12 December 2019
EMA/CVMP/CHMP/238375/2019
Committee for Medicinal Products for Veterinary Use (CVMP)
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on ''Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Categorisation of antimicrobials" (EMA/CVMP/CHMP/682198/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Prof Maiken Cavling Arendrup, MD, DMSci, PhD, Unit for mycology, Statens Serum Institute, Copenhagen Denmark
2	Professor Scott McEwen, Department of Population Medicine, Ontario Veterinary College, University of Guelph, Canada
3	Danish Medicines Agency
4	UK Sheep Antibiotic Guardian Group (includes SVS, NSA, SHAWG, AHDB, NFU; chair Fiona Lovatt)
5	Mr Gustavo Pappaterra from Laboratorios Calier in Spain
6	Dr. vet. med. Anette Hütt
7	Pig Veterinary Society (UK)
8	Dr Peter Scott MSc.BVSc.FRCVS
9	Danish Agriculture and Food Council
10	Dr Delphine ORAIN (SELARL)
11	National expert group of antimicrobial resistance control (MTKA), Finland
12	Elanco Animal Health
13	Association of Veterinary Consultants (AVC)
14	Triveritas Limited
15	Dr Gilles Chaudieu
16	British Veterinary Association (BVPA)
17	Comisión Nacional para el Control de la Resistencia Antimicrobiana de la República

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Stakeholder no.	Name of organisation or individual
	Argentina (CoNaCRA) – Ministerio de Salud y Desarrollo Social de la República Argentina
18	SOCIETE NATIONALE DES GROUPEMENTS TECHNIQUES VETERINAIRES
19	Dr. Thierry Azoulay, specialist in Veterinary Ophthalmology, President of the GEMO (Ophthalmology Department of the French Veterinary Society of Continuing Education – AFVAC).
20	Copa & Cogeca
21	Laboratory TVM (Global entity) TVM France (French affiliate)
22	National Office of Animal Health ltd (NOAH),
23	'Task force food safety' / Stabsstelle Ernaehrungssicherheit (Team of official veterinarians and pharmacists: inspections of veterinary medicinal products in veterinary practice premises and on farms), Baden-Wuerttemberg, Germany
24	Department of Agriculture, Food and the Marine, Ireland.
25	Italian Ministry of Health– Directorate General for Animal Health and Veterinary Medicinal Products – Italian CVO, and the Danish Medicines Agency (DKMA)
26	Phibro Animal Health Corporation. Richard Coulter, Senior Vice President Scientific and Regulatory Affairs
27	Andrea Holmström, Chief veterinarian,Växa Sverige
28	AnimalHealthEurope
29	German Pharmaceutical Industry Association (Bundesverband der Pharmazeutischen Industrie e.V., BPI)
30	EGGVP – European Group for Generic Veterinary Products
31	Ebba Schwan, Chief veterinarian, Farm and Animal Health, Sweden
32	Danish Veterinary and Food Administration
33	Advisory Committee on Veterinary Medicines, Denmark. Advisory committee to the Danish Government
34	Association de l'Aviculture, de l'Industrie et du Commerce de Volailles dans les Pays de l'Union Europeenne asbl (AVEC); European live poultry and hatching-eggs association (ELPHA)
35	Federation of Veterinarians of Europe (FVE), Federation of European Equine Veterinary Associations (FEEVA) and European Federation of Companion Animal Veterinary Associations (FECAVA)
36	German Federal Chamber of Veterinary Surgeons "Bundestierärztekammer (BTK)"
37	British Veterinary Association
38	Animal and Plant Health Association (APHA), Ireland
39	The United States Government
40	Public Health Agency of Canada
41	Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
1	Comment: Antimicrobial/antimicrobials covers antibacterial agents, antifungal agents and in principle also antiviral agents (not my topic), but the document only addresses antibacterial agents. Antifungal agents are used in veterinary medicine and some azole antifungal agents either cross reacts with or are identical with azoles used in human medicine (e.g. aerosolised azoles in turkey farms) and may therefore contribute to the emerging azole resistance witnessed in example in *A. fumigatus*. Therefore, it should be clearly indicated that this is a document that is limited to cover antibacterial agents in order not to imply that antifungals do not matter. Proposed change (if any): Replace antimicrobial with antibacterial throughout.	Thank you for your comment. To clarify the scope of the document, a new text box has been included: *Since the original AMEG scientific advice (2014), the terms 'antimicrobial' and 'antibiotic' have been defined in the Regulation on veterinary medicinal products (EU) 2019/6. In accordance with these definitions, the AMEG's categorisation includes specifically antibiotics, defined under the new legislation as '…any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious disease'. Substances with primarily antifungal, antiprotozoal or antiviral activity (included in the definition of antimicrobials) and disinfectants are out of scope. The term 'antimicrobial' was used in discussion of the first AMEG categorisation to reflect the reference to the WHO's list of 'Critically Important Antimicrobials for Human Medicine'. In the interests of consistency with Regulation (EU) 2019/6 and the scope of the AMEG's categorisation, the term 'antibiotic' is now used*	1.

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		except when referring to other publications which use the term 'antimicrobial' or when this term is used in the context of the definitions in the new legislation.'	
2	Although not European, I offer these comments as someone with long professional interest in containment of public health impacts of antimicrobial resistance arising from use of antimicrobial agents in food-producing animals. For several years I have been a member of the World Health Organization's Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), including the working group responsible for updating the WHO list of Critically Important Antimicrobials for Human Medicine (WHO-CIA list). Accordingly, I strongly believe that it is important to categorize the human health importance of antimicrobials in order to support risk assessment and risk management. Overall, I am very favourably impressed with the updated categorisation of antimicrobials put forward in the draft from AMEG. I think there are many improvements on the previous categorization, particularly the addition of a new category, the re-ordering of categories starting from highest risk, the new category names (Avoid, Restrict, etc.) and inclusion of the antimicrobial classes omitted from the previous advice. Clearly, much excellent work has gone into this report and my congratulations to everyone involved.	Thanks for the comments.	2.
3	Reviewed the draft AMEG report "Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Categorisation of antimicrobials" presented to IDWP in the first week of 2019 (AMEG 2018 - Categorisation of AMs - 20190108.doc). In July 2017, the EC asked the EMA to update its advice published in 2014. Regarding the categorisation of antimicrobials, the EC requested that the AMEG review the original classification and update as necessary taking account of the following specific points:		3.

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	• 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 World Health Organisation (WHO) 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 scope of the present AMEG document is limited to addressing the European Commission's request to update the 2014 advice on the categorisation of antimicrobials. As requested by the EC, all updated information should be considered in the updated AMEG categorisation. The Danish Medicines Agency has chosen to present its major concerns of the draft AMEG report under three focus areas: 1) **Major concerns about WHO CIA classes placed lower AMEG Catergories (Aminopenicillins, Macrolides, Aminoglycosides)** - Human and veterinary medicine share the use of some critically important antimicrobial (CIA) classes and thus resistance.	This is the case for most of Antimicrobial classes, not only the 3	

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	- There is a fundamental difference in common antimicrobial uses between veterinary and human medicine, including WHO CIAs. - Concerns about the AMEG categorization system is out of balance with WHO guidelines and scientific rationale for certain AB classes.	quoted. Agreed, but not a rationale for the concerns expressed. WHO guidelines recognise that the list "may vary from country to country".	
	2) **Major concerns about the description of AMEG Categories** - Description of categories forms the foundation of risk mitigation measures. - Concerns about the AMEG category description as lacking consistency and scientific rationale. - For example, the category that has some of the most important antimicrobial classes has the weakest description (Category A).	Agreed. More detailed explanations of the scientific rationale for the categorisation have been included. A very simple criterion was used for Category A (subclasses authorised for use in humans but not veterinary medicine in the EU). Some further changes have been made since the public consultation. See updated text in 4.1. As the formal AMR risk assessment and risk management measures that accompany use of an authorised veterinary medicine in the EU are not available, this might lead to an additional risk to public health.	
	3) **Major concerns about recent deletions of text as well as part of the unfulfilled EC mandate (route of administration)** - Recent deletions creates confusion about the previous methodology and the	Not understood as deletions are not	

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	shift away from this methodology. - Route of administration is a major factor contributing to likelihood of selection and transmission of resistant determinants. - When the oral route of administration is dominating the common use of an antimicrobial class, then it could be considered. **1) WHO CIA Classes** **Aminoglycosides** In the AMEG report it states the following for the justification of Aminoglycosides placed in Category C: "Firstly, with regard to the aminoglycosides (AGs), the CVMP's reflection paper recognises that in accordance with the categorisation criteria in the first AMEG report, all veterinary authorised AGs would be placed in Category 2. However, their use in veterinary medicine was considered to have a lower risk to human health compared with quinolones and 3rd- and 4th-generation cephalosporins. Therefore, it was suggested that a further stratification of the AMEG's categorisation should be considered." (Lines 431-443 AMEG)	specified. Agreed, a complete chapter is dedicated to routes of administration. The listing of routes of administration by preference, which should be used alongside the categorisation, is now also presented in the Summary.	
	It is unclear as to how veterinary usage of AGs was compared to quinolones and 3rd & 4th generation cephalosporins with regard to risk to human health, in the AG reflection paper? What methodology was used and how is this transparent in either the AG reflection paper or AMEG report? How was this part of the mandate given by CVMP for the AG reflection paper – in other words, was it part of the mandate to specifically compare AGs to quinolones and 3rd & 4th generation cephalosporins? In the AG reflection paper it states the following "The objective of the reflection paper is therefore to critically review the current knowledge on the usage of AGs, resistance development and the potential impact of this resistance on animal and human health." It seems a daunting task to compare AGs to quinolones and 3rd & 4th generation cephalosporins given that there are totally different mechanisms of resistance involved in AGs, quinolones and 3rd & 4th generation cephalosporins. Also, different indications for use in veterinary medicine, different levels of consumption and resistant rates. How was this factored into the comparison to different antimicrobial classes? The AMEG's	This comment is not relevant for the AMEG advice, but for the reflection paper on Aminoglycosides. WHO and OIE differentiate between quinolones and 3rd /4th generation Cephalosporins, that are classified as being the Highest priority CIA, and aminoglycosides (CIAs).	

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	own assessment of likelihood for transfer of resistance genes and resistant bacteria via different mechanisms from Table 3, scores aminoglycosides as high for all columns in table. **Macrolides** Previously the AMEG report 2014 concluded that the Macrolide class was placed in Category 1 (no restrictions). What has changed since 2014 that should be taken into account, as per the EC mandate includes: - WHO has published an updated list of critically important antimicrobial agents for human medicine (WHO, 2016). - WHO published a guideline on use of medically-important antimicrobials in food-producing animals (WHO, 2017). - As part of the WHO 2017 review, a new categorisation of antibacterials into three groups was specified: o ACCESS – 1st & 2nd choice antibiotics for the empiric treatment of most common infectious syndromes; o WATCH – antibiotics with higher resistance potential and should be limited to a small number of syndromes or patient groups; o RESERVE – antibiotics to be used mainly as 'last resort' treatment options. - OIE published an updated list of antimicrobial agents of veterinary importance (OIE, 2018). - Updated information from ESVAC about the EU sales of veterinary antimicrobials - Updated information from an EU antimicrobial resistance surveillance program (EFSA) of both indicator and zoonotic pathogens. - New peer-reviewed published scientific papers As a result of the AMEG 2014 report, the RONAFA (2016) report did not consider macrolides as critically important antimicrobials and thus the RONAFA recommendations do not apply to macrolides (EMA-European Medicines Agency and EFSA-European Food Safety Authority, 2017. EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA). [EMA/CVMP/570771/2015]. EFSA Journal 2017;15(1):4666, 245 pp. doi:10.2903/j.efsa.2017.4666). Thus, the primary change since the 2014 report is regarding the Macrolide class of antimicrobials as not only WHO CIAs, but also highest priority critically important antimicrobials. WHO CIAs are further discussed in a recent	All the information mentioned here has been taken into account.	

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	WHO guideline about medically important antimicrobials in food animals (WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.), where HPCIA classes (e.g. macrolides) are not recommended for prevention/prophylaxis or control/metaphylaxis, or first line treatment (as recommended in the AMEG 2014). In the new AMEG document, it reads: **"Category C** ("Caution") was therefore added in this report as an intermediate category. This category includes antimicrobial classes listed in different categories by WHO, including macrolides, which are listed by WHO as a 'highly prioritised CIA'. "There are in general alternatives in human medicine in the EU but there are few alternatives in veterinary medicine for certain indications." The proposal of placing macrolides in AMEG Category C may be at risk of offering arguments for not reducing the usage of macrolides via the oral route in animal productions (especially in pigs and poultry), which negatively impacts resistance towards macrolides in Campylobacter and other zoonotic Gram negative (*Salmonella*), Gram-positive (LA-MRSA) and opportunistic pathogens (*E. coli*) to humans. Also, the Category C for Macrolides also includes "**those (sub)classes which are not authorized in veterinary medicine in the EU**" (Lines 1045-1046 AMEG). These non-authorised Macrolide subclasses are NOT named in this AMEG report but would presumably include the new generation macrolides that are essential to human medicine (e.g. azithromycin, clarithromycin, etc …) and used off-label in companion animals (e.g. foals). It is unclear as to why these non-authorised macrolide subclasses are the exception to the rule of Catergory A and included in Category C. The main arguments/ brought for "few alternatives" for macrolides in veterinary medicine is for "*Lawsonia intracellularis* infection". *Lawsonia intracellularis* is a difficult organism to work with in standard laboratories where antimicrobial sensitivity is rarely performed. Diagnosis is typically via PCR tests. Thus, the potential exists to overuse macrolides for Lawsonia infections in pigs since prudent-use is difficult to apply. Additionally, in general and in the specific case of macrolides, the document does not take into account that valid alternatives to antibiotic "prevention, metaphylaxis or even treatment" with macrolides are available for porcine ileitis, such as attenuated and inactivated vaccines. It is worth noting that vaccines for immunization against *L. intracellularis* infection are available on the EU market (e.g. Enterisol Ileitis Vet), and more are currently under regulatory procedures. Also, tetracyclines can be used for *L. intracellularis* disease in pigs. The same arguments as above also apply to *Mycoplasma spp*. infections in poultry. A further justification for macrolides is stated in Table 4 as follows, "For the treatment	It should be noted that the status of Macrolides has changed, moving from the previous AMEG category 1 to the new category C 'Caution'. WHO do not categorize the different sub classes of Macrolides differently. In the updated AMEG document the ketolides have been separated into Category A. It is noted that alternative preventive treatments exist for certain animal diseases, but in terms of the categorisation, the criterion relates to alternative **antibiotics** to be used when there is disease outbreak when preventative measures have failed,	

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	of zoonotic pathogens (mainly *Campylobacter* spp.) in humans, there are alternative antimicrobials such as fluoroquinolones, although fluoroquinolone resistance in *Campylobacter spp.* is high in most EU/EEA countries.". Ciprofloxacin-resistant and ampicillin-resistant *Campylobacter* is already common throughout Europe and if macrolide resistance spreads then this would further compromise public health (Florez-Cuadrado D, Ugarte-Ruiz M, Quesada A, Palomo G, Domínguez L, Porrero MC. Description of an erm(B)-carrying Campylobacter coli isolate in Europe. J Antimicrob Chemother. 2016 Mar;71(3):841-3. doi: 10.1093/jac/dkv383.). Also, it is unclear if this statement about fluoroquinolone use for Campylobacter is consistent with other parts of the AMEG report, noting the following: - "Vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), as well as fluoroquinolone-resistant *Campylobacter* spp. and *Salmonella* spp., were listed among antimicrobial-resistant bacteria for which R&D of new effective antibiotics is of high priority." (Lines 374-377 AMEG) Macrolide resistance and it is also an emerging problem in *Salmonella* spp. (and *E. coli*) from animal productions in EU. Azithromycin (registered for human use only) has been chosen as the prototype macrolide antibiotic by the harmonised AMR monitoring according to the EU legislation. In some cases, azithromycin resistance in *Salmonella spp*. in broilers reaches 6% (Portugal) and 8% (Germany) in 2016. In indicator *E. coli*, it exceeds 10% in some EU countries (See Table 17, p. 81 and Table 45, p. 179, respectively, of the EU Summary Report AMR 2016 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5182). Thus, the arguments are unsatisfactory for placing macrolides in Category C, where they should be categorized the same as other HPCIAs. **Aminopenicillins alone (without inhibitor)** The main criteria for placing Aminopenicillins alone (without inhibitor) appears to be based on a Aminopenicillin Reflection Paper written by AWP. The Aminopenicillin Reflection Paper is not finalised and thus unclear as to why the conclusions are accepted at this time. Also, it is worth pointing out that the Aminopenicillin Reflection Paper does NOT actually recommend that aminopenicillins alone (without inhibitor) to be placed in Category D of the new AMEG classification system. Instead, the Aminopenicillin Reflection Paper concludes that:	or have not yet been applied. (See clarification section 3.3). See additional rationale regarding the categorisation of macrolides in Table.4. The CVMP/AWP's reflection paper	

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	- "The significance to public health of additional aminopenicillin resistance transferred from animals is considered to be low." (Lines 1582-1583) HOWEVER, "Considering that aminopenicillin resistance is at a very high level in some organisms and that aminopenicillins have been extensively used for decades both in animals and humans, it is currently **impossible to estimate** to what extent the use of these substances in animals, could create negative health consequences to humans at the population level." (Lines 123-126) - "All these factors should be taken into account for the AMEG's categorisation, which is currently under review. It is suggested that the AMEG could give consideration to a further stratification of the categorisation to allow a distinction in the ranking between those substances currently in Category 2 (fluoroquinolones, 3rd- and 4th-generation cephalosporins and colistin, for which there are fewer alternatives) and the amoxicillin-clavulanate combinations, and between the latter and the straight aminopenicillins. Amoxicillin-clavulanate has a wider spectrum and thus it is likely that it has higher chance to select multidrug resistant organisms compared to aminopenicillin alone." - "In case accumulating evidence from future scientific research indicates that veterinary use of aminopenicillins poses an added threat to public health due to animal-to-human resistance transfer, it could then be considered if a distinction in the categorisation should be made between straight aminopenicillins and narrow-spectrum penicillins" (Lines 174-177) It is unclear as to why the AMEG has interpreted these conclusions as justification for aminopenicillins alone (without inhibitor) in Category D. Furthermore, the Amino RP concludes that "The significance to public health of additional aminopenicillin resistance transferred from animals is considered to be low." However, the AMEG's own assessment of likelihood for transfer of resistance genes and resistant bacteria via different mechanisms from Table 3, scores aminopenicillins (with inhibitor) as high for all columns in table and aminopenicillins (without inhibitor) are not assessed in the table. It is unclear as to how the aminopenicillins (with inhibitor) scores high in Table 3, but aminopenicillins alone (without inhibitor) is interpreted by AMEG as Category D or concluded in the Amino RP as either 'low' probability of transmission OR 'impossible to estimate', when it is the same resistant mechanisms that could be selected and transmitted with either aminopenicillins (with or without inhibitor) (please see	has not been finalised due to the temporary suspension of certain EMA activities. The comments received during the consultation on the reflection paper will be addressed within that procedure when these activities resume. The differentiation in categorisation implies that use of Aminopenicillins without inhibitors is preferred over use of Aminopenicillins with inhibitors. Please see the updated rationale in Table 4.	

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	comments on the Aminopenicillin Reflection Paper). The major faults of the Aminopenicillin Reflection Paper, in the current version, concern the Conclusions that are not consistent with the evidence presented as well as other knowledge about aminopenicillins (please see comments on the Aminopenicillin Reflection Paper). In general, the reflection paper is not balanced and should include points of raising awareness to the possible misuse of aminopenicillins in an animal Health and a One Health perspective. Lack of balance of the RP is further evident by not examining the international scientific literature for evidence of the risk of transfer of relevant resistance from animals to humans. Also, there are examples where the RP is not consistent (or goes beyond) with the mandate given by the CVMP. For example, "…, based on the extent of use of these drugs in humans, the major resistance selection pressure in human pathogens caused by aminopenicillin use in European countries can be considered to be due to human consumption of these or other related beta-lactam drugs." (Lines 1543-1546 Aminio RP). The CVMP mandate was specifically for risk profiling of veterinary use of aminopenicillins on human and animal health. It was not about human medical use of aminopenicillins on human health. What methodology was used to assess EU human aminopenicillin data in relation to EU aminopenicillin resistance patterns? How is this methodology transparent in the RP? Does this specifically have an impact on human clinical isolates or the general human population? On the issue of stratification of aminopenicillin classes, the stratification of aminopenicillins is not justified in the Aminopenicillin Reflection Paper due to issues identified: - Stratification will lead to the same or higher consumption of aminopenicillins alone that also contributes to the same high EU resistant rates in animals or higher. - Evidence suggests that aminopenicillins alone can select for the same resistant bacteria as aminopenicillin combinations (with inhibitor). Evidence to the contrary has not been presented in this RP. For example, currently 3rd & 4th generation cepahlosporins are restricted in the EU for food animals. The benefits of these initiatives will be counter-acted by the high use of aminopencillins that can select the same resistant genes. - Stratification of aminopenicillins is not done in the WHO classification and since aminopenicillins are WHO CIAs then they are not recommended by WHO for mass medication purposes or first-choice treatments. - Aminopenicllins alone are more likely to be given both orally and for mass medications. This creates the highest risk for resistance selection and transfer and	Comments relevant for the aminopenicillins reflection paper, not for the AMEG report. The rationale for the AMEG categorisation of aminopenicllins with/without inhibitors has been clarified in Table 4 of the advice.	

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	contrary to statements made in this RP: ○ "Aminopenicillins are capable of selecting both aminopenicillin resistance and also resistance to other antimicrobials in the gut microbiota of dogs (Edlund and Nord, 2000; Grønvold et al., 2010). In a mouse model, oral *versus* injectable (i.v.) ampicillin significantly resulted in more ampicillin-resistant strains and resistance genes (*bla*CMY-2) in the gut microbiota (*E. coli*) (Zhang et al., 2013)." (Lines 1152-1155) ○ "Of importance, where oral antimicrobial treatments are given to large groups, the resistome in faecal indicator bacteria and pathogens in livestock is much more vulnerable to selection pressure compared to animals kept individually, or in small groups, and if injectable treatment is given (Catry et al., 2016). Therefore interventions to minimize the effect of oral administration of antimicrobials on AMR in the commensal bacteria and target pathogens should be considered." (Lines 1155-1160) On the issue of "In case accumulating evidence from future scientific research indicates that veterinary use of aminopenicillins poses an added threat to public health due to animal-to-human resistance transfer, …" (Lines 174-177), the following can be stated: - However, the AMEG report itself acknowledges the following: "As an example, co-selection exists between similar compounds such as amoxicillin and 3rd-generation cephalosporins (Persoons et al., 2012). Another example is tetracyclines, which facilitate spread of MRSA in livestock (Price et al., 2012). In other words, restrictions on one class alone might not have the desired impact because of co-selection of AMR." (Lines 261-264 AMEG) - It is further unclear as to why this statement about accumulating evidence is stated in the Amino RP. In the same Amino RP it is stated that "…, it is currently impossible to estimate to what extent the use of these substances in animals, could create negative health consequences to humans at the population level." (Lines 123-126). However, it is not clearly stated in the Amino RP as to what evidence is needed. Without specifying what is needed then any additional evidence is likely to also be deemed as 'impossible' to assess the impact of animal-associated aminopenicillin-resistance on public health. - Despite the 'impossibility' to conclude on the issues of zoonotic and transmissible resistance between animal and human bacteria clones, the Amino RP provides several examples of such transmission between animals and humans (please see		

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	comments on the Amino RP). **2) Description/Criteria for the four Categories** The AMEG reports states that it refines and builds on the previous AMEG categorisation. The reflinement includes new elements introduced into the methodology. Although several key words are mentioned with respect to the methodology of the AMEG classification system, it is not described in sufficient detail that the results could be repeated by an independent expert group. Limitations of the methodology are not outlined. Other limitations noticed include: - the WHO guideline about medically important antimicrobials in food animals does not appear to be consistently considered for the categorization (WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.). - Route of administration is not part of the methodology refinement as requested in the EC mandate. - Common use (determined from ESVAC sales data) for tonnes of bulk animal feed or common drinking water supply is not considered, whereby healthy animals are not separated from diseased. Also, it is worth noting that three WHO CIA classes are placed in Caetgory C that are also used in human medicine to treat tuberculosis (e.g. Aminogycosides, Macrolides, Rifamycins). Tuberculosis is infrequently treated in companion animals, with the potential for resistance selection. *Rhodococcus equi* is now recognised in immunocompromised people where several isolates share the same virulence factors as horse (foals) infections	Chapter 4 of the report lays out the criteria applied. The supporting evidence is included in Tables 2, 3 and 4. The final categorisation was based on the judgement of the AMEG, and therefore relies on the opinion of the experts involved. The WHO guideline does not address categorisation of antimicrobials, but makes recommendations on the use of antimicrobials according to their WHO CIA listing. Consistency with the WHO guideline is ensured when the WHO recommendations are considered in full. The route of administration has been addressed in chapter 3.3.1 and a listing of preferred options is provided. ESVAC data cannot give an indication of the actual use.	

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	(e.g VapA gene). Rifampin resistance is recognised in horse (foals) infected with *Rhodococcus equi*. Rifampin resistance is an increasing issue in MRSA in Europe (Bongiorno et al. 2018 Burden of Rifampicin- and Methicillin-Resistant Staphylococcus aureus in Italy. Microb Drug Resist. 24(6):732-738. doi: 10.1089/mdr.2017.0299.). ***Category A: "Avoid"*** The criteria for this category is simply stated as those antimicrobial (sub)classes **not authorised** in veterinary medicine. Also, it is worth noting that this basic definition (antimicrobial classes NOT authorised in veterinary medicine) is not strictly applied in the AMEG categorisation system. For example, Category C also includes the Macrolide class "**and those (sub)classes which are not authorized in veterinary medicine in the EU**" (Lines 1045-1046 AMEG). These non-authorised Macrolide subclasses are NOT named in this AMEG report but would presumably include the new generation macrolides that are essential to human medicine (e.g. azithromycin, clarithromycin, etc …) and used off-label in companion animals (e.g. foals). It is unclear as to why these non-authorised macrolide subclasses are the exception to the rule of Catergory A. However, it is actively mentioned that antimicrobials in this category can be used according to current EU 'cascade' legislation in veterinary medicine (e.g. off-label). Also, within the description of this category is the following text: "In the event of a future Marketing Authorisation application for a veterinary medicinal product containing a substance in this category, the benefits of use of the proposed veterinary medicine in animals are considered alongside a risk assessment that takes account of 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." (Lines 992-1004 AMEG) It is unclear as to the need of this text in the description of this Category that has the title and message of "Avoid". Thus, it is unclear as to how the concept of "Avoid" is	See previous comments regarding the criterion for Category A. Ketolides and Rifamycins (excluding rifaximin) have been placed in Category A. Macrolides (excluding ketolides) were maintained as one class as the main mechanisms of resistance are the same for all substances within this class. See updated Table 4 for rationale.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	represented, if at all, in this category when it is actively mentioned that these antimicrobials can be used off-label and only remain in this category unless the CVMP agree to a positive benefit:risk for authorisation in veterinary medicine. Certainly, there would be major concerns for public health for off-label and/or veterinary authorisation of certain antimicrobial classes in this category (oxaziladones, carbapenams, glycopeptides). It is unclear as to what should be avoided in this category. The AMEG concludes the following for this category: "*The extent of use of these classes, and hence overall selection pressure for AMR,* would be low provided the restrictions detailed in the prescribing cascade are complied with." (Lines 990-991) It is unclear as to how the AMEG could make this conclusion. No evidence is presented. It could be that low numbers of animals would potentially be treated if 'cascade' restrictions are complied with and hence low selection pressure for AMR. However, the following should be noted: - There is no EU data collected on off-label use of antimicrobials in veterinary medicine. It is unclear as how common off-label usage is in the EU. - Off-label use can itself lead to AMR because in many cases there are no clinical trials or basic PK/PD information for appropriate dosing regimens in most animal species. - ESVAC does not collect data on veterinary usage of non-authorised antimicrobials in this class. Veterinary consumption is unknown. - Food animals do NOT represent a small population for antimicrobials in this class for which an MRL (maximum residue limits) have been granted (e.g. Streptogramins in poultry) and thus the possibility to use off-label. - Current examples exist of resistance to some of these classes in animals (companion and food animals) in the EU (e.g. carbepenams, vancomycin). The significance of Category A antimicrobial classes are further downgraded in the AMEG report since part of the definition of inclusion into Category C is "The antimicrobial selects for resistance to a substance in Category A through specific multiresistance genes" (Lines 1020-1021). Category C antimicrobial classes are open for more common use in veterinary medicine (including healthy animals as metaphylaxis) compared to antimicrobial classes in	The cascade should be used in exceptional circumstances only. Provided that the legislative provisions of the cascade are followed, use of these substances will be low. The only criterion for placing certain classes in A is that they are not authorised for vet use. MRLs can only be set for substances for which there is intent to submit a MA application and therefore a product authorisation is anticipated.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	Category B that are supposed to be used under some type of restriction. Such multi-resistant bacterial genes that code for resistance to BOTH Category C and Category A antimicrobial classes, and present in animal bacterial isolates, include: *cfr* gene - encodes a 23S rRNA methyltransferase - resistance to Category C antimicrobial classes (Amphenicols, Pleuromutilins, Lincosamides) as well as Category A antimicrobial classes (Oxazolidinones, and Streptogramin A). - In LA-MRSA (EU) at a low level, emerging in *Campylobacter jejuni* (USA) *optrA* gene - ATP-binding cassette (ABC) transporter gene - resistance to Amphenicols (Category C) and Oxazolidinones (tedizolid) (Category A). Thus, use of these Category C antimicrobial classes (Amphenicols, Pleuromutilins, Lincosamides) can lead to selection and persistence of resistance genes/bacteria in animals coding for Category A antimicrobial classes (Oxazolidinones, and Streptogramin A), despite the fact that Category A antimicrobial classes are not authorized in veterinary medicine. Thus, the selection for AMR of Category A antimicrobial classes would be higher than stated in the AMEG description of Category A, when certain Category C antimicrobial classes are also factored into the assessment (i.e. it is NOT just off-label use of Category A that contributes AMR selection pressure of Category A antimicrobial classes). For example, it is acknowledged by the AMEG in the description of Category C that "Antimicrobials placed in this category present a higher AMR risk for human and/or animal health than antimicrobials placed in Category D, as assessed by AMEG." (Lines 1022-1023). The placement of these antimicrobial classes in Category C increases the risk of resistance selection and persistence to antimicrobial classes in Category A. ***Category B: "Restrict"*** This category includes classes in WHO HPCIA (Highest priority critically important antimicrobials), with the exception of macrolides and those (sub)classes which are not	This is why these substances are in category C, rather than D.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	authorized in veterinary medicine in the EU (Lines 1045-1046 AMEG). For this category the AMEG concludes the following: "Risk to public health resulting from veterinary use needs to be mitigated by specific restrictions. *Risk management measures: These antimicrobials should be considered only for the treatment of clinical conditions when there are no alternative antimicrobials in categories C or D that could be effective. Their use should be based on the results of antimicrobial susceptibility testing,* ***whenever possible****."* (Lines 1010-1014 AMEG) However, it is not mentioned in the AMEG report that currently in the EU there are several licensed quiniolones and polymyxins VMPs that are also indicated for healthy animals (metaphylaxis). Thus, veterinarians have a legal right currently in the EU to administer certain quiniolones and polymyxins VMPs for use as BOTH treatment and metaphylaxis, including administration to the common drinking water supply, where healthy animals are not separated from diseased. There is no suggestion/discussion in the AMEG report as to how a 'treatment only' restriction would be applied/accomplished for antimicrobial classes in Category B, given the current EU authorised indications for these VMPs. Thus, it is unclear as to how the word "restrict" is represented in the description of Category B. There is no acknowledgement in this category of the WHO guideline about medically important antimicrobials in food animals (WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.), where HPCIA classes are not recommended for prevention/prophylaxis or control/metaphylaxis. It is unclear as to the meaning of the term 'group treatment' in the Table 4 descriptions of Category B antimicrobial classes. Most experts would conclude that 'group treatment' is synonymous with 'metaphylaxis'. It is important to use the same term, as will be used in the upcoming new EU Veterinary legislation, throughout the document. The term	The definition of metaphylaxis is not the treatment of healthy animals. The definition in the new regulation (EU) 2019/6 is the following: *"metaphylaxis' means the administration of a medicinal product to a group of animals after the diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk which may already be subclinically infected****;"*** The WHO guideline is quoted in part, exemptions are foreseen "To prevent harm to animal health and	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	'treatment' is typically reserved for the administration of medicine to diseased individuals. ***Category C: "Caution"*** For this category, it is stated that the criteria include those antimicrobials for which there are alternatives in human medicine for their indications but which comply with one or both of the following criteria: • For the veterinary indication under treatment, there are few or no alternatives belonging to Category D. • The antimicrobial selects for resistance to a substance in Category A through specific multiresistance genes	welfare, exceptions to recommendations 4a and 4b can be made when, in the judgment of veterinary professionals, bacterial culture and sensitivity results demonstrate that the selected drug is the only treatment option. " Table 4 refers to '*Formulations for use in <group and> individual animals*…' The relevance is that 3/4G cephalosporins are available in formulations for individual treatment of animals only (e.g. injectables, intramammary tubes), whereas other Cat B classes are also available in formulations for group medication (premix, oral solution). The indication (treatment, metaphylaxis, prevention) does not consistently relate to one type of formulation.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	The Risk management measures stated include "These antimicrobials should only be used when there is no substance in Category D that would be effective." (Lines 1024-1025) Further risk management measures include that the AMEG report states that if certain bacterial genes (e.g. *cfr*, *erm* genes) are identified with increased prevalence in food animal isolates then AMEG will reconsider the classification. These genes have already been identified in EU food animal bacterial isolates. Unfortunately, *erm*-mediated macrolide resistance is a common feature in Gram-positive zoonotic pathogens such as LA-MRSA CC398, CC1, CC97, while emerging in *Campylobacter jejuni* and *C. coli*. High-level macrolide (azithromycin) resistance mediated by *mph* genes have been reported in the EU. It is unclear as to why the *mph* gene is not mentioned with the *erm* gene for the macrolide class. **What level (prevalence) of resistance will initiate a change by the AMEG? How will this be measured/monitored? Which bacterial species?** Previously, the presence of the *mcr-1* gene mediating transferable colistin (polymyxin) resistance in EU food animal bacterial isolates triggered a change in AMEG recommendations, without waiting for an increase in prevalence. ***Category D: "Prudence"*** Category D includes antimicrobials where there are alternative treatments in human and veterinary medicine for their indications and that do not select for resistance to Category A through specific multiresistance genes. Antimicrobials placed in this category present a lower AMR risk than antimicrobials placed in Category C as assessed by AMEG and should be used where possible as <u>first line treatments</u>. It is deeply concerning that a WHO (HICIA) antimicrobial class (aminopenicillins without inhibitor) is included in this Category and thus open for "first line" treatments including use in healthy animals (prophylaxis/metaphylaxis). This is NOT consistent and in balance	In the revision *mph* and *erm* genes are included in Table 2 for macrolides. See new chapter 6 that has been added to advise regarding the review of the categorisation. In addition to a change in AMR prevalence monitored under Directive 2003/99/EC [CID 2013/652/EC], a change in the categorisation will also be dependent on reports of public health significance as detailed in the final paragraph in chapter 6.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	with the WHO guideline about medically important antimicrobials in food animals (WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.), where HICIA classes are not recommended for prevention/prophylaxis or control/metaphylaxis OR "first line" treatment. This is not acknowledged by the AMEG. It states that antimicrobial classes cannot be Category D if they select for resistance in Category A. Carbapenam (Category A) resistance is present at a low level in companion and food animals in the EU. For example, three OXA-23-like enzymes: OXA-23, OXA-27, and OXA-146 are able to hydrolyze oxyiminocephalosporins, aminopenicillins, piperacillin, oxacillin, and aztreonam in addition to the carbapenems (Afzal-Shah M, Woodford N, Livermore DM. 2001. Characterization of OXA-25, OXA-26, and OXA-27, molecular class D β-lactamases associated with carbapenem resistance in clinical isolates of *Acinetobacter baumannii*. Antimicrob. Agents Chemother. 45:583–588. http://dx.doi.org/10.1128/AAC.45.2.583-588.2001.; Paton R, Miles RS, Hood J, Amyes SGB. 1993. ARI 1: β-lactamase-mediated imipenem resistance in *Acinetobacter baumannii*. Int. J. Antimicrob. Agents 2:81–88. http://dx.doi.org/10.1016/0924-8579(93)90045-7.). Furthermore, VIM (Verona integron-encoded metallo- β-lactamase) both hydrolyse all β-lactams except monobactams, and evade all β-lactam inhibitors and have been detected in food animals in the EU (Fischer, J., M. San José, N. Roschanski, S. Schmoger, B. Baumann, A. Irrgang, A. Friese, U. Roesler, R. Helmuth, and B. Guerra, 2017. 'Spread and persistence of VIM-1 Carbapenemase-producing Enterobacteriaceae in three German swine farms in 2011 and 2012', Veterinary microbiology, Vol. 200 pp.118-123.). Even though use of aminopenicillins in animals is unlikely responsible for the introduction of carbapenemase resistance in animals, the use of aminopenicillins (especially as first line treatment) can select for persistence of carbapenemase resistance in animals. This is in violation of the AMEG criteria for Category D and thus aminopenicillins (without inhibitor) cannot be included in Category D. Also, it is unclear as to why it is only resistance to Category A antimicrobial classes that constitute part of the exclusion criteria for antimicrobial classes to be placed in Category	Regulation 2019/6 includes provisions for use of antimicrobials for prophylaxis and metaphylaxis. As noted in Chapter 4 of the AMEG advice, these risk management measures should still be applied.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	D. For example, if antimicrobial classes in Category D also selected for resistance bacteria/genes for Category B antimicrobial classes then this would also be of equal major concern/s for EU public health. In that context, aminopenicillins (without inhibitor) (Category D) select for resistance to 3rd & 4th generation cephalosporins (Category B) (e.g. *CTX-M* and *AmpC* genes). Also, preliminary work shows that bacitracin (Category D) can select the *mcr-1* gene coding resistance to polymyxins (Category B) (Xu F, Zeng X, Hinenoya A, Lin J. 2018. The MCR-1 confers cross-resistance to bacitracin, a widely used in-feed antibiotic. mSphere 3:e00411-18. https://doi.org/10.1128/mSphere.00411-18.). 3) **Recent deletions of text and the unfulfilled EC mandate (route of administration)** In the previous AMEG (2014) report a system, described in Table 3 of the AMEG report, was developed to assist the classification of antimicrobial classes according to their likelihood for transfer of resistance genes and resistant bacteria via different mechanisms. This was based on based on certain criteria: - **Transmission of resistance through successful clone(s).** Defined as the vertical transfer of a resistance gene through the parent to the daughter bacterium in a successful, highly disseminated drug-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). - **Horizontal transmission** Defined as a transfer of resistance gene by means of mobile genetic elements. Probability (1 to 3). - **Co-selection of resistance**. Defined as a type of resistance where use of one antimicrobial favours the occurrence of resistance to other antimicrobial classes or sub-classes with a different spectrum. In this table, co-selection is limited to situations when different resistance genes are co-located on one mobile genetic element or are located in a genetic environment together with other resistance genes in such a way that there is a potential for mobilisation (e.g. IS-elements or resistance islands). A special case when one gene mediates resistance to several unrelated antimicrobial classes is also included. Probability (1 to 3).	The aim of the Categorisation is to present a pragmatic stratification of antibiotics. To this extent, there is particular concern regarding selection for resistance to substances in category A, and through certain resistance genes as highlighted in the rationale in Table 4.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	- **Transmission of resistance through zoonotic or commensal food-borne bacteria**. Defined as transmission of resistance through zoonotic pathogens (e.g. *Salmonella* spp., *Campylobacter* spp., MRSA, *E. coli* (VTEC/STEC) or transmission of resistance through commensal food-borne bacteria (e.g. *E. coli*, *Enterococcus* spp.). Probability (1 to 3). - **Similarity of resistance**: Genes: defined as a similar resistance gene detected in bacterial isolates of animal and human origin; Mobile genetic elements: defined as a similar resistance-conferring mobile genetic element detected in bacterial isolates of animal and human origin; Drug-resistant bacteria: defined as a similar bacterium harbouring a resistance gene (either chromosomally or mobile genetic element-encoded) of animal and human origin. Probability (1 to 3). The individual scores for each criteria per antimicrobial class were summed up to a semi-quantitative statement about the likelihood of transmission of known resistant determinants for the antimicrobial class as Low/Medium/High. The new AMEG classification was meant to include this previous assessment and build on other refinements. After completing the new AMEG classification and submission to CVMP/CHMP this semi-quantitative assessment (Low/Medium/High) has been deleted, with new statements added. - "In addition, further thought was given to the criterion on the likelihood of transfer of resistance. It was questioned if the scoring of the factors taken into consideration for this criterion could be integrated to provide a reliable qualitative assessment. It was also proposed that further consideration should be given to specific mechanisms of resistance/genes that might have particularly important consequences for human health. These elements are discussed in section 3.4." (Lines 451-455 AMEG) - "In the first AMEG report, for each antimicrobial class, influencing factors including those above were assigned a numerical score and crudely integrated to give a qualitative estimate of the overall probability of resistance transfer. For this		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	updated report, the AMEG agreed that these values (see 3.4.2 for explanation), although individually informative for each factor, are not 'mathematically scaled' and that there is no validation that they can be combined to predict the probability of resistance transfer. The qualitative assessment (high, medium, low) based on this information has therefore been removed from the tables in this updated advice. While the AMEG agreed that a qualitative estimate of the overall probability of resistance transfer should not be incorporated into the approach to categorisation of individual AM (sub)classes, the AMEG was of the view that account should be taken of specific resistance genes associated with certain classes where transmission of these specific resistance genes could have important consequences for human health (that is, where these are mobile and confer multi-resistance to antimicrobials that are 'last resort' or used solely in human medicine). Resistance mechanisms are documented in Table 2 and where particularly relevant for the final categorisation they are discussed in the 'rationale' column for each class in Table 4. - It was agreed that the criterion should be amended as follows: ~~*The*~~ *Knowledge of factors influencing the likelihood and possible consequences of AMR transfer from animals to humans. In the new categorisation individual mechanisms of resistance have been considered more specifically for e.g. those genes associated with mobile multiresistance.*" (Lines 821-838 AMEG) This raises some concerns. It is unclear as to the impact this assessment of the likelihood of transmission of known resistant determinants had on the new AMEG classification system and why this was deleted at this late stage. It is unclear if consideration was given to that while the semi-quantitative assessment (Low/Medium/High) may not have influenced expert opinion, it does provide a useful simple description for readers about a very complex topic (likelihood of transmission of known resistant determinants). This also suggests a shift in assessment between the AMEG 2014 and this new classification system	See explanation in chapter 3.4, as	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	which is not well described in the methods. If the shift is based on an emphasis of resistant determinants that may impact human health and/or "last resort" antimicrobials then it is unclear as to why this did not have more impact of the decision for aminopenicillins alone (Category D), macrolides (Category C) and antimicrobial classes that select for the *cfr* gene. Route of administration was requested in the EC mandate to be part of the refinements for the updated AMEG classification system. This task was not performed, as stated in the AMEG report: - "Given that AMs in each antimicrobial (sub)class are available in a number of different formulations and for administration by different routes, the AMEG chose not to include the route of administration as an additional criterion for the categorisation. It was the view of the group that to consider the relative AMR risk for all the different formulation/antimicrobial class combinations within the categorisation would be highly complex and difficult to evidence." (Lines 687-691) However, there are statements in the AMEG report that support the importance of route of administration as a major part of the likelihood of selection and transmission of known resistant determinants, noting the following: - "Across the EU as a whole, approximately 90% of all antimicrobials prescribed to livestock are given *via* the oral route (EMA/EFSA, 2017; EMA/ESVAC, 2017; Filippitzi et al., 2014; Timmerman et al., 2006)," (Lines 529-530 AMEG). - "For medication delivered via the drinking water supply or milk, the final concentration can be highly variable and may be further influenced by factors such as water hardness, pH, temperature, light (Luthman and Jacobsson, 1983) and complex formation (with e.g. Ca^{++} in the milk replacer diet). It may, therefore, be difficult to control dosing so that it is consistent with the Summary of Product Characteristics (SPC) of the VMP. Further, the same equipment may also be used	detailed by the interested party. The route of administration was an example of possible refinements. Extract from the mandate: *Further refinements of the criteria for the categorisation (e.g. including route of administration*)". The route of administration has been considered, and its importance is acknowledged, see previous comments. The listing of routes of administration, in order of	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	for the production, storage and/or transport of both medicated and unmedicated feed, with the potential carry-over of antimicrobial residues (Filippitzi et al., 2016).” (Lines 535-541 AMEG) - “Other factors contributing to variable intake of oral group medications include a relatively poor control over intake due to hierarchy in the flock/group, a lower intake by diseased animals, uncertain duration of therapy and potential for cross contamination of feed.” (Lines 577-579) - “Furthermore, the withdrawal time (the minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that such foodstuffs do not contain residues in quantities harmful to public health) is in general longer for VMPs administered by injection compared to VMPs administered orally.” (Lines 593-597 AMEG) - “Nevertheless, findings demonstrating substantial benefits of injectables over oral administration in relation to development of antimicrobial resistance in the digestive tract have been published in controlled studies in other animal species (Bibbal et al., 2007; Chantziaras et al., 2017; Checkley et al., 2010; Wiuff et al., 2003). Further research is needed into the impact on the selection of AMR in gastrointestinal microbiota by newer antimicrobial substances with long half-lives that are administered as a single injection (e.g. certain macrolides) (Zaheer et al., 2013). On a larger scale, microbiome studies have shown oral antimicrobials to have detrimental and persistent effects on the gut (Zaura et al., 2015). For this reason and also due to high livestock densities that facilitate rapid exchange of multi-resistance within and between production cycles (Heuer et al., 2002), the routine use of oral (group) medication has been questioned (Catry, 2017).” (Lines 610-619 AMEG)	preference associated with their potential impact on AMR has been included in the Summary and it is noted that this should be used alongside the Categorisation.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	- "The "Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety" (RONAFA report) stated that oral administration of antimicrobials in livestock is of particular concern in terms of promoting the development of AMR due to the high exposure of gastrointestinal commensal bacteria, and the sometimes prolonged duration of treatment or exposure, especially for products administered in feed (EMA/EFSA, 2017)." (Lines 620-664 AMEG) Thus, route of administration, especially oral, does appear to be a major factor in the likelihood of transmission of resistant determinants. The most common examples of zoonotic bacteria or transfer of bacterial genes via food of animal origin are from bacteria of the gut microbiota of animals (e.g. Salmonella, Campylobacter, *E. coli*). The main exception is LA-MRSA that is more transferred via direct contact. When "…, approximately 90% of all antimicrobials prescribed to livestock are given *via* the oral route (EMA/EFSA, 2017; EMA/ESVAC, 2017; Filippitzi et al., 2014; Timmerman et al., 2006)," (Line 530 AMEG), then it is unclear as to why it was route of administration was considered "different formulation/antimicrobial class combinations within the categorisation would be highly complex and difficult to evidence." (Lines 687-691). If 90% oral administration is dominanting the issue of route of administration then it is plausible that route of administration could have been given serious consideration in the catergorisation system. This might have influenced the placement of certain antimicrobial classes (e.g. aminopenicillins alone). Furthermore, ESVAC records data on VMP formulations per antimicrobial class to allow refinements of the impact of route of administration per antimicrobial class.		
4	We welcome the clarity that this document provides but we are concerned with the variation in categories between WHO, FDA, OIE, AMEG. We suggest that perhaps the formation of a number of different levels of categories as in this document gives retailers groups the opportunity to impose intermediary restrictions to	Variations in categories are inevitable as the objectives of the different classifications are different. For the AMEG, we have attempted	4.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	their competitive advantage.	to balance the impacts on animal and public health in a One Health perspective.	
6	- Good idea not to forbid any substance completely but to introduce a binding cascade/hierarchy. Suggested categorisation seems reasonable. - Good idea to expect more laboratory testing. - Both points can be difficult to check, as our experiences in Germany show (new TÄHAV since March 2018). Animal welfare demands effective treatment. - Guidelines could help with general decisions (lists of indications, list of possible sensitivity-tests). - Exceptions should be justified in writing by the treating veterinarian. - Hierarchy will improve awareness and careful use of antibiotics in animals and protect both animals and humans. - Changes in husbandry are necessary to improve health status. Reduction of the used amount seems also important.	Thanks for the comments.	5.
8	We are very concerned about the widening and all-inclusive nature of this document. The UK trout industry (and that in the rest of Europe) have few options for therapeutic antimicrobial usage, they have kept usage to a minimum, below that of more economic land based agriculture, they do not have any major resistance issues and drugs are still effective at the same levels as used 20 years ago. In UK we have only one drug actually licensed for trout – an oxytetracycline product, this and another containing amoxycillin are licensed in salmon, and florfenicol is licensed in salmon. All can be used on cascade which is vital. Possibly because the UK market is small manufacturers did not keep licenses for oxolinic acid, so this is currently brought into the UK on SIC from Denmark and Greece – again used on cascade although licensed in trout	The proposed categorisation does not propose any ban of the drugs mentioned as used in the aquaculture sector. The recommendation for category C is that these antibiotics should be only used if no substance in category D would be effective. Note that the categorisation should	6.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	in another country. Antimicrobials are all used in feed, therapeutically, at recommended dose rates for the recommended time periods, they are not used prophylactically or as growth promoters. Clinically these drugs have different uses (and my comments here affect trout in particular): Oxytetracycline has been used for many years and remains clinically useful and important against Flexibacteria/Flavobacteria, it is used occasionally on some sites for Aeromonas or Yersinia ruckeri problems but the large physical amount which has to be added to food is an issue. Amoxycillin is relatively little used, it requires large doses on feed and delivers poor clinical results although sensitivity is good. Florfenicol (listed as C/Caution as an amphenicol) is extremely useful in smaller fish, most <40g, where Flexibacteria/Flavobacteria is a major problem. Sensitivity is very good and it only requires a small physical amount to be added to feed (especially when compared to oxytetracycline. Oxolinic acid (a first generation, primary quinolone listed as B/restrict) is our mainstay for Aeromonas and Yersinia issues, it is used at standard dose rates for 10 days and produces an excellent clinical result. I understand that it is also used in salmon during the freshwater phase for similar gram-negative bacterial issues. These four drugs complete what we have available and losing any would be catastrophic in terms of disease and welfare. They have all been used for 35-40 years in UK and because that use was proper and veterinary regulated there are no systemic resistance issues to any of them within UK aquaculture. I believe that the same comment applies across Europe. A theoretical point	be used as one element when species-specific guidelines are developed. See Chapter 5 for detail.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	mutation risk may exist, but it is theoretical as it has not happened in 40 years and usage has fallen, not to zero because we do need it sometimes. In aquaculture metaphylaxis is normal, units of fish behave very much as one. Disease transmits through the 'shoal' easily, even with fish which are not naturally shoaling. The industry makes full use of such vaccines that are available, but over the last 3 years two have been lost and one other is under threat, this is because pharma chooses to manufacture bivalent/multivalent vaccines for salmon – used to great effect globally, rather than the simpler monovalent vaccines required for trout. Salmon attracts research, the smaller trout industry attracts less! Although the proposals in theory do not prevent use, merely asking for caution it would be naive to suppose that supermarkets will not seek to gold plate these recommendations by trying to prohibit their use. Usage is already restricted and done with caution, on veterinary direction only. Creating hurdles will encourage supermarkets to ask for bans to comply with their in-house standards. This will cause serious welfare problems. Recommendations which to be absolutely fair are already being observed by the industry and its veterinarians who already take great care prescribing because they already have such a limited arsenal of drugs available.		
9	Danish Agriculture and Food Council (DAFC) welcome the updated scientific advice on the impact on public health and animal health of the use of antibiotics in animals from European Medicines Agency (EMA). The proposal contains several positive elements, which	Thanks for the comments.	7.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	will promote a responsible use of antibiotics in animals. The DAFC fully recognizes that antibiotic resistance poses a serious threat to public health, and therefore the Danish agriculture and food sector is at the forefront of preventing antibiotic resistance and have for several years ago introduced a ban on the use of the highly prioritized antibiotics, colistin, fluoroquinolones and 3rd and 4th generation cephalosporins for treatment of infections in farmed animals. DAFC support the AMEG approach to classify the antimicrobials into four overall different categories allowing for additional criteria to be taking into account like the availability of alternative antimicrobials. We find that EMA with the classification into four groups have managed to find an appropriate balance between the risk of AMR to public health and the importance of the substance to animal health. We acknowledge the AMEG argumentation in line 130-138 that the categorization does not directly translate into a treatment guideline for use of antimicrobials in veterinary medicine but can be used as a tool by those preparing guidelines. However, we find that the categorization for two specific groups of antibiotics should be improved by taking into account the variety of species, type of production system and occurrence of resistance: **Classification of aminoglycosides** Aminoglycosides are classified as C in the AMEG-classification-scheme. We fully acknowledge, that aminoglycosides are important antibiotics for human infections with several bacteria, including Enterobacteriaceae and enterococci. However, the group of aminoglycosides is a highly diverse group of antibiotics, and some aminoglycosides are more important in human medicine than other aminoglycosides. Cross-resistance between different aminoglycosides is also variable as some resistance-mechanisms cause resistance towards several different aminoglycosides, and others are more specific. Danish clinical coli-isolates show close cross-resistance or co-selection between apramycin and	Spectinomycin has been moved to Category D as it is associated with a clearly different resistance mechanism. Moreover, WHO classified aminoglycosides as CIA while spectinomycin is classified as IA	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	gentamicin. But limited cross-resistance between gentamicin and the other aminoglycosides, streptomycin, neomycin and spectinomycin. The suggested antibiotics in class D are rarely useful for treating coli-infections, so in many cases only class C-antibiotics are a realistic choice. Diversifying the aminoglycosides, so streptomycin, neomycin and spectinomycin are in class D, and apramycin and gentamicin are in class C will provide a more beneficial risk-benefit ratio.	Streptomycin and neomycin have been kept in Category C as the mechanisms of resistance often are the same as for e.g. gentamicin. See previous comments.	
	Classification of quinolone In Denmark only two types of antimicrobial agents are approved for the treatment of fish in aquaculture: Oxolinic acid (quinolone) and a combination of sulfadiazine and trimethoprim. We fully acknowledge, that quinolones are important antimicrobial agents for treating many different infections in humans and are used against a wide variety of pathogens. However, a risk assessment carried out by the Danish Veterinary and Food Administration in 2017 concludes that the use of quinolones in marine aquaculture is assessed to constitute a low risk compared to how quinolones and fluoroquinolones are otherwise used in humans and for veterinary purposes and that quinolone resistance in marine aquaculture has not created and is not expected to create significant problems in foods or humans as the risk is deemed to be low. In Denmark the Water Framework Directive is fully implemented, which means that the use of different antibiotics is regulated for each fish farm as part of their environmental permit. It means that for each antibiotic treatment there is maximum amount of kg fish that can be treated. In many Danish fish farms this antibiotic specific limitation leads to a situation where only quinolones can be used for treatment of larger amounts of fish. We therefor encourage AMEG to take this species-specific situation for farmed fish into consideration and change the classification of oxolinic acid to group C allowing aquaculture to use this important quinolone. We have attached the risk assessment from the Danish	Since oxolinic acid can select for the same resistance genes that also code for fluoroquinolone resistance (e.g. *gyrA* gene) the AMEG does not agree to place oxolinic acid in Category C. A sentence has been added to Chapter 5 on the Use of the Categorisation to make reference that national policy and other legislative frameworks (e.g. the Water Framework Directive) should also be taken into account.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	Veterinary and Food Administration to our reply. If a change in classification of oxolinic acid to group C is not possible it is very important that it being highlighted that the use antibiotics from category B should not only be determined by antimicrobial susceptibility testing but can also be determined by restrictions for use of antibiotics introduced through the environmental regulation.		
10	Categorisation of all polymyxine while resistance problem is only with colistin (or polymyxin E) and not in polymixin B (only topical utilisation so a few selection and diffusion of resistant bacteria) High topical concentration is higher than MIC so it isn't probably to select bacteria There isn't any alternative in veterinary ophtalmology with bactericid antibiotic.	A separate listing of routes of administration in order of preference associated with their potential impact on AMR has been provided. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have least impact on AMR selection.	8.
11	The work of the AMEG group and EMA's scientific committees on categorisation document is thanked for. In our opinion, the revision of the categorisation of antimicrobials in veterinary use is important due to worsening resistance situation. There is an urgent need to strengthen the measures to slow down the resistance development. Especially restricting the veterinary use of those antimicrobials, which are considered last-resort antimicrobials in human medicine, is important. From the human health point of view, prohibiting also the cascade use should be considered as risk management option for group A antimicrobials. This has been used in Finland since late 1990's and the use of last resort antimicrobials in human medicine has been prohibited in animals by the Government Decree. Also, if there is an authorised veterinary medicinal product containing one of these last resort antimicrobials (for instance 3rd generation cephalosporin) the product may only be used for the indications in the target animal species (cascade use is not allowed).	Thank for your comments. Consideration of antimicrobials for which use should be restricted under the cascade will be considered in separate mandates from the Commission in relation to provisions in the new Regulation on veterinary medicines EU 2019/6.	9.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	We also support the revised 4-step categorisation. Addition of new group B highlights the need to take every measure to slow down the resistance development against 3rd and 4th generation cephalosporins, polymyxins and quinolones listed in this group B.		
12	Elanco Animal Health welcomes the opportunity to provide comments to this Answer to the request from the European Commission, which is well thought through, detailed, clear and comes to a rational approach which should be practical for the design and implementation of risk mitigation activities in different member states or regions within the EU. We support the general approach and in particular the creation of four categories. Sections putting this 'list' in the context of the other available lists are greatly appreciated because this is an area of significant confusion both within and outside the EU. We also appreciate that this categorisation takes into account not only the importance of the (sub)class or group to human medicine according to the WHO ranking but also the EU situation and the availability of alternative antimicrobial (sub)classes in veterinary medicine with lower AMR risk to animal and public health. Taking into account the need of veterinary medicine is critical.	Thanks for the comments.	10.
13	The AVC is in general agreement with this 4 February 2019 Draft document, but we do have some specific comments for consideration please.	Thank you for the comments.	11.
15	What is written in the answer to the request of the European Commission?	The finalised advice will be sent to the Commission at the end of 2019.	12.
16	The BVPA welcomes the opportunity to comment on this report and is broadly supportive although the Association does have concerns over the categorisation of streptogramins.	Thank you. Streptogramins are not authorised in veterinary medicines in Europe and are for that reason included in category A.	13.
17	The document turned out to be an excellent bibliographical revision since it puts into		14.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	context the different priorities for the use of antibiotics in animal health, taking into account the priority antibiotics in human health. Is a comprehensive framework that priorities for the use of antibiotics in animal health taking into account the AMR. The score for each class of antimicrobial was very novel according to its probability of transfer of resistance genes, the possible clonal expansion and the probability of co-resistance to be included. This classification was formative for health professionals who do not dedicate themselves specifically to the study of resistance mechanisms. It is very useful to have in one document the intersectoral analysis to make the decisions in the framework of One Health in an appropriate way. Comment: **Polymyxins in Category B** Proposed change (if any): Since it is one of the few treatment alternatives for multiresistant Gram-negative infections in humans, we suggest that it be included in Category A, even though the classification score has been included in Category B. Argentina has banned its Use by Resolution SENASA 22/19 (Official Bulletin 15-1-2019) Comment: **Bacitracin in Category D** Proposed change (if any): it is suggested to include Bacitracin in Category C because of the risk of co-selection of isolates with plasmid resistance transferable to Colistin mediated by the mcr-1 genes (Xu F, Zeng X, Hinenoya A, Lin J. 2018. The MCR-1 confers cross-resistance bacitracin, a widely used in-feed antibiotic. mSphere 3: e00411-18. https://doi.org/10.1128/mSphere.00411-18.) Comment: **Streptogramins en Categoría A**	The use of colistin in animals is authorised in animals with some restrictions in Europe. It therefore cannot be in category A. The AMEG provided a risk assessment for colistin in 2016 (Updated advice on the use of colistin product in animals within the European Union: development of resistance and possible impact on human and animal health EMA/CVMP/CHMP/231573/2016). The AMEG agreed to leave bacitracin in Category D based on the current level of evidence and in line with WHO categorisation as an IA. Recategorization of bacitracin might be needed if further evidence develops of co-selection of isolates with the *mcr* genes. Streptogramins are not authorised in veterinary medicines in Europe	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	Proposed change (if any): it would be interesting to know the rationale behind this decision, as this antibiotic has not been used for human infection since at least 5 year In our opinion, it should be placed in category C, along with the macrolides (probable co-resistance). From animal health we want to ask about the inclusion of the VIRGINIAMICINA in the "AVOID" category, considering that the EMA report declares that the human medical importance of the streptogramin class is "... considered obsolete"	and are therefore included in category A.	
	Comment: **Cephalosporin in Category A** Proposed change (if any): It is suggested to clarify that they refer to the 5th Generation Cephalosporin (ceftobiprole, ceftaroline)	Agreed, change made in the AMEG document: 'Other cephalosporins and penems' (ATC code J01DI) and 3rd generation cephalosporins with β-lactamse inhibitor are now included in Category A.	
	Comment: **Cephalosporin + inhibitors** Proposed change (if any): it is suggested to include in Category A the cephalosporins + inhibitors of beta lactamases (ceftolozano-tazobactam, ceftacidima-avibactam)		
	Comment: **Siderophores** Proposed change (if any): it is suggested to include in Category A the siderophores (cefiderocol)	Siderophores will be placed in Category A when authorised for use in human medicine in the EU.	
	Comment: **New aminoglycosides** Proposed change (if any): it is suggested to include new aminoglycosides in Category A	Very new, not approved yet The categorisation includes only antibiotic substances that have been authorised for human and/or veterinary use in the EU. This has been clarified in the report. The AMEG has proposed that any new antibiotic substance authorised	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	(plazomycin) Comment: **Fluorocyclines** Proposed change (if any): it is suggested to include them in Category A (eravaciclina) Comment: **Amidinopenicillins Categoría A** Proposed change (if any): it is suggested to correct writing by AMDINOPENICILLINS throughout the document	for use in human medicine after the publication of the Categorisation will be provisionally included in Category A regardless of the categorisation of its parent (sub)class, pending evaluation by the AMEG.	
18	Rifamycins, specially rifampicine, should be classified in A, except for horses because it is an essential substance, and this drug is only used in association with another antibiotic to reduce antibioresistance. Classification should distinguish individual and collective treatment. So, most of antibiotics in C could be in D for individual treatment and stay in C for collective treatment. This approach could be more scientific and realistic in point of view of antibioresistance and risk of diffusion/transmission to effluent and environment.	Rifamycins (excluding rifaximin, which is authorised for local use in a limited number of VMPs) are now placed in Category A. The rationale is provided in Table 4. A listing of routes of administration in order of preference associated with their potential impact on AMR has been provided. This takes into account routes used for treatment of individual animals and those used to treat groups. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have	15.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
		least impact on AMR selection.	
19	According to the following table and paper, Polymyxin is particularly efficient in the treatment of pseudomonas aeruginosa and staphylococcus sp, wich is of interest in the treatment of corneal infection in dogs and cats (Veterinary Ophthalmlogy, 5th edition- Slatter's Fundamentals of Vetrinary Ophthalmology) considering that very few medical specialities are available in veterinary medicine and considering the obligation for the veterinarian to follow the "cascade" law.	Noted. The use of the AMEG categorisation is addressed in Chapter 5.	16.
20	Copa and Cogeca welcome the updated scientific advice on the impact on public health and animal health of the use of antibiotics in animals from EMA. The proposal contains several positive elements, which will promote a responsible use of antibiotics in animals. Copa and Cogeca fully recognize that antibiotic resistance poses a serious threat to public health, and therefore the agricultural and food sector of the EU is at the forefront of preventing AMR. Copa and Cogeca support the AMEG approach to classify the antimicrobials into four overall different categories allowing for additional criteria to be taking into account like the availability of alternative antimicrobials. We find that EMA, with the classification into four groups, has managed to find an appropriate balance between the risk of AMR to public health and the importance of the substance to animal health. Copa and Cogeca acknowledge the AMEG argumentation in lines 130 to 138 that the categorization does not directly translate into a treatment guideline for use of antimicrobials in veterinary medicine, but it can be used as a tool by those preparing those guidelines. However, we find that the categorization for two specific groups of antibiotics (Aminoglycosides, quinolones) should be improved taking into account the variety of species, type of production system and occurrence of resistence. • **Aminoglycosides (class C):** the suggested antibiotics in class D are rarely useful for treatin *E. coli* infections, so in many cases only class C antibiotics are a realistic	Thank you for the comments. See previous response to comment 7. Streptomycin and neomycin have been kept in Category C as the	17.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	choice. Diversifying the aminoglycosides (streptomycin, neomycin and spectinomycin in class D; apramycin and gentamicin in class C) will provide a more beneficial risk-benefit ratio. **Quinolones:** we fully acknowledge that quinolones are important antimicrobial agents for treating many different infections in humans and are used against a wide variety of pathogens. Nevertheless, regarding the case of using quinolones in aquaculture we encourage the AMEG to take into consideration the species-specific situation for farmed fish, changing oxolinic acid to group C and allowing its use in aquaculture. If this is not possible, we want to highlight that the use of antibiotics from class B should not be only determined by antimicrobial susceptibility testing, but may be also determined by restrictions for use introduced through current environmental legislation.	mechanisms of resistance often are the same as for e.g. gentamicin; whereas spectinomycin has been moved to Category D. Since quinolones can select for the same resistance genes that also code for fluoroquinolone resistance (e.g. *gyrA* gene) the AMEG does not agree to place oxolinic acid in Category C. The requirements to comply with applicable legislative frameworks such as the Water Framework Directive is now mentioned in Chapters 4 and 5.	
21	Laboratory TVM is an independent French laboratory (Small and Medium company) specialized in ophthalmology, neurology and treatment of intoxications. Laboratory TVM welcomes the opportunity to participate to this consultation on the new categorisation of antimicrobials performed by the AMEG group. The addition of an intermediate category is considered as a positive point and this change fulfils the objective of an improvement of "the utility of the categorisation as a risk management tool by avoiding the counterproductive outcome of too many antimicrobials being placed in the higher risk category." However, Laboratory TVM wants to bring comments focusing on polymyxin B, antibiotic only used at topical level (notably in the eye) in pets. In dogs and cats, polymyxin B-based eye drops are widely used in case of ocular infections. Polymyxin B presented as eye drops is also essential in the veterinary	Please refer to Chapter 5 which outlines the Use of the Categorisation as a tool for those	18.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	therapeutic arsenal for the treatment of collagenase ulcers which threaten the functional integrity of the eye. In 2018, the French veterinary market for topical ocular antibiotics represented 530,000 units sold, of which 200,000 units for polymyxin B in the form of eye drops. This represents between 170,000 and 180,000 treated animals.	preparing treatment guidelines. The route of administration should be taken into account alongside the categorisation when making prescribing decisions and it is noted that local individual treatment (e.g. eye drops) are a preferred route.	
22	NOAH welcomes the opportunity to comment on this Answer to the request from the European Commission. We feel the approach is rational and allows for practical steps in the design and implementation of risk mitigation measures in different member states or regions within the EU. We are supportive of the general approach and the creation of four categories. NOAH members believe that once finalised, efforts will need to be made to ensure the categories are communicated clearly to prescribers and others with an interest in this area, (for example, veterinary organisations and retailer supply chains who have policies relating to antibiotic use) as there is much confusion about the different antibiotic classifications by different organisations. The Sections describing this 'list' in the context of the other available lists are greatly appreciated because this is an area of significant confusion both within and outside the EU. One area for consideration is that throughout the Answer, some of the references used are dated. We accept that a comprehensive and current literature review is complex, however we believe this is important. This would help ensure that some recent publications which address some of the previous assumptions about direct transfer of resistance from animals to humans (of course we realise that the AMEG is well aware of them). Examples include – Mather et al 2013 Distinguishable Epidemics Within Different Hosts of the Multidrug Resistant Zoonotic Pathogen *Salmonella* Typhimurium DT104. Science 341: 1513-1517, – Ewers et al 2012 Extended-spectrum b-lactamase-producing and AmpC-producing	Communication materials will be developed shortly after publication.	19.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	Escherichia coli from livestock and companion animals, and their putative impact on public health: a global perspective. Clinical Microbiology and Infection 18: 646–655, – de Been et al 2014 Dissemination of Cephalosporin Resistance Genes between Escherichia coli Strains from Farm Animals and Humans by Specific Plasmid Lineages. PLoS Genet 10(12): e1004776. doi:10.1371/journal.pgen.1004776. – Dorado-Garcia et al 2017 Molecular relatedness of ESBL/AmpC-producing Escherichia coli from humans, animals, food and the environment: a pooled analysis. Journal of Antimicrobial Chemotherapy doi: doi:10.1093/jac/dkx397 – and, admittedly after the Answer was prepared, Ludden et al 2019 One Health genomic surveillance of *Escherichia coli* demonstrates distinct lineages and mobile genetic elements in isolates from humans versus livestock. mBio 10:e02693-18. https://doi.org/10.1128/mBio.02693-18 to list a few.	Thank you. The references are now included in the advice.	
	Tables 2 and 3 should be updated in light of an updated literature review.		
	It is suggested that for completeness ketolides are missing from the list in Table 1.	Ketolides have been added in table 1.	
	As there has been a request for further scientific expertise from the EMA, regarding the list of antimicrobials reserved for human use NOAH would hope that the work of AMEG will serve as a basis for future scientific advice, for example the delegated and implementing acts under the new European Veterinary Medicines Regulations, 2019/6.	Noted. Recommendations in respect of Regulation 2019/6 will be made under separate mandates.	
	Although the route of administration is not included as a ranking criterion for the categorisation of antibiotic classes, NOAH believes that it is important to consider the route of administration at an individual product level. In order to fully reflect the different risks arising from different routes and modes of administration for the same class of	A listing of routes of administration in order of preference associated with their potential impact on AMR	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	substance, the concept of exceptions should be introduced into the AMEG categorisation so that where a MAH can demonstrate that there is a lower risk for a particular substance used via a particular route and/or mode then in that scenario the categorisation changes to a lower category. For example, for a specific antibacterial class or substance in Category B an exemption could be recorded specifying that in specified circumstances (e.g. use of antibiotic X in ear drops for use in individual animals) is considered to correspond to Category C. The entry could appear along the following lines: Category B Antibacterial Class or substance Y* *with the exception of antibiotic X when used in individual animals aurally = Category C In general, locally individual treatment (udder injector, eye or ear drop, as assessed in line 498), should be considered as exceptions for use of a given antimicrobial and lead to lower risk categorisation (from B to C or C to D). Throughout the document the word "effective" is used, and our interpretation is that this refers to clinical effectiveness, however, it might be helpful if it is expressed as "clinically effective" (lines 93, 115, 280, 294, 298, 301, 330, 757, 770, 850, etc). Adding a definition for "multiresistance genes" may be helpful– the term is used in lines 113, 766 and 774. This could be interpreted in 2 ways; the presence of a resistance determinant encoding resistance to multiple antimicrobial classes (e.g. MLSB, *OptrA* etc), but this could potentially also refer to the presence of several individual resistance determinants in one organism. We have assumed the former.	has been provided and is now included in the Summary. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antimicrobial that will have least impact on AMR selection. It was decided not to include the route directly in the categorisation due to the complexity it would introduce. Agreed – change included in AMEG document. It was agreed to modify criterion 3 (under Chapter 4): "The knowledge of factors influencing the likelihood and possible consequences of AMR transfer from animals to humans, in particular considering mechanisms where a single gene confers	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
		multiresistance (or resistance to several classes)"	
24	Welcome for New Categorisation DAFM welcomes the opportunity to provide comments to this consultation by the European Medicines Agency AMEG updating the advice on the impact on public health and animal health of the use of antibiotics in animals – Categorisation of antimicrobials. DAFM very much approves of the proposed categorisation which takes into account both the WHO and OIE lists of CIAs, thereby allowing an appropriate balance between animal health and welfare needs, human health needs and public health considerations. DAFM agrees with the approach taken whereby not only the importance of the antimicrobial class in human medicine and knowledge of factors influencing the likelihood of resistance transfer are considered, but emphasis is now also placed on the importance and the availability of alternatives antimicrobials in veterinary medicine. DAFM are pleased to see that the order of the categories, in terms of level of risk, has been reversed compared to the first AMEG report as many people felt that the previous categorisation was confusing with antibiotics posing the least risk to AMR development placed 1st in category 1. The use of key action words for each category A,B,C and D captures the meaning of each category very effectively and is user friendly, helping veterinary professionals, animal keepers and stakeholders in the animal health industry to remember the AMR risk posed by antibiotics in each different category. DAFM welcomes the fact that the reviewed categorisation considers all antimicrobials and ranks them according to the level of risk posed in terms of AMR. The proposed categorisation will be a very useful reference point for those preparing treatment guidelines serving to factor AMR risk into prescribing decisions. AMEG's ranking of the AMR risk posed by the route of administration is welcomed by DAFM	Thanks for the comments.	20.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	as a very prudent approach to antibiotic prescribing decisions. The use of the route of administration ranked from least to greatest risk together with the AMEG categorisation to select both the formulation/route of administration and class that will have the least impact on the selection of AMR should serve to promote the responsible use of antimicrobials.		
25	Reviewed the draft AMEG report "Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Categorisation of antimicrobials" presented to IDWP in the first week of 2019 (AMEG 2018 - Categorisation of AMs - 20190108.doc). It should be noted that recent changes/deletions made to this new draft have NOT been through consultation of the entire AMEG group. The comments have been drafted in collaboration with experts of the National Reference Laboratory for Antimicrobial Resistance (Reg. 2004/882/EC; Reg.(EU) 2017/625) Italy, and with the Italian and Danish members of the EMA CVMP. In July 2017, the EC asked the EMA to update its advice published in 2014. Regarding the categorisation of antimicrobials, the EC requested that the AMEG review the original classification and update as necessary taking account of the following specific points: • 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 World Health Organisation (WHO) as highly important and important (in addition to the critically important antimicrobials and their subgroup of Highest Priority Critically	Thank you for the detailed comments.	21.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	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 scope of the present AMEG document is limited to addressing the European Commission's request to update the 2014 advice on the categorisation of antimicrobials. As requested by the EC, all updated information should be considered in the updated AMEG categorisation. **Selected Issues with Critically Important Antimicrobial Classes** Previously the AMEG report 2014 concluded that the Macrolide class was placed in Category 1 (no restrictions). What has changed since 2014 that should be taken into account, as per the EC mandate includes: - WHO has published an updated list of critically important antimicrobial agents for human medicine (WHO, 2016). - WHO published a guideline on use of medically-important antimicrobials in food-producing animals (WHO, 2017). As part of the WHO 2017 review, a new categorisation of antibacterials into three groups was specified (20th WHO List of Essential Medicines, 2017): o ACCESS – 1st & 2nd choice antibiotics for the empiric treatment of most common infectious syndromes; o WATCH – antibiotics with higher resistance potential and should be limited to a small number of syndromes or patient groups; o RESERVE – antibiotics to be used mainly as 'last resort' treatment options. - OIE published an updated list of antimicrobial agents of veterinary importance (OIE, 2018).		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	- Updated information from ESVAC about the EU sales of veterinary antimicrobials - Updated information from an EU antimicrobial resistance surveillance program (EFSA) of both indicator and zoonotic pathogens. - New peer-reviewed published scientific papers Also, it is worth noting that the New Veterinary Regulations (NVR) and WHO recommendations for medically important antimicrobials in food animals (WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.) are NOT comparable but represent different types of important recommendations for antimicrobial usage in animals. For example, the NVR specifies conditions and restrictions for antimicrobial usage regarding prophylaxis and metaphylaxis, and allows for judgement by the prescribing veterinarian. The WHO food animal recommendations represent different types of recommendations compared to the NVR, which are focused on reductions in food animals based on the WHO classification of antimicrobial classes, with progressively more reductions on WHO CIA classes (both High Priority and Highest Priority). In the mandate given to AMEG, they are supposed to consider recent work by the WHO, which is not the case by specifying a High Priority-CIA class/subclass (aminopenicillins) for first choice use (Category D) and other CIAs (macrolides-Highest Priority, aminoglycosides, rifamycins, aminopenicillin combinations) with minimal restriction. The intention of the WHO recommendations is that CIAs in animals should only be considered when non-CIAs are used/evaluated first, which is not reflected in the new AMEG categorisation. It is worth noting that the WHO (AGISAR) that is responsible for the list of Critically Important Antimicrobials for Human Medicine also has veterinarians advising and agreeing to the CIA list and food animal recommendations.	The WHO list of CIAs has been taken into account. The AMEG categorisation considers the EU situation and there is some difference in the criteria used. The rationale for the categorisation of each class is provided in Table 4 of the advice.	
	Macrolides Summary Will restricting Macrolides have a negative impact on animal health? No, high levels of macrolide-resistance have already been identified for the major target pathogens in animals. Macrolides will still be available for veterinary prescription but should only be considered after alternatives. Macrolides tend to be overused, especially by oral route and for group administration, for some major target pathogens (e.g *Lawsonia spp*, *Mycoplasma spp*.) since prudent-use principles cannot be applied. No essential need		

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	for macrolides in animals has been established where alternatives do not exist. The majority of EU member states have demonstrated low consumption of macrolides in animals, despite having sizeable food animal industries in some member states. In the latest ESVAC report, several EU member states have demonstrated reductions of macrolides from their national action plans, recognizing that macrolides are HPCIAs. What alternatives are available in the EU for Macrolides for animal diseases? Depending on the major target pathogen, several EU alternatives are available including SPF systems, vaccines and other non-CIA antimicrobials including pleuromutilins, florfenicol, lincosamides, trimethoprim-sulfadoxine and tetracyclines. Will restricting Macrolides have a positive impact on public health? Yes, macrolide-resistance has been identified in Europe for major zoonotic pathogens (e.g. *Campylobacter spp*,. *Salmonella spp*., LA-MRSA), coded either by chromosomal mutations (e. g. in *C. jejuni* and *C. coli* most successful clones causing human disease), or even by horizontally transferable macrolide-resistance genes that can lead to a rapid spread of antimicrobial resistance (e.g. *erm*, *cfr* genes). Macrolides are necessary for the treatment of moderate-to-severe cases of campylobacteriosis in humans. Based on lifetime antimicrobial exposure in pigs, macrolide use is positively correlated with selection of the *ermB* and *ermF* genes (Birkegård *et al*., 2017). Based on a meta-analysis, the greatest reduction in pooled absolute risk difference in antimicrobial resistance from interventions (restrictions) were found with macrolides for both *Enterococcus spp*. in faecal samples and *Campylobacter spp*. in faecal samples (Tang *et al*., 2017). Macrolides are not only used in veterinary medicine, but also considered one of the highest priority critically important antimicrobials by the World Health Organization because of their need for treating *Campylobacter* infections in humans (World Health Organization: Critically Important Antimicrobials for Human Medicine: ranking of antimicrobial agents for risk management of antimicrobial resistance due to non-human use. In., 5th edn; 2016.). Since resistance to all clinical macrolides, plus lincosamides and streptogramin B compounds, is commonly conferred by ribosomal methylation (*erm* genes) (Weisblum B: Erythromycin resistance by ribosome modification. *Antimicrobial agents and chemotherapy* 1995, 39(3):577-585.; Valdivia L, Rice LB: Target-Mediated Antibacterial Resistance. 2017:89-95.), then the use of macrolides in animals can select for bacteria (e.g. *Campylobacter spp*.) that are resistant to all macrolides.	Macrolides are in AMEG's Category C, which means that substances in Category D should be used where possible in preference. Following consideration by the members of AMEG, the justification for the Categorisation of Macrolides is now given in Table 4: 'WHO categorises macrolides as HPCIA. Macrolides are also classified as critically important for veterinary use (VCIA) and few or no antimicrobial alternative treatments presenting a lesser risk are available for e.g. infections with *Lawsonia* in pigs. The class selects for macrolide resistance in e.g. *Campylobacter* spp, a food borne zoonotic organism with comparatively high prevalence. Only serious cases, however, need treatment and proportion of case fatalities is low. Furthermore, based on available knowledge and the group's expertise, it was concluded that, in the EU, the public health burden of infections of 3rd - and 4th-generation cephalosporin--and fluoroquinolone-resistant bacteria is	

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	In 2007, a Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials was convened in Rome to review both the WHO CIA and OIE Lists (Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials: report of the FAO/WHO/OIE Expert Meeting, FAO headquarters, Rome, 26–30 November 2007. Rome: Food and Agriculture Organization of the United Nations; 2008 http://www.fao.org/3/a-i0204e.pdf). The OIE List was developed using a survey of veterinarians and categorized the importance to animal health of antimicrobials used in food-producing animals. The experts from WHO and OIE concluded that because the two lists were developed for different purposes, and only the WHO CIA List considered the human health implications of use of antimicrobials in food-producing animals, it would not be possible to combine them. However, comparison of the two lists and consideration of relevant criteria (e.g. frequency and severity of human infections caused by resistant foodborne bacteria and preferred treatment for the infection) indicated that three classes of antimicrobials - fluoroquinolones, cephalosporins, and **macrolides** – should be the TOP priority when considering action on use of antimicrobials in food-producing animals. The AMEG has not acknowledged the outcomes of this conference when considering the categorization of macrolides, where the OIE and WHO agreed that actions were required on macrolides and equivalent actions as with fluoroquinolones and cephalosporins. Campylobacterosis is a leading cause of human bacterial enteritis (bloody diarrhoea, fever, abdominal cramps and vomiting lasting for approximately 5–7 days) in Europe (Spina *et al*., 2015 Spectrum of enteropathogens detected by the FilmArray GI Panel in a multicentre study of community-acquired gastroenteritis. *Clin Microbiol Infect* 21:719–28.), as well as one of the most costly foodborne diseases in Europe and worldwide (Skarp *et al*., 2016 Campylobacteriosis: the role of poultry meat *Clin Microbiol Infect* 22:103–109.). Campylobacteriosis is the most commonly reported gastrointestinal disease in humans in the European Union (EU), with around 246,000 cases in 2017 (ECDC-EFSA, 2017). Campylobacteriosis in Europe has undegone significantly increasing trends over the period 2008–2017 (ECDC-EFSA, 2017 European Food Safety Authority and European Centre forDisease Prevention and Control), 2018. The European Union summary report on trends and sources ofzoonoses, zoonotic agents and food-borne outbreaks in 2017. EFSA Journal 2018;16(12):5500, 262 pp.https://doi.org/10.2903/j.efsa.2018.5500.). Studies employing multilocus sequence typing and mathematical modelling have revealed that chickens are the most common reservoir/source of human *Campylobacter* spp. infections, with attribution rates varying from 38% to 77%, whereas cattle are regarded as the second most common source, with attribution rates varying between 16% and 54% (Skarp	higher than that for macrolide-resistant zoonotic bacteria Recently, transferable resistance (*erm*-genes) has been described in *Campylobacter* spp. This implies a higher probability of emergence and spread. The *erm* genes are currently considered to be of low prevalence in animal isolates of *Campylobacter* and other food borne pathogens in the EU. On the basis of new scientific evidence, or emerging information on changing patterns of antimicrobial use and/or resistance trends the categorisation of this antimicrobial class may need to be re-assessed. Altogether, macrolides are in category C rather than in B'.	

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	CPA, Hänninen ML, Rautelin HIK. 2016 Campylobacteriosis: the role of poultry meat. *Clin Microbiol Infect*. 22(2):103-109.). Similarly, based on comparative genomic fingerprints; MLST genes; 15 host segregating genes previously identified by whole genome sequencing, chicken was identified as the most important source of campylobacteriosis in France (31–63% of clinical isolates assigned), followed by ruminants with 22–55% of clinical isolates assigned (Thépault A, Rose V, Quesne S, et al. 2018 Ruminant and chicken: important sources of campylobacteriosis in France despite a variation of source attribution in 2009 and 2015. *Sci Rep*. 8(1):9305). Meat products are responsible for approximately 1.5 million foodborne illnesses in the U.S. annually (Painter JA, Hoekstra RM, Ayers T, Tauxe RV, Braden CR, Angulo 455 FJ, Griffin PM: Attribution of foodborne llnesses, hospitalizations, and deaths to food commodities by using outbreak data, United States, 1998-2008. *Emerg Infect Dis* 2013, 19(3):407-415.), with *Campylobacter* and *Salmonella* species (two commonly animal-associated bacteria) responsible for a majority of foodborne illnesses (Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, Jones JL, Griffin PM 2011 Foodborne illness acquired in the United States--major pathogens. *Emerg Infect Dis* 17(1):7-15.). The second antimicrobial regarded as critically important for treatment of campylobacteriosis in humans is erythromycin (EFSA, 2019). Recently, EFSA has released an updated AMR surveillance report (EFSA-European Food Safety Authority and ECDC-European Centre for Disease Prevention and Control, 2019. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2017. EFSA Journal 17(2):5598, 278 pp. https://doi.org/10.2903/j.efsa.2019.5598). EFSA (2109) noted the following, "In five countries, high to very high proportions of *C. coli* from humans were resistant also to erythromycin, leaving few options for treatment of severe *Campylobacter* infections.". The proportion of human *C. jejuni* isolates resistant to erythromycin was overall low (2.0%) but markedly higher in *C. coli* (12.8%) with high to very high (21.4–59.5%) proportions of *C. coli* being resistant to erythromycin in four of fourteen countries testing more than 10 isolates. The major reservoirs are pigs (harbour *C. coli* only) and poultry (broilers, turkeys: these productions harbour both *C. jejuni* and *C. coli*). At present, *C. coli* antimicrobial susceptibility monitoring is not mandatory at the EU level. Despite this, the overall erythromycin resistance in fattening pigs was moderate (15.6% for 7 MSs). Erythromycin resistance was undetected in Estonia (20 isolates tested) and in Norway (255 isolates tested) and very low in Sweden (0.7% out of 137 strains tested). Conversely, *C. coli* resistance to macrolides was very frequent in Spain (61.8% out of 170		

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	strains tested). This is further part of upward trend in Spain, where the proportion of *C. coli* isolates from fattening pigs exhibiting high-level resistance to erythromycin detected in 2017 (55.9%) was statistically significantly greater than that observed in 2015 (44.1%) (one-tailed z-test to compare proportions, p-value = 0.0148). Overall EU macrolide resistance rates in *C. jejuni* from food-producing animals are lower, however in some EU countries they have recently reached 8.1, 10.4% and 10.9% in Italy, Portugal, and Bulgaria, respectively (EFSA - European Food Safety Authority and ECDC - European Centre for Disease Prevention and Control, 2018. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. EFSA Journal 16(2):5182, 270 pp. https://doi.org/10.2903/j.efsa.2018.5182). Tang *et al*. (2017) performed a systematic review and meta-analysis to summarise the effects of interventions to reduce antibiotic use in food-producing animals on the presence of antibiotic-resistant bacteria in animals and humans (Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, Polachek AJ, Ganshorn H, Sharma N, Kellner JD, Ghali WA 2017 Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *Lancet Planet Health* 1: e316–27. doi.org/10.1016/S2542-5196(17)30141-9). In total, 81 studies were included in the meta-analysis showing that interventions that reduce antibiotic use in food-producing animals are associated with a reduction in prevalence of antibiotic resistance in these animals, by approximately 15% and multidrug-resistant bacteria by 24–32%. A meta-analysis of 13 studies showed similar results, with a 24% absolute reduction in the prevalence of antibiotic-resistant bacteria in humans with interventions that reduce antibiotic use in animals. Interventions were classified into four categories: externally imposed bans or restrictions of antibiotic use (36 animal studies, nine human studies); organic interventions, as defined by the study and the country-specific regulations for organic certification (87 animal studies and two human studies); self-labelled antibiotic-free, free-range, or pasture systems (38 animal studies, five human studies); and voluntary reduction of antibiotic use (29 animal studies, five human studies). The strongest reduction in pooled absolute risk difference in antimicrobial resistance from interventions were found with **macrolides** for both *Enterococcus spp*. in faecal samples (39% reduction – 95% confidence intervals 23%-56%) and *Campylobacter spp*. in faecal samples (15% reduction – 95% confidence intervals 4%-26%). In both cases, these were the largest reductions of any antimicrobial class studied. Tang *et al*. (2017) have identified and quantified that **macrolide** restriction in animals results is major reductions of		

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	antimicrobial resistance at the population-level. "The findings were consistent regardless of bacteria studied, food-producing animals in question, interventions implemented, samples studied, and regardless of the quality of the studies" (Tang *et al*., 2017). "Therefore, despite the limitations posed by the quality of studies and the methodological issues and assumptions that are made in them, it would be imprudent to entirely discount this body of evidence given its coherence and consistency" (Tang *et al*., 2017). Furthermore, the results of Birkegård *et al*. (2017) noted that "We found that exposure to macrolides and lincomycin was positively correlated with *ermB* and *ermF*, and tetracycline exposure was positively correlated with the levels of *tet(W)*." (Birkegård AC, Halasa T, Græsbøll K, Clasen J, Folkesson A & Toft N Association between selected antimicrobial resistance genes and antimicrobial exposure in Danish pig farms *Nature Scientific Reports* **7**:*9683* DOI:10.1038/s41598-017-10092-9). This was a study that quantified the relationship between the lifetime exposure of antimicrobials and seven antimicrobial resistance genes in Danish slaughter pig farms. AMR gene levels were quantified by qPCR of total-community DNA in faecal samples obtained from 681 batches of slaughter pigs. The lifetime exposure to antimicrobials was estimated at batch level for the piglet, weaner, and finisher periods individually for the sampled batches. Combined with the results of Tang *et al*. (2017), it is clear that macrolide use is positively correlated with selection of the *ermB* and *ermF* genes (Birkegård *et al*. 2017), the same genes identified by AMEG as concerns for public health, and that restriction of macrolides is positively correlated with a quantifiable reduction in AMR (Tang *et al*., 2017). It is unclear as to why the AMEG has not acknowledged this work that justifies the risk mitigation measure of placing macrolides into Category 'B' and not 'C'. The proposal of placing macrolides in AMEG Category C may be at risk of offering arguments for not reducing the usage of macrolides via the oral route in animal productions (especially in pigs and poultry), which negatively impacts resistance towards macrolides in *Campylobacter* and other zoonotic Gram negative (*Salmonella*), Gram-positive (LA-MRSA) and opportunistic pathogens (*E. coli*) to humans. Extra benefits identified of restricting macrolides in veterinary medicine, not mentioned in the AMEG report include: - Macrolide resistance genes can be linked to other resistance genes on mobile genetic elements or on chromosomes, resulting in co-selection of multiple resistances from the use of one antimicrobial class (Hasman H, Aarestrup FM: tcrB, a Gene Conferring Transferable Copper Resistance in Enterococcus faecium:	The latest data from ESVAC show that there has been a reduction in sales of macrolides in the EU from 12.2 to 8.08 mg/PCU between 2011 and 2017.	

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	Occurrence, Transferability, and Linkage to Macrolide and Glycopeptide Resistance. *Antimicrobial agents and chemotherapy* 2002, 46(5):1410-1416.). Therefore, restricting macrolides can result in a decrease in resistance to other Highest Priority Critically Important antimicrobial classes. This is also of major benefit for animal health. ○ For example, the prohibition of tylosin as a growth promoter in swine in Switzerland resulted in decreased enterococci resistance to macrolides, lincosamides and tetracycline (Boerlin P, Wissing A, Aarestrup FM, Frey J, Nicolet J: Antimicrobial growth promoter ban and resistance to macrolides and vancomycin in enterococci from pigs. *J Clin Microbiol* 2001, 39(11):4193-4195.). ○ Similarly, in Denmark, swine-associated enterococci retained glycopeptide-resistance until tylosin use was banned as a growth promoter because of a plasmid-mediated genetic linkage between macrolide (*erm*B gene) and glycopeptide resistance (*van*A gene – i.e. vancomycin resistance) (Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F 2001 Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrobial agents and Chemotherapy* 45(7):2054-2059.). Enterococci are common commensal opportunistic bacteria of the gastrointestinal tract that are also used as "indicator" bacteria when monitoring trends, or emergence and spread of antimicrobial resistance in animal productions (Directive 2003/99/EC; Dec 2013/652/EU). The *erm* genes [including *erm*(A), *erm*(B) *erm*(C)] continue to be common in *Enterococci* from food animals (Iweriebor BC, Obi LC, and Okoh AI 2016 Macrolide, glycopeptide resistance and virulence genes in Enterococcus species isolates from dairy cattle. *Journal of Medical Microbiology* **65**:641-648. DOI 10.1099/jmm.0.000275; Diarra MS, Rempel H, Champagne J, Masson L, Pritchard J, and Topp E 2010 Distribution of Antimicrobial Resistance and Virulence Genes in *Enterococcus* spp. and Characterization of Isolates from Broiler Chickens. *Applied and Environmental Microbiology* **76(24)**:8033–8043. DOI:10.1128/AEM.01545-10; Jackson CR, Fedorka-Cray PJ, Barrett JB,	A new chapter has been included in the report recommending review of the categorization if there is new evidence of changing patterns of antimicrobial use or AMR. Under Directive 2003/99/EC there is mandatory monitoring of AMR in zoonotic and commensal bacteria from food-producing animals and food. EFSA has recently issued a report to propose updates of the	

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	and Ladely SR 2004 Effects of Tylosin Use on Erythromycin Resistance in Enterococci Isolated from Swine. *Applied and Environmental Microbiology* **70(7)**: 4205–4210. DOI: 10.1128/AEM.70.7.4205–4210.2004). ○ In Denmark, after the ban of tylosin as growth promoters and restrictions on the use of macrolides for oral route in pigs, macrolide resistance rates in *Campylobacter coli* had dramatically decreased from around 60% in 1996 to around 15% in 2007 (DANMAP, 2007); ○ The *erm* genes continue to be common in both coagulase-positive and coagulase-negative *Staphylococcus* from animals, including Livestock-Associated methicillin resistant *S. aureus* (LA-MRSA). For example, a population-based survey at swine slaughter-houses in 2008, revealed that macrolide resistance among LA-MRSA was already at 60% (Battisti A, Franco A, Merialdi G, Hasman H, Iurescia M, Lorenzetti R, Feltrin F, Zini M, Aarestrup FM. 2010 Heterogeneity among methicillin-resistant Staphylococcus aureus from Italian pig finishing holdings. *Vet Microbiol.* 142(3-4):361-6. doi: 10.1016/j.vetmic.2009.10.008.). Thus, restricting macrolides is also an important part of the risk mitigation measure for LA-MRSA. The OIE concludes that macrolides are critically important antimicrobials for veterinary medicine, further stating that macrolides constitute essential treatments (few alternatives) for certain diseases in animals: "The wide range of applications and the nature of the diseases treated make macrolides extremely important for veterinary medicine. 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. This class is also used for respiratory infections in cattle.". Thus, it is in the interest for animal health to restrict macrolides as last-line treatments, similar to the strategy from the WHO on highest priority CIAs. However, these OIE essential indications do not necessarily reflect European conditions for macrolide use in animals. - Two major clinical presentations of *Lawsonia intracellularis* have been described in pigs. The first, an acute form known as proliferative hemorrhagic enteropathy (PHE), is characterized by bloody diarrhea and sudden death in mature pigs. The second, a chronic form called porcine intestinal adenomatosis (PIA), results in	harmonized monitoring technical specifications[1] to be used for future years' surveillance. As regards *Campylobacter*, it is proposed to include in the panel higher levels of erythromycin for better detection of isolates presumptively harbouring the *erm(B)* gene.	

[1] Scientific report on the technical specifications on harmonised monitoring of antimicrobial resistance in zoonotic and indicator bacteria from food-producing animals and food. EFSA Journal 2019:17(6):5709.

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	diarrhea and slow growth due to mucosal proliferation in the small intestine, particularly the ileum (Lawson GHK, Gebhart CJ. 2000 Proliferative enteropathy: review. *J Comp Pathol* 122:77–100.). However, the OIE only mentions the first, acute form (haemorrhagic disease) as essential for macrolide treatment. In Europe there are effective vaccines marketed for immunization against *Lawsonia intracellularis* infection (e.g. Enterisol Ileitis Vet), and more are currently under regulatory procedures. Vaccination against *L. intracellularis* has been previously reported in some successful field studies in Finland (Peiponen KS, Tirkkonen BT, Junnila JJT and Heinonen ML 2018 Effect of a live attenuated vaccine against *Lawsonia intracellularis* in weaned and finishing pig settings in Finland. *Acta Vet Scand* **60***:*18. https://doi.org/10.1186/s13028-018-0374-8), Denmark (Bak H, Rathkjen PH. 2009 Reduced use of antimicrobials after vaccination of pigs against porcine proliferative enteropathy in a Danish SPF herd. *Acta Vet Scand*. 51:1. https://doi.org/10.1186/1751-0147-51-1.), Australia (McOrist S, Smits RJ. 2007 Field evaluation of an oral attenuated *Lawsonia intracellularis* vaccine for porcine proliferative enteropathy (ileitis). *Vet Rec*. 161:26–8.), Korea (Park S, Lee JB, Kim KJ, Oh YS, Kim MO, Oh YR, *et al*. 2013 Efficacy of a commercial live attenuated *Lawsonia intracellularis* vaccine in a large scale field trial in Korea. *Clin Exp Vaccine Res*. 2:135–9.), Switzerland (Weibel H, Sydler T, Brugnera E, Voets H, Grosse Liesner B, Sidler X. 2012 Efficacy of simultaneous vaccination with Enterisol(R) Ileitis and Ingelvac(R) CircoFLEXTM in a Swiss breeding farm. *Schweiz Arch Tierheilkd*. 154:445–50.) and Hungary (Almond PK, Bilkei G. 2006 Effects of oral vaccination against *Lawsonia intracellularis* on growing-finishing pig's performance in a pig production unit with endemic porcine proliferative enteropathy (PPE). *Dtsch Tierarztl Wochenschr*. 113:232–5.). These studies reported increased weight gain, decreased mortality and lower antimicrobial use. Furthermore, *Lawsonia intracellularis* is a difficult organism to work with in standard laboratories where antimicrobial sensitivity is rarely performed. Laboratory diagnosis is typically via PCR (presence of the microorganism) or antibody tests (contact with the microorganism). Thus, there is a tendency to overuse macrolides for *Lawsonia* infections in pigs since prudent-use principles are difficult to apply. For example, most EU holdings will test seropositive, irrespective of their clinical status. Also, PCR-positive pigs occur without any pathological findings or clinical disease, demonstrating that *Lawsonia spp*. can be "present", without disease. Also, non-CIA EU alternatives can be used for *L. intracellularis* disease in pigs including tetracyclines, lincosamides and pleuromutilins. Macrolides are not an essential	It is agreed that as routine, infection prevention and control measures should be implemented to improve animal health and reduce the need to resort to the use of antibiotics. Despite this, animals may become sick when preventative interventions have not been effective and those with clinical signs of bacterial infection that is impacting on their health and welfare in many cases need to be treated with antibiotics. In these circumstances the categorisation may be taken into account for the prescribing decision. As part of the risk management measures, substances in Category C should only be used when there is no substance in Category D that would be clinically effective.	

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	treatment in Europe for *L. intracellularis* disease. - Mycoplasma-associated disease does occur in pigs (*M. hyopneumoniae*, *M. hyosynoviae* and *M. hyorhinis*) and poultry (*M. gallisepticum, M. synoviae, M. meleagridis*). Some Mycoplasma species, such as *M. bovis* and *M. hyopneumoniae*, are intrinsically resistant to 14-membered macrolides. Furthermore, *Mycoplasma spp.* is a difficult organism to work with in standard laboratories where antimicrobial sensitivity is rarely performed. For those specialized laboratories that have dedicated resources to study *Mycoplasma spp*., including detection of resistance through MIC or gene mutations, studies have revealed that the highest resistances of the main veterinary Mycoplasma species are observed for macrolides, followed by tetracyclines (Gautier-Bouchardon AV. 2018. Antimicrobial Resistance in Mycoplasma spp., *Microbiol Spectrum* **6(4)**:ARBA-0030-2018.). In general, macrolides are a poor choice to treat *Mycoplasma spp.* since macrolides are only bacteriostatic, and thus are not considered a long-term solution since macrolides will not eliminate *Mycoplasma* spp. infections from a herds/flocks (Hofacre CL, Fricke JA, and Inglis T 2013 Chapter 34: Antimicrobial Drug Use in Poultry. Antimicrobial Therapy in Veterinary Medicine. Fifth Edition Eds: Steeve Giguère, John F. Prescott, Patricia M. Dowling. 2013 by John Wiley & Sons, Inc). Furthermore, vaccines are available for *M. hyopneumoniae* and *M. gallisepticum*. *Mycoplasma spp*. is typically secondary to other viral diseases, such that adequate control from viral disease further reduces the incidence of *Mycoplasma spp*. In the Nordic countries, successful *Mycoplasma spp*. SPF systems have been developed in pigs and chickens and thus represent the cornerstone of *Mycoplasma spp*. prevention. Also, non-CIA alternatives can be used for Mycoplasma-associated disease including pleuromutilins, lincosamides, and tetracyclines. - Macrolides (e.g. tylosin) are approved in some countries for cattle for continuous oral use at 60 to 90 mg/head/day to reduce the incidence of liver abscesses (Elanco US Inc: NADA 012-491. In. Edited by Administration USFaD. Silver Spring, MD. 429 10.). It is used as a prevention and not as a treatment of a bacterial disease. Tylosin is hypothesized to prevent liver abscesses by suppressing the growth of *Fusobacterium necrophorum* in the rumen (Nagaraja T, Chengappa M: Liver abscesses in feedlot cattle: A review. *Journal of animal science* 430 1998, 76(1):287-298.), and increases feed efficiency and weight gain in cattle, likely because it reduces the severity of liver abscesses (Brown H, Bing R, Grueter H, McAskill J, Cooley C, Rathmacher R: Tylosin and chlortetracycline for the prevention of liver abscesses, improved weight gains and feed efficiency in feedlot		

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	cattle. *Journal of animal science* 1975, 40(2):207-213.). There are no European products with the indication to prevent liver abscesses. Tylosin is commonly used to prevent liver abscesses in beef cattle in the United States and Canada and also licensed for this use in Brazil, Mexico and Australia. - Macrolides are used for respiratory infections in cattle (prophylaxis, treatment and metaphylaxis), including Europe, often as mass medication (e.g. veal calves, feedlot cattle). The complex of viral, bacterial and/or mycoplasmal infections is described with blanket terms, 'enzootic pneumonia', 'shipping fever' or 'bovine respiratory disease complex', often used without precise definitions. Viruses and other stressors predispose cattle to opportunistic bacterial pneumonias, including bovine respiratory syncytial virus, parainfluenzavirus-3, infectious bovine rhinotracheitis virus, bovine herpes virus-1 and possibly bovine coronavirus (O'Neill RO, Mooney J, Connaghan E *et al.* Patterns of detection of respiratory viruses in nasal swabs from calves in Ireland: a retrospective study. *Vet Rec* 2014;**175**:351.). These viruses trigger BRD by damaging upper respiratory tract mucosa and/or modifying host pro- and anti-inflammatory immune responses. Bacterial BRD pathogens include *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, Arcanobacterium pyogenes*, *Mycoplasma dispar* and *M. bovis* that exist commonly as commensals, often as biofilms within the upper respiratory tract and tonsils. However, prevention through viral vaccines is a valid alternative to antibiotics, and macrolides are not an essential treatment for BRD with other non-CIA alternatives including- florfenicol, trimethoprim sulfadoxine, and oxytetracyclines. After oral administration, macrolides are absorbed incompletely (Pyörälä S, Baptiste KE, Catry B, van Duijkeren E, Greko C, Moreno M, Pomba C, Rantala M, Ružauskas M, Sanders P, Threlfall J, Torren-Edo J & Törneke K 2014 Macrolides and lincosamides in cattle and pigs: Use and development of antimicrobial resistance. *The Veterinary Journal* **200(2)**:230-239.). Macrolides antibiotics are eliminated mainly by the liver, with a variable part of the drug excreted in bile as the parent drug or metabolites. This leads to enterohepatic cycling and long terminal half-lives. These pharmacokinetic characteristics contribute to selection and persistence of AMR towards macrolides. As a result, more than 70 genes encoding for acquired macrolide resistance have been described hosted by more than 60 different bacterial species (Roberts, M.C., 2011. Environmental macrolide-lincosamide-streptogramin and tetracycline resistant bacteria. Frontiers in Microbiology 2,		

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	40.; van Hoek, A.H., Mevius, D., Guerra, B., Mullany, P., Roberts, A.P., Aarts, H.J., 2011. Acquired antibiotic resistance genes: An overview. Frontiers in Microbiology 2, 203.). Moderate-to-high levels of macrolide resistance has been in the EU for target animals pathogens, including nearly 100% for *Brachyspira spp*. in pigs, and variable levels in *Mannheimia haemolytica* in cattle (35%-France, 2008; 38%-Belgium, 2005) (AFSSA, 2009. French Antimicrobial Resistance Monitoring Program for Bacteria of Animal Origin. Report 2007–2008., Programme français 1999–2008, Vol. 2010. AFSSA.; Catry, B., Haesebrouck, F., Vliegher, S.D., Feyen, B., Vanrobaeys, M., Opsomer, G., Schwarz, S., Kruif, A.D., 2005. Variability in acquired resistance of Pasteurella and Mannheimia isolates from the nasopharynx of calves, with particular reference to different herd types. Microbial Drug Resistance 11, 387–394.). A multicenter study in some European countries revealed since 2008 that up to 22% of *Strep. uberis* and 17% of *Strep. dysgalactiae* isolates from bovine mastitis have been found to be resistant to erythromycin (Hendriksen, R.S., Mevius, D.J., Schroeter, A., Teale, C., Meunier, D., Butaye, P., Franco, A., Utinane, A., Amado, A., Moreno, M., et al., 2008. Prevalence of antimicrobial resistance among bacterial pathogens isolated from cattle in different European countries: 2002–2004. Acta Veterinaria Scandinavica 50, 28.); in a French study in 2010, 13–17% of *Strep. uberis* and 4–6% of *Strep. dysgalactiae* isolates from clinical and subclinical mastitis were already found resistant to erythromycin, spiramycin and lincomycin (Botrel, M.A., Haenni, M., Morignat, E., Sulpice, P., Madec, J.Y., Calavas, D., 2010. Distribution and antimicrobial resistance of clinical and subclinical mastitis pathogens in dairy cows in Rhone-Alpes, France. Foodborne Pathogens and Disease 7, 479–487.). Similarly, data from The Netherlands had already revealed that 43% of *Strep. uberis* and 8% of *Strep. dysgalactiae* were resistant to clindamycin (MARAN, 2007–2008. Monitoring of Antimicrobial Resistance and Antimicrobial Usage in The Netherlands in 2006–2008. http://www.cvi.wur.nl/NR/rdonlyres/A906A4C0-A458-423E-B932-28F222385988/83791/MARAN_2007_def3.pdf). For *Brachyspira* isolated from swine, high levels of macrolide resistance have been reported for tylosin in most EU countries, with close to 100% of the isolates being resistant (FINRES-Vet, 2005–2009. Finnish veterinary antimicrobial resistance monitoring and consumption of antimicrobial agents in 2005–2006. http://www.evira.fi/portal/en/evira/publications/?a=view&productId=17; SVARM, 2002–2010. Swedish Veterinary Antimicrobial Resistance Monitoring. http://www.sva.se/en/About-SVA/Reports-and-publications-in-english/Antibiotikaresistens/SVARM-rapporter/; MARAN, 2007–2008). Resistance to		

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	macrolides antimicrobials can develop rapidly in *B. hyodysenteriae* because only a single transversion mutation in one position of the 23S rRNA gene is required (Pringle, M., Landen, A., Unnerstad, H.E., Molander, B., Bengtsson, B., 2012. Antimicrobial susceptibility of porcine Brachyspira hyodysenteriae and Brachyspira pilosicoli isolated in Sweden between 1990 and 2010. *Acta Veterinaria Scandinavica* 54, 54.). For *A. pleuropneumoniae* isolated from swine, data are limited. In France, close to 80% of *A. pleuropneumoniae* were resistant to spiramycin, but only 2% to tilmicosin (AFSSA, 2009). In France in 2008, no resistance to tilmicosin was found in porcine isolates of *P. multocida*, but 86% of the isolates were resistant to tylosin (AFSSA, 2009). In selected EU countries in 2002, resistance of *Strep. suis* to erythromycin was 19–65% (Hendriksen et al., 2008). In France, resistance was reported to be as high as 72–77% towards spiramycin and tylosin and 69% for lincomycin (AFSSA, 2009). In the German surveillance data from 2008, 30–45% of isolates were resistant to erythromycin (BVL, 2008. Berichte Zur Resistenzmonitoringstudie 2008. Bundesamt für Verbraucherschutz und Lebensmittelsicherheit - BVL). According to the latest ESVAC report, the majority of EU member states have demonstrated a low consumption of macrolides, despite having sizeable food animal industries in some member states (European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2018. 'Sales of veterinary antimicrobial agents in 30 European countries in 2016'. EMA/275982/2018). Even Denmark, with the largest pig production in Europe, can manage an annual consumption under 5 PCU/kg. For example, 11/30 EU member states have >5 PCU/kg in the total annual consumption of macrolides in European veterinary antimicrobial sales. Some EU member states managed notable declines in macrolide sales for animals in 2016. For example, in Estonia the sales of macrolides decreased by 67 % in 2016 compared to 2015. In Germany, a 58 % decrease in the overall sales (mg/PCU) of veterinary antimicrobial agents was observed between 2011 and 2016, including a -69% in sales of macrolides. A change in the Swiss legislation forbidding stock delivery of products containing highest priority critically important antimicrobials lead to a strong reduction of 43% (4.29 mg/PCU in 2011 to 2.44 mg/PCU in 2016) in sales of this class. In Denmark, from 2010 to 2016, sales of macrolides decreased by 14%. In Portugal, the implementation of the National Action Plan for the Reduction of Use of Antibiotics in Animals, which emphasizes the need for the reduction of highest priority critically important antimicrobials for human medicine resulted in 2016 in a decrease in consumption (mg/PCU) of macrolides. Similar national action plans in Romania, Slovenia, Spain and the UK have resulted in declines in the sales of macrolides	It should be noted that Regulation (EU) 2019/6 includes various provisions in general around prescription of antimicrobials for metaphylaxis, including the need for diagnosis of an infectious disease by a veterinarian (Art 105) and restriction to use only when the risk of spread of infection in the group is high and when no other appropriate	

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	in 2016. In conclusion, we believe it would be necessary to place macrolides in Category B ("Restrict"). Restricting oral administration to groups of animals only to specific cases, and with specific diagnosis of bacterial disease, should be taken into consideration by the European Commission. **Aminopenicillins alone (without inhibitor)** Summary Will removing Aminopenicillins from 1st choice options (Category D) have a negative impact on animal health? No, high levels of ampicillin-resistance have already been identified for the major target pathogens in animals as well as indicator bacteria. Aminopenicillins will still be available for veterinary prescription but should NOT be used as 1st choice (Category D). No essential need for aminopenicllins in animals has been established where alternatives do not already exist. The Scandinavian countires have demonstrated lower consumption of aminopenicillins in animals with sizeable food animal industries in some member states. What alternatives are available in the EU for Aminopenicillins for animal diseases? Depending on the major target pathogen, several alternatives are available including SPF systems, vaccines and other non-CIA antimicrobials including natural (narrow-spectrum) penicillins, pleuromutilins, florfenicol, trimethoprim sulfadoxine and tetracyclines. Will removing Aminopenicillins from 1st choice options (Category D) have a positive impact on public health? Yes, moderate to high levels ampicillin-resistance have been identified in Europe for major zoonotic pathogens (e.g. *Salmonella spp*., LA-MRSA, *E. coli*). Reducing consumption of aminopenicillins is an important risk mitigation for preserving 3rd and 4th generation cephalosporins, since aminopenicillins select for the same antimicrobial resistant genes (e.g. AmpC gene family, CTX-M gene family, TEM/SHV mutants). The main criteria for placing Aminopenicillins alone (without inhibitor) appears to be based on a Aminopenicillin Reflection Paper written by AWP. The Aminopenicillin Reflection Paper is not finalised and work is suspended until after the finalization of the AMEG report. Thus, it is unclear as to why the conclusions of the Aminopenicillin Reflection paper are accepted	alternatives are available (Art 107(4)). It is agreed that non-antimicrobial infection and prevention control measures should be implemented as routine (see above). Some of the alternative antibiotic classes mentioned here were assessed by the AMEG of higher significance for public/animal health than aminopenicillins.	

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	by the AMEG at this time. Also, it is worth pointing out that the Aminopenicillin Reflection Paper does NOT actually recommend that aminopenicillins alone (without inhibitor) to be placed in Category D of the new AMEG classification system. Just before the release of the AMEG report for public consultation, some new text was added in Table 4 for aminopenicillins: "Narrow spectrum penicillins with a lower risk of AMR selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach." This new sentence actually strengthens the arguments ***against*** aminopenicillins as 1st choice in Category D. The AMEG finally acknowledges that narrow-spectrum penicillins are both a lower risk and should be used first; this is exactly the reasons that aminopenicillins should NOT be Category D. According to the EFSA (2019) report, both *Campylobacter spp*. and *Salmonella spp.* make up the majority of reported EU zoonosis cases. A high percentage of these cases were reported hospitalized cases, despite the fact that percentage of 'Status available' was low (Table 2; EFSA, 2019). Ampicillin resistance among human Salmonella cases was represented in the top three highest proportions of resistance in *Salmonella spp*. isolates from humans in 2017 (27.5% range:6.4%-81.4% - all non-typhyoid cases; 53.3% range:4.3%-85.7% - *S. Typhimurium* human cases) (EFSA, 2019). Ampicillin resistance in monophasic *Salmonella* Typhimurium 1,4,[5],12:i:- from humans is >80% in most EU countries (EFSA, 2019). The World Health Organization states that transmission of bacterial infection from non-human sources to humans, with the ability to cause disease, is more evident in particular bacteria, which includes non-typhoidal Salmonella. Additionally, a recent study inferred that multidrug-resistant nontyphoidal Salmonella infections may have more serious human health implications compared to those of pan-susceptible strains (Parisi A, Caruso M, Normanno G, Latorre L, Sottili R, Miccolupo A, Fraccalvieri R and Santagada G, 2016. Prevalence, antimicrobial susceptibility and molecular typing of methicillin-resistant Staphylococcus aureus (MRSA) in bulk tank milk from southern Italy. Food Microbiology, 58, 36–42. https://doi.org/10.1016/j.fm.2016.03.004). Furthermore, ampicillin can select for the Salmonella genomic island 1 (SGI1), known to contain a multi-drug resistant region located on a complex integron designated *In104*, which confers pentavalent resistance (ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline resistance phenotype) and has widely been documented in a range of	The following rationale is now included in Table 4 of the AMEG advice in regard to the Aminopenicillin class without β-lactamase inhibitors: 'Aminopenicillins are CIA in human medicine and are commonly used first line antimicrobials, but alternatives are available for most of the indications. Exceptions are infections with Listeria and with enterococci. In veterinary medicine aminopenicillins are VCIA, and important for treatment of infections in various animals, for example as first line treatment of urinary tract infections in companion animals and	

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	Salmonella serovars. In 2017, the monitoring of AMR in *Salmonella* isolates recovered from carcass swabs of fattening pigs and calves under one year of age at slaughter was mandatory, in accordance with Regulation (EC) No 2073/2005. Additionally, some MSs collected voluntary *Salmonella* AMR data from fattening pigs and cattle at slaughter, where one representative sample of caecal contents was collected per epidemiological unit (i.e. the holding) to account for clustering. The *Salmonella spp.* isolates from fattening pig carcasses corresponds with similar antimicrobial resistance patterns found in the human *Salmonella* data. For example, ampicillin resistance for pig *Salmonella* isolates was 53% (range 0-100%). A similar trend was found in ampicillin-resistance from isolates of *Salmonella spp*. recovered from caecal contents of fattening pigs at slaughter (54.9% range:0-76%) (EFSA, 2019). Carcass swabbing of calves (under 1 year of age) at slaughter revealed ampicillin-resistance among Salmonella at 24.4% (range: 0-66.7%), and 30% (range: 0-57.7%) from *Salmonella spp*. recovered from caecal contents of cattle at slaughter (EFSA, 2019). In EFSA 2018, ampicillin-resistance in *Salmonella spp*. from meat from broilers was 19.7% (range: 0-66.7%), and meat from turkeys was 23.1% (range: 0-60%). *Salmonella* Kentucky and from flocks of broilers, layers and turkeys is most concerning with 100% ampicillin-resistance in many EU member states. The Aminopenicillin Reflection paper concludes the following: "… it is currently **impossible to estimate** to what extent the use of these substances in animals, could create negative health consequences to humans at the population level. (Lines 123-126)" However, both the Aminopenicllin RP and AMEG report have NOT acknowledged the landmark European publication by Overdevest *et al*., (2011) (Overdevest I, Willemsen I, Rijnsburger M, Eustace A, Xu L, Hawkey P, Heck M, Savelkoul P, Vandenbroucke-Grauls C, van der Zwaluw K, Huijsdens X, and Kluytmans J 2011 Extended-Spectrum β-Lactamase Genes of Escherichia coli in Chicken Meat and Humans, the Netherlands. *Emerging Infectious Diseases* **17(7)**:1216-1222). This publication was one of the foundation issues that lead to change in Dutch antimicrobial policy regarding antimicrobial use in animals. The study determined the prevalence and characteristics of extended-spectrum β-lactamase (ESBL) genes of Enterobacteriaceae in retail chicken meat and humans in the Netherlands. Raw meat samples (262: chicken n=89; beef n=85; pork n=57; mixed or	respiratory tract infections in pigs, when group treatment is warranted. Use of aminopenicillins selects for betalactam resistance. Narrow spectrum penicillins with a lower risk of AMR selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach. Resistance is widespread in bacteria from both humans and animals. A range of different types of transferable resistance genes and mechanisms occur. Because of this, it is difficult to estimate to what extent use in animals may contribute to negative health effects in humans. The aminopenicillins class is thus placed in category D rather than in C'. In addition, the following is included in regard to Aminopenicillins in combination with β-lactamase inhibitors: 'CIA in human medicine. VCIA in veterinary medicine as there are few or no antibiotic alternative treatments presenting a lesser risk available for certain indications in veterinary medicine. Use of amoxicillin-clavulanate selects for resistance towards penicillins and cephalosporins including the higher generation cephalosporins in both Gram-	

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	ground meat n=22; other types of meat n=9) were obtained, and simultaneous cross-sectional surveys of human fecal carriage (927 rectal swab specimens from 876 patients: 461 male patients and 415 female patients, mean ± SD age 65.7 ± 16.8 years) were performed in four hospitals in the same area. Human blood cultures (31 clinical blood cultures) from these hospitals that contained ESBL genes were also included. A high prevalence of ESBL genes in bacteria were found in chicken meat (79.8%). A genetic analysis showed that the predominant ESBL genes in chicken meat and human rectal swab specimens were identical. These genes were also frequently found in human blood culture isolates. Based on multilocus sequence typing (MLST), the results of *Escherichia coli* strains showed a high degree of similarity between meat and humans. MLST results of 158 ESBL-positive *E. coli* strains isolated from chicken meat, other meat types, rectal swab specimens, and blood cultures showed a heterogeneous population that contained several clusters. Most clusters contained similar-to-identical strains isolated from both meat and humans. In other words, there were significant genetic similarities – based on the analysis of mobile resistance elements, virulence genes and genomic backbone – and concluded that chicken meat is a likely contributor to the recent emergence of ESBL-producing *E. coli* in human infections in the study region. MLST is a reference and well recognised molecular biology technique used today, very useful to reveal an insight into relatedness of a bacterial population structure level. Thus, it is not correct in the conclusions of the Aminopenicillin RP that it impossible to estimate the negative health consequences to humans at a population level. It is further noteworthy to point-out that a relative decrease from 44% to 25% in Dutch human carriage of CTX-M-1–like ESBL genes was observed over a 5-year period, coinciding with a >60% decrease in antimicrobial use in food animals in the Netherlands (Willemsen I, Oome S, Verhulst C, Pettersson A, Verduin K, Kluytmans J. 2015 Trends in extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae and ESBL genes in a Dutch teaching hospital, measured in 5 yearly point prevalence surveys (2010-2014). *PLoS One*; 10:e0141765.). This reduction in Dutch human carriage corresponded in-time with a reduction in extended-spectrum β-lactamase (ESBL) and plasmidic AmpC (pAmpC) producing *Escherichia coli* in food animals, especially broilers. For example, between 2009 and 2014 the total sales of antibiotics in veterinary medicine decreased by 58%, in the Netherlands. For example, in 2014 the ESBL/pAmpC *E. coli* prevalence in poultry meat was 67%, which was lower than found in 2013 (83%) and in 2012 (73%) (MARAN. Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2014. Lelystad, http://www.wageningenur.nl/upload_mm/2/2/2/0ab4b3f5-1cf0-42e7-a460-d67136870ae5_NethmapMaran2015.pdf). Human populations are exposed to	negative bacteria (ESBL) and in staphylococci (MRSA). Compared to aminopenicillins alone, amoxicillin-clavulanate has a wider spectrum and thereby a higher selection pressure for multidrug resistant organisms. Aminopenicillins with enzyme inhibitor are therefore in category C rather than in category D.'	

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	ESBL/pAmpC *E. coli* from food animals through direct contact (farm and slaughter-house workers), consumption of raw food products (filet americain, tartar and ossenworst) and the cooking preparation process by the consumer (heating and cross-contamination) followed by consumption. For example, a Belgian study assessing human exposure to 3rd generation cephalosporin-resistant *E. coli* found that the probability to be exposed to 10 CFU or more by the consumption of chicken meat was 7.0% (Depoorter P, Persoons D, Uyttendaele M, Butaye P, De Zutter E, Dierick K, et al. Assessment of human exposure to 3rd generation cephalosporin resistant E. coli (CREC) through consumption of broiler meat in Belgium. Int J Food Microbiol. 2012; 159:30±8. doi: 10.1016/j.ijfoodmicro.2012.07.026). Evers *et al*. (2017) found that a probability to be exposed to 1 CFU or more by the consumption of chicken meat of 6.85% with a mean exposure of 1.75 CFU per contaminated portion (Evers EG, Pielaat A, Smid JH, van Duijkeren E, Vennemann FBC, Wijnands LM, et al. 2017 Comparative Exposure Assessment of ESBL-Producing *Escherichia coli* through Meat Consumption. PLoS ONE 12(1): e0169589. doi:10.1371/journal.pone.0169589). Both Depoorter *et al*. (2012) and Evers *et al*. (2017) concluded that the majority of exposure through chicken meat was caused by cross-contamination. EFSA has ranked the *bla*CTX-M-1, *bla*CTX-M-14, *bla*TEM-52 and *bla*SHV-12 as the most common ESBL genes found in food-producing animals (EFSA. Scientific Opinion on the public health risks of bacterial strains producing extended-spectrum β-lactamases and/or AmpC β-lactamases in food and food-producing animals. *EFSA J.* 9(8), 2322 2011). The dissemination of these genes is more related to a horizontal transmission of these genes than to the spread of clones. These genes have been mainly associated with ESBL-producing *E. coli* and nontyphoidal *Salmonella* (e.g., *S*. Typhimurium, *S*. Newport and *S*. Heidelberg) found in healthy and diseased food-producing animals (e.g., calves, cattle, poultry and pigs) (Smet A, Martel A, Persoons D *et al*. Broad-spectrum β-lactamases among Enterobacteriaceae of animal origin: molecular aspects, mobility and impact on public health. *FEMS Microbiol. Rev.* 34(3), 295–316 2010). The ESBL genes have been found in poultry and/or poultry meat samples (Cloeckaert A, Praud K, Doublet B *et al*. 2007 Dissemination of an extended-spectrum-β- lactamase *bla*TEM-52 gene-carrying IncI1 plasmid in various *Salmonella enterica* serovars isolated from poultry and humans in Belgium and France between 2001 and 2005. *Antimicrob. Agents Chemother.* 51(5), 1872–1875.; AgersØ Y, Aarestrup FM, Pedersen K, Seyfarth AM, Struve T, Hasman H. 2012 Prevalence of extended-spectrum cephalosporinase (ESC)-producing *Escherichia coli* in Danish slaughter pigs and retail meat identified by selective enrichment and association		

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	with cephalosporin usage. *J. Antimicrob. Chemother.* 67(3), 582–588.), as well as *bla*CTX-M-1 as widely spread among food-producing animals. According to Leverstein-van Hall *et al*. (2011), the genetic correlation among *bla*CTX-M-1-producing isolates from human, poultry and poultry meat and the sequence types of IncI1 plasmids revealed that the transmission of CTX-M-1-producing isolates between food-producing animals and humans can occur through the food chain (Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J *et al*. 2011 Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin. Microbiol. Infect.* 17(6), 873–880.). Furthermore, a study by Dohmen *et al*., 2017 concluded that improved biosecurity, especially the presence of a hygiene lock, and pest control by a professional, were related to lower probabilities of farms being infected with extended spectrum beta-lactamase (ESBL)-*Escherichia coli* (Dohmen W, Dorado-García A, Bonten MJ et al. 2017 Risk factors for ESBL-producing Escherichia coli on pig farms: A longitudinal study in the context of reduced use of antimicrobials. PLoS One.12:e0174094.). Additionally, recent studies based on deep, whole genome sequence-based characterization and cluster analysis have demonstrated that ESBL-producing clones of "pure" zoonotic major pathogens like some *Salmonella* serovars, such as S. Infantis selected in food-producing animals, are transferred to humans via the food chain and have been causing human disease (Franco A, Leekitcharoenphon P, Feltrin F, Alba P, Cordaro P, Iurescia P, Tolli P, D'Incau M, Staffolani S, Di Giannatale E, Hendriksen RS, Battisti A: Emergence of a Clonal Lineage of Multidrug-Resistant ESBL-Producing Salmonella Infantis Transmitted from Broilers and Broiler Meat to Humans in Italy between 2011 and 2014. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0144802). Such *Salmonella* clones can acquire and disseminate not only transferable ESBL genes, but at the same time also transferable colistin resistance genes (Carfora V, Alba P, Leekitcharoenphon P, Ballarò D, Cordaro G, Di Matteo P,Donati V, Ianzano A, Iurescia M, Stravino F, Tagliaferri T, Battisti A, Franco A. Colistin Resistance Mediated by mcr-1 in ESBL-Producing, Multidrug Resistant Salmonella Infantis in Broiler Chicken Industry, Italy (2016-2017). Front Microbiol. 2018 Aug 17;9:1880. doi: 10.3389/fmicb.2018.01880. eCollection 2018). *E. coli* are important indicator bacteria in food animals as well as representing pathogens that can be zoonotic (e.g. ESBLs) or transferring resistant determinants to human-adapted clones. Ampicillin-resistance continues to be high in food animal *E. coli* isolates as well as part of the selection pressure for multi-resistant determinants that includes resistance to		

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	3rd & 4th generation cephalosporins (e.g. AmpC gene family, CTX-M gene family, TEM/SHV mutants) (also see Table 32; EFSA 2019). It is well known, and already been demonstrated in pigs, that besides ceftiofur or cefquinome (3rd-4th generation cephalosporins), the administration of amoxicillin results in the selection of ESBL(CTX-M)-producing *E. coli* in the intestinal flora (Cavaco LM, Abatih E, Aarestrup FM, Guardabassi L. 2008 Selection and persistence of CTX-M-producing *Escherichia coli* in the intestinal flora of pigs treated with amoxicillin, ceftiofur, or cefquinome. Antimicrob Agents Chemother. 52(10):3612-6. doi: 10.1128/AAC.00354-08.). Additionally, the semi-continuous use of oral aminopenicillins may also enhance the mutation rate of wild type beta-lactamase such as TEM-1 and SHV-1 that are widespread in *Enterobacteriaceae* from food-producing animals, and cause the spread of TEM- or SHV- ESBL, such as SHV-12 or TEM-52. Indeed, these ESBL genes have been already reported in food-producing animals by almost all EU Members States. Thus, placing aminopenicillins in Category 'D' directly counteracts the restrictions called for in 3rd & 4th generation cephalosporins, since aminopenicillins select the same highly mobile ESBL genes found in *E. coli* and *Salmonella spp*. Furthermore, ampicillin-resistance in indicator *Escherichia coli* from fattening pigs is at 38.5% (range: 8.6%-77.1%), and 29% (range: 1.7%-63.5%) in indicator *Escherichia coli* from calves under one year of age. In EFSA 2018, ampicillin-resistance in *E. coli* from broilers was high at 58% (range: 8.7%-100%), with 57.7% ampicillin-resistant *E. coli* in meat from broilers. In fattening turkeys, ampicillin-resistance in indicator *Escherichia coli* was 64.6% (range: 8.2%-85.9%), and 71.5% resistance in meat from turkeys. Since the usage of 3rd & 4th generation cephalosporins in poultry has never been authorised, then under current EU conditions, ESBL and AmpC-producing *E. coli* and *Salmonella* are persisting also by the selection pressure with antibiotics other than 3rd & 4th generation cephalosporins. Nevertheless, the most prevalent genes encoding for ESBL (e.g. CTX-M-1 family, SHV-12, and AmpC (e.g. CMY2) in Enterobacteriaceae are located on transferable elements (e.g. plasmids); this means that whether clones of the bacterial hosts in animals and humans are identical is NOT relevant, since transferable genes from animal-associated ESBLs can easily transfer to human bacterial clones. Plasmids do transfer many other different genes including AMR genes encoding for resistance to HPCIAs (WHO) (e.g. *cfr* gene, *erm* genes, *mcr* genes, carbapenemase-encoding genes etc.) across different clones and species (e.g. from an *E. coli* to another *E. coli*, or from one *E. coli* to one *Salmonella* etc.).		

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	The Aminopenicillin Reflection paper describes differences in beta-lactam antimicrobial consumption between Scandinavia and other parts of Europe. In the Aminopenicillin Reflection paper it states the following from ESVAC data: - "Extended spectrum penicillins (ampicillin, amoxicillin, and their inhibitor combinations) made up the major proportion (88%, 30.0 mg/PCU) of the total use of penicillins (Figure 2), although wide variation between the member states was observed. There were only six European countries (Denmark, Finland. Iceland, Luxembourg, Norway, Sweden) in which beta lactamase sensitive penicillins (benzyl penicillin, penethamate, phenoxymethylpenicillin) contributed more than half of the total beta-lactam sales, while in 23 out of 30 countries, amoxicillin and ampicillin consumption contributed more than half of the total penicillin sales. Aminopenicillins and their inhibitor combinations formed a very limited fraction of the total sales of aminopenicillins both at the European level (1%, 0.3 mg/PCU) and by country (Figure 2 and Figure 3)." (Lines 641-649) Scandinavia also have sizeable food animal production systems, where they have demonstrated that it is possible to use narrow-spectrum penicillins as first choice/major choice and not extended-spectrum beta lactam drugs. - Aminopenicillins are marketed for respiratory infections in cattle (treatment and metaphylaxis), including Europe particularly for *Mannheimia haemolytica,* and *Pasteurella multocida* that exist commonly as commensals, often as biofilms within the upper respiratory tract and tonsils. However, beside alternatives such as a preventive approach by using viral vaccines, aminopenicillins are not an essential treatment for BRD with other non-CIA alternatives including florfenicol, trimethoprim sulfadoxine, and oxytetracyclines. - Aminopenicillins are marketed for respiratory infections in swine (treatment and metaphylaxis), including Europe particularly for *Actinobacillus pleuropneumoniae*, *Streptococcus suis* and *Pasteurella multocida*. However, aminopenicillins are not an essential treatment for SRD with other non-CIA alternatives including florfenicol, penicillin (*Streptococcus suis*), trimethoprim sulfadoxine, and tetracyclines. - Aminopenicillins are marketed for infections in poultry (gram positive and necrotic enteritis). "Despite years of use, penicillin G is still an effective antimicrobial for Gram-positive bacterial infections in poultry. This drug is particularly important for the therapy of clostridial infections causing necrotic enteritis (Gadbois P, *et al*.		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	2008. The role of penicillin G potassium in managing *Clostridium perfringens* in broiler chickens.Avian Dis 52:407.). The one Gram-negative bacterium routinely treated with penicillin is *Pasteurella multocida*." (Hofacre CL, Fricke JA, and Inglis T 2013 Antimicrobial Drug Use in Poultry. Antimicrobial In Therapy in Veterinary Medicine Fifth Edition. Eds., Giguère S, Prescott JF, and Dowling PM). "The broader-spectrum beta-lactams, such as ampicillin and amoxicillin, theoretically are more effective for Gram-negative infections such as *E. coli* airsacculitis; however, there is limited data published on the use and clinical efficacy of these medications in poultry species." (Hofacre CL *et al*., 2013). Thus, aminopenicillins are not an essential "first choice" treatment for poultry with other non-CIA alternatives including narrow-spectrum penicillcin (e.g. phenoxymethylpenicillin), trimethoprim sulfadoxine, pleuromutilins and tetracyclines. In conclusion, it is not justified to have aminopenicillins as 1st choice (Category D) in the AMEG classification system. A suitable option could be to classify aminopenicillins in a category of "intermediate risk", i.e. one-step lower that potentiated aminopenicillins (in Veterinary medicine= amoxicillin+ clavulanic acid), or classify them the same as potentiated aminopenicillins. Here we further observe that the term "lower" does not mean "low", since the amount of usage of aminopenicillins alone (and the pattern of usage) in food-producing animals in the EU is high, while it is very high in certain MSs, and the selection pressure exerted by aminopenicillins alone is highly relevant. In some EU countries (including Italy), sales (in mg/PCU) of aminopenicillins can be 200 times higher than those of 3rd & 4th generation cephalosporins. This implies that higher levels of awareness should be raised to animal primary production systems, and among veterinary practitioners. Actions should to be taken to reduce the use of aminopenicillins, which are "typically" used by oral route and for "mass medication" (including prophylaxis/metaphylaxis), in food-producing animals. **Aminoglycosides** According to the previous criteria of the AMEG, then Aminoglycosides would be classified in Category 2. However, based on a non-quantified belief of a lower risk of veterinary-use of aminoglycosides to human health compared with (fluoro)quinolones and 3rd and 4th generation cephalosporins then the AMEG has classified aminoglycosides in Category C. It is worth pointing out that aminoglycosides represent the only CIA that are also used to treat protozoal diseases in animals. For example, paromomycin is used to treat	The following rationale for categorisation of the Aminoglycosides (except spectinomycin) has been included in	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	Cryptosporidia, *Giardia*, *Leishmania*, *Entamoeba histolytica* and *Balantidium coli* (Barr SC, Jamrosz GF, Hornbuckle WE, Bowman DD, and Fayer R 1994 Use of paromomycin for treatment of cryptosporidiosis in a cat. JAVMA 205(12):1742-1743.; Belloli C, Crescenzo G, Carli S, Villa R, Sonzogni O, Carelli G, and Ormas P 1996 Pharmacokinetics and dosing regimen of aminosidine in the dog. Vet Res Commun 20:533-541.; Poli A, Sozzi S, Guidi G, Bandinelli, and Mancianti F 1997 Comparison of aminosidine (paromomycin) and sodium stibogluconate for treatment of canine leishmaniasis. Vet Parasitol 71:263-271.). VMPs containing paromomycin are actively marketed on the European market for the prevention of cryptosporidium in calves. Cryptosporidium in calves is one of the most common causes of diarrhea in calves. Off-label use of aminosidine/paromomycin for the prevention or metaphylaxis/therapy of histomoniasis in turkey may be among the risk factors associated with the levels of gentamicin resistance in indicator commensal *E. coli* and Salmonella from turkeys in some Member States in 2014 (up to 22% and 30% respectively), as reported in the EFSA-ECDC Joint Summary Reports on Antimicrobial Resistance in EU (EFSA-ECDC, 2015). There are no products containing paromomycin approved for use in food-producing animals in the United States. Thus, it is unclear as to how the AMEG assessed a lower risk of veterinary-use of aminoglycosides to human health compared with (fluoro)quinolones and 3rd and 4th generation cephalosporins, when aminoglycosides are used against common non-bacterial protozoal diseases. Another example of non-prudent use of aminoglycosides occurs with apramycin. Apramycin is the major aminoglycoside responsible for the emergence, spread and persistence of apramycin-gentamicin resistance in cattle, since it was licensed for veterinary use in 1980s, mediated by the *ACC(3)*IV genes and carried by various conjugative plasmids (Wray C, Hedges RW, Shannon KP, Bradley DE. Apramycin and gentamicin resistance in Escherichia coli and salmonellas isolated from farm animals. J Hyg (Lond). 1986 Dec;97(3):445-56). Also, apramycin use in animals has been identified as responsible for apramycin-gentamicin resistance in zoonotic Salmonella (e.g. S. Typhimurium) and other Enterobacteriaceae causing disease both in animals and in humans (Threlfall EJ, Ward LR, Rowe B. R plasmids in Salmonella typhimurium in the United Kingdom. *J Antimicrob Chemother*. 1986 Suppl C:175-7; Threlfall EJ, Rowe B, Ferguson JL, Ward LR. Characterization of plasmids conferring resistance to gentamicin and apramycin in strains of Salmonella typhimurium phage type 204c isolated in Britain. *J Hyg (Lond)*. 1986 97(3):419-26; Pohl P, Glupczynski Y, Marin M, Van Robaeys G, Lintermans P, Couturier M. Replicon typing characterization of plasmids encoding resistance to gentamicin and apramycin in Escherichia coli and Salmonella typhimurium isolated from human and animal sources in Belgium. *Epidemiol Infect*. 1993 111(2):229-	Table 4: Aminoglycosides/aminocyclitols, except for spectinomycin, are CIA in human medicine. Aminoglycosides are VCIA in veterinary medicine and one of few treatment options presenting a lesser risk for Pseudomonas infections in companion animals and horses and weaning diarrhoea due to Enterobacterales in pigs. There is a high potential for transmission of resistance determinants e.g. 16S mRNA methylases between animals and humans. Patterns of cross-resistance are complex. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides other than spectinomycin are in cat C rather than in category B. For spectinomycin there is no/limited cross-resistance to the other aminoglycosides and it is therefore in category D.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	38; Johnson AP, Burns L, Woodford N, Threlfall EJ, Naidoo J, Cooke EM, George RC. Gentamicin resistance in clinical isolates of Escherichia coli encoded by genes of veterinary origin. *J Med Microbiol*. 1994 40(3):221-6; Wall PG, Morgan D, Lamden K, Griffin M, Threlfall EJ, Ward LR, Rowe B. Transmission of multi-resistant strains of Salmonella typhimurium from cattle to man. *Vet Rec*. 1995 136(23):591-2). In recent years, apramycin has been licensed in the EU for oral administration in poultry for colibacillosis. Colibacillosis is a systemic disease (multi-organ disease) caused by Avian Pathogenic *E. coli* (APEC). It is well known that APEC strains cause pulmonary or systemic infection following a respiratory exposure, not via the intestinal route (i.e. as a consequence of an enteritis). However, oral apramycin is marketed for the treatment of colibacillosis, despite the fact it is not appreciably absorbed by the gastrointestinal tract. This indication represents a non-prudent option to prevent or control avian colibacillosis. The philosophy exercised is that a reduction of the environmental contamination by APEC in the farm, via decolonisation of the GI tract will somehow improve flock management. It is neither scientifically sound nor cost beneficial. There are many other methods for reducing the environmental contamination by opportunistic pathogens (i.e. cleaning and disinfection procedures etc.). This approach using apramycin is untargeted because in order to reduce a minor representative (when really present) among the *E. coli* gastrointestinal and environmental populations of the flock, apramycin usage destroys many useful commensal *E. coli* sub-populations, creating dismicrobism, making animals more prone to disease. Additionally, it exerts selection pressure which favours the emergence, spread and persistence of gentamicin-apramycin resistance in animal pathogenic and in major zoonotic bacteria.		
26	**Categorizations should guide prudent use** Treatment of infectious diseases in food animals may require the administration of antimicrobials to meet the welfare and health needs of these animals. If equally effective treatment options include alternative antimicrobial classes, the principles of prudent use determine that the class with the lowest relative antimicrobial resistance risk should be the preferred alternative. Various competent authorities and international agencies have published antimicrobial categorizations on the relative medical importance and antimicrobial resistance risks of different classes of antimicrobials to provide guidance to veterinarians and the community at large. The community value of these categorizations	See previous comments. Although the categorisations from WHO and OIE have been used as a basis, the AMEG's categorisation both in 2014 and 2017 has been prepared from the perspective of human and veterinary antimicrobial use in the EU.	22.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	relies on the effectiveness and accuracy of the rankings to guide prescribing veterinarians to select low medical importance/low risk classes rather than high importance/high risk antimicrobial classes. Throughout EMA/CVMP/CHMP/682198/2017 (EMA-AMEG-17), the document recognizes the importance of appropriate categorization to drive prudent use. The authoring Expert Group succinctly summarizes the obligatory nature of this nexus in lines 845-846: "*The categorisation should also be considered as a guidance tool for assessing the importance of antimicrobials when implementing prudent use measures.*" The scope of AMEG-17 captures the WHO Critically Important and Highly Important antimicrobial classes, which appear unchanged from the predecessor document EMA/381884/2014 (EMA-AMEG-14), although it is noted that the streptogramin class was not included in AMEG-14, but has been included in AMEG-17. The current edition of the WHO Critically Important Antimicrobials for Human Medicine (5th edition) ranks the streptogramin class as "Highly Important", which is below the HPCIA and CIA groups, but above the "Important" group. It is unclear what functional utility the AMEG is seeking to achieve by departing from the underlying WHO categorization schema to place the streptogramins in the AMEG category designated as the most restrictive. That is more restrictive than the HPCIAs and CIAs, particularly as in this revision the Expert Group chose to downgrade some designated WHO HPCIAs. **European Parliament legislates for international coordination** European Parliament Regulation 2019/6 recognises the value of international collaboration and coordination in the fight against antimicrobial resistance: "(41)… … a global public health concern that affects the whole of society and requires urgent and coordinated intersectoral action in accordance with the 'One Health' approach." "(48) The prudent use of antimicrobials is a cornerstone in addressing antimicrobial resistance. All the stakeholders concerned should together promote prudent use of antimicrobials. It is therefore important that guidance on the prudent use of	Category A includes (sub) classes not authorised in veterinary medicine **in the EU** – now clarified in the report - but which are (or have been) authorised in human medicine in the EU. Novel substances to human use authorised after publication of this advice will also be included in Category A subject to further evaluation by AMEG. The indications, dosing regimen, formal AMR risk assessment and risk management measures that accompany use of an authorised veterinary medicine are not available for use of Category A classes in animals; therefore, their use might lead to an additional risk to public health. Please also see further responses in this document.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	antimicrobials in veterinary medicine be taken into account and further elaborated." "(49) It is important to consider the international dimension of the development of antimicrobial resistance when assessing the benefit-risk balance of certain veterinary antimicrobials in the Union… …measures restricting the use of veterinary antimicrobials in the Union should be based on scientific advice and should be considered in the context of cooperation with third countries and international organisations. For those reasons, it should also be ensured, in a non-discriminatory and proportionate manner…" **<u>Introduction of previously excluded streptogramin antimicrobials in AMEG-17</u>** The revised draft categorization of antimicrobials in EMA-AMEG-17 generally provides a proportional and well ranked categorization consistent with European Parliament Regulation 2019/6. There is, however, a striking exception to the general conformity with Regulation 2019/6 that is related to the addition of the streptogramin antimicrobial class and its inclusion in the most restrictive "Category A". The Expert Group recommends veterinary use of Category A compounds be "Avoided", consequently compounds from Category B, C or D are encouraged by AMEG for food animals use when streptogramins would actually present a lower risk to human health. Noting the EMA-AMEG-17 technical discussion describes the Streptogramin class to be "considered obsolete" in human medicine, this placement appears to be at odds with the concept of prudent use, the European Parliament recent Legislation and the Expert Group's reflection on the role of Categorization and stated Risk Management hierarchy (Lines 38-43, and elsewhere). The placement of streptogramins in Category A is apparently due to a mechanical approach being applied to this category, rather than the outcome of a science/risk determined process. As such, the outcome appears to be inconsistent with the intent of the European Parliament, the Expert Group itself and the principles of prudent use guidance. It is		

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	assumed that this unintended consequence arose from the Expert Group's self-tasked amendment of the categorization criteria. The assertion of this mechanical procedure resulting in an outcome that was likely unintended by the AMEG is based on: • The AMEG had not included streptogramins in the AMEG-14 process while other equivalent and lower WHO categorized (HIA, IA) antimicrobials were included. This suggests that the current AMEG-17 draft categorization is not a reinforcement of a previously considered ranking, but an initial draft position that will be more completely considered following comments from stakeholders during the public consultation period before the final categorizations of this edition are submitted to the European Commission as the EMA & AMEG's fully considered "**Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals**" • It being illogical for an internationally recognized Expert Group to note that the streptogramin class is considered functionally obsolete in human medicine, but then categorize this class in a manner that recommends the use of WHO HPCIAs and CIAs use in veterinary medicine in preference to streptogramins. This would directly contradict the endorsement of prudent use described in EMA-AMEG-14 & 17, European Parliament Regulation 2019/6 and many other international documents describing prudent use so is presumably not intended. • The Category A placement does not seem to conform to the revised categorization criteria of EMA-AMEG-17. Specifically, the "not currently approved for veterinary medicine" criteria is repeated many times through EMA-AMEG-17 and in fact is carried over from the predecessor 2014 document. The criteria is specifically contextualized in lines 814 to 818 of AMEG-17 which states: **"Category A… … includes antimicrobial classes not currently authorised in veterinary medicine",**		

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	while **"Category B… …[includes] those which are not authorised as veterinary medicines <u>in the EU</u>".** This clarification of context is consistent with the European Parliament Regulation 2019/6 and supports the contention that when the assessment criteria of AMEG-17 is followed the streptogramins should be not be placed in Category A. The AMEG-17 draft includes detailed sections on streptogramins to address: medical utility ("obsolete" – implying lower medical utility than any other antimicrobial); relevant resistance genes (same or fewer than lincosamides or macrolides and other Category C and D antimicrobials); and likelihood for transfer of resistance genes profile (similar to antimicrobial classes placed in Category C and D). Accordingly, the assessments already performed by AMEG-17 presents a lower risk profile than bacitracin (Cat D) supporting that the streptogramin profile may be consistent with Category D. Streptogramins were not included in the 2014 AMEG categorization (EMA-AMEG-14). As per section 4.3 of that document, the category included compounds "…not currently approved in veterinary medicine… … as maximum residue limits (MRLs) have not been established to allow their use in food producing animals." The categorization criteria for the AMEG-17 update were changed to omit the reference to the establishment of MRLs. Virginiamycin, the veterinary streptogramin is both widely approved for use in veterinary medicine, and has established MRLs for food animal species in many countries. European Union MRLs were established by the EMA in 2015, that is, after the 2014 AMEG report, but prior to the AMEG-17 draft revision. Based on the preceding material, it is hoped that this apparent mis-categorization of streptogramins in the draft for public consultation may be redressed during the revision phase prior to EMA-AMEG-17 being presented to the European Commission. An appropriate revision at this stage would avoid unnecessary international confusion, reinforce prudent antimicrobial selection globally, and support the validity of the review	Although MRLs have now been established for virginiamycin in Europe, no marketing authorisation has been granted yet. Should the situation change, the categorisation of streptogramins will be reviewed.	

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	process underlying EMA-AMEG-17. **<u>Consideration of genes conferring resistance to streptogramins</u>** While AMEG has summarized the medical utility of the streptogramins as "considered obsolete", the committee does note specific resistance genes, specifically those of the MLSb group and the cfr gene, confer resistance to high-value human antimicrobials and may also confer reduce sensitivity or resistance to streptogramins. The selection of the MLSb genes is widely regarded to result from the use of macrolides, the naming of the type *erm* (erythromycin ribosome methylation) genes reflecting this origin. The cfr gene selection is associated with the use of the human oxazolidinone, linezolid, however, it is hypothetically possible and maybe implied in EMA-AMEG-17 that streptogramins use in animals may potentially select for the *cfr* resistance genes which could ultimately compromise human linezolid therapy. It is not possible to demonstrate the negative case: that veterinary streptogramins use could definitively not have this selection role with regard to MLSb and *cfr* genes, however, it is highly implausible that streptogramins would select for MLSb resistance as this only confers streptogramin-b resistance without reducing streptogramin-a effectiveness. Unlike the situation for macrolides or lincosamides for which MLSb correlates with resistance, a bacterium would derive almost no biological advantage from the carriage of the MLSb determinants in the presence of streptogramin antibiotics which include both a and b factors. The *cfr* gene does confer resistance to streptogramin-a, and accordingly the combined streptogramin a + b compound. This is also true of cfr resistance with regard to phenicols, lincosamides, pleuromutilins and 16 member macrolides (Shen *et al*, line 1449 EAM-AMEG-17). The hypothetical potential for these classes to select for cfr resistance against linezolid therapy is not a differentiating criteria for the relative importance categorization of these antimicrobial classes by AMEG or similar bodies. As AMEG has placed other classes impacted by cfr resistance, notably the phenicols, lincosamides, pleuromutilins and 16 member macrolides in Category C, streptogramins should be categorized no higher than Category C based on consideration of the cfr gene. The same rationale can be applied		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	to categorization considerations of the MLSb gene. **<u>Medical and Veterinary Utility of Streptogramins</u>** The EMA / AMEG-17 states the streptogramin class is considered medically obsolete. While no veterinary streptogramin has a current marketing authorisation in the European Union, virginiamycin is an important agent for necrotic enteritis in chickens and ruminal acidosis/liver abscess complex in cattle outside the EU. Virginiamycin provides an effective therapy for these diseases combined with a very low AMR risk profile as the streptogramin class has such a low medical utility. There are other antimicrobials available for these veterinary diseases (macrolides, lincosamides), however, no other class provides the equivalent prudency combination of high veterinary efficacy and such low medical importance. Virginiamycin is approved in most of the major chicken and cattle producing countries of the world. It is noted that in 2015 the EMA published MRLs for virginiamycin for poultry species and tissues following a submission of supporting data by the sponsor. This EMA received prior advice from the sponsor that the MRL application would be a precursor to a subsequent EU marketing authorization. **<u>The 'Use in veterinary medicine' categorization criterion</u>** Placing streptogramins in Category A appears to be inconsistent with the overall international objectives of prudent guidance and those expressed by the European Parliament in Regulation 2019/6. The veterinary streptogramin virginiamycin is widely approved for veterinary medicine. Accordingly, it is appropriate to include streptogramins in the EMA-AMEG categorization. The 'use in veterinary medicine criteria' of AMEG-14 was not limited to use in the EU (ref		

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	AMEG-14 and lines 52-63 AMEG-17) and was described consistently throughout that document. The 'use in veterinary medicine criteria' is inconsistently phrased throughout AMEG-17 in some locations in the draft document it carries the additional text "…in the EU.", while in other locations it does not (lines: 736, 751, 815, 818, 826, elsewhere). Specifically lines 815, 818 and 826 support that only classes not approved at all in veterinary medicine meet the criteria for Category A. As noted elsewhere in this document there no suggestion that AMEG-17 would be seeking to do anything other than build on the work of AMEG-14, incorporate the direction from the European Parliament and support the global battle to combat antimicrobial resistance. As the "veterinary use" criterion is inconsistently presented throughout the AMEG-17 draft it is suggested that this can be resolved by uniformly considering any global approval for veterinary use as the criterion for EXCLUSION from Category A. As an alternative, the AMEG-17 may wish to consider EXCLUDING form Category A any antimicrobial class approval for veterinary use, OR, having EMA assessed and approved MRL(s) as both endorsements by EU competent authorities clearly confirm formal assessment and acceptability of the use of these antimicrobial classes in food animals. **<u>Summary</u>** The EMA-AMEG in strongly requested to amend the current draft to re-categorise streptogramins according to the stated scientific criteria and the assessed "obsolete" medical importance of this class. We note that the modification of the 'veterinary approval' criteria has changed from AMEG-14 and is inconsistently described throughout AMEG-17. Noting the European Parliament Regulation 2019/6 calls for the EU to take a global approach to combatting AMR two clarifications are proposed: that the criteria of AMEG-14 be retained. That is antimicrobials NOT be included in Category A if they 1. Are "approval for use in veterinary medicine" (no limitation to EU approvals only) 2. Are approved for use in veterinary medicine in the EU, or have one or more EU	See comments above.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	approved MRLs. We respectfully note that the “obsolete” description for human medicine is not consistent with the endorsed importance ranking of Category A and its related use directive of “Avoid”. As AMEG-17 has not determined any other antimicrobial class cited in EMA-AMEG-14 or 17 to be “obsolete” in human medicine the streptogramins are logically the least important antimicrobial class by AMEGs assessment. Additionally, considerations of other resistance issues (genes, transfer mechanisms) addressed in the AMEG-17 document with respect to streptogramins have allowed placement of those classes as low as Category D. Based on the scientific assessments of streptogramins presented in the draft AMEG-17 we request the EMA/AMEG strongly consider re-categorizing the streptogramins into Category D during the final review process following the public consultation period.		
27	Växa Sverige (Sweden´s largest advisory health service for dairy farmers) welcomes the initiative from the European Commission for requesting an update of the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Categorisation of antimicrobials, and we find the answer from EMA to be more or less in line with the Swedish guidelines and legislation for antibiotic use in dairy herds. Växa Sverige believes that the suggested categorisation will be more practical for veterinarians to follow than the one from WHO. For a Swedish setting, this suggestion seems to be a reasonable balance between practical use and risk of AMR. Moreover, the categories are well described, and the classifications are well motivated and easy to understand.	Thank you for your comments.	23.
28	AnimalhealthEurope welcomes the opportunity to provide comments to this Answer to the request form the European Commission which is well thought through, detailed, clear and comes to a rational approach which should be practical for the design and implementation of risk mitigation activities in different member states or regions within the EU. We support the general approach and in particular the creation of four categories. Sections putting this ‘list’ in the context of the other available lists are greatly appreciated because this is an area of significant confusion both within and outside the EU.	Duplicate comment. Please see response to comment 19.	24.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	One item, throughout the Answer which is apparent is that the references appear rather dated: while a comprehensive and current literature review is complex it is important to conduct this so that for example some of the more recent scientific publications are referred to *e.g.* those which have made some of the previous assumptions about direct transfer of resistance from animals to humans a bit more nuanced (although we anticipate that the AMEG is well aware of them). Examples include – Mather et al 2013 Distinguishable Epidemics Within Different Hosts of the Multidrug Resistant Zoonotic Pathogen *Salmonella* Typhimurium DT104. Science 341: 1513-1517, – Ewers et al 2012 Extended-spectrum b-lactamase-producing and AmpC-producing Escherichia coli from livestock and companion animals, and their putative impact on public health: a global perspective. Clinical Microbiology and Infection 18: 646–655, – de Been et al 2014 Dissemination of Cephalosporin Resistance Genes between Escherichia coli Strains from Farm Animals and Humans by Specific Plasmid Lineages. PLoS Genet 10(12): e1004776. doi:10.1371/journal.pgen.1004776. – Dorado-Garcia et al 2017 Molecular relatedness of ESBL/AmpC-producing Escherichia coli from humans, animals, food and the environment: a pooled analysis. Journal of Antimicrobial Chemotherapy doi: doi:10.1093/jac/dkx397 – and, admittedly after the Answer was prepared, Ludden et al 2019 One Health genomic surveillance of *Escherichia coli* demonstrates distinct lineages and mobile genetic elements in isolates from humans versus livestock. mBio 10:e02693-18. https://doi.org/10.1128/mBio.02693-18 to list a few. Tables 2 and 3 should be updated in light of an updated literature review.		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	As a matter of completeness, ketolides are missing from the list in Table 1. As further scientific expertise is requested from EMA regarding the list of antimicrobials reserved for human use, AnimalhealthEurope would like to emphasize that the work of AMEG should serve as a basis for future scientific advice, for example the delegated and implementing acts under 2019/6. Although the route of administration has not been retained as a ranking criterion for the categorisation of antibiotic classes, it is important to consider the route of administration at an individual product level. To properly reflect the different risks arising from different routes and modes of administration for the same class of substance, the concept of exceptions should be introduced into the AMEG categorisation so that where a MAH can demonstrate that there is a lower risk for a particular substance used via a particular route and/or mode then in that scenario the categorisation changes to a lower category. For example, for a specific antibacterial class or substance in Category B an exemption is recorded specifying that in specified circumstances (e.g. use of antibiotic X in ear drops for use in individual animals) is considered to correspond to Category C. The entry could appear along the following lines: Category B Antibacterial Class or substance Y* *with the exception of antibiotic X when used in individual animals aurally = Category C More generally, local individual treatment (udder injector, eye or ear drop, as assessed in line 498), should be considered as exceptions for use of a given antimicrobial and lead to lower risk categorisation (from B to C or C to D). The word “effective” is used throughout the document, and our interpretation is that this refers to clinical effectiveness, however, it might be helpful if it is expressed as “clinically		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	effective" (lines 93, 115, 280, 294, 298, 301, 330, 757, 770, 850, etc). We suggest adding a definition for "multiresistance genes" – the term is used in lines 113, 766 and 774. We are assuming this refers to the presence of a resistance determinant encoding resistance to multiple antimicrobial classes (e.g. MLSB, *OptrA* etc), but this could potentially also refer to the presence of several individual resistance determinants in one organism.		
29	The **BPI** generally welcomes a particularly prudent strategy in the use of antibiotics in both human and veterinary medicine to reduce the development of resistance in bacterial populations and to continue to ensure that people and animals in need of antibiotics receive them. An essential aspect for the future of the growing world population is whether the new division of antibiotics into four stages of this strategy ("world public health") is conducive. Because the success of an antibiotic in therapy depends above all on the right choice of the right bacterium. However, the reorganization of antibiotics has severely restricted this approach for the animal health sector from the outset. This is particularly the case for the "minor species and minor uses situation", but also for individual animal treatments of other species, which can only be treated adequately with antibiotics from human medicine in off-label use because of the pathogen situation. The restructuring of antibiotics therefore poses a major risk to global health. The proposed classification of antibiotics does not guarantee that there will be no gaps in the treatment of human diseases in the future, as there are or will be no corresponding approvals for animal health. The possibility of a flexible choice of antibiotics according to the results of appropriate diagnostics must therefore continue to exist. This is explained on the basis of three following aspects.		25.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	1st aspect: Zoonoses The danger of zoonoses is increasing worldwide, as humans and animals live ever closer together. Zoonoses, caused by pathogens that can be transmitted under natural conditions between vertebrates and humans, repeatedly cause outbreaks of disease on a global scale. This close coexistence will increase even further, as animal production must increase for a constantly growing world population in order to secure human nutrition in the future and in the long term. In addition, climate change is accompanied by an increase in zoonoses and in particular gram-negative bacteria (e.g. Pseudomonas aeruginosa, Klebsiella pneumoniae, E. Coli, Campylobacter, Yersinia Enterocolitica) (Impact of climate change and other factors on zoonotic diseases, Division of Medical Microbiology, Department of Pathology, Stellenbosch University, South Africa Corresponding author: preneshni.naker@nhls.ac.za Keywords: Climate change, Zoonotic diseases, Zoonoses Preneshni R. Naicker, 2011). Furthermore, the risk of zoonoses is increasing worldwide due to globalisation, not only in the EU. As an example, the importance of Streptococcus suis as a zoonotic agent should be mentioned here. This has been known for decades, but may have been underestimated so far. Last year, for example, a much-noticed outbreak occurred in Sichuan province in China, in which over 200 people fell ill and 38 died despite treatment. The World Health Organization (WHO) has now established that "human health is inextricably linked to animal health and animal husbandry" (ISSN 0947-0956 Forschung fürs Leben 2007, dgfz, Bonn), on the basis of the current expanded state of scientific knowledge, and also on the basis of the above-mentioned events, on the definition of zoonotic triggers in the form of diverse and reciprocal transmission pathways between animals and humans. If only limited anibiotics are available for the veterinary sector in the future, as in the proposed 4-class division, the risks described would increase and the fatal consequences for animals and humans would reach even greater proportions.	Thank you for these comments. It is agreed that there is a need to keep a range of antibiotic classes available for the treatment of animal diseases. Alongside consideration of the importance of the antibiotic classes for human health, the revised categorisation	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	2nd aspect: Promotion of resistance A reorganization of the use of selected antibiotics - preferably only for human health or animal health - promotes the risk for global health with regard to the promotion of resistance, as the reorganization of antibiotics inevitably forces the use of the same antibiotics in ever larger quantities in the animal health area, and thus the antibiotics to be given preference in the animal health area develop higher resistance rates through more frequent use. **3rd aspect: High research demand on epidemiology and speed of adaptation of bacterial pathogens** It is important to have a high level of expertise in the use of antibiotics, as this is one of the key pillars for safeguarding public health (one-health strategy). There is still a very high need for research in this area, as there are still serious gaps in the international state of science on the successful effect of antibiotics. One of the reasons for this is that the properties of infectious pathogens can change relatively quickly, making it possible to adapt to changing habitats in a short space of time. Depending on environmental conditions, it is therefore not unlikely that new subpopulations will develop that are (even) better adapted to the human host organism. In order to clarify this zoonotic relevance it is therefore important to know the survival mechanisms of the pathogens in the various habitats and to investigate them further. In addition, there is still a great need for research into many pathogens relevant to veterinary medicine for which no clinical limit values are yet available, so that a classification of the bacterial pathogens into "sensitive/sensitive", "intermediate" and "resistant" on the basis of the MHK values determined for certain pathogen/active substance combinations is ultimately not possible. The research results to be expected in this context may lead to the proposed four-class	has aimed to take a One Health approach by introducing a new criterion considering the indications for veterinary use and availability of alternative antibiotic classes for their treatment (see Chapter 3.3).	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	classification of antibiotics running counter to the one-health strategy and the safeguarding of world health and nutrition of the world population.		
30	EGGVP welcomes the opportunity to comment on the AMEG proposal for categorisation of antimicrobials for veterinary use. The following elements are positively valued by EGGVP: - The creation of a new intermediate category for important and commonly used antibiotics. - The significant emphasis which is placed on veterinary responsibility and freedom of treatment based on the veterinarians' knowledge - The considerations regarding transmission of resistance from human to animal origin is also a risk factor (reinforcing the ONE HEALTH approach) On the other hand, and regarding the classification of full categories of antibiotics, it is of concern that further stratification and refinement have not been considered for some cases (see specific comments re. polymyxin B). In particular the administration route has not been taken into account, i.e. topical route which generate less antimicrobial resistance than systemic route. Topical route ensures that the antibiotic remains at the site of administration without causing any selection pressure on bacteria of the gut and thus not spreading resistant bacteria in the environment.	See previous comments. A separate listing of routes of administration in order of preference associated with their potential impact on AMR has been provided and is now also included in the Summary. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have least impact on AMR selection.	26.
31	Our company, Gård & Djurhälsan AB (Farm & Animal Health Ltd), the main advisory	Thanks for the comments.	27.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	company in veterinary medicine and production for food producing animals (pig, sheep and beef) in Sweden, are happy to answer the initiative from the European Commission requesting an update of the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Categorisation of antimicrobials. We are satisfied with the answer from EMA which we find is in line with the Swedish guidelines and legislation for antibiotic use in meat production herds in Sweden. The suggested categorisation is preferable to the one from WHO and will be easier to follow as the different substances of antimicrobials are categorised in a more logical way. The suggestion appears to be well motivated, easy to follow and in balance with the risk for AMR.		
32	The Danish Veterinary and Food Administration recognizes the work group's great work and the importance of seeing the antibiotic groups in relation to both human and veterinary health. However, the Danish Veterinary and Food Administration considers it important to continue to adhere to the call from the working group on the development of national evidence-based treatment guidelines. The report's categorization of antimicrobials can be used as a starting point for the national guidelines. However, it is important that the individual countries can consider factors such as the composition of livestock production and national risk profiles in the preparation of new treatment guidelines. The Danish Veterinary and Food Administration will therefore point at line 130 - 138 "This categorisation does not directly translate into a treatment guideline for use of antimicrobials in veterinary medicine, but can be used as a tool by those preparing guidelines. In veterinary medicine, the variety of animal species, the different routes of administration (from intramammary treatment of individual cows to treatment of many hundreds of fish by in-feed medication) and diversity of indications are all factors that have to be taken into account for treatment guidelines. Further, types of production systems, the presence of different diseases and occurrence of antimicrobial resistance may differ between regions. Therefore, treatment guidelines need to be regionally or even	Thank you for this comment and for highlighting the importance of the development of evidence-based, national/regional treatment guidelines.	28.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	locally developed and implemented. Development and implementation of evidence-based national and regional treatment guidelines are encouraged" as very essential to the Danish way of regulating antimicrobials for use in animals.		
33	We appreciate the AMEG' effort on drafting the report on Categorisation of AMs. Please find below some aspects that may be considered for clarification: 1. Due to lack of supportive evidence (systematic reviews and/or meta-analysis) we suggest to include the WHO positions and recommendations. Ref: WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.: a. WHO recommends that antimicrobials classified as critically important for human medicine should not be used for prevention/prophylaxis or control/metaphylaxis of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals. b. WHO recommends that antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed disease. 2. Therefore we lack a rationale for the choice that a. Macrolides are classified as WHO highest priority critically important antimicrobials (HPCIAs) for human medicine, but recommended by AMEG for veterinary use in food animals (Category C), without restriction (Category B). b. WHO high priority CIAs (specifically aminoglycosides, aminopenicillins) are recommended by AMEG for veterinary use in food animals (Category C or D), without restriction (Category B); this includes both treatment purposes and for healthy food animals (prophylaxis/metaphylaxis). c. Polymyxins and quinolones (WHO HPCIAs) are recommended by AMEG for use in food animals with restrictions (Category B), but the restrictions are not stated;	1.The WHO guidelines and recommendations are included in the report. The recommendations quoted are accompanied by 'remarks' or comments permitting exceptions and are in line with EU recommendations. (See WHO report) 2. An EMA/CVMP reflection paper is available on macrolides, lincosamides and streptogramins (EMA/CVMP/SAGAM/741087/2009). An updated rationale is given in Table 4. EMA/CVMP Reflection papers are available for Aminoglycosides (EMA/CVMP/AWP/721118/2014) and Aminopenicillins (EMA/CVMP/AWP/842786/2015-draft). Risk management measures have	29.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	3. We wonder what trigger points will encourage a change in EU AMEG recommendations? The AMEG report states that if certain bacterial genes (e.g. cfr, erm genes) are identified with increased prevalence in food animal isolates then AMEG will reconsider the classification. These genes have already been identified in EU food animal bacterial isolates. Unfortunately, erm-mediated macrolide resistance is a common feature in Gram-positive zoonotic pathogens such as LA-MRSA CC398, CC1, CC97, while emerging in *Campylobacter jejuni* and *C. coli*. High-level macrolide (azithromycin) resistance mediated by mph genes have been reported in the EU. 4. What level (prevalence) of resistance will initiate a change by the AMEG, especially for aminopenicillins? Oral aminopenicillin use in food-producing animals exerts selection pressures for beta-lactam resistance in both Gram-positive and Gram-negative animal and zoonotic pathogens (e. g. *S. aureus*, LA-MRSA, *E. coli*, Salmonella), as well as maintaining resistance towards 3rd & 4th generation cephalosporins (e. g. mediated by mec genes in LA-MRSA and by ESBL/AmpC	been proposed previously by the CVMP for Colistin (EMA/CVMP/CHMP/231573/2016) and (Fluoro)quinolones (EMEA/CVMP/SAGAM/184651/2005. In addition, specific risk management measures for Cat B substances are given in the AMEG report. *These antibiotics should be considered only for the treatment of clinical conditions when there are no alternative antibiotics in categories C or D that could be clinically effective. Especially for this category, use should be based on the results of antibiotic susceptibility testing, whenever possible.* It should be noted that the new Regulation (EU) 2019/6 provides restrictions around prophylactic and metaphylactic use for all classes. 3 & 4. A new Chapter 6 has been added proposing conditions for review of the Categorisation. Findings from the European monitoring of AMR under Directive 2003/99/EC, as well as new	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	genes in *E. coli* and Salmonella). 5. We would like to see an elaboration on the effect of route of administration, formulations and particularly oral medication on the development of AMR - the mere magnitude of use could pose an unacceptable (risk) impact on AMR development. 6. The passage(s) concerning the likelihood and possible consequences of AMR transfer from animals to humans – should be updated. 7. Further elaboration on the criteria on condition of use would be beneficial; there is only a brief mention of dose and duration. 8. It would be appropriate to highlight that the New Veterinary Regulation, does not allow preventive group treatment with antibiotics. 9. It is mentioned that approximately 90 % of all AMs prescribed to livestock are given via the oral route. This is true for most of the European countries, but fortunately, the rare opposite can be found – thus this could form the basis for future inspiration? 10. A bid for prudent use of the different classes stratified according to species, disease, dose, dose regime, formulation etc. would be useful. 11. How is the categorization translated to practical strategies for reducing AM consumption and subsequently reducing AMR ? – in the following we have a bold suggestion: 12. Apply the Danish VETSTAT ='Yellow card system' in EU and/or refine the ESVAC system 13. Minimum national Goals within 1-6 years for AM use and AMR <u>reduction strategy</u> applying the 4 AM categories: ○ A - Avoid: max 0.01% of total AM consumption. (in principle a total ban)	scientific evidence or information on changing patterns of antibiotic use or resistance can trigger review of the categorisation. 5.The route of administration is addressed in chapter 3.3.1. A separate listing of routes of administration in order of preference associated with their potential impact on AMR has been provided and is now also included in the Summary. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have least impact on AMR selection. 6.Not clear to which specific part of the text/tables this relates. 7. Detailed consideration on dose regimens and duration of treatment are out of scope. 8. The provisions of the NVR regarding pro/metaphylaxis are included in Chapter 4.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	○ B - Restrict: max 0.05% of total AM consumption – effort to substitute specific AM with lower AM Category or find alternatives e.g. vaccines ○ C - Caution: max 5% of total AM consumption - effort to substitute specific AM with AM Category D or find alternatives e.g. vaccines ○ D - Prudence: min 95% of total AM consumption - effort to substitute specific oral AM with other routes of administration or find alternatives e.g. vaccines 14. Common motivational drivers and incentives for prudent and transparent AM use and AMR reduction: 1. Species, gender, age 2. Disease (agent) 3. Mode of action of AM 4. Dose, dose regime and duration. 5. ERA – Environment risk 6. Pharmacovigilance data including accumulating evidence that prudent AM use (timely use of diagnostics, appropriate use of treatments, etc) will improve animal health outcomes 7. 'Enforcement' of the B:R – benefit : risk analysis of antibiotics. E.g. exercising SPC harmonisation and referrals, in case of e.g. a negative B:R, in the regulatory system within the current National, DCP, MRP and CP	9. A discussion of different husbandry practices, disease epidemiology etc is interesting but out of scope. 10. This would go beyond the current categorisation and move towards development of treatment guidelines. The categorisation is one part of this process (see Chapter 5). 11. to 14. Please refer to the RONAFA report[2] which addresses many of these issues.	

[2] https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/advice-impacts-using-antimicrobials-animals/reducing-use-antimicrobial-agents-animal-husbandry

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	marketing authorisations procedures. 8. AMR surveillance data - enhance quality and applicability, safety, access and reduce variations 9. Herd Health Management/Husbandry in focus – exchange know-how and enhance education of farmers, health care professionals, veterinarians, and stakeholders in general – e.g. a model could be the curriculum of the Danish 100+year old farmer training colleges. 10. Develop 'twinning' projects for the purpose of dissemination of *lessons learned* from mature to immature EU members as to curbing 'over-consumption' of AM (categories/formulations) 11. Alternatives to AM: a. existing alternatives to AM with a marketing autorisation should be implemented as 'drug of choice' where relevant and in a fast track manner – primarily vaccines. b. Awareness of development within i. feed additives (e.g.organic acids, ZnO), ii. borderline (e.g. phage therapy, pro-/symbiotics, gene-editing technologies (CRISPR) in feed antibodies etc.) iii. VMPs (e.g. combination therapy, antimicrobial peptides, auto vaccines, immune stimulators, phytochemicals etc.). c. Fast-track scientific advice and marketing authorisation subject to alternatives to AM candidates. 12. Policies – the new delegated and implementing acts of the Veterinary Regulation (NVR) 2019/6 of the European Parliament and of the Council Directive 2001/82/EC of 11 December 2018 on veterinary medicinal products and repealing)		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	13. Animal welfare and *One Health* issues 14. Awareness – Refinement of consumption figures (ESVAC, VETSTAT) emergence and implantation of systems to measure quality and performance and ability to extract detailed data for actions for reducing AM consumption. 15. Optimisation and intelligent utilization of the new (NVR) EU databases complementing existing national databases: a. Union pharmacovigilance data system b. Union product (VMP) data base c. Union sales and use of AM database d. Union manufacturing and wholesale distribution database 16. Market, trends – e.g. promotion of *'the pig produced free of AM'* by supermarket chains in EU and US. 17. Legal (New) payment agreements for National Competent Authorities, Veterinarians, health care professionals and farmers. Distil the international and cross sectorial experience with pay for performance 18. Implementing a *One Health* approach is necessary for regulating the use of AM in veterinary and human medicine in a balanced and proportionate way, so as to retain an adequate and relevant range of AM 19. Development of new antimicrobials for pivotal production animal diseases 20. Curb illegal (internet) promotion, advertisement and sales of AM 21. Minimize the (mis)use of Medicated Feed and transport over borders. Questions related to the report:		

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	1. What EU conditions would allow the AMEG and AWP to differ from WHO recommendations? 2. What trigger points will encourage a change in EU AMEG recommendations? - *Trækkes ud som en kommentar.* 3. What level (prevalence) of resistance will initiate a change by the AMEG, especially for aminopenicillins? 4. Is it a concern that WHO recommendations are not fully reflected by allocating some CIA classes for common use in animals? Is it a concern that the route-of-administration is essential in the methodology of a veterinary antimicrobial classification system, as specified in the EC mandate?	1.Although it is appreciated that AMR is a global problem due to global trade and travel, there are still differences between geographical regions in disease epidemiology, availability of antimicrobials, patterns of AMR and animal husbandry. 2. to 4. Addressed in comments above.	
34	AVEC representing the European poultry processors and ELPHA representing the European live poultry and hatching-eggs association, generally agree with the AMEG categorization. Furthermore, AVEC and ELPHA promote and support an appropriate use of antimicrobials is the key to mitigating the risk of widespread antimicrobial resistance. Administration of antimicrobials should be complementary to good farm-management practice including strict bio-security policies and properly designed vaccination programs. Both associations encourage a review of the use of all antimicrobials during production with the objective to reduce the usage and advise on alternatives to antibiotics; AVEC and ELPHA agree with the need for more R&D of new effective antibiotics is of high priority expressed by several guidelines on the use of antimicrobial substances.	Thank you for the comment.	30.
35	FVE welcomes very much the updated AMEG classification finding it a very clear, evidence-based and well developed document. We especially welcome that AMEG moved away from looking only at the public health risk (based on WHO listing) and instead considered additional criteria such as indications in veterinary medicines ('need for this product'),		31.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	animal health and welfare aspects, route of administration and availability of alternatives in veterinary medicine. We regret that despite the overwhelming evidence of difference in AMR risk profiling, the route of administration was not fully utilised and was not used further in the risk categorisation as it was felt to be '*too complex and the difficult to evidence*'. FVE strongly feels, that seen the route of administration makes such a difference in risk towards public health, that this should be taken stronger into account. We welcome the categorisation to go from 3 to 4 categories (with the extra category C – 'Caution'), allowing for refinement of the risk and for avoiding a too restrictive approach by placing too many antimicrobials in the highest risk category. In addition, the new classification (Avoid (A) - Restrict (B) - Careful (C) - Cautious (D)) is better understandable or not as misleading as the old one (Highly Important-Critically Important-Highest Priority Critically Important) from 2014. It is to be welcomed that all antimicrobial agents authorised in veterinary medicine are classified in category B/C/D and none in category A, so that the authorised antimicrobial agents would remain untouched, if category A substances were defined within the new Veterinary Medicines Regulation as antimicrobial agents reserved for the treatment of certain human infections. There is some confusion in the document regarding the use of the term 'class', 'subclass' and 'substance' (e.g. line 114, table 141, etc.). The document mainly refers to classes, not to substances. To make this document practical and useful for veterinarians it needs to include all antimicrobials as referred in the veterinary pharmacopeia. Otherwise it will create a lot of doubts. Some examples are given in the detailed comments. In addition, it could be worth to further divide some of the antimicrobials in the same class	A listing of routes of administration in order of preference associated with their potential impact on AMR has been provided. This has now been included in the Summary. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have least impact on AMR selection. Category A substances will not automatically be reserved for human use. Delegated and Implementing acts will define the criteria for and antimicrobials that will be reserved to human use only. Text amended. These suggestions are welcomed for	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	when their risk profile differs. Some other reflections: - it would be worth to include some data on the spectrum of activity of each class of antimicrobial in their categorization; - the report lacks indications regarding association of antimicrobials; - some definitions are missing (e.g. cascade, …); - the advice is focused on livestock and has little date on companion animals, aquatic and exotic animal species. FVE welcomes that after adoption an Infograph and other communication materials will be developed. Experience from the communication of the first AMEG classification showed that it was insufficient, as it could only be found inside the answers to the EC request, so it was very hard for veterinary practitioners to retrieve. Nevertheless, also the current advice is too broad, too long and not easy to read for veterinary practitioners. In order to be practical, it must contain the precise antimicrobials. Good and clear communication is essential to inform veterinarians about this classification, so that they can act accordingly (line 143). FVE would be happy to assist EMA to develop a practical and user-friendly Infograph and communication materials for veterinary practitioners. A couple of points remain for us unclear how they will work in practice, such as the classification and the cascade or regarding the need for susceptibility testing and intermediate treatment before getting the results back. We would very much appreciate if this could be further clarified including some examples. To allow veterinarians to make better use of this categorisation of antimicrobials, we must underline the urgent need for a practical, user-friendly and up-to-date product database allowing veterinary practitioners to see which lower class antibiotics are available across Europe, as well as, the need for a better functioning of the internal market allowing them to import easily from other Member States medicines to prevent diseases, e.g. vaccines,	future revisions. Some examples of indications in companion animals where there are few alternatives are included in Table 4, but further examples would be welcome. A sentence regarding combinations has been added: For products containing a combination of antibiotics, the categorisation of the individual substance with the highest risk level should be taken into account for prescribing decisions. Noted. Thank you for the offer. The recommended criteria to designate antimicrobials to be reserved for human use in accordance with Article 37(5) of Reg 2019/6 differ in part from those for the categorisation and have been proposed under a separate Commission mandate. The choice of antibiotic to use whilst awaiting AST results would be better addressed in locally	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	or the most appropriate antibiotic per case according to responsible use rules. We would appreciate to add this point in the EMA advice.	developed treatment guidelines. Noted. Development of the Union Product Database is out of scope of this mandate.	
36	BTK welcomes very much the updated AMEG classification; finding it a very clear, evidence-based and well developed document. We especially welcome that AMEG moved away from only looking at the public health risk (based on WHO listing) and instead considered additional criteria such as indications in veterinary medicines ('need for this product'), animal health and welfare aspects, route of administration and availability of alternatives in veterinary medicine. We regret that despite the overwhelming evidence of difference in AMR risk profiling, the route of administration was not fully utilised and was not used further in the risk categorisation as it was felt to be 'too complex and the difficult to evidence'. BTK strongly feels, that seen the route of administration makes such a difference in risk towards public health, that this should be taken stronger into account.	Thanks for the comments See previous comments A listing of routes of administration in order of preference associated with their potential impact on AMR has been provided. This has now been included in the Summary. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have least impact on AMR selection. Spectinomycin has been separated	32.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	We welcome the categorisation to go from 3 to 4 categories (with the extra category C – 'Caution'), allowing for refinement of the risk and for avoiding a too restrictive approach by placing too many antimicrobials in the highest risk category. It could be worth to further divide some of the antimicrobials in the same class when their risk profile differs. BTK welcomes that after adoption an Infograph and other communication materials will be developed. This was certainly lacking for the first AMEG classification, which was very hard to retrieve. Good communication is essential to inform veterinarians about this classification so that they can act accordingly (line 143).	from the Aminoglycosides and placed Category D. Ketolides have been placed in Category A. Noted.	
37	Who we are The British Veterinary Association (BVA) is the national representative body for the veterinary profession in the United Kingdom. With 18,000 members, our primary aim is to represent, support and champion the interests of the United Kingdom's veterinary profession. We, therefore, take a keen interest in all issues affecting the profession, including animal health and welfare, public health, regulatory issues and employment matters. Introduction Antimicrobials are essential to both veterinary and human medicine to treat infectious and zoonotic bacterial diseases. Continued availability of all existing antimicrobial classes and the development of new ones for veterinary use are essential to maintain the health and welfare of companion, equine and food animals and for the protection of public health. Each use of antimicrobials increases the risk of selection for resistant bacteria, so we must ensure the use of antimicrobials is responsible across human and animal health. The UK veterinary community is concerned by the implications of the development of antimicrobial	Thank you for your comments.	33.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	resistance. According to a survey of the UK veterinary profession undertaken by BVA, nearly all (97%) vets are concerned about antimicrobial resistance, with nearly half (46%) describing themselves as very concerned. The timespan of the UK Five Year Antimicrobial Resistance Strategy 2013-2018, has seen considerable success, reflected in October 2017 by the publication of the Veterinary Antimicrobial Resistance and Sales Surveillance (VARSS) 2016 report which marked several important milestones: • The commitment to reduce antibiotic use in livestock and fish farmed for food to a multi-species average of 50 mg/kg by 2018 was achieved two years early. Antibiotic use in food-producing animal species decreased by 27% to 45 mg/kg. • The lowest UK veterinary antibiotic total sales figure recorded (337 tonnes) since regular UK antibiotic sales reporting began in 1993. • Reductions across sales of all highest-priority critically important antibiotics (HP-CIAs), including an 83% reduction in sales of colistin use for food producing animals, from an already very low level. The VARSS 2017 report demonstrated further progress. Total sales of veterinary antibiotics, adjusted for animal populations, was 37 mg/kg in 2017. This result signals an additional 18% reduction from 2016 and a 40% reduction since the publication of the UK AMR strategy in 2013. Sales of HP-CIAs dropped a further 29% from levels in 2016, to 0.8% of total sales in 2017. This improvement at a UK level, coincided with a Europe wide improvement. According to the latest ESVAC report, published in October 2018, sales of antibiotics for use in animals across Europe fell by 20% between 2011 and 2016.		

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	Advice of the Antimicrobial Advice Ad Hoc Expert Group BVA welcomes the action taken by the Antimicrobial Advice Ad Hoc Expert Group (AMEG) to provide updated advice on the classification of antimicrobials used in animals. We particularly welcome that this categorisation brings together human health, animal health and welfare and public health considerations, which we believe is a worthwhile and useful process. This supports a 'One-Health' approach, which spans people, animals, agriculture and the wider environment. We note the scope of this categorisation, as outlined within the consultation document, is not intended to directly translate into a treatment guideline for use of antimicrobials in veterinary medicine. It is instead intended to be utilised as "one element" within a wider consideration when deciding on whether to use a certain class/substance in veterinary medicine. We agree with this approach, because as the document notes there are several factors that may differ between regions (the variety of animal species, the different routes of administration, types of production systems, the presence of different diseases, and occurrence of antimicrobial resistance). As such, treatment guidelines need to be developed and implemented at the appropriate local level. We appreciate that this update seeks to take into account the experience gained since the initial publication of the categorisation of antimicrobials in 2014. We also welcome an effort to refine the criteria used to determine the categorisation of antimicrobials. The inclusion of two additional criteria (route of administration and indications for veterinary use and availability of alternative antimicrobials of lesser risk) are welcome. We would appreciate further detail of how these new criteria were taken into account. Route of administration is particularly relevant within the companion animal sector where veterinary surgeons will often apply topical treatment for conditions such as ear disease. Similarly, there are also considerations for antimicrobial use in aquaculture, where	A listing of routes of administration in order of preference associated with their potential impact on AMR has been provided. This has now been included in the Summary. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have least impact on AMR selection.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	administration is generally by immersion. Further, we would note that there are limits to how effectively these criteria can be applied within more minor use species where there are fewer alternative antimicrobials available. Communications BVA believes that this categorisation can act as a useful foundation for developing treatment guidelines. It can also act as a useful tool to raise awareness and facilitate behaviour change amongst veterinary surgeons and animal keepers. The presentation of the categorisation appears cogent. Classifying antimicrobials within four categories is helpful for treatment choice. Clarity has been provided by aligning the hierarchy to place category A as the most restricted class. However, we would note the labels attached to the categories may be confusing as the meaning of each label is not clearly distinct and may be open to misinterpretation. Further consideration should be given to how this categorisation and associated communications will best influence behaviour. In particular we would note that it is important for an intervention to be Easy, Attractive, Social and Timely (EAST). These principles for applying behavioural insights are based on the work of the Behavioural Insights Team and a large body of evidence on what influences behaviour. We would advise that several organisations categorise antimicrobials (e.g. WHO, OIE) and there are cases where the EMA ranking will diverge. We would note that there will likely be some confusion caused by the variety of different categories, and communications strategy should consider this to ensure this potential confusion does not become a barrier that could potentially limit the use of this categorisation as a tool by those preparing guidelines.	In regard to minor species, the limited range of authorised products is acknowledged. It is proposed that treatment guidelines should be developed by species specialists; although the categorisation can be taken into account to inform about the potential human health AMR risk (chapter 5). Thank you for this advice.	
38	Welcome for New Categorisation: Animal and Plant Health Association (APHA) Ireland welcomes the opportunity to provide	Thank you for the comments.	34.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	comments to this consultation by the European Medicines Agency AMEG updating the advice on the impact on public health and animal health of the use of antibiotics in animals – Categorisation of antimicrobials. In general, APHA welcomes the proposed classification of antibiotics, which will bring greater clarity to Member States (MS), as they strive to prevent and curtail the growth of antimicrobial resistance. A singular agreed classification system at EU level provides a reference framework for all stakeholders at member state level, which should be practical for the design and implementation of risk mitigation activities in different member states or regions within the EU. Greater Clarity: Sections putting this 'list' in the context of the other available lists are greatly appreciated because this is an area of significant confusion both within and outside the EU. In addition the relabelling of categories will remove confusion created by the current categorisation based on labelling as Priority 1, 2 or 3. Removing Ambiguity – Reg 06/2019 and New Categorisation: It is important to understand the relationship between the proposed Category A (Avoid) and the reservation of antibiotics under the new Regulation. As the AMEG description of Category A permits the use of these substances in companion animals in exceptional circumstances and since the new Regulation specifies reserved substances cannot be used under the cascade, please confirm that substances listed in Category A are the only potential candidates for reservation but according to their individual risk profiling they may or may not be included on the reserved list i.e. any substance in Category B, C or D won't be reserved for use in humans given they have a lower risk than category A substances. A sub-division of Category A should be considered which sets out those substances which may never be used in animals (i.e. reserved) and those which can't be authorised for	The provision of advice on the delegated act on Criteria to designate antimicrobials for human use only has been addressed under a separate mandate from the Commission and it is probable that these criteria will need to differ to some extent from those used for the AMEG's Categorisation. The criteria will apply in principle to all antimicrobials authorised or not in	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	veterinary use but can be used in companion animals in exceptional circumstances under the cascade.	veterinary medicine.	
40	• PHAC appreciates the efforts made by the authors to provide transparent documentation (i.e., the history, background references, and rationale) and the consultative approach for development of this new categorisation. • PHAC supports the four category system over the previous three category system. In particular, PHAC supports the intermediate category (i.e., Category B) to make the distinction between the aminoglycosides and the 3 and 4th generation cephalosporins/fluoroquinolones. Canada too has a four category system; though different criteria were used to develop the Canadian system. • Comments about the drugs included under the various categories: o Category B – polymyxins. Are polymyxin B products included here too? o Future categorisation activities could also include an additional criterion: "The availability and feasibility of implementing alternative farming practices that may reduce the need for that particular antimicrobial use."	Polymyxin B is included with other polymyxins in Category B. See response to comments 8 and 18. Noted.	35.
41	Au Québec, nous nous fions beaucoup à la catégorisation des antimicrobiens de Santé Canada (version avril 2009). Le Règlement modifiant le Règlement sur l'administration de certains médicaments découlant de la Loi sur la protection sanitaire des animaux y fait notamment référence. Ce réglement est entrée en vigueur le 25 février 2019. L'Antimicrobial Advice ad hoc Expert (AMEG) propose une catégorisation différente de celle de Santé Canada. Bien que les deux listes (AMEG et Santé Canada) soient composées chacune de 4 catégories, la signification des catégories et les implications sont différentes. Le niveau d'importance accordé à un antimicrobien (classe ou sous-classe) donné comparé au niveau accordé à un autre est différent entre les deux listes. Des antimicrobiens de certaines classes ou sous-classes pourraient alors être moins utilisés dans l'Union	Thanks for the comments.	36.

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	européenne qu'au Canada et au Québec. Bien que le nouveau classement proposé par l'AMEG ne remplace pas les lignes directrices, il propose également des recommandations spécifiques pour l'usage des antibiotiques des différentes catégories. Le système de classification de Santé Canada n'inclut pas ce genre de recommendation. Il y a un risque que l'UE se serve de ces recommandations pour ajuster ses exigences envers les pays partenaires commerciaux, par exemple en exgieant que les antibiotiques de classe B soient utilisés uniquement lorsqu'un antibiogramme est disponible. Ce genre d'exigence pourrait entrer en conflit avec les politiques adoptées par différentes juridictions comme le Québec. Cependant, ce nouveau classement proposé par l'AMEG semble plus complet puisqu'il considère les risques de transmission de résistance de l'animal vers l'humain, incluant les phénomènes de cosélection. Translation: In Quebec, we rely a great deal on Health Canada's categorization of antimicrobial drugs (April 2009 version). For example, the *Regulation to amend the Regulation respecting the administering of certain medications* under the *Animal Health Protection Act* refers to it. This regulation came into force on February 25, 2019. The Antimicrobial Advice Ad Hoc Expert Group (AMEG) proposes a categorization that differs from that of Health Canada. Although the two lists (AMEG and Health Canada) are each composed of four categories, the meaning of the categories and the implications are different. The level of importance given to one antimicrobial (class or subclass) compared to the level given to another is different between the two lists. Antimicrobials of certain classes or subclasses may therefore be used less in the European Union than in Canada and Quebec. Although the new classification proposed by AMEG does not replace the guidelines, it also	The purpose of this categorisation is only to serve as a basis for National treatment guidelines in the EU member states.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)	
	proposes specific recommendations for the use of antibiotics in the different categories. Health Canada's classification system does not include this type of recommendation. There is a risk that the EU will use these recommendations to adjust its requirements for trade partner countries, such as requiring that class B antibiotics be used only when antibiotic sensitivity results are available. This type of requirement could conflict with the policies adopted by different jurisdictions such as Quebec. However, AMEG's proposed new classification proposed seems more comprehensive since it considers the risks of resistance transmission from animals to humans, including coselection phenomena.		

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
Table A2	5	Comment: you place amoxicillin with the code ATC and ATC-vet QJ01CA03, when according to the page - https://www.whocc.no/atcvet/atcvet_index/ - corresponds to carbenicillin. On this page, as well as in the SPCs of registered veterinary products with amoxicillin, the correct code is QJ01CA04. Is this correct?, If not, on what are you based on the classification of amoxicillin with the ATC and TAC-vet code QJ01CA03?	Accepted. For amoxicillin the ATC code should be J01CA04 and the ATCvet code is QJ01CA04. This has been revised in Table A2.	37.
55	35	Comments: risk of spread from animals or animal products Proposed change (if any): Insert animal products	The text is a direct reference to text in the original AMEG report (2014) and therefore it is proposed that it should not be amended. The foodborne route is intrinsic as a route of AMR transfer from animals to humans in the previous and new AMEG reports but, for reasons of brevity, is not always stated.	38.
64	35	Comments: colistine (also known as polymyxin B) Proposed change (if any): Insert (also known as polymyxin B)	In order to keep the text succinct, a footnote has been added instead to advise that colistin is also known as 'polymyxin **E**'.	39.
80-144	23	Comment:	Thank you for the comment.	40.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		We welcome and strongly support this categorisation of antibiotics in veterinary medicine in the classes A to D and the explanatory text for each class. Especially placing colistin (polymyxins) in category B together with quinolones and cephalosporins 3rd and 4th generation.		
82 option 1 82 option 2	26	classes not currently authorized in veterinary medicine ~~in the EU~~ classes not currently authorized in veterinary medicine ~~or having approved MRLs~~ in the EU Rationale: The criteria of EMA-AMEG-14 did not limit its consideration of veterinary authorization to the EU. The specific phrasing of this criterion in EMA-AMEG-17 is inconsistent throughout the document, however, it does appear to be specifically clarified in lines 814 to 818. Additionally, specific limitations to considerations of AMR strategy within the EU is inconsistent with the position taken by the European Parliament Regulation 2019/6. The criterion should be consistent throughout the document. This could be achieved by deleting the "in the EU" to reflect to the EMA-AMEG-14 text, or the alternative is provided to ensure clarity and reflect consistency with European Parliament Regulation 2019/6.	It has been clarified in the Summary that 'The categorisation includes only antibiotic classes that have been authorised for human and/or veterinary use in the EU'. This has also been noted in Section 4 of the report. The AMEG categorisation has been developed for use in the EU. Additionally, it is not possible to take account of the authorisation status of antibiotics in third countries as this may change over time and the relevant information may not be easily accessed. The Commission provided a separate mandate (Ares(2019)688882) for development of criteria to	41.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
			designate antimicrobials that should be reserved for human use in the EU (Article 37.5, Reg EC 2019/6) and which should not be used in animals/products to be imported from third countries (Article 118.1). There should be no assumption that these criteria will be identical to those for the AMEG's Category A. Clarification has been added in section 4.1. Substances that have EU MRLs should either not be in category A (as they are authorised in veterinary medicines), or only be in Category A temporarily since MRLs are only granted when there is the intent for a marketing authorisation application (when/if receiving approval, the Categorisation for the substance would be changed); therefore the MRL status is not useful for designating Category A.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
82-86, and Table 1 line 141	13	Comment: Category A does not correspond to Category 3 in the first AMEG report (as incorrectly written on line 82), because important details have been changed. The first AMEG report states: ***"Category 3 as antimicrobials not approved for use in veterinary medicine."*** Streptogramins are not mentioned in the first AMEG report, and one of these (virginiamycin) is approved in many countries for veterinary therapeutic use (*e.g.* USA, Australia, Canada, South Africa, Argentina, *etc.*). It is possible that the apparently global approach taken in the first AMEG report resulted in Streptogramins not being put into Category 3 (or possibly not being mentioned at all, or simply an oversight). In contrast, the current 04 February 2019 draft states: "***Category A ("Avoid") corresponds to Category 3 in the first AMEG report, and includes antimicrobial classes not currently authorised in veterinary medicine in the EU. In the absence of established maximum residue limits for foodstuff of animal origin, use of these classes of AM in food-producing animals is prohibited and they may only be administered to individual companion animals exceptionally, in compliance with the prescribing "cascade"."*** Streptogramins appear in Category A (Table 1, line 141). Rationale: the first AMEG report did not restrict Category 3 antimicrobials to those not approved **in the EU** – but appeared to take a "One Health" globally coordinated approach which is in line with the recommendations of EU Regulation 2019/6. In 2019/6 it is stated for example:	The original AMEG categorisation (2014) included the classes that met the WHO's Criterion 1, hence Streptogramins were not included. This has changed in the new report as the 2017 mandate requested that the Categorisation should be broadened to include WHO's HIAs and IAs. From its initiation, the Categorisation was developed for use in the EU. It has been further clarified in the report that Category A includes classes not currently authorised in veterinary medicines in the EU, but that are authorised in human medicine in the EU. The formal risk assessment/management measures that accompany use of authorised VMPs in the EU are not available and they may only be used under the Cascade (see response to stakeholder 39, below).	42.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		"(41)… … a global public health concern that affects the whole of society and requires urgent and coordinated intersectoral action in accordance with the 'One Health' approach." "(48) The prudent use of antimicrobials is a cornerstone in addressing antimicrobial resistance. All the stakeholders concerned should together promote prudent use of antimicrobials. It is therefore important that guidance on the prudent use of antimicrobials in veterinary medicine be taken into account and further elaborated." "(49) It is important to consider the international dimension of the development of antimicrobial resistance when assessing the benefit-risk balance of certain veterinary antimicrobials in the Union… …measures restricting the use of veterinary antimicrobials in the Union should be based on scientific advice and should be considered in the context of cooperation with third countries and international organisations. For those reasons, it should also be ensured, in a non-discriminatory and proportionate manner…" The report (EMA/CVMP/CHMP/682198/2017) should be in line with the legislation Regulation 2019/6 and not taking an "EU only" approach to AMR which is a global problem as indicated in 2019/6. The use of "in the EU" in line 83 could act against antimicrobials that have an EU MRL but no MA – for example virginiamycin. An MRL is a pre-requisite to obtaining an MA for a food species product in the EU. The result is virginiamycin being a streptogramin has now appeared in Category A ("Avoid") – see Table 1, Line 141. This could accidentally send a message to most users of the report whom do not read all details of its 67 pages - the message being to avoid that antimicrobial. *- In fact, the MRL of Virginiamycin has been set in 2016, so just 3 years ago.*	The Commission has provided a separate mandate (Ares(2019)688882) for development of criteria to designate antimicrobials that should be reserved for human use in the EU (Article 37.5, Reg EC 2019/6) and which should not be used in animals/products to be imported from third countries (Article 118.1). There should be no assumption that these criteria will be identical to those for the AMEG's Category A. Clarification has been added in section 4.1. Proposed changes not accepted.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Why now to ban? This has huge trade implications. If the antimicrobial is already approved outside of the EU it could suffer decreased use as a result – for example due to farmers, supermarkets or purchasers of meat products avoiding the use of EU Category A antimicrobials on their farms. This is NOT the intention of the AMEG report to adversely affect approved suitable veterinary antimicrobials (for example virginiamycin – is "considered obsolete" in human medicine – as indicated in Table 2, Streptogramins, pages 26-27). However, it is likely to happen because many readers will just read Table 1 (line 141) without studying the details in the report. If EMA/CVMP/CHMP/682198/2017 considered antimicrobials that have an EU MRL or an EU MA then the situation would be resolved and would not accidentally act against virginiamycin. Proposed change (if any): Lines 82 to 86 are proposed to be changed to: ***"Category A ("Avoid") corresponds to Category 3 in the first AMEG report, and includes antimicrobials ~~classes~~ without an MRL or not currently authorised in veterinary medicine in the EU. In the absence of established maximum residue limits for foodstuff of animal origin, use of these ~~classes of~~ AM in food-producing animals is prohibited and they may only be administered to individual companion animals exceptionally, in compliance with the prescribing "cascade"."*** Another proposal for changing lines 82 to 86, could be:		

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		"Category A ("Avoid") corresponds to Category 3 in the first AMEG report, and includes antimicrobial classes not currently authorised in veterinary medicine in ~~the EU~~ VICH territories/worldwide. In the absence of established maximum residue limits for foodstuff of animal origin, use of these ~~classes of~~ AM in food-producing animals is prohibited and they may only be administered to individual companion animals exceptionally, in compliance with the prescribing "cascade"." *Dear David, I prefer the first proposal rather than this one.* Either of the above proposals would result in a global approach as required by 2019/6, and virginiamycin being moved out of Category A (line 141, Table 1). Based on current scientific knowledge it is suggested that virginiamycin should be moved into Category D (Table 1, line 141).		
82-86, 141	16	Comment: The BVPA wishes to draw attention to the inclusion of streptogramins in Category A ("Avoid") in the present report EMA/CVMP/CHMP/682198/2017. Streptogramins include the antibiotic virginiamycin, which is a veterinary-only antibiotic and is not used in human medicine. Streptogramins are described as "presently considered obsolete" in human medicine ((see line 620, table 1, pages 26-27). Virginiamycin is placed in Category A as it is not currently authorised for use in the EU. However, virginiamycin does have a European MRL for poultry, granted in 2015 (EPMAR EMA/CVMP/643658/2014), with the prospective use for treatment of necrotic enteritis (NE). NE is a common and often fatal	Please refer to the comments to stakeholders 26 and 13, above. From its initiation, the Categorisation was developed for use in the EU. Section 4.1 of the report already clarifies that, in the event of a future marketing authorisation application for a VMP containing a substance in Category A, the benefits to animal health will be	43.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		gastrointestinal disease toxigenic strains of *Clostridium perfringens*. Virginiamycin has been used in animals since 1975 and is currently widely used outside the EU. Approvals include treatment and control of ruminal acidosis / liver abscess in cattle (Argentina, Australia, Brazil – submitted, Canada, Mexico, South Africa, USA, several Central and South American countries, and pending in some SE Asian countries). It is also approved for treatment of swine dysentery in pigs in Canada, USA, Brazil – in process, China – in process. Virginiamycin is not currently used in human medicine. The BVPA proposes that virginiamycin be placed in Category D ("Prudence"). This change would retain the potential development of virginiamycin for use in chickens, for example for treatment of NE, thus extending the choice of antibiotics available in poultry. Use of more important antibiotics such as amoxicillin could thus be spared. BVPA makes it clear that any subsequent marketing authorisation of virginiamycin should be restricted to therapeutic use only, and be available as a prescription-only veterinary medicine. The unintended consequence of placing virginiamycin in Category A would be removing it from potential development as a therapeutic antibiotic in the EU. In addition importation of poultry treated with virginiamycin into the EU could be banned.	considered alongside the AMR risk assessment. Therefore there is still potential for VMP development. There is no assumption that all substances in Category A will be disallowed from use in animals/produce imported to the EU from third countries (see above). The Commission has provided a separate mandate for development of criteria to designate antimicrobials that should be reserved for human use in the EU (Article 37.5, Reg EC 2019/6) and which should not be used in animals/products to be imported from third countries (Article 118.1). There should be no assumption that these criteria will be identical to those for the AMEG's Category A.	
82-84	39	Comment: It is important that the categories be science-based to enhance rather than confuse global understanding and that there is consistency in establishment of this list with future lists of antimicrobial drugs that may be	Please see the response to the comments on lines 82 → from stakeholders 26, 13 and 16, above.	44.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		prohibited for use in countries exporting to the EU as per Article 118. Authorization status in the EU is not a scientific basis for a list. For example, the drug class, Streptogramins are included in Category A. While not authorized for use in the EU, virginiamycin, a streptogramin, is authorized for use in the U.S. and in many other countries outside the EU. Further, it is difficult to determine the extent of use for off-label or unauthorized uses (e.g. rifamycins) of antimicrobials and as such should not be a factored in a categorization. Further, a point of confusion is on lines 814-815, where the text reads that Category A is for drugs not authorized for use in veterinary medicine and does not include the qualifier "in the EU" as in lines 82-83. Drug categorization should be based on scientifically justifiable risks to human health rather than lack of authorization status in the EU. Further, any risk management measures associated with the use of these drugs in veterinary medicine should consider the results of risk assessments, MRLs and authorized uses in other countries.	Further clarification has been added in section 4.1 regrading Category A: *'The formal AMR risk assessment and risk management measures that accompany use of an authorised veterinary medicine are not available for use of these classes in animals. This might lead to an additional risk to public health'.* It is acknowledged that this risk cannot be fully assessed at this time, but risk management measures in line with Cascade use are considered to be relevant. The risk assessments conducted in third countries may not be applicable to the unforeseeable off-label use in the EU. Please also note the EMA/CVMP reflection paper on off-label use of antimicrobials in the EU (EMA/CVMP/AWP/237294/2017).	
82 - 86 & 141 (Table)	41	Comment :	Please see the response to comments from stakeholders 26,	45.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Selon la catégorisation de l'Antimicrobial Advice *ad hoc* Expert Group (AMEG), la catégorie A (Avoid) comprend les antimicrobiens dont l'utilisation chez les animaux de production est interdite. **Important : Potentiel d'impact** Les antimicrobiens qui ne sont pas autorisés dans l'Union européenne (par autorisés, nous assumons que cela veut dire commercialisés) sont inclus dans la catégorie A de l'AMEG, en raison notamment de l'absence d'établissement de LMR. Les streptogramines (catégorie 2 selon Santé Canada) se retrouvent alors dans cette catégorie. La virginiamycine (une streptogramine) est un antimicrobien commercialisé au Canada (homologué par exemple chez les poulets à griller pour prévenir l'entérite nécrotique, les porcs pour traiter et réprimer la dysenterie porcine et les bovins de boucherie pour réduire l'incidence d'abcès au foie avec 0 jour de retrait selon les notices sur les substances médicatrices de l'ACIA). L'entérite nécrotique est une maladie importante dans le secteur de la volaille. Les données de surveillance à la ferme du PICRA (2016) montrent bien que la virginiamycine est un des antimicrobiens le plus utilisé chez les poulets de chair et les dindons. Le retrait de cet anibiotique de la liste des antibiotiques permis en médecine vétérinaire pourrait avoir un impact important sur ces secteurs de production.	13 and 16, above. The Categorisation was developed for use in the EU. There is no assumption that all substances in Category A will be disallowed from use in animals/produce imported to the EU from third countries. Proposed change not accepted.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Proposed change (if any) : Proposer de revoir la catégorisation des streptogramines pour les inclure dans la catégorie B. Translation: According to the categorization of the Antimicrobial Advice Ad Hoc Expert Group (AMEG), Category A (Avoid) includes antimicrobials that are prohibited for use in livestock. **Important: Potential impact** Antimicrobials that are not authorized in the European Union (we assume that "authorized" means marketed) are included in AMEG Category A, owing in part to the lack of established MRLs. Streptogramins (Health Canada Category II) therefore fall under this category. Virginiamycin (a streptogramin antibiotic) is an antimicrobial marketed in Canada (approved, for example, in broilers to prevent necrotic enteritis, in pigs to treat and suppress swine dysentery and in beef cattle to reduce the incidence of liver abscesses with 0 days of withdrawal according to the CFIA's medicating ingredient brochures). Necrotic enteritis is a major disease in the poultry sector. On-farm surveillance data from CIPARS (2016) clearly show that virginiamycin is one of the most widely used antimicrobials in broilers and turkeys. The removal of this antibiotic from the list of antibiotics permitted in veterinary medicine could have a significant impact on these production sectors.		

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Proposed change (if any): Propose reviewing the categorization of streptogramins for inclusion in Category B.		
83-86 738-741	30	Comment: Classifying antibiotics to this category ("avoid"), which have no MRL may be misleading. If these categories were established according to risk of bacterial resistance to human health, it has no relevance whether any antibiotic has MRL or not. Proposed change: Remove the MRL reference from this category.	The possession or not of an MRL is not a criterion for designation to Category A. However, the absence of MRLs for substances in this category (MRLs can only be granted when there is intent for a marketing authorisation application), means that they cannot be used in food-producing species and this coincidentally acts as a risk management measure.	46.
87 - 106 & 141 (Table)	41	Comment : Selon la catégorisation de l'AMEG, la catégorie B (Restrict) comprend les antimicrobiens qui ne devraient être utilisés que pour le traitement de conditions cliniques quand il n'y a pas d'alternative efficace d'antimicrobiens appartenant à des catégories inférieures (C ou D). De plus, leur utilisation devrait être basée sur des résultats de tests de sensibilité, si possible. Au Québec, le Règlement modifiant le Règlement sur l'administration de	The public statement on the use of (fluoro)quinolones in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMEA/CVMP/SAGAM, 2007) indicates "In Enterobacteriaceae resistance to fluoroquinolones is	47.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		certains médicaments découlant de la Loi sur la protection sanitaire des animaux va dans le même sens, avec quelques différences. Le Réglement encadre l'utilisation des antimicrobiens de catégorie 1 (en faisant référence à la catégorisation de Santé Canada). L'utilisation de l'antibiogramme n'est pas obligatoire mais un exemple d'outil. Lien URL vers le Règlement. : http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=1&file=69441.pdf Étant donné les différences entre la catégorisation de l'AMEG et celle de Santé Canada, une des classes (ou sous-classes) d'antimicrobiens de la catégorie B de l'AMEG n'est pas visée par notre Réglement. En effet, la catégorie B de l'AMEG inclut l'ensemble des quinolones (fluoroquinolones et autres quinolones) alors que la catégorie 1 de Santé Canada inclut les fluoroquinolones seulement. Les autres quinolones sont dans la catégorie 2. Dans les autres quinolones, il y a notamment l'acide nalidixique qui est homologué chez les porcs et les bovins de boucherie. Le fait d'inclure l'ensemble des quinolones dans la catégorie B pourrait demander des ajustements de la part des producteurs canadiens, particulièrement au Québec puisqu'elles seraient considérées comme un équivalent des catégories 1 selon Santé Canada. Proposed change (if any) : Demander de considerer de séparer les fluoroquinolones des autres quinolones. Translation : According to the AMEG categorization, Category B (Restrict) includes	most commonly acquired by mutations in two steps. One mutation in the *gyrA* gene mediates full resistance to first generation quinolones such as nalidixic acid and flumequine and reduced susceptibility to fluoroquinolones. A second mutation in either *gyrA* or *gyrB* genes mediates 'full resistance' to fluoroquinolones". The same document indicates that in *Campylobacter* one single mutation causes full resistance to both fluoroquinolones and nalidixic acid. In addition, the *qnr* gene is a plasmid-borne resistance mechanism in Enterobacteriaceae which confers low level resistance and is selected by both quinolones and fluoroquinolones (Machuca et al., 2014). As quinolones can select for genes conferring resistance to fluoroquinolones, the AMEG	

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		antimicrobials that should be used only for the treatment of clinical conditions when no antimicrobials in the lower categories (C or D) are an effective alternative. In addition, the use of Category B antimicrobials should be based on sensitivity test results, if possible. In Quebec, the *Regulation to amend the Regulation respecting the administering of certain medications* under the *Animal Health Protection Act* runs along the same lines, with some differences. The *Regulation* provides a framework for the use of Category I antimicrobials (under Health Canada's categorization). Antibiotic sensitivity testing is not mandatory but an example of a tool. link to the *Regulation*: http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=1&file=69441.pdf. Given the differences between the AMEG categorization and the Health Canada categorization, one of the antimicrobial classes (or subclasses) in AMEG Category B is not covered by our regulation. AMEG Category B includes all quinolones (fluoroquinolones and other quinolones), while Health Canada Category I includes fluoroquinolones only. The other quinolones are in Category II. Other quinolones include nalidixic acid, which is approved for pigs and beef cattle. Including all quinolones in Category B could require adjustments from Canadian producers, particularly in Quebec, since they would be considered equivalent to Health Canada's Category I. Proposed change (if any): Request to consider separating fluoroquinolones from other quinolones.	considers that they should remain in Category B. Proposed change not accepted.	
89	8	Comment:	See Response to comment above	48.

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		This simply states quinolones, bringing in the early ones such as oxolinic acid Proposed change (if any): List fluoroquinolones rather than quinolones	from stakeholder 41 (comment No47). 'Quinolones' includes fluoroquinolones and other quinolones. Proposed change not accepted.	
93-94	20	Comment: if a change in classification of oxolinic acid to group C is not possible, we want to highlight that the use of antibiotics from class B should not be only determined by antimicrobial susceptibility testing, but may be also determined by restrictions for use introduced through current environmental legislation. Proposed change (if any): change of wording of these two lines "*especially for this category, use should be based on the results of antimicrobial susceptibility testing, whenever possible or by restrictions on the use of antibiotics based on the current environmental legislation".*	See full response to stakeholder 41 (Comment No 47). As quinolones can select for genes conferring resistance to fluoroquinolones, the AMEG considers that they should remain in Category B. The proposed text is not accepted as the context is not clear for many readers. It has been noted in chapters 4 and 5 that in addition to the Categorisation, other applicable legislative frameworks (e.g. the Water Framework Directive) should be taken into account.	49.
95-106	4	Comment: We very much welcome this rational approach as we consider that oral aminoglycosides are the only appropriate product for the justified and targeted metaphylactic treatment of neonatal lambs when necessary in the face of an outbreak of neonatal colibacillosis (watery mouth). There are no other licensed products for oral administration in lambs and we have	Thank you for your comment. Please note that in the revised categorisation the AMEG now proposes that spectinomycin should be moved to category D	50.

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		been working very hard to ensure that UK vets do not prescribe unlicensed products for this purpose. There have been communications throughout the UK sheep industry to iterate responsible use messages specific to these products. Proposed change (if any):	as the resistance mechanisms are different to those for otheraminoglycosides. Spectinomycin is available in the EU as an oral solution for treatment of individual lambs. Streptomycin and Neomycin remain in Category C.	
102	35	Comments: worth to specify that quinolones are fluoroquinolones and other quinolones. Proposed change: quinolones (fluoroquinolones and other quinolones)	A footnote has been added to clarify.	51.
107 - 115 & 141 (Table)	41	Comment : La catégorisation de l'AMEG accorde un ordre d'utilisation en fonction des catégories. La catégorie C (Caution) ne doit être utilisée seulement s'il n'y a pas d'antimicrobien dans la catégorie D qui est efficace. Nous n'avons pas d'équivalent à cette règle au Québec, outre le Règlement modifiant le Règlement sur l'administration de certains médicaments qui réserve en quelque sorte les antimicrobiens de catégorie 1 en dernière option. Translation: The AMEG categorization provides an order of use based on the categories. Category C (Caution) should be used only if there is no antimicrobial in Category D that is effective. We have no equivalent to this rule in Quebec, other than the *Regulation to amend the Regulation respecting the administering of certain medications*, which reserves Category I	Thank you for the comment.	52.

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		antimicrobials as a final resort.		
122	35	Comment: prudent and **responsible** use Proposed change (if any): add responsible	The two words are frequently used interchangeably in the AMR context. As this is a summary, 'prudent' has been substituted for the more commonly used word, 'responsible'.	53.
133	35	Comment: The example of treatment of fish by in-feed medication is not an ideal example. While in some countries antibiotics are provided in-feed to aquatic animals, in many major aquaculture producing countries this is extremely rare e.g. Norway, UK, etc. A better example would be the treatment of broiler flocks, although there also some countries have almost completely moved away from this (e.g. in Scandinavia; where group treatment of broilers has become rare and if done, usually via in water not in feed). Proposed change (if any): change the example of in-feed group treatment with antibiotics either to broilers or even better leave it out.	The intention is to demonstrate the diversity of treatment methods; therefore, the example has been changed, but not omitted.	54.
136	35	Comment: Therefore, treatment guidelines need to be **nationally**, regionally or even locally developed and implemented. Proposed change (if any): add nationally	Change accepted.	55.
137-138	35	Comment: '*Development and implementation of evidence-based national and regional treatment guidelines are encouraged*.' FVE, several of our members and several of our sister organisations, e.g. FECAVA, have already developed treatment guidelines.	A reference has been included in section 5 of the report to the European Commission's Guidelines for the prudent use of	56.

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		Proposed change (if any): recognise some treatment guidelines	antimicrobials in veterinary medicine (Practical examples) and the RONAFA report, both of which include examples of treatment guidelines in effect in EU member states.	
137-138, 836-837	39	Guideline states, "*…development and implementation of evidence-based national and regional treatment guidelines are encouraged.*" Comment: It is unclear what "evidence-based" means in this context. Could you please provide further clarification? Use of the word 'evidence' could imply a hazard identification is not based on scientific data.	The evidence required will depend on the purpose of the guidelines. In the RONAFA report it was recommended that sector-specific treatment guidelines should be developed. It was recognised that the approach to developing guidelines should include consideration of evidence of clinical effectiveness, PKPD factors, local AMR surveillance etc. Additional clarification has been added in Section 5 of the AMEG report.	57.
141	7	Comment:concern that cat D is highly restrictive and if followed in the field will put intense selection pressure on few products available with wide therapeutic gaps (NB Bactitracin, nitrofurans,nitroimidazoles and fusidic acid have no therapeutic indication or value in pigs Proposed change (if any): consider a less restricted approach to C/D	We are aware that category D does not contain appropriate alternatives for all species-indication combinations. Category C are antibiotics that should only be used when there	58.

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		allocation esp wrt aminoglycosides and pleuromutilins see below considering this document is about animal use rather than human use and proven spread of resistance from animal orgs to human orgs is vastly overstated	is no substance in Category D that would be effective. This covers the therapeutic gaps – for certain indications Category C would be first choice. Preferably, national or regional treatment guidelines can specify indications and species where Category C is appropriate as first choice.	
141	8	Comment: This simply states quinolones, bringing in the early ones such as oxolinic acid Proposed change (if any): List fluoroquinolones rather than quinolones	Quinolones are HPCIA in the WHO categorisation. They select for the first step of the mutations that lead to fluoroquinolone resistance and are therefore in Category B. From a "microbiological resistance" perspective it would not be appropriate to make a distinction between these substances (quinolones and fluroquinolones) as they have the potential to select for resistance (mutations, as well as plasmid-mediated).	59.
141	9	Comment: the group of aminoglycosides is a highly diverse group of antibiotics, and some aminoglycosides are more important in human medicine than other aminoglycosides and a differentiation between the	Partly agreed. Aminoglycosides, except for spectinomycin, are CIA in human	60.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		different groups of aminoglycosides should be applied to the categorization. Proposed change (if any): Diversifying the aminoglycosides, so streptomycin, neomycin and spectinomycin are in class D, and apramycin and gentamicin are in class C will provide a more beneficial risk-benefit ratio.	medicine. There is a high potential for transmission of resistance determinants between animals and humans. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides other than spectinomycin are in category C rather than in category B. For spectinomycin there is no/limited cross-resistance to the other aminoglycosides and it is less important in human medicine compared to other aminoglycosides. Spectinomycin is therefore now in included category D.	
	9	Comment: a risk assessment carried out by the Danish Veterinary and Food Administration in 2017 concludes that the use of quinolones in marine aquaculture is assessed to constitute a low risk compared to how quinolones and fluoroquinolones are otherwise used in humans and for veterinary purposes and that quinolone resistance in marine aquaculture has not created and is not expected to create significant problems in foods or humans as the risk is deemed to be low. Proposed change (if any): We therefor encourage AMEG to take this species-	Quinolones are HPCIA in the WHO categorisation. They select for the first step of the mutations that lead to fluoroquinolone resistance and are therefore in Category B. From a "microbiological resistance" perspective it would not be appropriate to make a distinction between these substances	61.

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		specific situation for farmed fish into consideration and change the classification of quinolones to group C allowing for aquaculture to use quinolones	(quinolones and fluroquinolones) as they have the potential to select for resistance (mutations, as well as plasmid-mediated). Species-specific aspects (risk, need) can be taken into account in national, regional or species-specific guidelines or regulation.	
	9	Comment: If a change in classification of oxolinic acid to group C is not possible it is very important that it being highlighted that the use antibiotics from category B should not only be determined by antimicrobial susceptibility tests but can also be determined by restrictions on the use of antibiotics based on the Water Framework Directive or other environmental legislation Proposed change (if any): Line 93-94 should be changed to following wording: Especially for this category, use should be based on the results of antimicrobial susceptibility testing, whenever possible or by restrictions on the use of antibiotics based on the Water Framework Directive or other environmental legislation.	See responses to comments 7 and 47.	62.
141	12	Comment: We feel that it is inappropriate to place all formulations of polymyxin molecules under Category B. Polymyxin B is used in companion animals as an individual aural treatment and we feel that polymyxin B should be, for companion animal use, placed into Category D for the following reasons:	Please see section 3.3.1 of the report, where it is acknowledged that local individual treatments are likely to have a lower impact on selection of AMR than other	63.

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		• Polymyxin B is used as an individual patient treatment, and not herd treatment as it is only licensed in companion animal, additionally polymyxin B is not used in food producing animals; Polymyxin B is only used therapeutically and only after diagnosed infection as topical individual treatment in companion animals • Cat welfare is at risk with very few other antibiotic classes licensed for cats' Otitis Externa containing antibiotics for aural use (e.g. aminoglycosides – Category C) • Studies have demonstrated non-absorption of polymyxin B reducing the risk of systemic exposure and resistance induction (Voget, *Et al*., Antibiotic plasma levels in dogs with Otitis externa treated routinely with various topical preparations. Berliner und Münchener Tierärztliche Wochenschrift 125, Heft 11/12 (2012), Seiten 44–48); • As such, the expert's answer highlight line 194 "*The chain of events that may follow from use of antimicrobials in animals resulting in compromised antimicrobial treatment in humans*." In case of aural and ophthalmic treatments with Polymyxin B the step 2 *"selection pressure leading to increase number of resistant bacteria and/or resistance genes in the animal microbiota"* appears to be weak. This could also be a reason to reconsider Polymyxin B classification. NB : please note there is a typo in the answer step 2 : "seletion" instead of "selection" • Synergistic effect of polymyxin B & miconazole in some aural treatments enhances efficacy against the bacteria, the synergistic effects may reduce risk of resistance (Chiavassa *et al*. Evaluation of *In Vitro* Synergistic Interaction of Miconazole and Polymyxin B Against Clinical Strains of *Malassezia pachydermatis. The Open Mycology Journal,* 2013, *7,* 7-10; Pietschmann et al. Synergistic effects of Miconazole and Polymyxin B on microbial pathogens. Vet Res Commun (2009) 33:489–505) ; • Since 2013, the ESVAC report on sales of veterinary antimicrobial agents	routes. More emphasis has also been given in section 5 on the importance of consideration of the route of administration when prescribing. To include each substance/subclass + route of administration combination separately would make the categorisation very complex for the user and in most cases, the antibiotic class is available for administration via a variety of routes. Therefore, we have chosen to keep separate rankings for route and class, both to be considered when making a prescribing choice.	

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		do not report sales of Polymyxin B: indeed, ATCvet group QD and QS are voluntary excluded. The latest ESVAC report states that *"The contribution from these pharmaceutical forms, in tonnes of active ingredient, to the total amount of veterinary antimicrobials sold is shown to be negligible and thus the underestimation of total sales is insignificant".* Regarding Polymyxin B, only two ATCvet codes belonging to the ATCvet group QS could have been considered: QS01AA18 and QS02AA11. → **the fact that ESVAC do not consider Polymyxin B in the ESVAC report is consistent with the fact that Polymyxin B is probably not a key contributor to AMR.** • We believe that our suggestion is fully in accordance with the expert answer that clearly states that : (line 72) *"Hence in the updated categorisation proposal, more emphasis is placed on the availability of alternative antimicrobials in veterinary medicine."* → **we do consider that this is an additional reason to reconsider Polymyxin B classification as an exception due to the few alternatives** • We understand why the experts choose not to take into account the route of administration for categorisation *"Given that antimicrobials in each (sub)class are available in a number of different formulations and for administration by different routes, the AMEG chose not to include the route of administration as an additional criterion for the categorisation."(line 509-511)* Nevertheless, in the case of Polymyxin B it appears that there are only 2 species concerned – cat and dogs –, 2 formulations – eyewash and suspension - and only 2 routes of administration –ophthalmic and aural – that are clearly considered as very low risk. → **This is an additional reason to consider our proposal** • Overall, we consider that what is taken in consideration line 355 and 356 for reviewing aminoglycosides categorisation from 2 to C fully apply to Polymyxin B: *"their use in veterinary medicine was considered to have a lower risk to human health compared with quinolones and 3rd- and 4th-*		

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		generation cephalosporins." **On top of that, Polymyxin B being prescribed only in pets and as aural or ophthalmic topicals, it does make sense to consider them in Category D.** • This exception will also be consistent with the one referred to lines 689-692 of the expert's answer : *"With regard to the route of administration, this has not been included as a criterion for the categorisation for reasons discussed in 3.3.1. The exception is for steroid antibacterials (fusidic acid) where it was taken into account that this class is only administered locally in animals."* → **Like fusidic acid, Polymyxin B is only administred locally in dogs and cats.** Proposed change: • For local administration and companion animal use, we propose moving polymyxin B into Category D as an exception, taking into account above points • Additionally a foot note should be included – as per fusidic acid - to reinforce the point that use of polymyxin B in companion animals, as single animal aural/opthalmic route of administration is acceptable and not subject to the same restrictions as other members of the polymyxin class i.e. colistin.		
	12	Comment: With respect to macrolides being placed in Category C, we feel that this is inappropriate and that macrolides, or at least a sub-set of macrolides, should be placed into Category D for the following reasons: • As per OIE CIA (May 2015) macrolides are VCIA and the only drug of choice for some food animal infections e.g. Lawsonia and Mycoplasma • Lack of field reports of treatment failure when using macrolides for Lawsonia and Mycoplasma is indicative that after over 40 years of use, macrolides remain an effective treatment option for Lawsonia and	Macrolides are HPCIA according to WHO. Other HPCIAs are placed in B. Therefore, macrolides cannot be placed in D due to their importance in human medicine. The rationale in Table 4 has been revised to improve clarity. The importance of macrolides for treatment of	64.

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		Mycoplasma infections Proposed change (if any): We recommend that macrolides as a group, or select macrolides at the very least, be placed into Category D for food animal use	Lawsonia and mycoplasma infections has been taken into account.	
141	20	Comment: the group of aminoglycosides is a highly diverse group of antibiotics, and some of them are more important in human medicine than others; a differentiation between these different groups should be applied at the categorization. Proposed change (if any): Diversifying the aminoglycosides (streptomycin, neomycin and spectinomycin in class D; apramycin and gentamicin in class C) will provide a more beneficial risk-benefit ratio. Comment: the use of quinolones in marine aquaculture is assessed to constitute a low risk compared to how quinolones and fluoroquinolones are otherwise used in humans and for veterinary purposes, and that quinolone resistance in marine aquaculture has not created and is not expected to create significant problems in foods or humans, as the risk is deemed to be low (Danish Veterinary and Food Administration, 2017). Proposed change (if any): we encourage the AMEG to take into consideration the species-specific situation for farmed fish, changing oxolinic acid to group C and allowing its use in aquaculture.	Aminoglycosides: Partly agreed. Aminoglycosides, except for spectinomycin, are CIA in human medicine. There is a high potential for transmission of resistance determinants between animals and humans. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides other than spectinomycin are in cat C rather than in category B. For spectinomycin there is no/limited cross-resistance to the other aminoglycosides and it is less important in human medicine compared to other aminoglycosides. Spectinomycin is therefore now placed in category D.	65.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
			Quinolones: Quinolones are HPCIA in the WHO categorisation. They select for the first step of the mutations that lead to fluoroquinolone resistance and are therefore in Category B. From a "microbiological resistance" perspective it would not be appropriate to make a distinction between these substances (quinolones and fluroquinolones) as they have the potential to select for resistance (mutations, as well as plasmid-mediated). The rationale has been further clarified in Table 4. Species-specific aspects (risk, need) can be considered in national, regional or species-specific guidelines or regulation.	
141 Table 1: (aminoglycosides)	22	**Comment:** Regarding AMGs, the nature of the genetic support of resistance primarily involves numerous plasmid-mediated, AG-modifying enzymes (**Vakulenko S.B. *et al*, 2003**). When screening antibiotic profiles generated through these enzymes, it is important to note that, unlike the	Aminoglycosides: Partly agreed. Aminoglycosides, except for spectinomycin, are CIA in human medicine. There is a high	66.

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		other AG drugs, the oldest AMG generation such as streptomycin only induces the expression of a limited series of enzymes in the bacterium (AG phosphotransferases, type APH(3")-Ia, Ib and APH(6)-Ia, Ib, Ic and Id encoded by the strA-strB genes (**Sunde M. *et al,* 2005**); and no AG acetyl transferase (enzymes very commonly expressed in the inducible resistance towards more recent AGs); AG nucleotidyltransferases, types ANT(3')-I and ANT(6')-I encoded by the aadA gene (**Sunde M. *et al*, 2005**). The article published by **Vakulenko S.B. *et al*, 2003** clearly demonstrates that the potential for cross-resistance between streptomycin and the others AGs is very low since the majority of the inducible enzymes recognise streptomycin as it was rightly highlighted in the reflection paper EMA/CVMP/AWP/721118/2014 adopted by CVMP the 21st of June 2018. Another mode of bacterial resistance to AGs involves the genetic modification of ribosomal receptor sites to prevent the binding of the antibiotic and induce misreading as well as inhibiting protein synthesis. Small differences in the structure of the AG, and particularly the presence and position of 2'-amino groups, can result in substantial differences in the inhibition of protein synthesis. For example: the molecular structure of streptomycin differs from that of kanamycin or amikacin and the bacterial resistance, which results from ribosomal modification and inhibited binding capability, is also different (**Benveniste R. *et al*, 1973**). The induction of this type of resistance to streptomycin does not confer full cross-resistance to more recent generations of AGs (gentamycin, kanamycin, amikacin). This point is in accordance with the reflection paper EMA/CVMP/AWP/721118/2014 (page 22, first paragraph). Indeed, it is well known that amikacin binds strongly to the 50S ribosomal sub-unit, unlike streptomycin, which binds with varying degrees of affinity to the 30S	potential for transmission of resistance determinants between animals and humans. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides other than spectinomycin are in cat C rather than in category B. For spectinomycin there is no/limited cross-resistance to the other aminoglycosides and it is less important in human medicine compared to other aminoglycosides. Spectinomycin is therefore now placed in category D. The rationale has been further clarified in Table 4.	

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		ribosomal sub-unit. Furthermore, gentamycin shares some common binding sites with amikacin on the 50S ribosomal sub-unit, which is not the case for streptomycin (**Bryan L.E. *et al*, 1983**). On the basis of this scientific data, AMGs belonging to the group of (dihydro)streptomycin and spectinomycin should be differentiated from the more recent and more efficient aminoglycosides such as gentamicin, kanamycin and amikacin. **Proposed change:** In the new context of antibiotic categorization, these 2 very old generations of AMGs ((dihydro)streptomycin and spectinomycin) not classically used in human medicine should be classified in category D and desoxystreptamines 4-5 and 4-6 substituted should be classified in category C. **Comment:** In Table 1, 1st and 2nd generation cephalosporins (C1-C2) are classified in Category C. This classification should be based on the 4 categorisation criteria for a given (sub)class or group which have been updated (lines 680 and following) as: 1) Use as a veterinary medicine 2) Importance to human medicine according to WHO ranking 3) Likelihood of AMR transfer from animals to humans 4) Availability of alternatives with lower AMR risk However, when comparing assessment of these 4 criteria between C1-C2 and substances which have been classified in Category D, the rationale is not totally clear as C1-C2 do not belong to the highest priority from WHO (C1-C2 are highly important rather than critically important antimicrobials), their risk of AMR transfer is not higher than for some of the substances in Category D (from Table 3) whereas scarcity of alternatives for some indications in veterinary medicine is highlighted (from Table 4).	Cephalosporins: Criterion 3 considers not only likelihood of transfer, but also the possible consequences. Specific genes have also been considered. These subclasses may select for resistance to penicillins and higher generation cephalosporins in both Gram-negative bacteria (ESBL, *ampC*, even would select for carbapenemases if they become more widespread in	

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		Proposed change: Please consider the inclusion of C1-C2 in Category D**.**	animal populations) and in staphylococci (MRSA).	
141 Table 1 : (florfenicol)	22	**Comment:** In the previous antibiotic categorization, florfenicol was the only phenolic compound used in veterinary medicine as a first intention to treat respiratory diseases infections caused by gram-negative *Pasteurellaceae* bacteria and mycoplasmosis. Indeed, florfenicol can pass through biological membranes to reach lung intracellular pathogens. Chloramphenicol is rarely used in human health due to the probability of the inhibition of mitochondrial protein synthesis causing irreversible idiosyncratic aplastic anaemia and the availability of many alternative antimicrobial agents that possess better safety profiles. (**Schwarz S. et al; 2005**). Because of the high importance of phenicol based compounds in veterinary medicine to treat efficiently and quickly respiratory diseases, a safer alternative to chloramphenicol and exclusively for veterinary medicine has been used, namely florfenicol (**Schwarz S. *et al*; 2004**). Chloramphenicol and thiamphenicol resistance among bacteria is frequently due to the presence of antibiotic inactivating enzyme chloramphenicol acetyltransferase (CAT) which catalyses the acetyl-S-CoA-dependent acetylation of chloramphenicol at the 3-hydroxyl group. The fluorinated more potent and less toxic phenicol derivative, florfenicol, is a synthetic drug, which substitutes a fluorine atom for the hydroxyl group on the 3' carbon of thiamphenicol, leading this molecule to be considerably less affected by enzymatic modifications (**Neu HC. *et al*; 1980**; **Syriopoulou VP. *et al*; 1981**). The synthesis of CAT is constitutive in gram-negative bacteria, which naturally harbour plasmids bearing the structural gene for the enzymes (**Schwarz S. et al; 2005**).	Amphenicols select for *cfr*-genes that mediate resistance to oxazolidinones in MRSA and enterococci. It is acknowledged that these genes still seem to be of low prevalence. As oxazolidinones are of critical importance for human medicine, amphenicols have been placed in C.	67.

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		Most of the genes cited in the scientific literature such as OptrA and cfr which confer resistance to phenols have mainly been found on gram-positive bacterial species (**Jing Qi. *et al* ;2012**) and often belonging to the digestive flora. Florfenicol used as an injectable preparation against respiratory infections is mainly eliminated by the urine (EMA –Committee for veterinary medicinal products – on line florfenicol summary report). The impact on the intestinal bacteria of the treated animals is therefore extremely low. A recent study was conducted in Germany in order to evaluate the spread of cfr gene between calves, pigs on 27 farms and 22 farmers in direct contact with these animals (**Cuny C. *et al*; 2017**). The study was then extended to 169 veterinarians from all over Germany and 363 humans from the German municipal community. The results of this study highlight the very low rate of presence of cfr-carrying Staphylococci in humans. Florfenicol is not used to target Gram-positive bacteria but only Gram-negative bacteria found in the respiratory tree, including *Pasteurellaceae* and *Mycoplasma*. The scientific literature does not mention that the genes concerned such as OptrA and cfr have been isolated in this bacterial families. Furthermore, it has been demonstrated by the recent CEESA data that florfenicol exhibits a with very low occurrence of antibiotic resistance towards *Pasteurellaceae* (Vetpath IV 2015-2016). Recent scientific work by experts in the field of phenolic antibiotics highlights that mechanisms of resistance involving genes such as OptrA are not yet fully understood (**Wang Y. *et al*; 2018**). Given that there is not a single agent in category D that can be used to effectively treat acute multifactorial diseases such as the BRD complex we suggest the classification of florfenicol is changed to category D. **Proposed change:** In the new context of antibiotic categorisation, please consider classifying florfenicol in category D.		

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
141 (Table 1) (sub lines 16-18)	26	• Riminofenazines • ~~Streptogramins~~ • Sulfones Rationale: Streptogramins are an old class of antimicrobial regarded as obsolete in human medicine. Virginiamycin is widely approved as a therapeutic veterinary medicine. The rationale of conserving classes not approved for veterinary medicine is well founded for new classes with high medical utility, but not for old classes that have demonstrated low human medical utility. Placing streptogramins in Category A provides inappropriate selection advice as it encourages the selection of higher importance human use classes. Moving streptogramins to Category D is consistent with European Parliament Regulation 2019/6 clause 49 "…restricting the use of veterinary antimicrobials in the Union should be based on scientific advice and should be considered in the context of cooperation with third countries and international organisations"	The present categorisation is not linked to recital 49 of Regulation 2019/6. Please refer also to the response to your earlier comment 22 and to comment 43.	68.
141 (Table 1) (insert at end of table)	26	• Nitroimidazoles* • Penicillins: Anti-staphylococcal penicillins (β-lactamase-resistant penicillins) • NEW: Streptogramins Rationale: See prior point. Additionally, the rationale for re-categorising streptogramins to Category D specifically is based on the medical importance of this class relative to other antimicrobial classes. As a class that is regarded as obsolete in human medicine, the streptogramins are appropriately classified below those classes with significant utility in human medicine. Category D is the most appropriate category, and provides the EU categorisation with international utility.	Streptogramins currently fulfil the criterion for A, i.e. the class is not authorised for use in animals in the EU. In the event of a future application for Marketing Authorisation, the risk and benefits will be assessed at that time, and the class will be categorised accordingly. Please also refer to responses to your earlier comments.	69.
141 Table 1:	28	**Comment:** Regarding AMGs, the nature of the genetic support of resistance	Aminoglycosides: Partly agreed.	70.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
(aminoglycosides)		primarily involves numerous plasmid-mediated, AG-modifying enzymes (**Vakulenko S.B. *et al*, 2003**). When screening antibiotic profiles generated through these enzymes, it is important to note that, unlike the other AG drugs, the oldest AMG generation such as streptomycin only induces the expression of a limited series of enzymes in the bacterium (AG phosphotransferases, type APH(3")-Ia, Ib and APH(6)-Ia, Ib, Ic and Id encoded by the strA-strB genes (**Sunde M. *et al*, 2005**); and no AG acetyl transferase (enzymes very commonly expressed in the inducible resistance towards more recent AGs); AG nucleotidyltransferases, types ANT(3')-I and ANT(6')-I encoded by the aadA gene (**Sunde M. *et al*, 2005**). The article published by **Vakulenko S.B. *et al*, 2003** clearly demonstrates that the potential for cross-resistance between streptomycin and the others AGs is very low since the majority of the inducible enzymes recognise streptomycin as it was rightly highlighted in the reflection paper EMA/CVMP/AWP/721118/2014 adopted by CVMP the 21st of June 2018. Another mode of bacterial resistance to AGs involves the genetic modification of ribosomal receptor sites to prevent the binding of the antibiotic and induce misreading as well as inhibiting protein synthesis. Small differences in the structure of the AG, and particularly the presence and position of 2'-amino groups, can result in substantial differences in the inhibition of protein synthesis. For example: the molecular structure of streptomycin differ from that of kanamycin or amikacin and the bacterial resistance, which results from ribosomal modification and inhibited binding capability, is also different (**Benveniste R. *et al*, 1973**). The induction of this type of resistance to streptomycin does not confer full cross-resistance to more recent generations of AGs (gentamycin, kanamycin, amikacin). This point is in accordance with the reflection paper	Aminoglycosides, except for spectinomycin, are CIA in human medicine. There is a high potential for transmission of resistance determinants between animals and humans. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides other than spectinomycin are in cat C rather than in category B. For spectinomycin there is no/limited cross-resistance to the other aminoglycosides and it is less important in human medicine compared to other aminoglycosides. Spectinomycin is therefore now placed in category D. The rationale has been further clarified in Table 4.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		EMA/CVMP/AWP/721118/2014 (page 22, first paragraph). Indeed, it is well known that amikacin binds strongly to the 50S ribosomal sub-unit, unlike streptomycin, which binds with varying degrees of affinity to the 30S ribosomal sub-unit. Furthermore, gentamycin shares some common binding sites with amikacin on the 50S ribosomal sub-unit, which is not the case for streptomycin (**Bryan L.E. *et al*, 1983**). On the basis of this scientific data, AMGs belonging to the group of (dihydro)streptomycin and spectinomycin should be differentiated from the more recent and more efficient aminoglycosides such as gentamicin, kanamycin and amikacin. **Proposed change:** In the new context of antibiotic categorization, these 2 very old generations of AMGs ((dihydro)streptomycin and spectinomycin) not classically used in human medicine should be classified in category D and desoxystreptamines 4-5 and 4-6 substituted should be classified in category C.		
141	28	**Comment:** In Table 1, 1st and 2nd generation cephalosporins (C1-C2) are classified in Category C. This classification should be based on the 4 categorisation criteria for a given (sub)class or group which have been updated (lines 680 and following) as: 1) Use as a veterinary medicine 2) Importance to human medicine according to WHO ranking 3) Likelihood of AMR transfer from animals to humans 4) Availability of alternatives with lower AMR risk However, when comparing assessment of these 4 criteria between C1-C2 and substances which have been classified in Category D, the rationale is not totally clear as C1-C2 do not belong to the highest priority from WHO (C1-C2 are highly important rather than critically important antimicrobials), their risk of AMR transfer is not higher than for some of the substances in	Cephalosporins: Criterion 3 is not only likelihood of transfer, it is likelihood and possible consequences. Specific genes have also been considered. These subclasses may select for resistance to penicillins and higher generation cephalosporins in both Gram-negative bacteria (ESBL, *ampC*, even would select for carbapenemases if they become more widespread in animal populations) and in staphylococci (MRSA).	71.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Category D (from Table 3) whereas scarcity of alternatives for some indications in veterinary medicine is highlighted (from Table 4). **Proposed change:** Please consider the inclusion of C1-C2 in Category D**.**		
141 – Table 1 : (florfenicol)	28	**Comment:** In the previous antibiotic categorization, florfenicol was the only phenolic compound used in veterinary medicine as a first intention to treat respiratory diseases infections caused by gram-negative *Pasteurellaceae* bacteria and mycoplasmosis. Indeed, florfenicol can pass through biological membranes to reach lung intracellular pathogens. Chloramphenicol is rarely used in human health due to the probability of the inhibition of mitochondrial protein synthesis causing irreversible idiosyncratic aplastic anaemia and the availability of many alternative antimicrobial agents that possess better safety profiles. (**Schwarz S. et al; 2005**). Because of the high importance of phenicol based compounds in veterinary medicine to treat efficiently and quickly respiratory diseases, a safer alternative to chloramphenicol and exclusively for veterinary medicine has been used, namely florfenicol (**Schwarz S. *et al*; 2004**). Chloramphenicol and thiamphenicol resistance among bacteria is frequently due to the presence of antibiotic inactivating enzyme chloramphenicol acetyltransferase (CAT) which catalyses the acetyl-S-CoA-dependent acetylation of chloramphenicol at the 3-hydroxyl group. The fluorinated more potent and less toxic phenicol derivative, florfenicol, is a synthetic drug, which substitutes a fluorine atom for the hydroxyl group on the 3' carbon of thiamphenicol, leading this molecule to be considerably less affected by enzymatic modifications (**Neu HC. *et al*; 1980**; **Syriopoulou VP. *et al*; 1981**). The synthesis of CAT is constitutive in gram-negative bacteria, which naturally harbour plasmids bearing the structural gene for	Amphenicols select for *cfr*- genes that mediate resistance to oxazolidinones in MRSA and enterococci. It is acknowledged that these genes still seem to be of low prevalence. As oxazolidinones are of critical importance for human medicine, amphenicols have been placed in C. Other criteria were also assessed for the current classification.	72.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		the enzymes (**Schwarz S. et al; 2005**). Most of the genes cited in the scientific literature such as OptrA and cfr which confer resistance to phenols have mainly been found on gram-positive bacterial species (**Jing Qi. *et al* ;2012**) and often belonging to the digestive flora. Florfenicol used as an injectable preparation against respiratory infections is mainly eliminated by the urine (EMA –Committee for veterinary medicinal products – on line florfenicol summary report). The impact on the intestinal bacteria of the treated animals is therefore extremely low. A recent study was conducted in Germany in order to evaluate the spread of cfr gene between calves, pigs on 27 farms and 22 farmers in direct contact with these animals (**Cuny C. *et al*; 2017**). The study was then extended to 169 veterinarians from all over Germany and 363 humans from the German municipal community. The results of this study highlight the very low rate of presence of cfr-carrying Staphylococci in humans. Florfenicol is not used to target Gram-positive bacteria but only Gram-negative bacteria found in the respiratory tree, including *Pasteurellaceae* and *Mycoplasma*. The scientific literature does not mention that the genes concerned such as OptrA and cfr have been isolated in this bacterial families. Furthermore, it has been demonstrated by the recent CEESA data that florfenicol exhibits a with very low occurrence of antibiotic resistance towards *Pasteurellaceae* (Vetpath IV 2015-2016). Recent scientific work by experts in the field of phenolic antibiotics highlights that mechanisms of resistance involving genes such as OptrA are not yet fully understood (**Wang Y. *et al*; 2018**). Given that there is not a single agent in category D that can be used to effectively treat acute multifactorial diseases such as the BRD complex we suggest the classification of florfenicol is changed to category D. **Proposed change:** In the new context of antibiotic categorisation, please		

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		consider classifying florfenicol in category D.		
141	34	Comment: Table 1. Summary of the AMEG categorisation – categorisation of penicillin Proposed change (if any): AVEC suggests including a more clear categorisation of penicillin considering the use across category B to D; Comment: Table 1. Summary of the AMEG categorisation – use and categorisation of colistin Proposed change (if any): AVEC agrees on restricting and/or banning colistin, besides this we agree with the classification in category "B"; Comment: Table 1. Summary of the AMEG categorisation – categorisation and use of macrolides Proposed change (if any): As the categorisation stands there are limited alternatives for macrolides (cat C) AVEC suggests clarifying if it is possible to use these antibiotics as soon as there are no alternatives in cat. D;	Penicillin subclasses that are currently not authorised in animals are in category A, aminopenicillins with enzyme inhibitors are in category C and remaining penicillins are in D. The rationale for the categorisation of each (sub)class has been clarified in Table 4. Colistin: thank you for your comment. Macrolides: The interpretation is correct. According to the risk management measures proposed for category C (4.3), substances from this category should only be used when there is no substance in category D that would be effective. Preferably, national or regional species-specific guidelines should define for the indications or situations where this is the case.	73.
141	35	Comment: The text used to explain each category is unclear and in order to	In agreement with the mandate	74.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		be practical should be more precise and include the substance (while now it is mostly only listing classes). For example class glycopeptides include substances such as vancomycin, teicoplanin, telavancin, ramoplanin, decaplanin and only vancomycin is cited. Enrofloxacin, flumequine, danofloxacin, etc. are not cited. The fluoroquinolones especially for pet animals are not included. Tetracycline is cited but not oxytetracycline, chlortetracycline, doxycycline and other tetracyclines. To be practical, you need to include the substances, as these are very important for veterinary practitioners. Comment: Category A: We suggest, before summing up all antimicrobials for Category A in the table, to add that these are all antimicrobials not authorised in veterinary medicine. In addition, please correct a typo in the list of Category A antibitics, namely '~~Cephalosporins~~, Other Cephalosporins and penems (ATC code J01DI)' Proposed change (if any): Add at beginning of Category A before listing the antimicrobials: **Antimicrobials not authorised in veterinary medicine, such as** … and remove double reference to cephalosporins. Comment: It is also to be welcomed that the macrolides have been classified in category C and not in B Proposed change: none	received, communication tools including an infographic will be provided after the advice is published. A comprehensive list of the veterinary authorised substances and their categorisation is also be provided in an Annex. Please refer to the revised description for Category A in section 4.1 of the report.	
141	36	Comment: Category A: We suggest in the table to add for Category A before summing up all antimicrobials that these are all antimicrobials **not authorised in veterinary medicine**. In addition, also in Category 1, typo - the first cephalosporins need to be	Amended in part. The explanation for category A is clearly stated earlier in the Summary.	75.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		removed in 'Cephalosporins, Other cephalosporins and penems (ATC code J01DI)' Proposed change (if any): Add at beginning of Category 1 before listing the antimicrobials: Antimicrobials not authorised in veterinary medicine, such as … and remove double cephalosporins.		
141 Table 1: (aminoglycosides)	38	**Proposed change:** In the new context of antibiotic categorisation, two very old generations of AMGs (streptomycin and spectinomycin) not classically used in human medicine should be classified in category D and desoxystreptamines 4-5 and 4-6 substituted should be classified in category C.	Partly agreed. Aminoglycosides are CIA in human medicine. There is a high potential for transmission of resistance determinants between animals and humans. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides, not including spectinomycin, are in category C rather than in category B. Aminocyclitols are categorized as 'Important' by WHO. For spectinomycin there is no/limited cross-resistance to the other aminoglycosides and it is less important in human medicine compared to other aminoglycosides. Spectinomycin is therefore now in category D.	76.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
141 – Table 1 : (florfenicol)	38	**Comment:** In the previous antibiotic categorisation, florfenicol was the only phenolic compound used in veterinary medicine as first intention to treat respiratory diseases infections caused by gram-negative *Pasteurellaceae* bacteria and also against intracellular bacterial pathogens such as *Mycoplasma* because such antibiotic is able to pass through biological membranes to reach lung intracellular pathogens. Chloramphenicol is rarely used in human health due to the probability of the inhibition of mitochondrial protein synthesis causing irreversible idiosyncratic aplastic anaemia and the availability of many alternative antimicrobial agents that possess better safety profiles. (**Schwarz S. et al; 2005**). Chloramphenicol was banned from veterinary medicine because of possibility of trace residues in animal food product. Because of the high importance of phenicol based compounds in veterinary medicine to treat efficiently respiratory diseases, a safer alternative to chloramphenicol has been used namely florfenicol (**Schwarz S. *et al*; 2004**). **Proposed change:** In the new context of antibiotic categorisation, florfenicol should be classified in category D.	Amphenicols select for *cfr*- genes that mediate resistance to oxazolidinones in MRSA and enterococci. It is acknowledged that these genes still seem to be of low prevalence. As oxazolidinones are of critical importance for human medicine, amphenicols have been placed in category C.	77.
143-144	30	Comment: It is paramount to ensure that the new classification will be widely communicated to the concerned parties so as to ensure a correct enforcement and implementation. As such, a broader communication campaign (not limited to infographic) should be envisaged so as to warrant that relevant parties (mainly veterinary students and practitioners) are correctly informed.	Thank you for your comment. This will be considered in the communication phase.	78.
145	7	Comment: Aminoglycosides & aminocyclitols (spectinomycin) are the last groups of Abs available to treat enterobacterial enteritis in pigs and with the	Spectinomycin is now placed in category D.	79.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		impending ban on Zinc Oxide welfare problems could occur (accepting that use of A-Gs is permissible within conditions set for cat C) Pleuromutilins and lincoamines only products available to treat Swine Dysentery Proposed change (if any): Would appreciate an acknowledgement that animal health and welfare are important and working within these guidelines animals should not be denied essential treatment/metaphylaxis	With the addition of the fourth criterion, the importance of each class for animal health and welfare is balanced against public health risks (section 3.3) and more emphasis has been given to a One Health approach. It is acknowledged in chapter 3.3 that infection prevention and control measures should be implemented to improve animal health and reduce the need to resort to the use of antibiotics. Despite this, animals may become sick and those with clinical signs of bacterial infection that is impacting on their health and welfare in many cases need to be treated with antibiotics.	
186	2	Comment: Since the revised categorization now explicitly includes animal health considerations, I think a brief statement to that effect directly following section 3.1 would be helpful. Granted, some information that is provided later in the document regarding refinement to criteria (lines 395-414) touches on this but I think its importance could escape many readers, particularly those who may wonder why this categorization is different from WHO's etc. Proposed change (if any): Add section 3.2. Risk to animal health, or revise	The comment is acknowledged. The focus of this section has not been changed but a sentence was added on the risk to animal health and welfare at the end of 3.1.	80.

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		3.1 to include both human health and animal health.		
186	35	Comment: Please redraft the paragraph on risk to public health in the One Health perspective, briefly explaining the different transfer routes. Now it looks like the use of antimicrobials in animals is the sole route for human AMR. Take into account the different species: food producing and companion animals. Proposed change: Reword this paragraph, putting it more in a holistic One Health Perspective.	The text has been amended: 'Other routes for the development and spread of resistant bacteria and /or resistance genes to humans include use of antibacterials in humans, varying infection prevention and control/hygiene practices to prevent cross-transmission between humans, as well as environmental sources'.	81.
200-201	36	Comment: "restrictions on one class alone might not have the desired impact because of co-selection of AMR." This is a very important, factual statement that has been missed in the legislation.	Except for specific public health concerns, co-selection was not considered as a full criterion for the categorisation. It is outside the mandate to comment on the legislation.	82.
205-247	2	Comment: WHO recently drafted a 6th revision of its list of Critically Important Antimicrobials for Human Medicine. Proposed change (if any): If the 6th revision is released in time, incorporate any relevant changes into the draft advice.	The advice was updated with the 6th revision of the WHO list.	83.
268-269	35	Comment: add an example e.g. amoxicillin in pneumonia	An example was added.	84.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
272	35	Comment: add an example e.g. colistin and some cephalosporins	An example was added.	85.
327	35	Comment: replace 'the results of bacteriological tests ' by ' culture and antimicrobial susceptibility testing'.	Text was amended.	86.
333 and forward	21	Comment: In the sections 3.3 Refinement of AMEG criteria and 3.3.1 Impact of the route of administration on antimicrobial resistance, the information regarding the selection pressure of resistant bacteria are the following: - « As the largest reservoir of AMR following the administration of antimicrobial results from the exposure of the gut flora, the route of administration is discussed extensively in Chapter 3.3.1 of this report." - « Of utmost importance with respect to the selection and containment of resistance is that oral antimicrobials may induce changes in the digestive tract microbiota, starting from the oropharynx, and ending in the faeces, and by consequence in the environment. » - "[…] oral administration of antimicrobials in livestock is of particular concern in terms of promoting the development of AMR due to the high exposure of GI commensal bacteria, and the sometimes prolonged duration of treatment or exposure, especially for products administered in feed. » These 3 extracts concern antibiotic molecules intended to be administered by oral route, that will induce selection pressure on bacteria of the gut and may cause the emergence and development of antimicrobial resistance that could subsequently spread into the environment via faeces. The longer the treatment duration and the higher the number of animals treated (e.g.	It is important to note that route of administration is considered as a main driver of antimicrobial resistance selection. However, as stated in the section 3.3.1 of the AMEG reports, given that antimicrobials in each (sub)class are available for administration by different routes, the AMEG chose not to include the route of administration as an additional criterion for the categorisation. It was the view of the group that to consider the relative AMR risk for all the different formulation/antimicrobial class combinations within the categorisation would be highly complex and difficult to evidence. Nevertheless, when factoring AMR risk into prescribing decisions, the aim should be to use the list above together with the AMEG categorisation to select both the formulation/route of administration and class that will have the least impact on the selection of AMR.	87.

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		groups of food-producing animals), the higher the risk. Consequently, in the section 3.3.1 Impact of the route of administration on antimicrobial resistance, a ranking of the routes of administration related to their impact on the risk of development of antimicrobial resistance is presented. The topical route is that which presents the lesser risk. Indeed, the antibiotic remains at the site of administration without causing any selection pressure on bacteria of the gut and thus not spreading resistant bacteria in the environment. However, for the new categorisation of antimicrobials, it has been decided not to make the distinction between the formulations and therefore between the routes of administration for antimicrobials within a class, as described below: - « Given that antimicrobials in each (sub)class are available in a number of different formulations and for administration by different routes, the AMEG chose not to include the route of administration as an additional criterion for the categorisation. » Choosing not to retain the route of administration as a ranking criterion induces an irregularity in the categorisation of certain antibiotics used locally and only in pets (which very few alternatives are available). As a result, certain molecules will undergo the same level of restrictions as the antibiotic molecules used by oral route in food-producing animals. This appears as unjustified according to the use of these molecules (local administration in pets only). This approach does not foster the innovation supported by the new veterinary medicinal product regulation. For information, in France, polymyxin B in eye drops represents a very small percentage of veterinary antibiotics sold (0.57% in terms of turnover) for an annual turnover of 1 million euros. This figure remains significant for a laboratory the size of TVM France (Small and Medium company) to maintain the innovation on the vet market. In the context of the new categorisation of antimicrobials and in the same manner that it has been considered for fusidic acid (exception due to local	Concerning the reconsideration of the level of classification of polymyxin B in a lower category than colistin as we did for fusidic acid, it should be noted that fusidic acid is identified as HIA by the WHO compared to polymyxin B which is categorised as CIA. Finally, as agreed upon in the section 3.3.1., the topical route of administration is in favour of a reduced antimicrobial resistance selection pressure compared to systemic administrations. The message regarding the importance of considering the route of administration has been emphasised and is included in the Summary and chapter 5.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		administration in pets, lines 691-692), it seems crucial that exceptions of classification be done for antibiotic molecules specifically administered locally in pets. Proposed change (if any): With a similar approach than fusidic acid (local administration in pets only), it is appropriate to reconsider the level of classification of polymyxin B in a lower category than colistin.		
341-349	26	No amendments recommended. Rationale: this section refers back to EMA-AMEG-14, clarifying that the criteria for veterinary use in the prior document was global, rather than limited to the EU.	The objective of the present advice as well as the former one was to consider antibiotic use in the EU, yet acknowledging the WHO categorisation during the process.	88.
353	35	Comment: better not use abbreviation of Aminoglycosides but write it out completely to make it easier to read.	Corrected.	89.
379	35	Comment: Criteria relating to conditions of use: add pharmacokinetics.	Added.	90.
396	35	Comments: include animal welfare Proposed change: The impact on animal health **and welfare** may be considered as part of the approach to categorisation. Same in line 398, 402 and 404!	Added.	91.
400-410:	39	This guideline states, "*Consideration of the risk to public health has to be balanced with the importance of the substance for animal health. The importance of the substance for animal health is determined to a great extent by the availability of alternative treatment options for given indications in given species.*"	As routine, infection prevention and control measures should be implemented to improve animal health and reduce the need to	92.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Comment: Can the EMA define what is meant by "alternatives"? It is unclear if these alternatives belong to the same or different drug class(es) of antimicrobials or if EMA is referring to non-antimicrobial products such as probiotics, herbs etc.	resort to the use of antimicrobials. Despite this, animals may become sick and those with clinical signs of bacterial infection that is impacting on their health and welfare in many cases need to be treated with antibiotice. Therefore, in the context of use of the categorisation, the focus is on the availability of alternative antibiotic treatments. This has been clarified in the document.	
412-414 585-613	2	Comment: In these sections it is not very clear how the criteria were used to achieve categorization. It is stated in some places that expert judgement was used, but I wonder if it is possible to provide more transparency in how the criteria were applied to drug classes and how the outcomes were weighted and pooled to place the classes into categories? I found it most difficult to see how criterion 3 was applied (even with the explanation on lines 591-598). Proposed change (if any): Add a new section to the document that describes in some detail and as clearly as possible how the criteria for categorization were applied. As is pointed out earlier in the draft document, the WHO and OIE lists utilize yes/no criteria (of implied equal weight) which lend themselves to straight-forward application to categorization that goes some way to transparency (although it can be argued that this simply masks the subjectivity inherent in expert opinion). It seems to me that the four new	More information is now included in Table 4 in regard to the main rationale for the categorisation of each (sub)class.	93.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		criteria could be stated in yes/no or categorical terms and then a table &/or flow chart could be prepared to supplement the text in explaining how the criteria are applied, weighted and pooled for categorization.		
427	35	Comment: specify that this is for broilers not laying hens	Not agreed. See e.g. Woodward, M. J., Mappley, L., Le Roy, C., Claus, S. P., Davies, P., Thompson, G., & La Ragione, R. M. (2015). Drinking water application of Denagard® Tiamulin for control of Brachyspira pilosicoli infection of laying poultry. *Research in veterinary science, 103*, 87-95.	94.
448	11	Comment: A lower intake of feed by diseased animals is true but if animals are seriously ill they do not eat at all. Proposed change (if any): a lower intake <u>of feed</u> by diseased animals <u>or seriously ill individuals not eating at all</u>, uncertain…	Agreed. Changes made accordingly.	95.
Lines 482-503	3	Comment: It is unclear as to why the AMEG considers as a main decision criteria "The importance of the substance for animal health is determined to a great extent by the availability of alternative treatment options for given indications in given species." It is well known that non-antimicrobial preventative measures (e.g. vaccines, parasite control, animal husbandry and welfare) are the cornerstone of veterinary animal health concepts (both	Modified to more clearly express the concern into: *"The presence of a certain*	96.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		companion and food animal). This is basic veterinary knowledge. Treatment represents a breakdown of preventative measures, where there is currently an over-dependence of antimicrobials for control (metaphylaxis) and prevention (prophylaxis) in healthy food animals. Proposed change (if any): The sentence requires further explanation to avoid misinterpretation.	*substance for animal health in the current veterinary compendium is and has historically been determined to a great extent by the availability of alternative treatment options for given indications in given species."* See also Comment 92.	
Lines 495-505	12	Comment: - we do consider that it is unfair to consider that "oral medication via feed/premixes" has a higher impact on resistance than *"Oral group medication via drinking water/milk replacer"* - We agree that "top feeding" may be the route of administration that is the worst but it should not be put on the same level as medicated feed - Medicated feed enables an accurate dosing of the drug and this is subject to control as per the actual directive and the future Regulation 2019/04. Feed manufacturers guarantee the dosage of antimicrobial in medicated feed; and if the feed is the unique feed given to animals and that vet considers when prescribing that the current disease do not affect consumptions, there is no issue. In case there is a decrease in consumption, vets could anyway prescribe a higher posology to take this into account - Top feeding is totally different: the molecule is usually highly concentrated and vets have no clue on the quantity that will be consumed by individual animals. There is no way to guarantee the posology isrespected. For these reasons, top feeding indeed should be banned - Water medication is theoretically a good way to treat animals but the quality of the medicated water fully relies on the capacity of the farmer. It can also be dramatically affected by, amongst others, the quality of the water, the concurrent use of sanitation agent to clear the water of bacterial compensation and even the material of the water pipes. The French agency conducted a study (CABALE) that	We appreciate the relevant comments received in relation to the route of administration. In macrolides a borderline non-significant effect was found in favour of drinking water compared to in-feed medication (Wu et al, 2019) in relation to macrolide resistance in enterococci. Other cross-sectional studies have shown for different compounds a benefit of antimicrobials given via water over in feed (Varga et al. 2009 a & b). Concerns on deviating dosing are of relevance, in particular with regard to drinking water, but have already been addressed in the document for consultation and are fully in line with the argumentation provided by the stakeholder. Of note, accurate dosing in the referenced regulation has been centered around clinical efficacy and this	97.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		has demonstrated that the potency of antibiotics in drinking water can be dramatically reduced: in some circumstances and for some VMP we can find only 25% of the expected dose of antibiotic. Proposed change (if any): - We suggest below ranking - Ideally, we would also recommend to ban the use of top dressing or restrict it to exceptional situations and individual or small group treatment 495 A suggested listing of routes of administration and formulations, ranked in order from those with in 496 general lower effect on the selection of AMR to those that would be expected to have higher impact on 497 resistance, is proposed as follows: 498 ☐ Local individual treatment (e.g. udder injector, eye or ear drops); 499 ☐ Parenteral individual treatment (intravenously, intramuscularly, subcutaneously); 500 ☐ Oral individual treatment (tablets, oral bolus, top dressing); 501 ☐ Injectable group medication (metaphylaxis), only if appropriately justified; ☐ Oral medication *via* feed/premixes (EMA/EFSA, 2017) (metaphylaxis), only if appropriately justified ☐ Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified. ☐ Oral medication *via non-individual* top dressing (EMA/EFSA, 2017) (metaphylaxis), only if appropriately justified under exceptional circumstances that should be justified by the vet	is not questioned in the present document. We share concerns in particular for top-dressing (due to deviations regarding optimal dosing, duration, stability and intake), yet the evidence related to the subject is to the best of our knowledge limited to an outbreak investigation (Holmbert et al. 1987).For now, top-dressing has been removed from the list below. The revised listing: • Local individual treatment (e.g. udder injector, eye or ear drops); • Parenteral individual treatment (intravenously, intramuscularly, subcutaneously); • Oral individual treatment (i.e. tablets, oral bolus); • Injectable group medication (metaphylaxis), only if appropriately justified; • Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified. • Oral group medication via feed/premixes (EMA/EFSA, 2017) (metaphylaxis), only if appropriately justified.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
			New references were added to this statement: "Oral administration *via* drinking water can be more precisely dosed compared to medication administered in food (Filippitzi, 2018), with a potential benefit over in feed administration related to antimicrobial resistance (Holmberg et al., 1987; Varga et al., 2009a; Varga et al., 2009b; Wu et al., 2019)."	
Lines 495-505	15	**- In the section <u>3.3.1 Impact of the route of administration on antimicrobial resistance</u>**, the following paragraph indicates : "A suggested listing of routes of administration and formulations, ranked in order from those with in general lower effect on the selection of AMR to those that would be expected to have higher impact on resistance, is proposed as follows: • Local individual treatment (e.g. udder injector, eye or ear drops); • Parenteral individual treatment (intravenously, intramuscularly, subcutaneously); • Oral individual treatment (tablets, oral bolus); • Injectable group medication (metaphylaxis), only if appropriately justified; • Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified. • Oral medication *via* feed/premixes or top dressing (EMA/EFSA, 2017) (metaphylaxis), only if appropriately justified."	Agreed.	98.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
498	19	Comment: /Polymyxin B is only used in local route and is not crossing the cornea. Therefore, the risk of systemic bacterial resistance with Polymyxin B is very low. Moreover, if the concentration of Polymyxin B is over the MIC (wich is the case in Tevemyxine®), the selection of resisting bacterias is unlikely. Proposed change (if any):/ Local individual treatment (e.g. ~~udder injector,~~ eye ~~or ear~~ drops should be an exclusion of the restriction)	No change needed since AMEG agrees that local individual treatment has lesser effect on resistance selection and therefore eye drops are at the very top of formulations in terms of lower impact on resistance.	99.
502-504	22	**Comment**: It is not clear on what grounds the differentiation between in-feed and drinking water is made. These two methods of administration present similar risks and we are not aware of any scientific reason to rank one above the other. **Proposed Change:** Both these forms of administration, have advantages and disadvantages and might be classified at the same level of risk**.**	Addressed above (comment 97).	100.
502-504	28	**Comment**: It is not clear on what grounds the differentiation between in-feed and drinking water is made. These two methods of administration present similar risks and we are not aware of any scientific reason to rank one above the other. **Proposed Change:** Both these forms of administration, have advantages and disadvantages and might be classified at the same level of risk**.**	Addressed above (comment 97).	101.
Lines 506-508	3	Comment: It is unclear as to how 'the availability of alternative treatment options' forms the foundation of potentially negative impacts on animal health, when the majority of antimicrobial consumption is for healthy animals either through tonnes of bulk animal feed (premixes) or added to the common drinking water supply, whereby healthy animals are not separated from diseased? Proposed change (if any):	See previous comments. The concerns regarding the impact of the route of administration are addressed in chapter 3.3.1 and further emphasis has been given in the Summary.	102.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
510-511 & 691	22	**Comment:** It is stated "the AMEG chose not to include the route of administration as an additional criterion for the categorization". Later an exception to this is given "The exception is for steroid antibacterials (fusidic acid) where it was taken into account that this class is only administered locally in animals." It has not been explained why this exception is permitted and other possibilities not considered. This is contrary to the key principle that veterinary medicines should be authorized and use permitted according to the products benefit/risk assessment. We acknowledge that due to the many different formulation/antimicrobial class combinations which create a high level of complexity, it is not easy to systematically incorporate the route of administration as a criteria for the categorisation. However, local individual treatments for which there is negligible systemic absorption (such as topical ear antibiotics) are delivered at concentrations well above the Minimum Inhibitory Concentration (MIC) of the relevant organism and the selection pressure on the emergence of bacterial resistance is very low. Hence, for such very specific use, antibiotics listed in Category B should not be restricted to second intent treatments. **Proposed change:** As set out in the general comments, please introduce a consideration of the route and mode of administration which will enable lower risk uses to be identified and if appropriate categorized in a lower group.	Agreed, we have removed this sentence and we have added the ranking of formulations in the Summary in a response to this concern.	103.
510-511 & 691	28	**Comment:** It is stated "the AMEG chose not to include the route of administration as an additional criterion for the categorization". Later an exception to this is given "The exception is for steroid antibacterials (fusidic	Duplicate comment. See response to comment 103.	104.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		acid) where it was taken into account that this class is only administered locally in animals." It has not been explained why this exception is permitted and other possibilities not considered. This is contrary to the key principle that veterinary medicines should be authorized and use permitted according to the products benefit/risk assessment. We acknowledge that due to the many different formulation/antimicrobial class combinations which create a high level of complexity, it is not easy to systematically incorporate the route of administration as a criteria for the categorisation. However, local individual treatments for which there is negligible systemic absorption (such as topical ear antibiotics) are delivered at concentrations well above the Minimum Inhibitory Concentration (MIC) of the relevant organism and the selection pressure on the emergence of bacterial resistance is very low. Hence, for such very specific use, antibiotics listed in Category B should not be restricted to second intent treatments. **Proposed change:** As set out in the general comments, please introduce a consideration of the route and mode of administration which will enable lower risk uses to be identified and if appropriate categorized in a lower group.		
510-511 & 691	38	**Comment:** It is stated "the AMEG chose not to include the route of administration as an additional criterion for the categorisation". Later on an exception to this is given "The exception is for steroid antibacterials (fusidic acid) where it was taken into account that this class is only administered locally in animals." It has not been explained why this exception is permitted and other possibilities not considered. This is contrary to the key principle that veterinary medicines should be authorized and use permitted according	Duplicate comment. See response to comment 103.	105.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		to the products benefit/risk assessment. We acknowledge that due to different formulation/antimicrobial class combinations, it is not possible to systematically incorporate the route of administration as a criteria for the categorisation. However, local individual treatments for which there is negligible systemic absorption (such as topical ear antibiotics) are delivered at concentrations well above the Minimum Inhibitory Concentration (MIC) of the relevant organism and the selection pressure on the emergence of bacterial resistance is very low. Hence, for such very specific use, antibiotics listed in Category B should not be restricted to second intent treatments. **Proposed change:** As set out in the general comments, please introduce a consideration of the route and mode of administration which will enable lower risk uses to be identified and if appropriate categorized in a lower group.		
516	22	**Comment:** It is important to acknowledge & remind here the importance of SPC of each VMP and the fact that specific claims have been validated through the registration process. While taking into account the proposed AMEG classification and the route of administration in the prescription choice, the importance of the SPC should be reinforced especially for antibiotics in classes B, C & D **Proposed change:** new sentence at the end of the paragraph: It is also acknowledged that these choices should be made also in agreement with the Summary of Product Characteristic for each given product. Table 4:	Agreed, modification made.	106.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Comment: For cephalosporins 3G and 4G, polymyxins and quinolones; the final column only says "See chapter 4.2" – this basically says these are HPCIA with the exception of macrolides. In this same column of the table for macrolides it sets out in summary the rationale e.g. information on probability of resistance transfer, prevalence of resistance genes, alternatives etc. Ideally taking account of all available published literature the probability of deaths occurring in people due to authorised use of these antimicrobials in animals should be calculated and used as the basis for ranking. **Proposed change:** For transparency and ensuring consistency of approach please add this same level of summary in the final column for cephalosporins 3G and 4G, polymyxins and quinolones.	Agreed. Modifications in the table have been made for more consistency.	
516	28	**Comment:** It is important to acknowledge & remind here the importance of SPC of each VMP and the fact that specific claims have been validated through the registration process. While taking into account the proposed AMEG classification and the route of administration in the prescription choice, the importance of the SPC should be reinforced especially for antibiotics in classes B, C & D **Proposed change:** new sentence at the end of the paragraph: It is also acknowledged that these choices should be made also in agreement with the Summary of Product Characteristic for each given product. Table 4: **Comment:** For cephalosporins 3G and 4G, polymyxins and quinolones; the final column only says "See chapter 4.2" – this basically says these are HPCIA with the exception of macrolides. In this same column of the table for	Agreed. Duplicate comment, see above (comment 106).	107.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		macrolides it sets out in summary the rationale e.g. information on probability of resistance transfer, prevalence of resistance genes, alternatives etc. Ideally taking account of all available published literature the probability of deaths occurring in people due to authorised use of these antimicrobials in animals should be calculated and used as the basis for ranking. **Proposed change:** For transparency and ensuring consistency of approach please add this same level of summary in the final column for cephalosporins 3G and 4G, polymyxins and quinolones.		
532-534	36	Comment: "Nevertheless resistance can persist in the absence of antimicrobial use (Enne et al., 2001). 532 If this is the case (or in cases of co-resistance), reduction of consumption of a certain substance, in 533 both veterinary and human medicine, will not necessarily lead to consequent reduction in AMR." This is a very important, factual statement that has been missed in the legislation.	Thank you. No change needed.	108.
599	35	Comment: Typo, remove The	. Thank you, done.	109.
620	7	Comment: PVS welcomes the separation of the old Cat 2 products into 2 subcategories . In principle the groupings now match the PVS Prescribing Principles operating since 2013 (see https://www.pigvetsoc.org.uk/resources/pvs-documents) Proposed change (if any):	No change needed.	110.
620-621 (Table 2) and 141-142 (Table 1)	14	Comment: The purpose of the AMEG report is to consider the risk to public health from AMR due to the use of antimicrobials in veterinary medicine.	See previous responses to comments 22 and 43.	111.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Table 2 shows that Macrolides and Lincosamides have significant and important indications in human medicine, but the Streptogramins are "*presently considered obsolete*" in human medicine. Macrolides and Lincosamides are considered more important than Streptogramins by AMEG for public health (Table 2). There is shared MLSB resistance between these three classes of antimicrobials which is confirmed by EMA in EMA/CVMP/643658/2014 (EPMAR for Virginiamycin for poultry, second bullet point in 2.1.5 of that EMA report). Therefore, based on the AMR risk to Public Health it is scientifically incorrect to have Streptogramins in Category A ("Avoid") but Macrolides and Lincosamides in Category C ("Caution"). It should be remembered that the purpose of the report is as stated above and should not be based on the EU veterinary MA status of antimicrobials, but on a "One Health" basis as indicated in EU Regulation 2019/6. Leaving Streptogramins in Category A ("Avoid") is likely to cause the global therapeutic use of virginiamycin in veterinary medicine to be replaced by other antimicrobials in lower categories in Table 1 (such as macrolides, lincosamides, aminopenicillins in combination with β-lactamases inhibitors) which have far greater and more valuable utility to public health. This replacement use is considered likely because purchasers of chicken products (*e.g.* fast-food chains, supermarkets) will use Table 1 as their guide to advise their suppliers and will not read (or perhaps not technically understand) the entire 67-page AMEG report to make their buying decisions to try to protect public health.		

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Proposed change (if any): Streptogramins should be in the same (C) or a lower (D) AMEG category in Table 1 than Macrolides and Lincosamides in order to protect the risk to public health on a "One Health" global basis.		
620	15	**In the section <u>3.4.1 Consideration of AM classes not taken into account in AMEG 1 advice and those given further consideration,</u>** the Table 2 presents an overview of indications in human medicine and relevant mechanisms of resistance for antimicrobials not covered by AMEG 1 advice. If we focus on polymyxins (eg colistin), the hazard of potential zoonotic relevance are the enterobacteriaceae. In the column "Overview of indications in human medicine and resistance mechanisms", it is written notably: • "Resistance also due to plasmid-mediated *mcr* gene reported globally from animals, food products, the environment and as well in human clinical and non-clinical (screening) specimens. • Presence of horizontally transferable colistin resistance in food animals, food products, the environment, paired with high rates of *in vitro* transfer between bacteria, worrisome for human medicine, as presence confers full resistance to colistin, rendering bacteria pandrug-resistant and likely resulting in poor patient outcomes." Comment: **These 2 parts written above are the basis of the following comments regarding the use of polymyxin B in the veterinary practice for the treatment of ocular infections in pets:** - The topical administration, as written above in the section 3.3.1 is the one which has the lowest impact on the selection of AMR, regardless of the drug used. *More in details: Polymyxin B is only used as a topical drug in dogs and cats.*	Proposed change: not agreed. The AMEG categorization is a general classification not separating specific indications, different animal species, or individual product formulations. Furthermore, the AMEG categorisation is not a full risk assessment or a treatment guideline and categorization in category B does not prevent an antibiotic's use when it is needed. It is acknowledged in the report that the route of administration may have an important impact on AMR selection and that local application is relatively lower risk, but for reasons given (3.3.1), it was decided not to	112.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		- The inability to pass the healthy corneal epithelial barrier and the hemato-aqueous barrier in case of epithelial defect; *More in details: As reported by several publications, polymyxin B is unable to penetrate the anterior segment of the healthy eye. The drug passes neither through the corneal epithelium, nor through the hemato-aqueous barrier (HAB).So, even if a corneal epithelial injury (corneal ulcer) is involved, a systemic diffusion of the drug cannot occur, as polymyxin B is currently used in bacterial conjunctivitis or simple ulcers (defined as simple epithelial defects with a smooth bottom and very mild corneal oedema, without anterior uveitis, recovering in 4 to 6 days of treatment).* - The confirmation or at least the strong suspicion of bacterial infection before using; *More in details: Bacterial conjunctivitis in dogs and cats are often consecutive to a surinfection by opportunistic germs living on the conjunctival surface.* *Antibiotic treatment of a conjunctivitis is justified when mucopurulent or purulent discharged is observed, epidemiological and/or clinical circumstances are in favour of Chlamydophila infection in the cat, a predisposing cause is observed (as a KCS for example), or a corneal ulcer is associated.* - The short duration of the treatment; *More in details: the duration of treatment is comprised between 8 and 10 days.* - The very useful association polymyxin B-neomycin for the treatment of infectious conjunctivitis/keratitis in small animal ophthalmology. *More in details: In cases of bacterial infections, the association neomycin-polymyxin B is an excellent first intention treatment. When vets decide on the treatment of a simple corneal ulcer, they widely use a combination neomycin-polymyxin: the goal is to treat non-specific infections of the ocular surface because the association is bactericidal (remains in surface), has an appropriate spectrum, and is non expensive.*	incorporate this into Table 4.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		All items are <u>not in favour</u> to class polymyxin B as a restricted use antimicrobial drug. Proposed change: It is proposed to make an exception for the classification of polymyxin B (lower category) due to its veterinary clinical use in pets. *** Note: *Product available in France with polymyxin B* In France, there is one product with polymyxin B available for the treatment of ocular infections in companion animals (dogs and cats): Tévémyxine® eyedrops, aqueous excipients (Dextran 70 ; EDTA ; monosodic dihydrated phosphate ; dodecahydrated disodic phosphate; sodium chloride ; benzalkonium chloride ;water), active substances : polymyxin B (10000 UI/mL) + neomycin (3400 UI/ml)		
620 Table 2- aminoglycoside	28	**Comment:** The oldest generations of AMGs (spectinomycin and (dihydro) streptomycin) do not confer all the resistance mechanisms profiles described for AMGs. Their usage has indeed little impact on the future use of wider spectrum AMGs molecules which by definition traces a possible escalation process amongst AMGs **(Sunde M. et al, 2005).** it is therefore not appropriate to classify all AMGs in the same category. **Proposed change:** add the information: separate spectinomycin/ (dihydro)streptomycin from the others AMGs.	Partly agreed. Aminoglycosides, except for spectinomycin, are CIA in human medicine. There is a high potential for transmission of resistance determinants between animals and humans. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides other than spectinomycin are in cat C rather than in category B. For spectinomycin there is no/limited cross-resistance to	113.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
			the other aminoglycosides and it is less important in human medicine. Spectinomycin is therefore now in category D.	
669-688	14	Comment: There appears to be significant and confusing typographical errors on page 36? Presumably the updated criteria (lines 680-688) should not be 1,2,3 and 4 – but should be A, B, C and D? Proposed change (if any): Replace 1,2,3 and 4 with A, B, C and D.	Proposed change: not agreed. The numbers 1-4 give a listing of the criteria used to perform the categorization whereas the letters are used to label each of the categories.	114.
679 to 688, 814 to 828, compared to 82 to 86	14	Comment: Lines 82- 86 are contradicted by lines 679-688 and lines 814-828 in the draft AMEG report. This is because Category A and B as defined in lines 814-819 are respectively considered re. authorisations in veterinary medicine (A), or those veterinary medicines not authorised in the **EU** (B). This is the same approach as shown in lines 680-682 (assuming criteria 1 and 2 are typographical errors and will be replaced by A and B). However, in contrast lines 82-86 Category A includes antimicrobial classes not currently authorised in the **EU**. Proposed change (if any): Category A in lines 82-86 should be changed to be the same as the	Proposed change: not agreed. There seems to be a misunderstanding. This categorization is limited to the EU. In category A, antibiotics are not authorized for veterinary medicine in the EU. The numbers 1-4 give a listing of the criteria used to perform the categorization whereas the letters are used to label each of the categories. Streptogramins are currently not authorised in the EU.	115.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		definitions used in the report (lines 679-688, and 814-828). This change would mean that Streptogramins would need to be moved from Category A in Table 1 (lines 141 -142) to another category because they are widely authorised for veterinary therapeutic use outside of the EU (*e.g.* in Argentina, Australia, Canada, Mexico, South Africa, USA, other South & Central America countries).		
680	26	~~1. If the (sub)class or group is authorised for use as a veterinary medicine~~ 1. If the class is new generation of antimicrobial and has not yet been approved for veterinary use in the EU or other countries. Rationale: Authorisation of a class of antimicrobial for veterinary use is not in itself a science based assessment criteria. If the intent is to conserve new generation antimicrobials for human use, the language can be modified to reflect that intent. "Over-ranking" selected antimicrobial classes inappropriately will lead to inappropriate antimicrobial selection and the potential unavailability of low risk antimicrobial choices in the EU and elsewhere. Classifications in the EU medical importance Categorisations that do not provide appropriate relative ranking potentially undermine the domestic and international credibility of the EU document as a reference list. The amendment makes clear that the EU is taking a global, rather than parochial, approach to AMR.	Proposed change: not agreed. Criterion 1 is to establish if the (sub)class has been authorised in a veterinary medicine in the EU. If the class does not have an authorization for animals it goes automatically in category A. No formal risk assessment or risk management measures are available for use in the EU as would be the case when an authorized VMP is used. This could lead to an additional public health risk.	116.
688 – 692	35	Comment: FVE suggests to insert a 5th criterion: namely route of administration. It is contradictory to first explain in the text how important this criteria is (which we totally support) and afterwards to say we do not include it because it is '*too complex*'. At least use it for the antimicrobials for which it is most relevant e.g. the 3 and 4th generation cephalosporins are mainly used parentally or locally (e.g. intramammary).	Proposed change: not agreed. The relative AMR risk for all the different formulation/antibiotic class combinations within the categorisation would be highly complex and difficult to	117.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Proposed changed: insert 5th criterion, route of administration and use this criterion for more antimicrobials than fusidic acid.	evidence. A separate listing is provided which suggests routes of administration and types of formulation which, in general, are preferred in terms of their estimated impact on the selection of AMR (see section 3.3.1. as well as the Summary). It has been noted that this list should be used together with the categorisation when factoring AMR into prescribing decisions. The number of randomized control trials related to the route of administration is currently too limited to extrapolate these findings to all classes of antibiotics.	
688 - 692	36	Comment: BTK suggests to insert a 5th criterion: namely **route of administration**. It is contradictory to first explain in the text how important this criteria is (which we totally support) and afterwards to say we do not include it because it is 'too complex'. At least use it for the antimicrobials for which it is most relevant e.g. the 3 and 4th generation cephalosporins are mainly used parentally or locally (e.g. intramammary). Proposed change: insert 5th criterion, route of administration and use this criterion for more antimicrobials than fusidic acid.	See response to comment 117.	118.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
705-706	26	No amendments recommended. Same notation as for lines 341- 349	Noted.	119.
707-711	35	Comment: Categorisation and cascade should be explained more clearly, preferably with the use of an example, e.g. if a veterinarian does not have a category D antimicrobial authorised in its country for a specific indication/species but one exists in another EU Member State, should the product from the other MS be used (recognising it might take him long to get access to this product) or does the categorisation apply only depending on what is available in the country of origin? Seen the practical importance of this, we suggest to also include it the summary of the assessment and recommendations part. Another example is the use of gentamycin in horses. Gentamicin (Category C) is one of the few antibiotics used in hospital based clinical practice for the management of MRSA, enterobactericae and pseudomonas, which are all important pathogens of the horse. Recent data collected by FEEVA has shown the worldwide importance of this medicine in equine clinical practice (Redpath, et al 2018). Currently Gentamicin is only licensed for use for the management of respiratory tract infection, which makes up a small amount of its clinical use in this study. As such, cascade use of gentamicin represent good clinical practice and responsible use of antibiotics. Proposed change: Clarify the categorisation versus the cascade both in the detailed text as well as in the summary and add some examples	The proposed changes are not agreed. The text is deemed sufficiently clear. Definition of "cascade" is indicated in a footnote and risk management measures to be applied to each category are given at high level. It is clearly stated that the categorisation does not override the rules of the prescribing cascade and that AMEG categories should be seen as being complementary to provisions of the Regulation 2019/6. Adding of examples goes beyond the scope of this scientific advice on categorisation of antibiotics and could rather be subject of treatment guidelines. In chapter 5 it is outlined how the Categorisation may be used in the development of treatment guidelines.	120.
712-734	8	Comment:	Comment noted. No changes	121.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Does not take account of shoaling behaviour in fish and that metaphylactic treatment is normal. Nor does it take into account the necessity for availability using the cascade, most drugs are licensed for the high value fish ie salmon, rather than lower value trout, char, carp, tilapia etc. Proposed change (if any):	necessary. Risk management measures related to the provisions of the Regulation 2019/6 and to individual AMEG categories are indicated at high level, only. Please note the earlier statement '*Although the categorisation may be used to help with prescribing decisions made under the "cascade", it cannot take account of all the principles to be considered and importantly the welfare of the individual animal(s). Therefore the categorisation does not override the complete rules of the prescribing "cascade" in which AMR risk is a factor to consider alongside other criteria as laid out in legislation'*. The use of the Categorisation in the development of species-specific treatment guidelines is laid out in chapter 5.	
Lines 735-737	3	Comment: This sentence is spun in a way as an example of the spread carbapenem resistance from humans to animals. A reference by Fischer et al. (2017) is given in support of the statement (Fischer, J., M. San José, N. Roschanski, S. Schmoger, B. Baumann, A. Irrgang, A. Friese, U. Roesler, R. Helmuth, and B. Guerra, 2017. 'Spread and	Proposed change agreed. We agree with the comment and we have removed the carbapenemase example.	122.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		persistence of VIM-1 Carbapenemase-producing Enterobacteriaceae in three German swine farms in 2011 and 2012', Veterinary microbiology, Vol. 200 pp.118-123.). Upon reviewing this article there is NO mention of spread of VIM-1 Carbapenemase-producing Enterobacteriaceae in German swine farms between humans and animals. Humans were NOT even sampled in the study for VIM-1 Carbapenemase-producing Enterobacteriaceae. The discussion about 'spread' between swine farms and animals was under the hypothesis of either environmental spread using animal slurry as fertilizer or exposures to heavy metals as a selection factor. It is unclear as to why this reference is misrepresented in this context. It is interesting to note that the other reference quoted by Fernádez et al. (2018) does not mention VIM-1 as an example of carbapenem resistance genes from human-adapted bacteria to animals. Also, the examples cited by Fernádez et al. (2018) of carbapenem resistance genes from human-adapted bacteria to animals were all from outside Europe. Fernádez et al. (2018) also proposes that antimicrobial use in animals could also be responsible for selection and persistence of carbapenem resistance genes in animals. "Moreover, the high level of MDR among carbapenemase producers, and the frequent linkage of resistance genes within discrete genetic elements, including self-transferable and mobilizable plasmids, could allow co-selection by antimicrobials other than carbapenems used in agriculture." "It has also been proposed that the widespread use of extended spectrum beta-lactams such as ceftiofur (third-generation cephalosporin) in nearly all food animal species worldwide could exert a selective pressure not only for resistance to extended-spectrum cephalosporins, but also for carbapenem resistance [74], since most carbapenemases confer resistance to extended spectrum cephalosporins." Proposed change (if any): The issues of carbapenemase resistance in animals has not been appropriately represented in the AMEG report.		

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
735-748	22	**Comment:** According to the current criteria for inclusion in category A absence of a veterinary authorisation in the EU automatically places an antibiotic in Category A. This approach may help preserve the most important human only antimicrobial classes for human use. However, it is a blunt instrument in terms of selection. Care should be taken to avoid the inclusion of antibiotics in category A solely on the basis that there is no current EU authorisation. There are some antibiotics in therapeutic use globally which are not authorised in the EU and an automatic inclusion into category A could stifle innovation and deter companies from seeking authorisation for those products in the EU. Some consideration should also be given to the importance in human medicine before placing in category A. As an example, the streptogramins are currently in Category A. AMEG describes streptogramins as "…considered obsolete" in human medicine and therefore presumably of low medical importance. In contrast to the obsolete importance characterisation of the class for human medicine, virginiamycin has widespread international therapeutic use in veterinary medicine (for necrotic enteritis in broilers, swine dysentery in pigs and ruminal acidosis/liver abscess complex in cattle), and no human use. Since November 2015 virginiamycin has had EU MRLs for all key poultry species. Relative to many other antimicrobial classes, virginiamycin has a narrow spectrum of activity with little effect against gram negative bacteria meaning that unlike broader spectrum compounds, virginiamycin has little collateral effect on gram-negatives when used for the gram-positive bacterial diseases for which it is approved outside Europe. **Proposed Change:** Please review the inclusion of antibiotics in category A solely on the lack of an EU authorisation, for example the status of	Proposed change: not agreed. Criterion 1 is to establish if the (sub)class has been authorised in a veterinary medicine in the EU. If the class does not have an authorization for animals it goes automatically in category A. No formal risk assessment or risk management measures are available for use in the EU as would be the case when an authorized VMP is used. This could lead to an additional public health risk.	123.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		streptogramins in category A and amend the document according to the outcome.		
735-748	28	**Comment:** According to the current criteria for inclusion in category A absence of a veterinary authorisation in the EU automatically places an antibiotic in Category A. This approach may help preserve the most important human only antimicrobial classes for human use. However, it is a blunt instrument in terms of selection. Care should be taken to avoid the inclusion of antibiotics in category A solely on the basis that there is no current EU authorisation. There are some antibiotics in therapeutic use globally which are not authorised in the EU and an automatic inclusion into category A could stifle innovation and deter companies from seeking authorisation for those products in the EU. Some consideration should also be given to the importance in human medicine before placing in category A. As an example, the streptogramins are currently in Category A. AMEG describes streptogramins as "…considered obsolete" in human medicine and therefore presumably of low medical importance. In contrast to the obsolete importance characterisation of the class for human medicine, virginiamycin has widespread international therapeutic use in veterinary medicine (for necrotic enteritis in broilers, swine dysentery in pigs and ruminal acidosis/liver abscess complex in cattle), and no human use. Since November 2015 virginiamycin has had EU MRLs for all key poultry species. Relative to many other antimicrobial classes, virginiamycin has a narrow spectrum of activity with little effect against gram negative bacteria meaning that unlike broader spectrum compounds, virginiamycin has little collateral effect on gram-negatives when used for the gram-positive bacterial diseases for which it is approved outside Europe.	Duplicate comment, please see response to comment 123.	124.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		Proposed Change: Please review the inclusion of antibiotics in category A solely on the lack of an EU authorisation, for example the status of streptogramins in category A and amend the document according to the outcome.		
735	35	Comment: The possibility to allow very exceptionally the use of Category A products for companion animals under the cascade is welcome. This kind of use is extremely minimal but in some cases necessary. An example is the use of amikacin, a human medicine in the aminoglycoside category, which is recognised as essential for the treatment of horses specifically for the management of septic arthritis. As such, continued access to this medicine remains important, while the risk for public health is extremely limited. What is really important, is that this exceptional use must be retained into the new Veterinary Medicines Regulation, especially in relation to Article 107 (5) of the Regulation (EU) 2019/6. Proposed change: No change.	Thank you for the comment.	125.
735-741	36	Comment: The possibility to very exceptionally use Category A products for companion animals under the cascade is welcome. This use is extremely minimal but in some cases necessary.	Thank you for the comment.	126.
752	8	Comment: This simply states quinolones, bringing in the early ones such as oxolinic acid Proposed change (if any): List fluoroquinolones rather than quinolones	Proposed change not agreed. Use of quinolones can lead to development of resistance that also includes fluoroquinolones. See response to comments 7 and 47.	127.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
752-753 Table 4	30	Comment: The fact that all polymyxins have been classified under category B is of high concern. Colistin is primarily administered to food producing animals, whereas polymyxin B is only contained in veterinary medicinal products indicated for the topical treatment of infections with susceptible bacteria in companion animals. While the mechanisms of development of resistance are considered to be the same for colistin and polymyxin B the likelihood of development of resistance and of transfer of AMR from animals to human is expected to be significantly lower for polymyxin B. The route of administration has been identified by the AMEG to have a high impact on antimicrobial resistance with local individual treatment being considered to have the lowest effect. Based on the fact that most antibiotics are contained in veterinary medicinal products approved for various routes of administration, the route of administration has not been included as a criterion for the categorisation with the exception of steroid antibacterials (fusidic acid) where it was taken into account that this class is only administered locally in animals. EGGVP is of the opinion that the same reasoning applies to polymyxin B. Published data on the use of polymyxin B for the treatment of otitis externa in dogs and cats and for the treatment of ocular infections in dogs and cats indicate that there is a very low risk for the development of resistance. MCR-1, a horizontally transferable resistance gene identified in bacteria of food animal origin has not yet been detected in companion animals in Europe despite the wide-spread use of polymyxin B for the treatment of otitis externa and ocular infections in dogs and cats[3,4]. Polymyxin B is	Proposed change: not agreed. As stated by the stakeholder - the mechanisms of development of resistance are considered to be the same for colistin and polymyxin B. Placement in category B does not prevent prudent use of polymyxin B when needed. The AMEG categorization is a general classification not separating specific indications, different animal species, or individual product formulations. Furthermore, the AMEG categorisation is not a treatment guideline. Please also see the responses to comments 63 and 87.	128.

3 S. Simmen et al. Investigation for the Colistin Resistance Genes mcr-1 and mcr-2 in Clinical Enterobacteriaceae Isolates from Cats and Dogs in Switzerland. *ARC Journal of Animal and Veterinary Sciences* 2016; 2: 26–29.
4 E. Olsson et al. 2018. *Swedres-Svarm 2017: Consumption of antibiotics and occurrence of antibiotic resistance in Sweden.* 18003: 87–91.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		administered topically at concentrations far above the MIC and is not absorbed systemically[5], thus limiting the risk of development of resistance. Polymyxin B in companion animals is used in combination with an antimycotic and a synergistic effect for the combination has been demonstrated[6,7]. The classification of polymyxin B (as well as several other antibiotics approved for topical treatment of otitis externa and ocular infections in companion animals) into AMEG category B, drastically limits the number of antibiotics available as first line treatment. EGGVP is of the opinion that this would negatively affect animal health without material impact on the risk to humans. Proposed change: It is proposed to classify polymyxin B in a lower category than colistin.		
755	35	Comment: Use of Category B is advised to be on the basis of susceptibility testing. While we totally support the use of culture and sensitivity for medicines in category B it should be recognised that getting the results back can take several days. In some cases, for example with neonatal sepsis in foals, early use of 3rd generation cephalosporins may enhance outcomes and therefore limit AMR through early effective management. It would be worth clarifying that it is allowed to start the treatment while waiting for the susceptibility results and based on knowledge of the epidemiological	Not agreed. The limitations in regard to application of culture and susceptibility testing are acknowledged ('…*based on the results of AST, whenever possible*'); however, this advice is not intended as a treatment guideline and therefore further	129.

5 M. Voget, M. Armbruster & M. Meyer. Antibiotic plasma levels in dogs with otitis externa treated routinely with various topical preparations. *Berliner und Münchener tierarztliche Wochenschrift* 2012; 125: 441–448.
6 S. Pietschmann et al. Synergistic effects of miconazole and polymyxin B on microbial pathogens. *Veterinary research communications* 2009; 33: 489–505.
7 S. Pietschmann et al. The joint in vitro action of polymyxin B and miconazole against pathogens associated with canine otitis externa from three European countries. *Veterinary dermatology* 2013; 24: 439-45, e96-7.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		situation. Change proposed: Clarify treatment options when waiting for susceptibility results.	guidance is not provided.	
769	35	Comment: need to specify that the antimicrobial alternative must be available. Some countries have a limited number of authorised products or/and alternative products might be unavailable *e.g.* when there is a shortage. Therefore it is worth adding 'when available' Change: '*These antimicrobials should only be used when there is no* ***available*** *substance in Category D that would be effective.'*	Accepted.	130.
769	36	Comment: need to specify that the antimicrobial alternative must be available. Some countries have also a limited number of authorised products or/and alternative products might be unavailable e.g. when there is a shortage. Therefore it is worth adding 'when available' Proposed Change: 'These antimicrobials should only be used when there is no available substance in Category D that would be effective.'	Accepted.	131.
783-798	2	Comment: Table 4. It is not easy to appreciate at a glance (without turning back to the definitions on lines 680-688) how the columns relate to the actual criteria and how the information is combined for classification. Proposed change (if any): For example, perhaps the criteria could be incorporated into the column headings of table 4, e.g. fourth column "Use in veterinary medicine (Criterion 1)" etc. Including the criteria definitions in footnotes could also improve clarity. Furthermore, I think the column	More information is included in Table 4 in regard to the main rationale for categorisation (Category B and C).	132.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		heading used in Table A1 "Bacterial targets in human medicine (for which availability of class/substance is critically important due to few alternatives)" is more indicative of criterion 2 than the heading used in table 4 "Examples of important indications in human medicine".		
783 Table 4	23	Comment: Polymyxins, e.g. colistin: We welcome the awareness that there do exist cases of colibacillosis (e.g. weaning pigs or broilers) that need treatment with colistin after bacterial culture and sensitivity testing	Thank you for your comment. This was identified in the AMEG's updated advice on colistin (EMA/AMEG 2016).	133.
785 (Table 4 selected row)	26	*Streptogramins* | *Staphylococci (e.g. MRSA), MDR Enterococcus spp. (e.g. VRE)* | *HIA* | *VIA* | | | *N/A* *Rationale: See previous entries.*	There is no marketing authorisation available for veterinary medicine. Thus there is no need to revise currently the categorisation of this family as the criteria for category A is antibiotic (sub)classes not authorised in veterinary medicine in the EU but authorised in human medicine.	134.
799 and forward	21	Comment: In the Section 5. Use of AMEG Categorisation, it is explained that the aim of this guideline is to help the vet in the choice of antibiotic treatment. However the route of administration is not taken into account for the ranking of antibiotic (sub)classes. Consequently this document is not very helpful to do a specific choice of treatment and does not fulfil to the objective of an improvement of "the utility of the categorisation as a risk management tool by avoiding the counterproductive outcome of too many antimicrobials being	Agreed. The emphasis on the importance of the route of administration has been increased with the addition of new text in in Section 5. In addition, the A separate listing of routes of administration in order of preference associated with	135.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		placed in the higher risk category." Proposed change (if any): It is proposed to add a sentence specifying that "Although the route of administration has not been retained as a ranking criterion for the categorisation of antibiotics, it is important to consider the route of administration for the veterinary prescription to prevent antimicrobial resistance."	their potential impact on AMR has been provided and is now also included in the Summary. It is noted in the report that the route of administration should be considered together with the categorisation to select the route and class of antibiotic that will have least impact on AMR selection.	
799 and forward	30	Comment: In the Section 5. Use of AMEG Categorisation, it is explained that the aim of this guideline is to help veterinarians in the choice of antibiotic treatment. However the route of administration is not taken into account for the ranking of antibiotic (sub)classes. Consequently this document is not very helpful to do a specific choice of treatment. Proposed change: It is proposed to add a sentence specifying that "Although the route of administration has not been retained as a ranking criterion for the categorisation of antibiotics, it is important to consider the route of administration for the veterinary prescription to prevent antimicrobial resistance." An alternative suggestion is to make a cross reference in section 5 to the suggested listing of routes of administration and formulations given in section 3.3.1 (lines 513-516) which mentions 'when factoring AMR risk into prescribing decisions, the aim should be to use the list above together with the AMEG categorisation to select both the formulation/route of administration and class that will have the least impact on the selection of	See response to comment 135, above.	136.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		AMR'.		
807	35	Comment: Please recognise the national difference in available alternatives and the different epidemiological situations. Change: Add '*…and the availability of alternative antimicrobials in veterinary medicine,* ***which may depend according to the country and local epidemiological situation***'.	Agreed. Sentence added	137.
807	36	Comment: Please recognise the national difference in available alternatives and the different epidemiological situations. Proposed Change: Add '…and the availability of alternatives antimicrobials in veterinary medicine, which may depend according to the country and local epidemiological situation'.	Agreed. Sentence added	138.
814-818	26	No amendments recommended. Same notation as for lines 341- 349, 705-706 Rationale: this section apparently clarifies the limitation of compounds not approved for veterinary use in the EU as being relevant to category B, and therefore, following the complete criteria established by AMEG will actually be categorized based on the result of scientific risk assessment.	See also response to comment 88.	139.
843-844	2	Comment: In section 5 "Use of AMEG Categorization" it is stated that "The categorization itself is not a risk assessment.. (line 838)" and "The categories could be used to provide background for the consequence assessment…(line 843). I think these are valid points but here and there in the text of the draft advice the distinction is not so clear. For example, line 116-17 it is stated "Category D ("Prudence") is the lowest risk category. While the risk to public health associated with the use in veterinary medicine	It is acknowledged that important elements of a complete risk assessment, e.g. probability of exposure to AMR, are not fully addressed, and may not be relevant to use of the Categorisation (e.g. the overall	140.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		of substances included in this category is considered low,…". This wording suggests that the categories are reflective of risk assessment – but it is not clear whether that the intention. I wonder if there are some places where the term "consequence" might be a more appropriate term than "risk" – to the extent that the consequence of resistance to a category B drug is expected to be greater than from category D? Proposed change (if any): Where appropriate use "consequence" rather than "risk" when comparing categories.	risk to the population due to use of an antibiotic in animals may be low at present due to low prevalence of resistance genes, but the antibiotic may be included in category A/B in order to limit its use and preserve it's efficacy as a last resort antibiotic for use in humans). However, the criteria for the categorisation include some aspects of a risk assessment in addition to consideration of consequences to human health. The term 'risk' has been retained in the document for consistency with AMEG 1 and the terminology used in the Commission's mandate.	
843	39	The document states, "*The categories could be used to provide background for the consequence assessment of a risk assessment for antimicrobial medicines*". Comment: For each of the four categories the EMA has provided pre-determined risk management conditions. It is unclear how these conditions could be	Table 2 in particular relates to a consequence assessment. The risk management measures proposed are at high level. It is anticipated that the	141.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		established in the absence of an overall risk assessment process which factors the potentials for release and exposure. It is unclear how the current categorization would be used to inform a consequence assessment in a preliminary risk profiling or full risk assessment when the outcome of the risk assessment should result in the development of risk management options related to the use of the drug.	categorisation would be used as a tool to develop treatment guidelines which would address specific species, indications, the local AMR situation etc. (Chapter 5). More detailed risk management measures could then be proposed based on the more complete evaluation of the risk possible once the full circumstances of use of a particular formulation are known.	
855 – 867	35	Comment: These are very important observations made to the categorisation. It would be good to incorporate them also in the summary. Change: include the messages of line 855-867 also in the summary of the assessment and the recommendations (part 1).	Agreed. This information was partially already included in Section 1. Sentence changed: This categorisation does not directly translate into a treatment guideline for use of antibiotics in veterinary medicine, but can be used as a tool by those preparing guidelines, for making decisions about prescribing under the "cascade" or when deciding on risk mitigation activities. In veterinary medicine, the variety of animal species, the different	142.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
			routes of administration…." Added after line 140: *"In the categorisation process, defined criteria, based on evidence and experts' considerations, have been applied to provide a rationale for the ranking.* And: '*It is recommended that this categorisation should be reviewed in the light of the data collated annually in the mandatory EFSA/ECDC monitoring programme for AMR in zoonotic and indicator bacteria (at least within 5 years) and, if necessary, on the basis of new ad hoc scientific evidence or emerging information on changing patterns of antibiotic use and/or resistance trends.'*	
892 (Table A2 selected row)	26	~~*A*~~ *D* | *Streptogramins* | *J01FG* | *Q01FG, QJ01FG90 (virginiamycin)* *Rationale: See previous entries.*	Not agreed. See comment 134.	143.
Table 2	13	Comment: In Table 2 under Macrolides (P23), in the 'Overview of indications in human medicine and resistance mechanisms' it describes treatment of	As macrolides are defined in the Annex 2 with ATC codes,	144.

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		shigellosis and salmonellosis. This does not apply to all macrolides in general but specifically to the azalide, azithromycin. Therefore, under 'Antimicrobial class should it not specify Macrolides and azalides? Subsequently in Table 3 (P31) It refers to 'Macrolides (including ketolides)'. At some stage, dividing the macrolide group of antibiotics into their respective sub-groups may be beneficial. Ketolides tend to be more advanced macrolides. Proposed change (if any): Change to 'Macrolides (including azalides)'	azithromycin (J01FA) is a macrolide.	
Table 3 (page 29-35)	40	Comment: We noted that a few antibiotics received scores of 1 across the board, while the most of the antimicrobial classes have probability ratings of 3 with a few having mixed ratings. For those that received only scores of 1, is it possibly to clarify the factors contributing to this? For example, is this due to the newness of the compounds, the restricted use, a lack of data, etc.?	No, it is due to the data available indicating a limited risk of transfer of resistance genes.	145.
Table 4 **Lincosamides**	3	Comment: The warning for the *cfr* gene is not included in the last column for this antimicrobial class. The *cfr* gene encodes a 23S rRNA methyltransferase, which leads to resistance to Category C antimicrobial classes (Amphenicols, Pleuromutilins, Lincosamides) as well as Category A antimicrobial classes (Oxazolidinones, and Streptogramin A). Proposed change (if any): The warning for the *cfr* gene must be included in this antimicrobial class.	Agreed. The "Main rationale for categorisation" column of Table 4 for Lincosamides was revised.	146.
Table 4 **Pleuromutilins**	3	Comment: The warning for the *cfr* gene is not included in the last column for this antimicrobial class. The *cfr* gene encodes a 23S rRNA methyltransferase, which leads to resistance to Category C antimicrobial classes (Amphenicols, Pleuromutilins, Lincosamides) as well as Category A antimicrobial classes	Agreed. The "Main rationale for categorisation" column of Table 4 for Pleuromutilins was revised.	147.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		(Oxazolidinones, and Streptogramin A). Proposed change (if any): The warning for the *cfr* gene must be included in this antimicrobial class.		
Table 4 Rifamycins	3	Comment: A new comment was included in this section of the Table: "No hazard of zoonotic importance is identified, and extent of use in vet medicine is low." It is unclear as to the basis of this comment. Rifamycin testing is not included in surveillance programs for zoonotic bacteria. The extent of use in veterinary is UNKNOWN since human authorised formulations are used off-label in companion animals and foals. There is no data about this off-label consumption. Tuberculosis is infrequently treated in companion animals, with the potential for resistance selection. *Rhodococcus equi* is now recognised in immunocompromised people where several isolates share the same virulence factors as horse (foals) infections (e.g VapA gene). Rifampin resistance is recognised in horse (foals) infected with *Rhodococcus equi*. Rifampin resistance is an increasing issue in MRSA in Europe (Bongiorno et al. 2018 Burden of Rifampicin- and Methicillin-Resistant Staphylococcus aureus in Italy. Microb Drug Resist. 24(6):732-738. doi: 10.1089/mdr.2017.0299.). **Proposed change (if any): The new statement included is NOT true and should be deleted.**	Rifamycins have now been included in Category A, with the exception of rifaximin which remains in Category C as there are some veterinary medicines authorised for local use. The rationale in table 4 has been amended: Rifamycins are essential in human medicine for treatment of *Mycobacterium tuberculosis* infections. They are also CIA for treatment *of Staph aureus* infections associated with prostheses. Rifamycins are VHIA in veterinary medicine. Although there is cross-resistance in the class, resistance is not horizontally transferable. Mtb is not treated in food animals and transfer of resistant Mtb organisms is not a potential zoonotic hazard in context of authorised local use of rifaximin in veterinary medicine. Use of	148.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
			rifaximin could select for cross-resistance to rifampicin in *Staph aureus* which may be a zoonotic hazard, although risk is low with appropriate hygiene measures and alternatives in human medicine are available. Resistance to rifamycins develops rapidly and responsible use is essential.	
Table 4	13	Comment: Similarly, in Table 4, under Macrolides, it refers to 'invasive MDR *Salmonella* spp. and *Shigella* spp. infections.' Should the 'Antimicrobial classes and subclasses, substances' section include 'Macrolides and azalides'. Proposed change (if any): Change to 'Macrolides (including azalides)'	Not accepted.As macrolides are defined in the Annex 2 with ATC codes, azithromycin (J01FA) is a macrolide.	149.
	13	Comment: In table 4, (P45) Lincosamide (lincomycin, clindamycin) resistance is also linked to *vga*(A) resistance and *cfr* resistance but it is not mentioned here in the same light as Pleuromutilins. Should it not have the same statements? 'Antimicrobial class with high probability of resistance transfer. May lead to resistance to last resort antimicrobial class especially to linezolid (oxazolidinone)'? The resistance is probably by co-selection, similar to tiamulin and is likely to be uni-directional from linezolid use/resistance in man (Miller et al, 2008). There may be a more direct link to amphenicol use in animals, as the *cfr* gene is the 'chloramphenicol, florfenicol resistance' gene (Schwarz et al, 2000). There is also the cross-resistance link to macrolides and streptogramin B via the *erm* genes (Kadlec et al, 2012). Proposed change (if any): Insert 'Antimicrobial class with high probability of resistance transfer. May lead to co-selection of resistance to last resort	Partly agreed. The text has been revised in Table 4. The *erm* and *cfr* genes are now included in the 'main rationale' for categorisation of lincosamides. *Vga* is not included as this gene has less significance.	150.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		antimicrobials class, especially to linezolid (oxazolidinone)' Comment: Under Pleuromutilins (P45) this class is generally not associated with a high probability of resistance transfer, even after 40 years of use. It is stated under 'Examples of important indications in human medicine' as *Staphylococcus* spp. (e.g. MRSA) only. The pleuromutilins are not active against *E. coli* or *Salmonella* spp. and have been shown not to be active against *Enterococcus* spp. (Fard et al, 2011) using a pathogenic enteric bacteria, *Brachyspira hyodysenteriae,* MIC breakpoints of only 0.25µg/ml (SWEDRES/SVARM 2018). The same would apply to *Campylobacter* spp. Tiamulin resistance has been reported in porcine MRSA but the majority of the resistance is chromosomal and clonal, associated with gene mutations affecting the RNA and tiamulin's binding to the ribosome. In the case of *cfr* or *vga* genes, regarding pleuromutilin resistance transfer risk, the incidence might only be 'very low' or 'low'. Peeters et al. (2015) demonstrated the presence of 1 (0.47%) *cfr* gene and 4 (1.9%) *vga*(A) genes in 211 Belgian MRSA isolates from pigs and Sönksen of the Statens Serum Institut, Denmark, (2019 – Personal communication) reported that in a survey of 257 Danish LA-MRSA CC398 isolates there were zero (0%) *cfr* genes found and only 1 (0.4%) *vga* gene. It might be more suitable to state 'Antimicrobial class with low to very low probability of resistance transfer.' There are other treatments for MRSA in man such as glycopeptides (vancomycin) and the streptogramins (although 'considered obsolete'), as well as the oxazolidinones (linezolid). This then questions why the pleuromutilins are in Category C and not Category D? Proposed change (if any): change to 'Antimicrobial class with low to very low probability of resistance transfer. However, may lead to co-selection of	The rationale in Table 4 for the categorisation of pleuromutilins has been revised. They have been retained in Category C – 'Pleuromutilin use in animals selects for the multidrug-resistance gene *cfr* in MRSA, including LA-MRSA, which is a hazard of zoonotic relevance. *cfr* mediates cross resistance to oxazolidinones.'	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome	
		resistance to last resort antimicrobials class, especially to linezolid (oxazolidinone)' Switch Pleuromutilins from Category C to Category D.		