Antimicrobial Resistance: EMA/AMEG categorisation in Veterinary Medicine in EU

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14 December 2018

The priorities for legislators and institutions are:

1) the man

2) the environment in which he lives

No government or institution will allow man to die for:

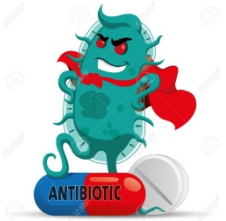
- ✓ Workplace accidents (in Italy, 1.029 deaths in 2017 – INAIL data)

  → *'Testo Unico sulla salute e sicurezza sul lavoro',* D.Lgs. n.81/2008 updated version of July 2018.

- ✓ Car accidents (in Italy, 3.378 deaths in 2017 – ISTAT data)

  → *'Decreto sicurezza'* (D.Lgs. 113/2018), Road Traffic Code amendments

- ✓ Antimicrobial Resistance (in EU 33,000 deaths/year – Ears-Net data in Italy, 10,000 deaths/year - Ar-Iss data)



  → **strategies to prevent and control antimicrobial resistance requiring global European coordination and specific national strategies, able to face local situations**

  → **strategies to prevent global warming**

Zero risk does not exist…

A recent study published in *Nature Climate Change* suggest that a link between climate change and bacterial resistance exists.

Epidemiologist from Boston Children's Hospital and the University of Toronto found that **higher local temperatures** and **population densities** correlated to a greater level of antibiotic resistance among a number of common bacterial strains (*E. coli, K. pneumoniae, S. aureus*).

The strongest associations between temperature and resistances was found in **fluoroquinolones and beta-lactam antibiotics**, suggestiong that warmer temperatures may affect the way bacteria respond to certain drug mechanisms.

MacFadden et al., 2018

Critically Important Antimicrobials (CIAs)

The concept of **"critically important antimicrobials"** was originally developed following recommendations from two expert workshops (Geneva, Switzerland, 2003; Oslo, Norway, 2004) organized by Food and Agriculture Organization of the United Nations (FAO), World Organization for Animal Health (OIE), and World Health Organization (WHO), to address public health consequences of antimicrobial agents use in food producing animals.

The workshops recommended that **WHO should develop such a list of critically important antimicrobial agents in human medicine (CIAs)** and that **OIE should also develop a list of critically important antimicrobial agents in veterinary medicine (VCIAs).**

The WHO CIA List was first developed in 2005, while the OIE VCIA List in 2007.

A third FAO/OIE/WHO expert meeting (Rome, Italy, 2007), considered WHO and OIE CIA lists and concluded that they should be **revised on regular basis**, in a collaborative and coordinated approach by FAO, OIE and WHO.

World Health Organization

The **World Health Organization** (**WHO**) is a specialized agency of the United Nations that is concerned with international public health.

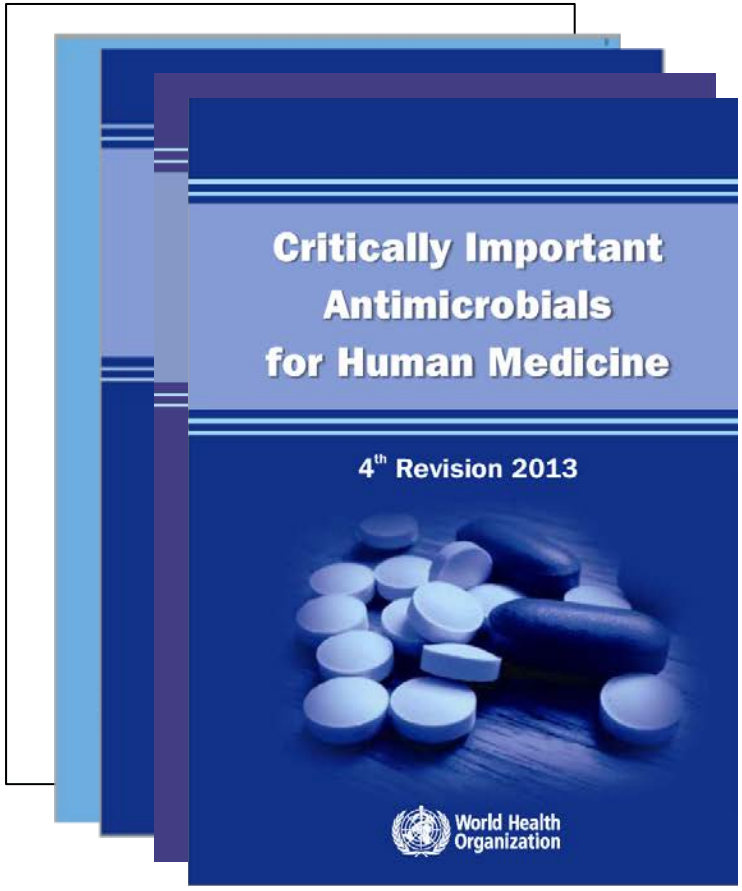
It was established on 7 April 1948, and is headquartered in **Geneva, Switzerland.**

Its current priorities include communicable diseases, in particular HIV/AIDS, Ebola, malaria and tuberculosis; the mitigation of the effects of non-communicable diseases such as sexual and reproductive health, development, and aging; nutrition, food security and healthy eating; occupational health; substance abuse; and driving the development of reporting, publications, and networking.

The WHO is financed by contributions from member states and outside donors.

WHO Headquarters building in Geneva

The WHO CIA List



The WHO CIA List was first developed in 2005, and then updated every 2 years.

During the first WHO Expert Meeting on CIA for Human Health (Canberra, Australia; 2005), participants categorized antimicrobial agents used in human medicine into three groups:

- ✓ **Critically important**
- ✓ **Highly important**
- ✓ **Important**

based on two criteria developed at the meeting:

Criterion 1: The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.

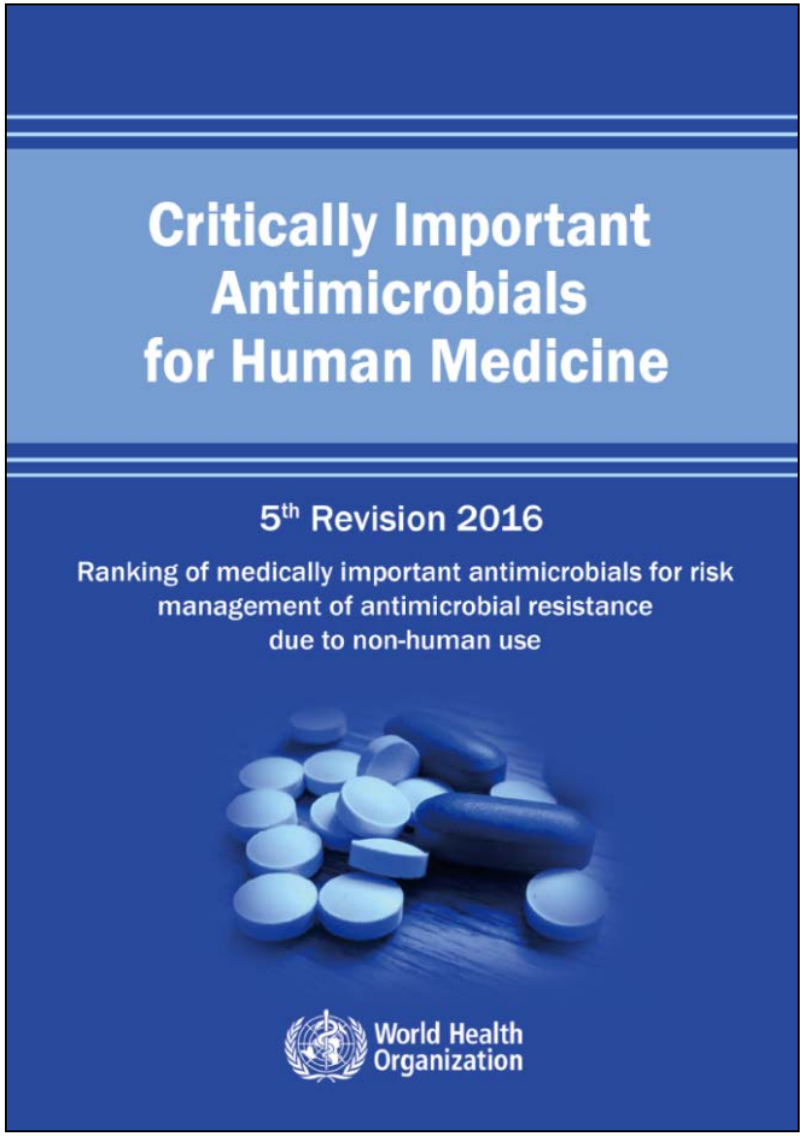
Criterion 2: The antimicrobial class is used to treat infections in people caused by either:

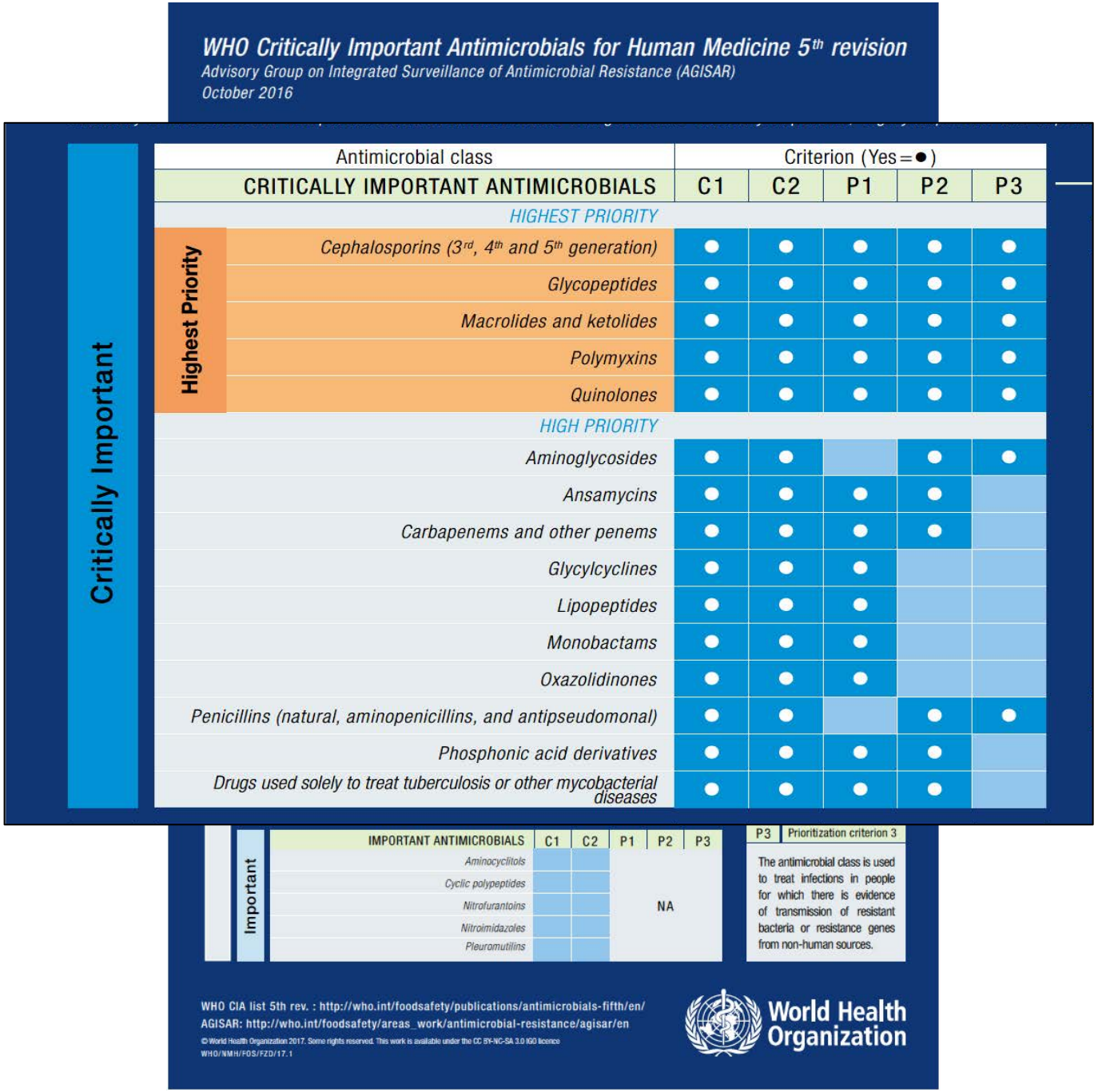
(1) bacteria that may be transmitted to humans from nonhuman sources, or

(2) bacteria that may acquire resistance genes from nonhuman sources.

The list was last updated in 2016 (**5th revision of the CIA list**).

This document is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.





WHO Critically Important Antimicrobials for Human Medicine 5th revision

Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)
October 2016

Critically Important

Antimicrobial class	Criterion (Yes = ●)				
CRITICALLY IMPORTANT ANTIMICROBIALS	**C1**	**C2**	**P1**	**P2**	**P3**
HIGHEST PRIORITY					
Highest Priority — *Cephalosporins (3rd, 4th and 5th generation)*	●	●	●	●	●
Glycopeptides	●	●	●	●	●
Macrolides and ketolides	●	●	●	●	●
Polymyxins	●	●	●	●	●
Quinolones	●	●	●	●	●
HIGH PRIORITY					
Aminoglycosides	●	●		●	●
Ansamycins	●	●	●	●	
Carbapenems and other penems	●	●	●	●	
Glycylcyclines	●	●	●		
Lipopeptides	●	●	●		
Monobactams	●	●	●		
Oxazolidinones	●	●	●		
Penicillins (natural, aminopenicillins, and antipseudomonal)	●	●		●	●
Phosphonic acid derivatives	●	●	●	●	
Drugs used solely to treat tuberculosis or other mycobacterial diseases	●	●	●	●	

Important

IMPORTANT ANTIMICROBIALS	C1	C2	P1	P2	P3
Aminocyclitols			NA		
Cyclic polypeptides					
Nitrofurantoins					
Nitroimidazoles					
Pleuromutilins					

P3 Prioritization criterion 3

The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria or resistance genes from non-human sources.

WHO CIA list 5th rev. : http://who.int/foodsafety/publications/antimicrobials-fifth/en/
AGISAR: http://who.int/foodsafety/areas_work/antimicrobial-resistance/agisar/en

World Health Organization

WORLD ORGANISATION FOR ANIMAL HEALTH

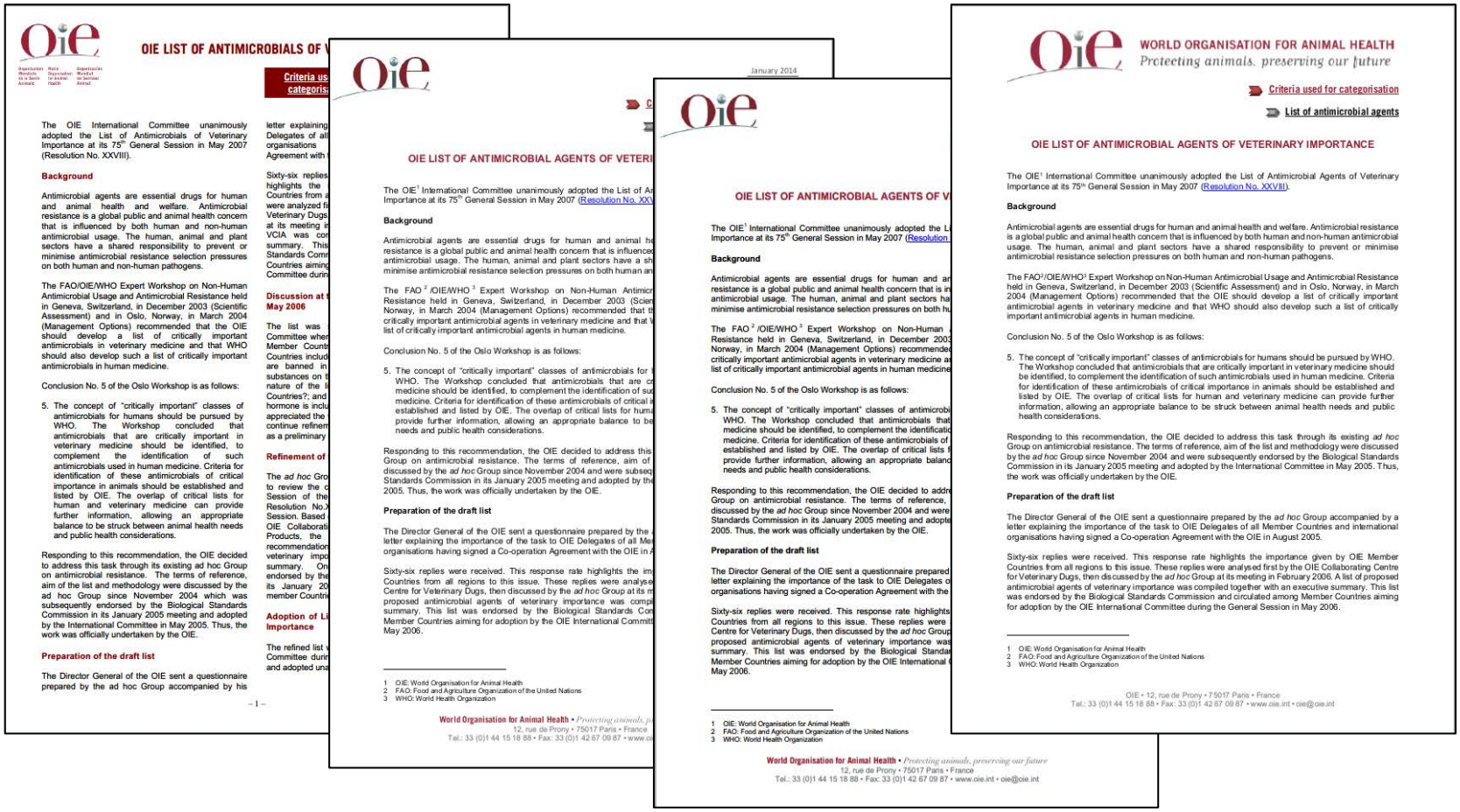
Protecting animals, preserving our future

World Organisation for Animal Health (OIE) Headquarters building in Paris

- ✓ The need to fight animal diseases at global level led to the creation of the **Office International des Epizooties (OIE)** in 1924.
- ✓ In 2003, the Office became the **World Organisation for Animal Health** but kept its historical acronym OIE.
- ✓ The OIE is the intergovernmental organisation responsible for improving animal health worldwide.
- ✓ The OIE maintains permanent relations with nearly 75 other international and regional organisations and has Regional and sub-regional Offices on every continent. In 2018, it has a total of 182 Member Countries.
- ✓ The day-to-day operation of the OIE is managed at the Headquarters situated in **Paris, France**.
- ✓ The OIE's financial resources are derived principally from compulsory annual contributions backed up by voluntary contributions from Member Countries.

The OIE List of Antimicrobial agents of veterinary importance

The OIE List of Antimicrobial agents of veterinary importance (VCIA) was first developed in 2007 and then was further updated in 2013, 2015 and 2018.



Criteria used for categorisation of veterinary important antimicrobial agents (OIE List)

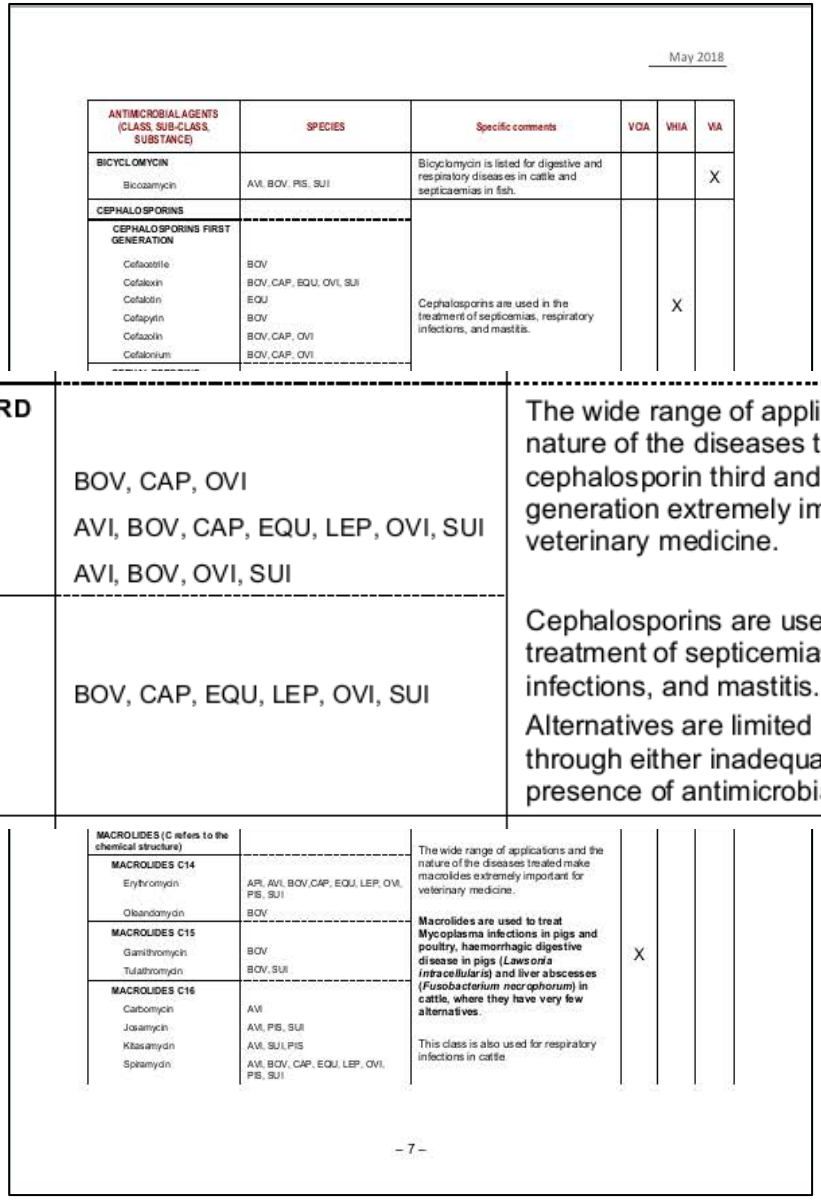
On the basis of two criteria:

1. **importance of the antimicrobial class**
2. **treatment of serious animal diseases and availability of alternatives**

the following categories were established:

- **Veterinary Critically Important Antimicrobial Agents (VCIA)** - criteria 1 and 2
- **Veterinary Highly Important Antimicrobial Agents (VHIA)** - criteria 1 or 2
- **Veterinary Important Antimicrobial Agents (VIA)** - neither criteria 1 or 2

Antimicrobial classes/sub classes used only in human medicine are not included in the 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.



May 2018

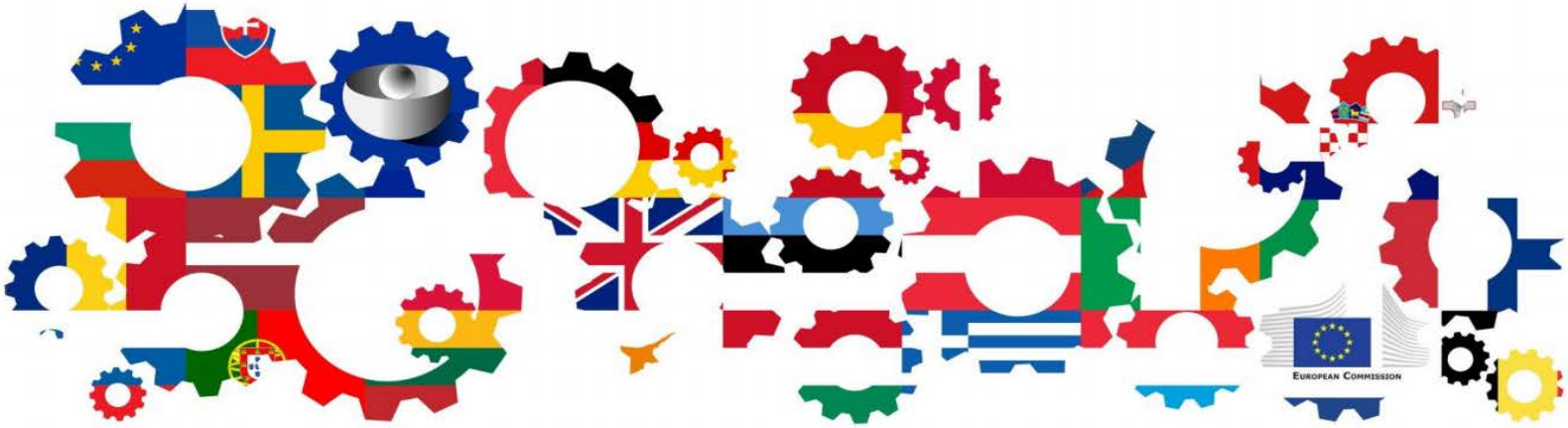
ANTIMICROBIAL AGENTS (CLASS, SUB-CLASS, SUBSTANCE)	SPECIES	Specific comments	VCIA	VHIA	VIA
BICYCLOMYCIN		Bicyclomycin is listed for digestive and respiratory diseases in cattle and septicaemias in fish.			
Bicozamycin	AVI, BOV, PIS, SUI				X
CEPHALOSPORINS					
CEPHALOSPORINS FIRST GENERATION					
Cefaoxitile	BOV				
Cefaloxin	BOV, CAP, EQU, OVI, SUI				
Cefalotin	EQU	Cephalosporins are used in the treatment of septicemias, respiratory infections, and mastitis.		X	
Cefapyrin	BOV				
Cefazolin	BOV, CAP, OVI				
Cefalonium	BOV, CAP, OVI				
CEPHALOSPORINS THIRD GENERATION		The wide range of applications and the nature of the diseases treated make cephalosporin third and fourth generation extremely important for veterinary medicine.			
Cefoperazone	BOV, CAP, OVI				
Ceftiofur	AVI, BOV, CAP, EQU, LEP, OVI, SUI				
Ceftriaxone	AVI, BOV, OVI, SUI				
CEPHALOSPORINS FOURTH GENERATION		Cephalosporins are used in the treatment of septicemias, respiratory infections, and mastitis.	X		
Cefquinome	BOV, CAP, EQU, LEP, OVI, SUI	Alternatives are limited in efficacy through either inadequate spectrum or presence of antimicrobial resistance.			
MACROLIDES (C refers to the chemical structure)		The wide range of applications and the nature of the diseases treated make macrolides extremely important for veterinary medicine.			
MACROLIDES C14					
Erythromycin	API, AVI, BOV,CAP, EQU, LEP, OVI, PIS, SUI				
Oleandomycin	BOV				
MACROLIDES C15		**Macrolides are used to treat Mycoplasma infections in pigs and poultry, haemorrhagic digestive disease in pigs (*Lawsonia intracellularis*) and liver abscesses (*Fusobacterium necrophorum*) in cattle, where they have very few alternatives.**	X		
Gamithromycin	BOV				
Tulathromycin	BOV, SUI				
MACROLIDES C16					
Carbomycin	AVI				
Josamycin	AVI, PIS, SUI				
Kitasamycin	AVI, SUI, PIS	This class is also used for respiratory infections in cattle			
Spiramycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI				

– 7 –

The use of WHO list, in conjunction with the OIE list of antimicrobials of veterinary importance and the WHO Model Lists of Essential Medicines, will allow for prioritization of risk management strategies in the **human sector**, the **animal sector**, and in **agriculture**, through a coordinated One Health approach.

Which is the CIA list to be considered in Veterinary Medicine in EU?

The European medicines regulatory network



The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 EEA countries (28 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and EMA.

The European Commission is the Executive body of the EU responsible for proposing legislation, implementing decisions, upholding the Union's treaties and day-to-day running of the EU.

European Commission headquarters building in Brussels

The Commissioners (2014-2019)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- The European Medicines Agency (or EMA) is the EU regulatory body responsible for the scientific evaluation and supervision of medicine developed by pharmaceutical companies for use in the EU (= it ensures that medicines are safe and that they work as expected).

- EMA's main responsibility is the protection and promotion of public and animal health, by carrying out scientific evaluations of medicine for human and veterinary use.

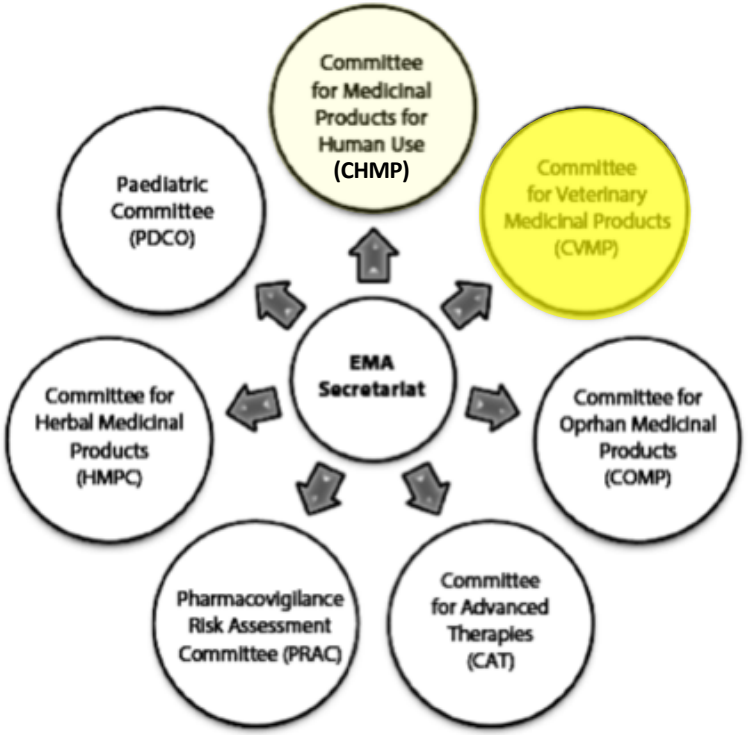
- The Agency also supervises the safety of medicines in the EU after they have been authorised. It can also give scientific opinions on medicines at the request of Member States or the European Commission.

- It is located in London (UK) but will relocate to Amsterdam (NL) following the UK's withdrawal from the EU on 30 March 2019 at the latest.

European Medicines Agency (EMA) headquarters building in London

EMA and its scientific committees

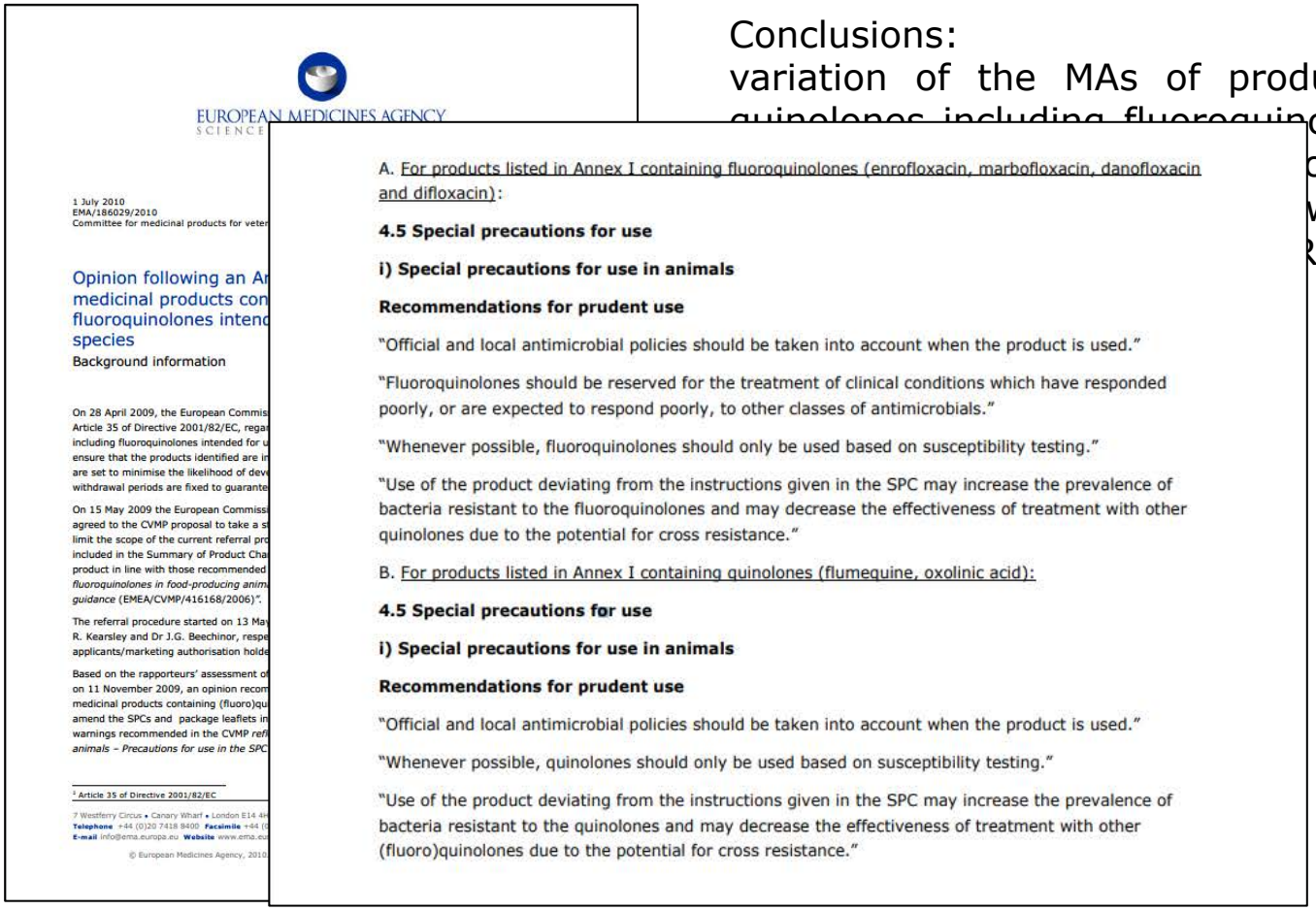
There are 7 scientific committees that evaluate medicines at the EMA – 6 of these are for medicines for human use and one, the CVMP is for veterinary products.



The EMA Committees contain members nominated by the medicine regulatory authorities of the EU Member States (the 'National Competent Authorities')

Urgent restrictions before 2013:

EMA/186029/2010 - Article 35 referral for all veterinary medicinal products containing quinolones including fluoroquinolones intended for use in food-producing species (1 July 2010)



EUROPEAN MEDICINES AGENCY
SCIENCE

1 July 2010
EMA/186029/2010
Committee for medicinal products for veter

Opinion following an Ar
medicinal products con
fluoroquinolones intend
species

Background information

On 28 April 2009, the European Commis
Article 35 of Directive 2001/82/EC, regar
including fluoroquinolones intended for u
ensure that the products identified are in
are set to minimise the likelihood of deve
withdrawal periods are fixed to guarante

On 15 May 2009 the European Commissi
agreed to the CVMP proposal to take a st
limit the scope of the current referral pro
included in the Summary of Product Cha
product in line with those recommended
fluoroquinolones in food-producing anim
guidance (EMEA/CVMP/416168/2006)".

The referral procedure started on 13 May
R. Kearsley and Dr J.G. Beechinor, respe
applicants/marketing authorisation holde

Based on the rapporteurs' assessment of
on 11 November 2009, an opinion recom
medicinal products containing (fluoro)qu
amend the SPCs and package leaflets in
warnings recommended in the CVMP *refl*
animals – Precautions for use in the SPC

[1] Article 35 of Directive 2001/82/EC

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A. For products listed in Annex I containing fluoroquinolones (enrofloxacin, marbofloxacin, danofloxacin and difloxacin):

4.5 Special precautions for use

i) Special precautions for use in animals

Recommendations for prudent use

"Official and local antimicrobial policies should be taken into account when the product is used."

"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."

"Whenever possible, fluoroquinolones 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 fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance."

B. For products listed in Annex I containing quinolones (flumequine, oxolinic acid):

4.5 Special precautions for use

i) Special precautions for use in animals

Recommendations for prudent use

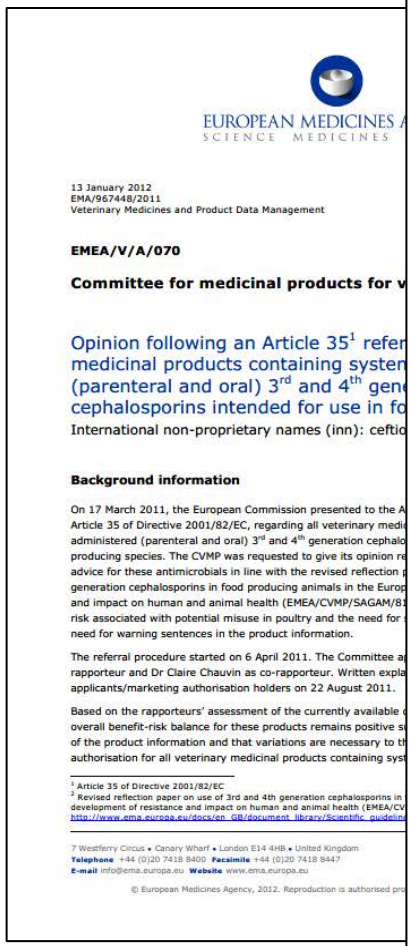
"Official and local antimicrobial policies should be taken into account when the product is used."

"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."

Conclusions:
variation of the MAs of products containing quinolones including fluoroquinolones intended order to amend where there are Reflection Paper

EMA/967448/2011 … medicinal products containing … oral) 3rd and 4th generation … roducing species (13 January …



EUROPEAN MEDICINES A…
SCIENCE MEDICINES

13 January 2012
EMA/967448/2011
Veterinary Medicines and Product Data Management

EMEA/V/A/070

Committee for medicinal products for v…

Opinion following an Article 35[1] refer… medicinal products containing systen… (parenteral and oral) 3rd and 4th gen… cephalosporins intended for use in fo…
International non-proprietary names (inn): ceftio…

Background information

On 17 March 2011, the European Commission presented to the A… Article 35 of Directive 2001/82/EC, regarding all veterinary medi… administered (parenteral and oral) 3rd and 4th generation cephalo… producing species. The CVMP was requested to give its opinion re… advice for these antimicrobials in line with the revised reflection … generation cephalosporins in food producing animals in the Europ… and impact on human and animal health (EMEA/CVMP/SAGAM/81… risk associated with potential misuse in poultry and the need for … need for warning sentences in the product information.

The referral procedure started on 6 April 2011. The Committee a… rapporteur and Dr Claire Chauvin as co-rapporteur. Written expla… applicants/marketing authorisation holders on 22 August 2011.

Based on the rapporteurs' assessment of the currently available … overall benefit-risk balance for these products remains positive s… of the product information and that variations are necessary to th… authorisation for all veterinary medicinal products containing syst…

[1] Article 35 of Directive 2001/82/EC
[2] Revised reflection paper on use of 3rd and 4th generation cephalosporins in … development of resistance and impact on human and animal health (EMEA/CV… http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guidelin…

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Amendments in the relevant sections of the summary of product characteristics

4.1 Target species

.....

Delete, where applicable, poultry (poultry, chicken, etc) as target species.

.....

4.2 Indications for use, specifying the target species

.....

Delete, where applicable, all indications related to poultry (poultry, chicken, etc).

.....

Add, where applicable, for products indicated for bovine metritis:
The indication is restricted to cases where treatment with another antimicrobial has failed.

.....

4.3 Contraindications

.....

Add, to all products:
Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

.....

4.5 Special precautions for use

.....

Add, to all products:
"Product name (to be completed nationally)" selects for resistant strains such as bacteria carrying extended spectrum betalactamases (ESBL) 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)"* 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.
"Product name (to be completed nationally)" is intended for treatment of individual animals. Do not use for disease prevention or as a part of heard health programmes. Treatment of groups of animals should be strictly restricted to ongoing disease outbreaks according to the approved conditions of use.

.....

Add, where applicable, for products indicated for bovine metritis:
Do not use as prophylaxis in case of retained placenta.

.....

4.11 Withdrawal period(s)

.....

Delete, where applicable, all withdrawal period(s) related to poultry (poultry, chicken, etc) as target species.

.....

59/60

…veterinary medicinal …nd 4th generation …mically administered …nded for use in food …amend the SPC and

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Director General

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

Dear Professor G. Rasi,

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

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

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

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

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

Professor G. Rasi
European Medicines Agency
7, Westferry Circus – Canary Wharf
London E14 4 HB United Kingdom
Email: guido.rasi@ema.europa.eu

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 (4 Questions).

Antimicrobial Advice Ad Hoc Expert Group (AMEG)

AMEG was set up to answer four questions posed by the European Commission **in April 2013** when it requested scientific advice from the EMA on the impact of the use of antibiotics in animals on public health and animal health and measures to manage the possible risk to humans.

The AMEG is an ad hoc group of 15 experts established jointly under the Committee for Medicinal Products for Veterinary Use (CVMP) and the Committee for Medicinal Products for Human Use (CHMP).

AMEG's tasks include:

- the **categorisation of antimicrobials** based on their risk to public health due to the development of antimicrobial resistance (AMR) following use in animals. Categorisation may have a significant impact on veterinarians' selection and use of antimicrobial medicinal products, and on national treatment guidelines;

- the development of an **early hazard characterisation assessment.** This is intended to address the risk to public health from AMR and will be assessed prior to the submission of a MAA. It will inform decisions on restricting or banning the use of a substance in food-producing species, and on the need to introduce risk management measures.

The response to Question 1 was published in July 2013 and includes advice from the Agency on the use of colistin and tigecycline in animals (EMA/443757/2013 - *Antimicrobial resistance - European Medicines Agency provides advice on use of colistin and tigecycline in animals*) as follows:

There is no available evidence on the transfer of resistance to colistin from animals to man but information on the subject is limited and more research and surveillance should be done. The advice recommends:

- ✓ **maintaining the responsible use of colistin in veterinary medicine** but restricting its use to the treatment of infected animals and those in contact with them, and to remove all indications for preventive (or prophylactic) use.
- ✓ **strengthening the systems for surveillance for resistance to colistin** in order to increase the likelihood of early detection of any rise. The benefit-risk balance for colistin to be re-evaluated if a substantial increase of resistance is detected.

Tigecycline, an antibiotic of the glycylcycline class, is not currently approved for use in animals; there is some evidence of off-label use in dogs and cats of tigecycline products authorised for human use.

The Agency advised that currently no need is foreseen for the authorisation of tigecycline for use in animals and it is unlikely that a marketing authorisation could be granted in light of the need for this antibiotic in human medicine.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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

Answer to the second request from the EC (ranking of antibiotics)
Answer to the third request from the EC (new antibiotics)
Answer to the fourth request from the EC (risk mitigation options)

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

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The answers to Question 2, 3 and 4 were provided in December 2014 in the publicly available document EMA/381884/2014 - *Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals*).

The answers were prepared by the Antimicrobial Advice ad hoc Expert Group (AMEG).

AMEG has performed an evaluation on all human CIAs based on the degree of risk to man due to resistance development following use in animals.

The EMA/AMEG 2014 Categorisation

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

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

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

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

The EMA/AMEG 2014 Categorisation

The **Category 1**, with low risk of resistance included different antimicrobials like macrolides (spiramycin, tylosin), penicillin with natural and narrow spectrum, polymyxins (e.g. colistin), rifamycins (rifaximin) and tetracyclines.

Category 2, with higher risk of resistance for humans, includes 3rd and 4th generation cephalosporins (ceftiofur, cefoperazone, cefquinome), fluoroquinolones (enrofloxacin, marbofloxacin), aminoglycosides and aminopenicillins including β-lactamase inhibitors (e.g. co-amoxiclav). The use of these antimicrobials in veterinary medicine is considered acceptable provided that specific restrictions are placed on their use like not being used as first choice antibiotic.

Category 3 regards forbidden antimicrobials in veterinary medicine.

The AMEG categories take into account:

- ✓ the WHO categorisation of antimicrobials,
- ✓ the consumption of those antimicrobials in veterinary medicine,
- ✓ the hazards of zoonotic relevance in EU and
- ✓ the risk of resistance transfer to humans.

The AMEG classification is published on the EMA webpage:
https://www.ema.europa.eu/documents/other/answers-requests-scientific-advice-impact-public-health-animal-health-use-antibiotics-animals_en.pdf

Data summary table

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

Table 1: Summary table

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

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

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

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

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

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

Restrictions after 2014:

Polymyxins (e.g.colistin)

May 2014 - Referral procedure under Article 35 of Directive 2001/82/EC for **all veterinary medicinal products containing colistin as sole active substance for oral administration to food-producing species**.
March 2015 – Adoption of EC Decision to restrict the indications (prophylactic use of oral colistin products in food-producing species excluded, salmonellosis claim deleted), target species (horse deleted), and duration of treatment (restricted to maximum 7 days) of the concerned products, as well as to add prudent use warnings to the product information.

May 2015 - Referral procedure under Article 35 of Directive 2001/82/EC for **all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally**.
July 2016 - EC recommended the withdrawal of the marketing authorisations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally.

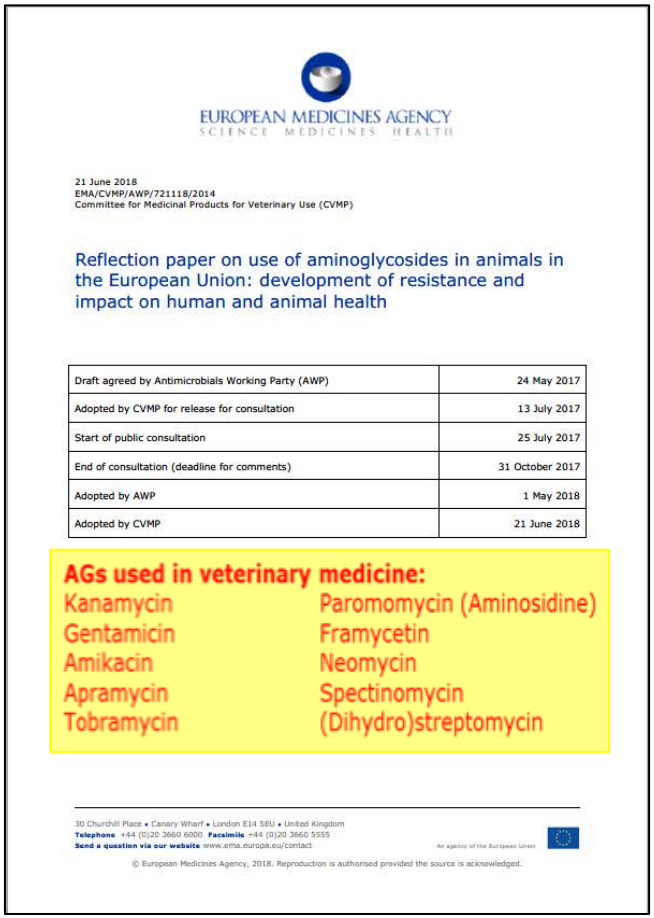
July 2016 - following the discovery of *mcr-1*, a horizontal transferable resistance gene in bacteria of food animal origin, **the impact of the current or future use of colistin products in veterinary medicine for animal health and welfare has been re-assessed**:

- ✓ colistin moved from AMEG Category 1 of antimicrobials to Category 2, to be used as fluoroquinolones only as 2nd choice, after the Category 1 antimicrobials have not been effective. The opinion will be reviewed in 3-4 years.
- ✓ in 3-4 years the consumption should be reduced of 65-80% in the countries with the highest consumption, such as Italy and Spain, without increasing the use of fluoroquinolones, cephalosporins of 3rd and 4th generation and total consumption of antibiotics

Currently in progress:

EMA/CVMP/AWP/721118/2014 - Reflection paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health (21 June 2018)

All veterinary-authorised AGs, **including spectinomycin**, would be placed in Category 2 (higher risk for public health), a further stratification is foreseen for some AGs, based on active substances and/or route of administration.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2018
EMA/CVMP/AWP/721118/2014
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health

Draft agreed by Antimicrobials Working Party (AWP)	24 May 2017
Adopted by CVMP for release for consultation	13 July 2017
Start of public consultation	25 July 2017
End of consultation (deadline for comments)	31 October 2017
Adopted by AWP	1 May 2018
Adopted by CVMP	21 June 2018

AGs used in veterinary medicine:

Kanamycin	Paromomycin (Aminosidine)
Gentamicin	Framycetin
Amikacin	Neomycin
Apramycin	Spectinomycin
Tobramycin	(Dihydro)streptomycin

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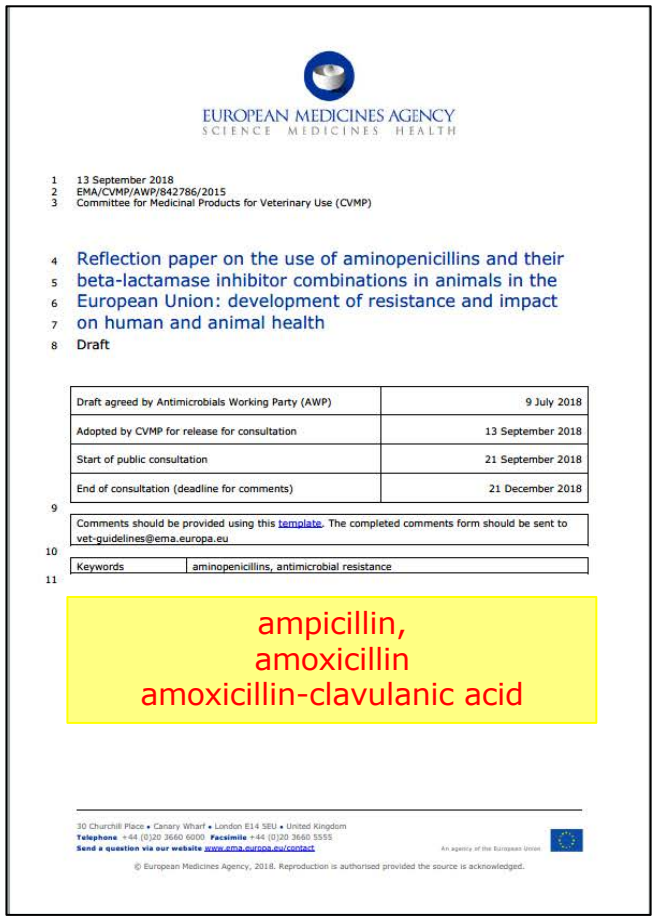

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2018
EMA/CVMP/AWP/842786/2015
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of aminopenicillins and their beta-lactamase inhibitor combinations in animals in the European Union: development of resistance and impact on human and animal health

Draft

Draft agreed by Antimicrobials Working Party (AWP)	9 July 2018
Adopted by CVMP for release for consultation	13 September 2018
Start of public consultation	21 September 2018
End of consultation (deadline for comments)	21 December 2018

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	aminopenicillins, antimicrobial resistance

ampicillin,
amoxicillin
amoxicillin-clavulanic acid

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Aminopenicillins, especially those in association with clavulanic acid, have a similar spectrum to cephalosporins of 2nd and 3rd generation. They can also select and/or facilitate the development of bacteria with extended spectrum beta-lactamases (ESBLs), similar to cephalosporins of 3rd and 4th generation and fluoroquinolones. They are classified as CIA for humans (WHO) and as VCIA for animals (OIE) and for this they have been included by AMEG in **Category 2**.

Based on the assessment of the possible development of resistance and consequent impact on animal and human health, **the CVMP suggests to AMEG to consider a further stratification of the current categorization**, in order to review the priority among the substances currently present in Category 2 (fluoroquinolones, cephalosporins of 3rd and 4th generation and colistin, for which there are fewer alternatives) and the association amoxicillin-clavulanic acid, and between the latter and the aminopenicillins (amoxicillin, ampicillin). The association amoxicillin-clavulanic acid, having a broader spectrum, is indeed more likely to select multiresistant bacteria than single aminopenicillins.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 November 2018
EMA/CVMP/AWP/237294/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union

Draft agreed by Antimicrobials Working Party (AWP)	24 May 2017
Adopted by CVMP for release for consultation	11 July 2017
Start of public consultation	25 July 2017
End of consultation (deadline for comments)	31 January 2018
Adopted by AWP	19 September 2018
Adopted by CVMP	8 November 2018

Keywords	off-label use, antimicrobials, antimicrobial resistance, veterinary medicines

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SCIENCE MEDICINES HEALTH

19 July 2018
EMA/CVMP/849775/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on dose optimisation of established veterinary antibiotics in the context of SPC harmonisation

Draft

Adopted by CVMP for release for co	
Start of public consultation	
End of consultation (deadline for co	

Comments should be provided usin
vet-guidelines@ema.europa.eu

Keywords	antimicrobi Dose optim target anim risk assessr

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 November 2018
EMA/CVMP/ERA/632109/2014
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products

Draft

Draft agreed by the Environmental Risk Assessment Working Party (ERAWP)	30 April 2018
Draft agreed by the Antimicrobial Working Party (AWP)	30 May 2018
Adopted by CVMP for release for consultation	8 November 2018
Start of public consultation	16 November 2018
End of consultation (deadline for comments)	31 August 2019

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	antibiotic, environmental fate, human health, animal health, risk assessment, antimicrobial resistance bacteria (ARB), antimicrobial resistance genes (ARGs)

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The updated EMA/AMEG 2014 Categorisation

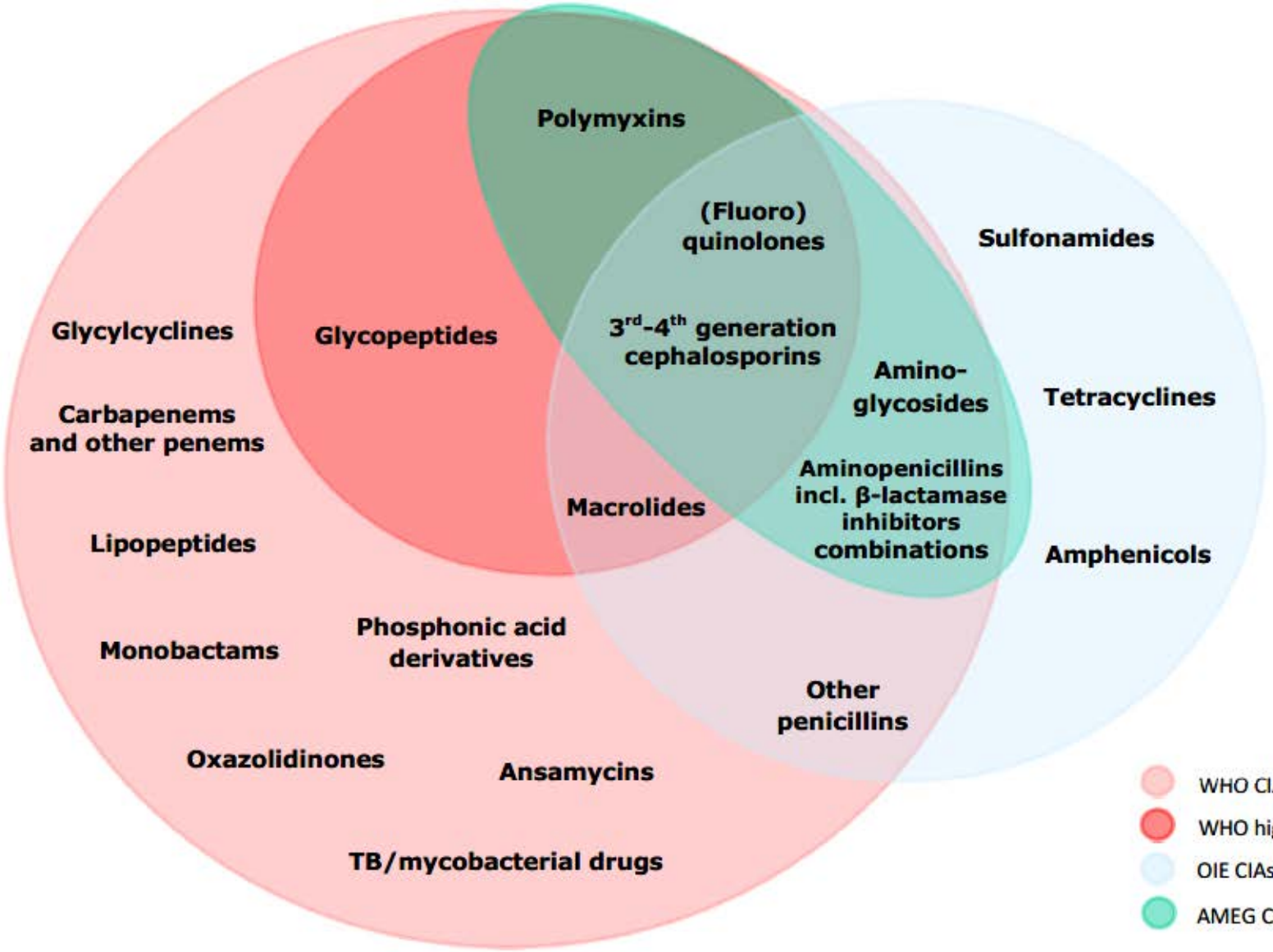
Category 1	
Class	**Substances**
Macrolides	Erythromycin Gamithromycin Spiramycin Tildipirosin Tulathromycin Tylosin Tylvalosin Tilmicosin
Penicillins, Natural	Benzylpenicillin Benethamine penicillin Penethamate (hydroiodide) Benzylpenicilline procaine Benzathine penicillin
Penicillins: Narrow spectrum, β-lactamase-resistant penicillins	Cloxacillin Dicloxacillin Nafcillin Oxacillin
Rifamycins	Rifaximin
Tetracyclines	Chlortetracycline Doxycicline Oxytetracycline Tetracycline

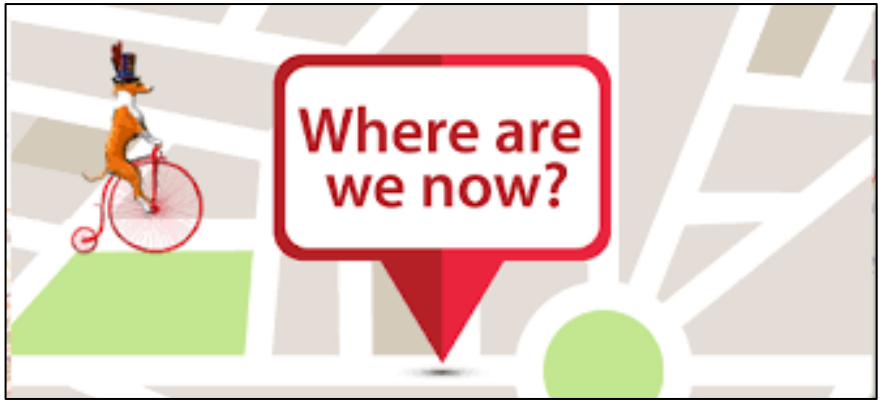
Category 2	
Class	**Substances**
Cephalosporins 3rd- and 4rd- generation	Ceftiofur Cefquinome
Fluoroquinolones and other quinolones	Danofloxacin Marbofloxacin Difloxacin Enrofloxacin Flumequin Oxolinic acid
Polymixins (e.g. colistin)	Colistin
Aminoglycosides	Amikacin (Dihydro)streptomycin Framycetin Gentamicin Kanamycin Neomycin Paromomycin (aminosidine) Apramycin Spectinomycin Tobramycin
Penicillins: Aminopenicillins including β-lactamase inhibitors combinations (e.g. co-amoxiclav)	Amoxicillin Ampicillin Amoxicillin + clavulanic acid

AMEG classification vs WHO classification

Antimicrobial class	WHO 2016 classification	AMEG 2014 classification
3rd- and 4th-generation cephalosporins	Highest priority CIAs (3rd- and higher-generation cephalosporins)	Category 2
Fluoroquinolones and other quinolones	Highest priority CIAs	Category 2
Macrolides	Highest priority CIAs	Category 1
Polymyxins	Highest priority CIAs	Category 2
Aminoglycosides	CIAs	Provisionally included in Category 2 (but no risk profiling has been provided) Category 2 confirmed by Reflection Paper EMA/CVMP/AWP/721118/2014 dt 21.06.2018
Certain penicillins (amoxicillin, ampicillin, metampicillin)	CIAs	Provisionally included in Category 2 (but no risk profiling has been provided) Category 2 confirmed by draft Reflection Paper EMA/CVMP/AWP/842786/2015 dt 13.09.2018

Classes of antibiotics included in the WHO, OIE and AMEG 2014 list of critically important antimicrobial agents





Ref. Ares(2017)3482661 - 11/07/2017

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Director-General

Brussels,
SANTE/E5/DB/mcd Ares (2017) 3584639

Dear Professor Rasi, dear Guido,

Subject: **Request for an update of the advice on the impact on public health and animal health of the use of antibiotics in animals (categorisation of antimicrobials and early hazard characterisation)**

On request of the European Commission in April 2013, the European Medicines Agency (EMA) provided in 2014 the scientific advice on the impact on public health and animal health of the use of antibiotics in animals. This advice included a categorisation of critically important antimicrobials from the World Health Organisation list, based on
resistance development following use in
dvice Ad Hoc Expert Group (AMEG). The
EMA in 2016, resulted in a re-classification

t risk assessment of new antimicrobial
should be reinforced by introducing e.g. an
prior to the submission of a marketing

ref. EMA/139924/2017) about the need to
crobials and to further elaborate on the
ating the need for a mandate for EMA to
e of 2014 accordingly. I also acknowledge
he Committee for Medicinal Products for
inal Products for Human Use scientifically

MA to update its advice regarding the
y hazard characterisation, in line with the
nt, to closely collaborate on this matter with
nd Control (ECDC) and the European Food

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The EMA should address the following points:

1. Categorisation of antimicrobials

- Categorisation of aminoglycosides and penicillins,
- Further refinements of the criteria for the categorisation (e.g. including route of administration),
- Improved communication of the categorisation,
- Consideration of additional categorisation for antimicrobials categorised by the WHO[8] as highly important and important (in addition to the critically important antimicrobials),
- Consideration of other recent work of the WHO on classification of antimicrobials and pathogens (e.g. the 20th edition of the WHO Model List of Essential Medicines and the WHO Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics),
- Consideration of any other relevant work in this area (e.g. OIE list of antimicrobial agents of veterinary importance).

The route of administration has been already used as refinement of the criteria for the EMA/AMEG Categorisation in 2014 (e.g. for rifamycins/rifaximin).

Antimicrobial class	Summary of veterinary use in the EU	Risk management measures implemented by some countries
Rifamycins	Limited use in veterinary medicine. • Indications: Rifamixin is the only substance of the group authorised for use in food producing species with indications limited to intramammary or intrauterine use • Pharmaceutical Form: intramammary • Species: cattle. Comment: Rifampicin is included in the list of essential substances for horses for the treatment of *Rhodococcus equi* infections in equines.	Those recommended by responsible use.

(from Table 8 EMA/381884/2014)

Application of EMA/AMEG 2014 categorisation

OJ of the EU, 2015/C 299/04 Guidelines for the prudent use of antimicrobials in veterinary medicine, 2015

COMMISSION NOTICE

Guidelines for the prudent use of antimicrobials in veterinary medicine

(2015/C 299/04)

Table of Contents

3.2. Particular issues to be considered before using critically important antimicrobials

Many of the antimicrobials used in animals are also used in humans. Some of these antimicrobials are critical ([4]) for preventing or treating life-threatening infections in humans. Special consideration is necessary to ensure the continued efficacy of such antimicrobials and to minimise the development of resistance.

Before using these antimicrobials in animals, consideration should be given to the following (in addition to the points already mentioned):

— These antimicrobials should only be used in situations where a veterinarian has assessed, on the basis of antimicrobial susceptibility testing and relevant epidemiological data, that there is no non-critically important effective antimicrobial available.

— In exceptional cases where the use of these antimicrobials under off-label use (cascade) is unavoidable and legally permissible, prescription and final use should be sufficiently justified and recorded. Such use should be based on clinical grounds, i.e. the prescribing veterinarian considers the use of a particular critically important antimicrobial necessary in order to avoid the suffering of diseased animals, and should also take into consideration ethical and public health concerns. The use of critically important antimicrobials should be limited to cases where no other alternative is available.

([1]) http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/

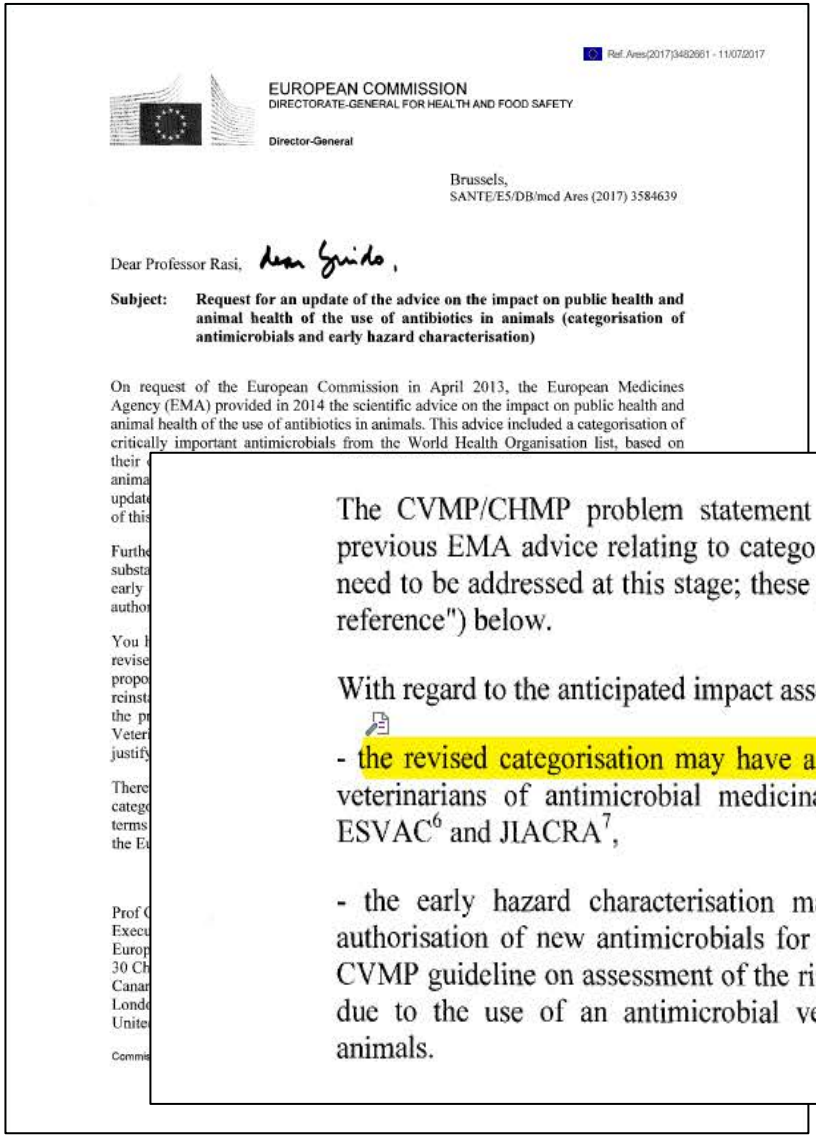
([2]) Article 10, Article 11 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).

([3]) Commission Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin (OJ L 15, 20.1.2010, p. 1).

([4]) In April 2013, the Commission requested advice from the European Medicines Agency on the impact of the use of antibiotics in animals on public and animal health. The response to this request should be used to identify the antimicrobials to be considered in this chapter.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000385.jsp&mid=WC0b01ac058080a585

Application of EMA/AMEG 2014 categorisation

EC letter to EMA, 2017



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The CVMP/CHMP problem statement provides further details on the points of the previous EMA advice relating to categorisation and early hazard characterisation which need to be addressed at this stage; these points are reflected in the section II. ("Terms of reference") below.

With regard to the anticipated impact assessment, this problem statement indicates that:

- the revised categorisation may have a significant impact on the selection and use by veterinarians of antimicrobial medicinal products, on national treatment guidelines, ESVAC[6] and JIACRA[7],

- the early hazard characterisation may have an impact on the development and authorisation of new antimicrobials for veterinary use and on the revision of the draft CVMP guideline on assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals.

Application of EMA/AMEG 2014 categorisation

AEMPS; 2017

REFERENCIAS:

- Report of the 3rd Meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, 14-17 june 2011, Oslo, Norway. Disponible en:

  http://apps.who.int/medicinedocs/documents/s21642en/s21642en.pdf

- ECDC. 2015 The bacterial challenge: time to react. Stockholm: EMEA doc. ref. EMEA/576176/2009. Disponible en:

  http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.

- EMA. 2014 Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals: 18 December 2014 EMA/381884/2014. Veterinary Medicines Division/CVMP/CHMP

  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf

- WHO. 2011. WHO list of Critically important antimicrobials in human medicine. Third revision. In W. L. C.-i.-P. Data, editor

  http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf

- OIE LIST OF ANTIMICROBIAL AGENTS OF VETERINARY IMPORTANCE

  http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pd

9

Application of EMA/AMEG categorisation

Eighth European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report, 2018

Application of EMA/AMEG categorisation

UK-VARSS (2018). UK Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS 2017). New Haw, Addlestone: Veterinary Medicines Directorate.

1.4.4.3 Sales of antibiotics of particular relevance to human health (mg/kg)

In VARSS reports, HP-CIAs are identified according to the categorisation by the Antimicrobial Advice *ad hoc* Expert Group (AMEG) of the EMA, and therefore include fluoroquinolones, 3rd and 4th generation cephalosporins and colistin (European Medicines Agency, 2014, 2016). Sales of HP-CIAs for food-producing animal species represented 0.28 mg/kg, a small proportion (0.8%) of the overall antibiotic sales. The sales decreased by 0.12 mg/kg (30%) between 2016 and 2017 and by 0.36 mg/kg (56%) since 2013 to 0.28 mg/kg in 2017. Between 2016 and 2017, sales of 3rd and 4th generation cephalosporins decreased by 0.03 mg/kg (21%), sales of fluoroquinolones decreased by 0.07 mg/kg (30%) and sales of colistin decreased by 0.017 mg/kg (94%) to very low levels (0.001 mg/kg), see **Figure 1.5**.

To conclude:

The best choice:

- **Cephalosporins 1st -2nd generation:** cefacetrile, cefadroxil, cefalexin, cefalonium, cefapyrin
- **Sulfonamides:** sulfadiazine, sulfadimethoxine, sulfadimidine, sulfadoxine, sulfaguanidin, sulfamethoxypyridazine, sulfaquinoxaline…
- **Amphenicols:** florphenicol, thiamphenicol
- **Others:** bacitracin, fusidic acid
- **Lincosamides:** lincomycin, pirlimycin (prudent use recommended since 2011)

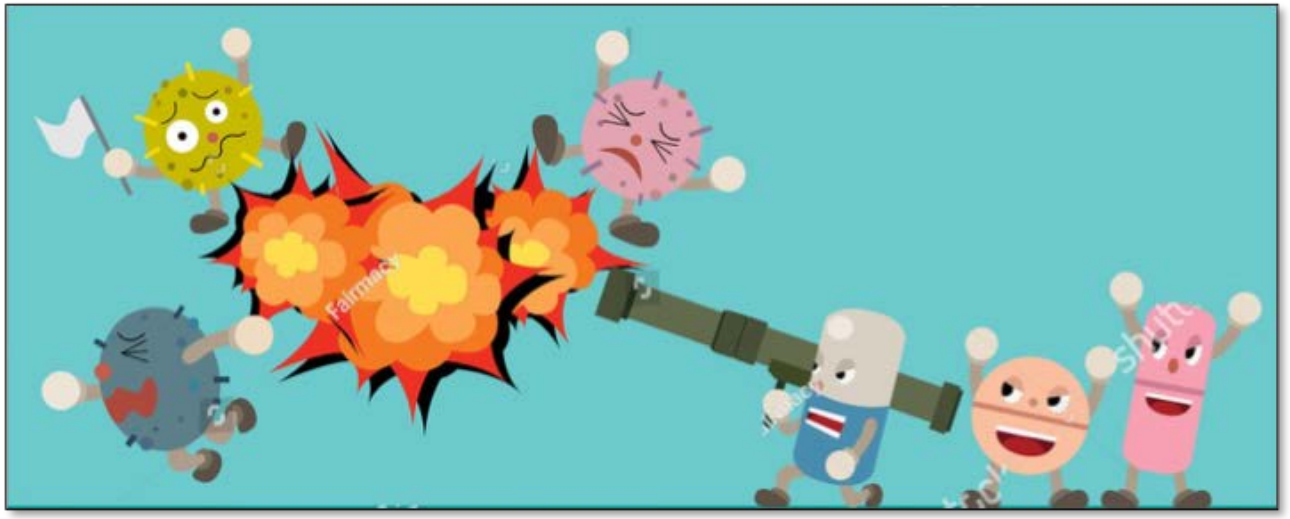
The first choice:

- **Macrolides:** erythromycin, gamithromycin, spiramycin, tildipirosin, tulathromycin, tylosin, tylvalosin, tilmicosin)
- **Penicillins, natural:** benzylpenicillin, benethamine penicillin, benethamate (hydroiodide), benzylpenicilline procaine, benzathine penicillin
- **Penicillins, narrow spectrum, β-lactamase-resistant penicillins:** cloxacillin, dicloxacillin, nafcillin, oxacillin
- **Rifamycins:** rifaximin
- **Tetracyclines:** chlortetracycline, doxycicline, oxytetracycline, tetracycline

The second choice:

- **Cephalosporins 3rd- 4rd generation (for systemic use):** ceftiofur, cefquinome
- **Fluoroquinolones and other quinolones:** danofloxacin, marbofloxacin, difloxacin, enrofloxacin, flumequin, oxolinic acid
- **Polymixins (e.g. colistin):** colistin
- **Aminoglycosides:** amikacin, (dihydro)streptomycin, framycetin, gentamicin, kanamycin, neomycin, paromomycin (aminosidine), apramycin, spectinomycin, tobramycin
- **Penicillins, aminopenicillins including β-lactamase inhibitors combinations (e.g. co-amoxiclav):** amoxicillin, ampicillin, amoxicillin/clavulanic acid)

Awaiting EMA/AMEG 2018 Categorisation…



…thank you for your attention!