Mycoplasma hyopneumoniae* in pigs. It is also indicated for treatment of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis* in herds where there is a diagnosis based on clinical history, post-mortem findings and clinical pathology results. Further for treatment of clinical outbreaks of swine dysentery, caused by *Brachyspira hyodysenteriae* in herds where the disease has been diagnosed and prevention of further clinical cases. In chickens and pheasants it is indicated for the treatment of *Mycoplasma gallisepticum* and in turkeys for the treatment of sensitive strains of *Ornithobacterium rhinotracheale*.

**Ceftiofur** is a third generation cephalosporin first authorised in 2005. In pigs it is authorised for the treatment of bacterial respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis* and *Streptococcus suis* and treatment of septicaemia, polyarthritis or polyserositis associated with *Streptococcus suis*. In cattle it is authorised for the treatment of acute interdigital necrobacillosis also known as Panaritium or foot rot, and for treatment of acute post-partum (puerperal) metritis, in cases where treatment with another antimicrobial has failed.

**Cefovecin** is a third generation cephalosporin first authorised for use in 2006, authorised for use in dogs (treatment of skin and soft tissue infections including pyoderma, wounds and abscesses associated with *Staphylococcus pseudintermedius*,  $\beta$ -haemolytic Streptococci, *Escherichia coli* and/or *Pasteurella multocida*, treatment of urinary tract infections associated with *Escherichia coli* and/or *Proteus* spp. and as adjunctive treatment to mechanical or surgical periodontal therapy in the

treatment of severe infections of the gingiva and periodontal tissues associated with *Porphyromonas spp.* and *Prevotella spp.*) and cats (treatment of skin and soft tissue abscesses and wounds associated with *Pasteurella multocida*, *Fusobacterium spp.*, *Bacteroides spp.*, *Prevotella oralis*,  $\beta$  haemolytic Streptococci and/or *Staphylococcus pseudintermedius* and the treatment of urinary tract infections associated with *Escherichia coli*).

**Gamithromycin** is a macrolide first authorised in 2008. Authorised for therapeutic and preventive treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

**Pradofloxacin** is a fluoroquinolone first authorised in 2011 for the treatment of dogs and cats. Dogs treatment of wound infections caused by susceptible strains of the *Staphylococcus intermedius* group (including *S. pseudintermedius*), superficial and deep pyoderma caused by susceptible strains of the *Staphylococcus intermedius* group (including *S. pseudintermedius*), acute urinary tract infections caused by susceptible strains of *Escherichia coli* and the *Staphylococcus intermedius* group (including *S. pseudintermedius*) and as adjunctive treatment to mechanical or surgical periodontal therapy in the treatment of severe infections of the gingiva and periodontal tissues caused by susceptible strains of anaerobic organisms, for example *Porphyromonas spp.* and *Prevotella spp.* In cats it is authorised for the treatment of acute infections of the upper respiratory tract caused by susceptible strains of *Pasteurella multocida*, *Escherichia coli* and the *Staphylococcus intermedius* group (including *S. pseudintermedius*).

**Tildipirosin** is a macrolide first authorised in 2011. In pigs it is authorised for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica* and *Haemophilus parasuis*. In cattle it is authorised for the treatment and prevention of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* sensitive to tildipirosin.



### ***Annex III – Summary of regulation of medicinal products for use in animals in the EU - Maximum residue limits (MRLs) and marketing authorisations***

For a detailed explanation of the regulation of medicinal products for use in animals please refer to the legislation quoted in this Annex.

The authorisation of veterinary medicinal products requires data on the quality, safety (including possible impact on the environment) and efficacy of the intended medicinal product. In addition, data on the potential emergence of resistant bacteria of relevance for human health have to be provided, and when required, possible measures to limit resistance development from the intended use of the veterinary medicinal product (Official Journal of the European Communities, 2009).

The EU requires by law that foodstuffs, including milk, obtained from animals treated with veterinary medicines must not contain any residue that might represent a hazard to the health of the consumer. As a result, before a veterinary medicinal product intended for food-producing animals can be authorised in the EU, the consumer safety of its pharmacologically active substances and their residues must first be evaluated. The substances must then be included in Table 1 (Allowed substances) of the Annex to Commission Regulation (EU) No 37/2010 (Official Journal of the European Communities, 2010). The mentioned Table 1 specifies for each pharmacologically active substance: the marker residue (which will be used for residue control), the animal species (e.g. cattle) and the MRL and related target tissues or food commodities, which might be a numerical value in µg/kg or a statement like “no MRL required”. The MRL values are also used for the calculation of the withdrawal period(s).

For the evaluation of the safety of residues for antimicrobials data has to be provided to the regulatory authorities on: 1) the potential effects on the human gut flora, 2) the potential for emergence of resistant bacteria of relevance for human health and 3) the potential effects on the microorganisms used for industrial food processing, including the effects of low concentrations of microbiologically active residues.

The EMA is responsible for the scientific evaluation of applications for EU marketing authorisations for medicinal products (i.e. the centralised procedure). In the EU, medicinal products can be authorised by a centralised procedure or through decentralised procedures as established in Regulation No 726/2004 and Directive 2001/82/EC of the European Parliament and of the Council, as amended (Official Journal of the European Communities, 2001; Official Journal of the European Union, 2004). Under the centralised procedure, pharmaceutical companies submit a single marketing-authorisation application to the EMA. The application is assessed by the CVMP which if positive is submitted to the EC for adoption. If a Marketing Authorisation is granted by the EC, a centralised marketing authorisation is valid in all the EU Member States, as well as in the European Economic Area (EEA) countries. A pharmaceutical company can only commercialise a medicinal product once a marketing authorisation has been granted.

Article 10 of Directive 2001/82/EC of the European Parliament and of the Council, as amended (Official Journal of the European Communities, 2001) indicates that *“Member States shall take the necessary measures to ensure that, if there is no authorised veterinary medicinal product in a Member State for a condition affecting a non food-producing species, by way of exception, the veterinarian responsible may, under his/her direct personal responsibility and in particular to avoid causing unacceptable suffering, treat the animal concerned with:...”* after which a series of conditions under which medicinal products can be used if there is no authorised veterinary medicinal product are detailed. Article 11 of the above mentioned Directive addresses the same subject in reference to food producing species, this article also indicates that *“Paragraph 1 shall apply provided that pharmacologically active substances included in the medicinal product are listed in Annex I, II or III to Regulation (EEC) No 2377/90, and*

*that the veterinarian specifies an appropriate withdrawal period."* Which means that the pharmacologically active substances contained in the medicinal products to be used off label must be listed in the Table of Allowed Substances in Commission Regulation EU No 37/2010 (Official Journal of the European Communities, 2010). Detailed explanations on the "cascade" use are provided on the Veterinary Medicines Directorate guidance on the use of cascade<sup>19</sup> and by the FVE (Cascade Guide for veterinarians if NO authorised medicinal product is available)<sup>20</sup>.

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<sup>19</sup> See <http://www.vmd.defra.gov.uk/pdf/vmgn/VMGNote13.pdf>

<sup>20</sup> See [http://www.fve.org/uploads/publications/docs/fve\\_bro\\_cascade\\_jan2014.pdf](http://www.fve.org/uploads/publications/docs/fve_bro_cascade_jan2014.pdf)

## **Annex IV - Abbreviations**

AGISAR – WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance  
AM - antimicrobial  
AMEG - Antimicrobial Advice ad hoc Expert Group  
AMR - Antimicrobial resistance  
ANSES - French Agency for Food, Environmental and Occupational Health & Safety  
ASOA - Alliance to Save Our Antibiotics  
AVC - Association of Veterinary Consultants  
BRD - Bovine respiratory disease  
BSAVA - British Small Animal Veterinary Association  
BVA - British Veterinary Association  
CHMP - Committee for Medicinal Products for Human Use  
CIA - Critically Important Antimicrobials  
COGECA - General Committee for Agricultural Cooperation in the European Union  
COPA - Committee of Professional Agricultural Organisations  
CVMP - Committee for Medicinal Products for Veterinary Use  
DANMAP - Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans  
DDDA – Defined Daily Dose Animals  
DCDA – Defined Cure Dose Animals  
EC - European Commission  
ECDC – European Centre for Disease Prevention and Control  
EEA - European Economic Area  
EFSA - European Food Safety Authority  
EGGVP - European Group for Generic Veterinary Products  
EMA - European Medicines Agency  
ESBLs - Extended-Spectrum Beta-Lactamases  
ESVAC - European Surveillance of Veterinary Antimicrobial Consumption  
EU - European Union  
FECAVA - Federation of European Companion Animal Veterinary Associations  
FVE - Federation of Veterinarians of Europe  
IDWP - Infectious Disease Working Party  
IFAH-Europe - International Federation for Animal Health Europe  
JIACRA - Joint Interagency Antimicrobial Consumption and Resistance Analysis  
MA - Marketing authorisation  
MAA - Marketing Authorisation Application  
MAH – Marketing Authorisation Holder  
MBL - Metallo-Beta-Lactamases  
MDR - Multidrug-resistant  
MLST - Multi Locus Sequence Types  
MRLs - Maximum Residue Limits  
MRSA - Methicillin-resistant *Staphylococcus aureus*  
MRSP - Methicillin-resistant *Staphylococcus pseudintermedius*  
MS - Member State  
OIE - World Organisation for Animal Health  
PCU - Population Correction Unit  
PNSP - Penicillin non-susceptible *Streptococcus pneumoniae*  
RMM – Risk Management Measures  
RPUE - Représentation permanente de la France auprès de l'Union européenne  
RUMA - Responsible Use of Medicines in Agriculture Alliance  
SAGAM - Scientific Advisory Group on Antimicrobials  
SNGTV - Société Nationale Groupements Techniques Vétérinaires  
SPC - Summary of Product Characteristics  
SRD - Swine Respiratory Disease  
SVARM - Swedish Veterinary Antimicrobial Resistance Monitoring  
UTI - Urinary tract infection  
VCIA - Veterinary Critically Important Antimicrobials  
VMP - Veterinary Medicinal Product  
VRE - Vancomycin-Resistant enterococci  
VTEC/STEC - Verocytotoxin/Shiga toxin-producing *Escherichia coli*



## Annex V - References

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