8 November 2018
EMA/CVMP/AWP/30098/2018
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union' (EMA/CVMP/AWP/237294/2017)

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

Stakeholder no.	Name of organisation or individual
1	Pig Veterinary Society
2	Responsible Use of Medicines in Agriculture (RUMA) Alliance
3	A.F.V.P.Z : Association Francophone des Vétérinaires de Parc Zoologique
4	EVIRA - Finnish Food Safety Authority
5	BVPA - British Veterinary Poultry Association
6	FVE - Federation of Veterinarians of Europe
7	BEVA - The British Equine Veterinary Association
8	EGGVP – European Group for Generic Veterinary Products

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Mainly a good descriptive narrative of the current situation. However is undermined by a presumption that off label use is undesirable (it is essential given the increasingly narrowly restrictive terms of SPCs) and an unproven presumption that off label use creates increased risk of AMR - no evidence given for this. No reference is made to short term high dose use for disease elimination strategies – one of the major off label uses of antibiotics in pigs.	Partly accepted The paper discusses the legitimate needs for the cascade in section 3. In the subsequent sub-sections of section 5 many examples of responsible off-label use are given in addition to examples of more concerning practices. In the reflections and conclusions it is clearly noted that there is a lack of published studies on this topic and that 'it is only possible to speculate about the risks to animal and public health based on general principles.' Reference to short term high dose off-label use of antimicrobials for disease elimination strategies in pigs has been included in the annex, 1.2 Pigs.
2	RUMA welcomes this reflection paper and supports most of the recommendations made subject to taking account of our detailed comments.	Thank you for your comments.
3	Veterinary practice on wild captive animals (zoo, circus,…) involves use of antibiotics; this use is almost always relying on the cascade principle of the directive 2001/82/EC, article 10 (translated into French regulation through the article L5143-4 of Code de la Santé Publique), and also the directive 2004/28/ modification of article 10 that allows use of VMP allowed in other member states. Main reason of this off label use is the obvious lack of VMP allowed for non-domestic	Thank you for your advice. Section 5.1 has been updated.

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	species, moreover zoo species. Those treatments mainly concern individual animals (with limited AMR public impact as stated on line 356). While they're obviously non food producing species, the importance of treating them could be sometimes paramount considering the potentially high conservation value of endangered species. There are more and more published studies on pharmacokinetics of antimicrobial drugs in wild species in peer reviewed journals, they must be promoted and used as reference by clinician vets before prescribing antibiotics to these species. Moreover, datas and knowledge spreading do exist among zoo vets through 3 different tools / medias: 1. European College of Zoological Medicine, recognized by EBVS, with exotics speciality (Avian, herps,..) and recent Zoo Health Management specialty 2. European Association of Zoo and Wildlife Veterinarians (more than 700 members) and all national association, such as AFVPZ. Scientific conferences are running each year, where information' are gathered and spread to/from members. 3. Use of a web-based information management application "ZIMS" from Species360, with a medical module that has – among others- a part dedicated to drug prescription/usage/administration/report and thus gather a lot of information on VMP / species (Available only in ZIMS: Drug usage information for more than 1,200 species).	
4	Evira thanks for the opportunity to comment the draft reflection paper on off-label use of antimicrobials and makes the following general comments: 1) On a small market like Finland the cascade use of antimicrobials cannot be avoided as all the necessary products are not available on the market. 2) In case of old VMPs the dosage is not always up-to-date with the scientific knowledge, thus referring to label use as better option is not always true. This needs to be addressed in the document. In case of food-producing animals these out-dated	Partly accepted 1) The issue on product availability varying in different member states has been included in section 3. 2) It is acknowledged that dosing regimen in old VMPs may not always be up to date. Nevertheless as outlined in section 5.9 the

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	SPCs are probably due to the fact that carrying out residue studies is considered too expensive. Keeping old substances on the market is absolutely necessary. During the last couple years there have been shortage of benzyl penicillin procaine, sulpha – trimethoprim and the marketing authorisation of the only short-acting oxytetracycline injectable has ceased. 3) Off-label or cascade use can be prudent use e.g. when choosing a efficacious narrow spectrum product authorised for humans or other animal species instead of choosing an unnecessary broad spectrum product authorised for animal species in question. In addition, in countries with small markets cascade rules have to be applied more often than in some other countries and it does not mean that in countries with small markets antimicrobials are not used prudently. From the point of view of bacteria there is no difference if the exposure is due to label, off-label, cascade or misuse. Even the most prudent use may cause resistance. The most sustainable way to fight against antimicrobial resistance is to reduce the need for antimicrobials.	basis for recommendations to change dosages is often not clear and the impact on the risk to public health when changing the dose is usually not taken into account. From a regulatory point of view there is need to be informed via the pharmacovigilance system about lack of efficacy in authorised VMPs. This issue has been addressed in section 5.7 and was included in the recommendations, new bullet point (9). The concern to avoid loss of older antimicrobial products or species and indications is indicated in point 6 of the CVMP recommendations for action and the CVMP's strategy on antimicrobials 2016-2020. 3) The use of a narrow spectrum AM authorised for other species instead of broad spectrum product could be interpreted as "prudent OLU". However, this practice would take into account that efficacy and safety has not been proven for a non-authorised product. The concern on the use of less critical antimicrobials in countries with small markets or with limited treatment options (MUMPs) has been

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		included in section 5.1.With regard to "the most sustainable way to fight antimicrobial resistance by reduction the need for antimicrobials", this has been extensively described in the RONAFA report.
5	This reflection paper is to be welcomed and in general makes sensible and constructive recommendations. Reduction in off-label use of antimicrobials will no doubt help control the development of resistance. This shows a pragmatic approach and recognises the welfare aspects of continuing justified off-label use. The off-label use of antimicrobials in the poultry industry is believed to be low, and to a large extent related to use in species where few products are approved, and for treatment of diseases where no specific indications exist. Observance of statutory withdrawal periods receives due recognition, however it must be clarified that where treatment of the indicated species with the approved posology is given, no changed to the withdrawal period is required. This permits treatment of a specific infection not indicated on the SPC provided the above conditions are met.	Thank you for your comments. Line 192. Directive 2001/82 lays the responsibility with the veterinarian for establishing a withdrawal period. Further interpretation in national law may vary between member states, therefore this will not be addressed further in the paper.
6	FVE welcomes the intention of CVMP to look into off-label use in veterinary medicine. Off-label use or use of a medicine under the cascade system is an indispensable tool in veterinary medicine, especially -but not only- for minor species or indications (MUMS), as it is also acknowledged in this document. It needs to be recognised that the amount of marketing authorisations of veterinary medicinal products greatly differs between the different EU member states (see	Partly accepted. Thank you for your comments. To address some of the additional issues raised by FVE would significantly change the scope and focus of the paper. In addition, it has to be considered that the evidence base around OLU is limited. It is

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	commission impact report – with more than 6000 veterinary medicinal products authorised in some EU member states and less than 400 in others). In EU member states with only limited veterinary medicinal products authorised (which are not even all marketed!), the need for off-label use will be much greater. Although FVE welcomes the overall initiative and can agree with the main CVMP recommendations for actions, we believe the concept of the reflection paper misses to address some major points and misses clear action to prevent the need for off-label use and which will increase the availability of authorised VMPs and vaccines. - The paper is only focused on the off-label use of antimicrobials. It should also look at off-label use of other VMPs or vaccines in relation to AMR risk. For example, some alternatives to antimicrobials in animal feeding and preventive vaccines, the use of which can reduce the risks of antibacterial resistance (AMR), are also used off-label. - The reflection paper should not only look at the risks but also at the benefits which can be given by off-label use of antimicrobials. Off-label use of veterinary medicines is often in line with responsible use practices, for example in case of (i) off-label use of an older or narrow spectrum antibiotic that is authorised in another Member State vs a CIA authorised in the home country, (ii) off-label use of a vaccine to prevent from disease and which reduces the need to treat animals with antimicrobials, (iii) off-label use of the right antibiotic for the underlined disease as indicated by the sensitivity tests, (iv) etc. Practical reasons, such as package sizes, strength, convenience of application, are correctly acknowledged in this document as they are very important in veterinary practice (try to give tablets to an aggressive cat or to a critically ill animal which refuses to eat) and should be considered in decision making for the right medicine.	acknowledged that the reasons for OLU are numerous and often complex. The paper tries to capture the main reasons at high level but cannot address every situation. The issue on varying product availability in different member states has been included in section 3 and 5.1. The concern on the use of less critical antimicrobials in countries with small markets or with limited treatment options (MUMS) has been included in section 5.1.

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	- If veterinary medicinal products, which are more effective for the indication and which are known to give a lower risk for AMR, are prescribed off-label can be beneficial. To give an example, for some species, only CIA's are authorised and marketed for certain indication and species in some EU member state. In this case, it might be beneficial to use off-label an antimicrobial veterinary medicinal product of a lower AMEG category from another EU member state. Another example is that for certain clinical indications scientific research has shown that a shorter treatment time is possible, in which case again off-label use will reduce the AMR risk. - The definition of off-label is incomplete or even questionable. We tend to consider the use of a medicine off-label when it is used outside of terms laid down in the summary product characteristics (SPC) without considering that SPCs especially of older veterinary medicinal products are not following the recent scientific developments in veterinary medicine and that the information and data on the SPCs even for the same veterinary medicinal product differs greatly among different marketing authorisations and from Member State to Member State. There are examples where the same veterinary medicinal product is licensed for different clinical indications, different animal species, different dosage regime, and different withdrawal periods. What may be off-label in one member states could be according to the label in other Member States of EU. The same applies also for combination of antimicrobials vs authorised combination products. Veterinarians have been trained to follow science-based information and have an ethical and professional obligation to prevent and relief animal suffering (see veterinary Oath and Codes of Conduct). Veterinarians have been trained on how to use veterinary medicinal products in the interest of animal health, animal welfare and public health. This is why veterinarians have ranked "training/literature as well as their own experience	The definition of off-label is in line with the existing European Directive 2001/82/EC. As long as the new veterinary regulation has not yet been adopted alignment to other definition cannot be made. The problem of existing SPC differences among different marketing authorisations and Member States is acknowledged in the CVMP's strategy on Antimicrobials and SPC harmonisation is envisaged in the new regulation. The issue on "not up to date" dosing regimen and the practice of veterinarians to follow off-label recommendations by changing the dosage regimen according to treatment guidelines, scientific based information or own experience is acknowledged. There is concern on the

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	higher than SPC" (see De Briyne et al. (2013) report). In the same report is mentioned that veterinarians "viewed the SPC only occasionally and/or seldom before treatment", however has it to be acknowledged that veterinarians have usually access only to the Product Information Leaflet (PIL) included in the package of the product and not to the detailed SPC approved by the authorities. - Off-label use clearly plays a potentially important role in contributing to the overall safety profile of medicinal products and could play a role in extending product marketing authorisations to more animal species or more clinical indications. - Systematic (on-label or off-label) preventive use of antimicrobials in groups of animals is not any more considered an acceptable practice. FVE has been promoting best practices, such as biosecurity, proper hygiene and husbandry, good nutrition, holistic health plans through regular veterinary visits and prevention from disease through proper vaccination programmes, etc. FVE is pleased to see that these recommendations have been taken into consideration and included in the proposal for a new regulation on veterinary medicinal products. In conclusion, the reflection paper misses to present an overall risk-benefit analysis and misses important veterinary aspects. FVE feels that the reflection paper needs to be refined and extended in order to ensure a holistic, science-based, ethical and compliant to best-practices approach of the impact of off-label use of veterinary medicinal products – not only antibiotics – against antimicrobial resistance. FVE agrees with the CVMP recommendations for action and would like to contribute towards that direction. Nevertheless, recommendations should also consider more actions - to increase the availability of the currently authorised medicines as well as	basis for these dose adjustments which is often not clear. Thus, veterinarians are encouraged to report on the lack of efficacy of authorised VMPs via the pharmacovigilance system. This issue has been addressed in section 5.7 and has been included in the recommendations, new bullet point (9). It is noted that public access to SPCs is possible via the HMA/VMRI Product Index, websites of various NCAs and is also available on request from MAHs. This problem (availability of medicines/SPC harmonisation) is noted in the final paragraph of section 3 of the paper and has been acknowledged in the CVMP's strategy on Antimicrobials.

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	- the update and harmonisation of SPCs content throughout the EU member states. We note that many of the examples presented in the Annex of the reflexion paper, just demonstrate that there is a need to improve availability of medicines, to harmonise SPCs and to update SPCs to follow recent scientific and technical developments in veterinary medicine. Veterinarians very much prefer to use authorised veterinary medicines, instead of relying on off-label use which has to be done on their own liability. Increasing the availability of veterinary medicines, such as through allowing a true single market of veterinary medicines, will reduce at large extend the need for using of veterinary medicines by the cascade system (off-label use). In conclusion, FVE would like to highlight that more and more restrictions on the use of antimicrobials in animals may have the opposite results, i.e. the increase of the need of off-label use of antimicrobials or the increase of bacterial diseases due to lack of available treatment options. We must therefore be mindful and make risk-benefit considerations through the holistic One-Health approach.	
7	BEVA is broadly supportive of the proposals in the CVMP consultation document and has championed the responsible use of antimicrobials within the equine veterinary profession for several years through initiatives such as the *Protect ME* campaign to equine practitioners and to horse owners. The goal of this on-going campaign has been to reduce overall antimicrobial use, to promote appropriate prescription (which may actually require off-label use), and to reduce the use of CIA's.	Partly accepted.

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	BEVA wishes to emphasise the critical importance of Cascade/off-label prescribing for a minor-use, minor-species animal like the horse. Cascade prescribing is a vital measure to safeguard equine health by ensuring there is an adequate range of medicines available, and BEVA has long-supported and valued the measures put in place to this end through the provisions of Cascade prescribing and the Essential List. There are frequent clinical situations where it is necessary to prescribe off-label by varying the dose or frequency of antimicrobial treatment to follow an evidence-based approach based on published scientific evidence, which may be at variance with the SPC.	The unmet medical need has been described in section 5.1 in general and with regard to horses in detail in 1.3 of the annex. Any need to "prescribe off-label by varying the dose or frequency of antimicrobial treatment" is addressed in section 5.7 and suspected lack of efficacy should be reported by the PV system. This has been included in a new point (9) of the CVMP recommendations.

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8	Many thanks to CVMP/AWP for addressing off-label use of antimicrobials and for the opportunity to comment. The provisions and goals of the concept paper are explained in a clear way; the paper gives a good overview of the reasons of off-label use and potential risks (in particular related to AMR), which is welcomed. EGGVP also generally agrees with the recommendations given. However, "off-label use" is, in essence, a privilege of the freedom of treatment based on the veterinarians' knowledge. For certain conditions it is still an important tool for a veterinarian to practice his clinical knowledge, such as local therapy (intra-synovial), unmet medical needs (indications for which no products are registered of registered anymore due to recent adjustment of the SPC's, minor target species…). The cases treated by off-label are different from each other. If a veterinarian treats an animal in a certain way, it is not evident that another veterinarian would treat the same animal with the same diagnosis the same way. So, even if recommendations are welcome, during the development of any future guideline or provisions, some perspective may be needed so as not to overregulate a practice that is based on professional knowledge with full responsibility. The evaluation of the off-label use shall be in the hands of the specialists, the veterinarians in the field, and they should not be hindered when there is a clear indication for an off-label use. As a general comment, EGGVP perceives more focus should be given to **withdrawal periods** in case of off-label use in food producing animal. Especially when animals are treated at a higher dose than prescribed and/or when not target species in the SPC are treated by off-label use.	Partly accepted. The paper aims to give a balanced view of both responsible OLU and other practices that could lead to unjustified AMR risk. Final provisions for regulation of OLU rest with EU and national legislative bodies. The issue of withdrawal periods for OLU is to be addressed in the new VMP Regulation. The risk that AM residues exceeding the microbiological ADI may result due to inadequate withdrawal periods after OLU is noted in section 5, but there is limited research on this topic.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
13-107	8	Comment: Suggestion to stress the need for training activities and sensitivity campaigns (not limited to the publication of guidelines guidelines). It is important to raise awareness in veterinarians and farmers about, i.e. - Veterinarians - consequences of off-label use on AMR, for instance in situations where antibiotics are combined (sometimes mentioned in formularia as an option) or post-operative situations (not 100% prove that this is useful). - Veterinarians - sensibility testing, training in reading the results of these type of tests, drawing the right conclusions from it to take the right actions. - Farmers – understanding a label. Labels of VMP's are not always clear to farmers (which can result in under and overdosing) Comment: Section 5 gives some considerations on combinations of AMs, but there are no specific reccomendations. EGGVP suggests that **veterinarians should be encouraged to use fix combinations than arbitrarily using different single products**. Because in the second case, when products are freely mixed, positive or negative interactions are not well tested and neither the withdrawal perod.	The CVMP recommendations (4) already cover consequences of off-label use and trainings to raise awareness of the use of treatment guidelines. Training of veterinarians in antimicrobial susceptibility testing is a good advice but this is not specific to OLU. In EU, all VMPs containing antimicrobials are under veterinary prescription. It is GVP that prescribing veterinarians help farmers understanding the label. It has been included in recommendation 5 that the concomitant use of two or more antimicrobials without proper diagnosis cannot be considered as cascade use. The importance of diagnostic investigation and AST for OLU is already emphasised in Recommendation 2. We prefer to keep the recommendations focused on issues relating to AM aspects rather than aspects that could relate to other combination products.

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14-17	6	Comment: The definition of off-label is incomplete or even questionable as there is no harmonisation of the SPCs of authorised products and not a true single market in EU. Align the definition with the new regulation.	Not accepted. The definition of off-label is in line with the existing European Directive 2001/82/EC. As long as the new veterinary regulation has not yet been adopted alignment to other definition cannot be made.
20-23	4	Comment: The statement "Although it is preferable that VMPs are used in-line with an evidence-based summary of product characteristics (SPC)…" is true only for the newer VMPs. There are still old products on the market which do not have dosage information up-to-date probably due to the fact that carrying out new residue studies is not economically feasible. Proposed change (if any): "Although it is preferable that VMPs are used in-line with an up-to-date, evidence-based summary of product characteristics (SPC)…"	Partly accepted. The concern on potential "not-up to date" dosing regimen is discussed further down in the document in chapter 5. For clarification the sentence was amended to "Although it is preferable that VMPs are used in-line with the summary of product characteristics (SPC) as approved,…"
23	6	Comment: The concept of 'unacceptable suffering' is totally confusing. What is the difference between 'acceptable suffering' and 'unacceptable suffering'? When does suffering become 'unacceptable? (e.g. 'Unnecessary suffering' as a concept in animal welfare legislation and standards by F. Lundmark). FVE suggests to replace this confusing concept with 'in the interest of animal health, animal welfare and public health'. This would also include the aspect of evaluating the AMR risk to public health.	Not accepted. Although the concern is acknowledged, 'unacceptable suffering' is not a concept but a citation of the wording used in the Articles 10 and 11 of Directive2001/82/EC, as amended.

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		Proposed change (if any): …**~~to avoid causing unacceptable suffering~~ in the interest of animal health, animal welfare and public health.**	
24	5	It should be pointed out that moves towards pathogen / disease specific indications whilst justifiably encouraging accurate diagnosis, reduces the flexibility of use with many antimicrobials, and may necessitate off-label prescribing.	This concern is already addressed in the last paragraph of section 3, no need for additional inclusion in the recommendations.
26	6	Comment: The benefits from off-label use should be also acknowledged and presented in this document. Proposed change (if any): … it is only possible to speculate about the potential **benefits and** risks to animal and public health…	Accepted.
37-38	6	Comment: Practical reasons, such as package sizes, strength, convenience of application, are correctly acknowledged in this document as they are very important in veterinary practice and should be considered in decision making for the right medicine. Please see also comment below about Lines 396-410. Unintentional under- or over- dosing is an accident. Only intentional under- or over- dosing should be considered as off-label use and in that case has to be justified and a science-based decision. Proposed change (if any):	Partly accepted. Sentence changed to: These include use of antimicrobials for practical or economic reasons <u>alone</u>, systematic preventive use in groups of animals, ~~un-~~intentional under~~- or over-~~dosing and concomitant use of two or more antimicrobials without proper diagnosis. Off-label use of antimicrobials alone for 'practical or economic reasons' cannot be considered as cascade use and will

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		These include **~~use of antimicrobials for practical or economic reasons,~~** systematic preventive use in groups of animals, **~~unintentional~~** under- or over-dosing and concomitant use of two or more antimicrobials without proper diagnosis **and scientific evidence**.	therefore, be kept. "and scientific evidence" not included because it adds no further clarification to the condition to make a diagnose before the concomitant use of antimicrobials.
43-53	2	Comment: RUMA has regularly called for decisions on the use of antimicrobials to be based on evidence so we welcome the proposal for "a limited research initiative to investigate the major off-label uses, particularly of antimicrobials that are currently only authorised for human use." However, as stated in lines 190-193, it should be noted that such antimicrobials may not be used legally under the cascade in food producing animals unless there is a MRL for the active ingredient. This will be particularly relevant when considering the results of the research initiative and any possible control measures.	Accepted. To address the point a footnote was included.
43-55	4	Comment: From the point of view of bacteria it does not make any difference if the use is in accordance with the label or off-label use. All use should be prudent and an effort should be made to collect indication-based usage data of all antimicrobial usage not only about off-label use. It is important to consider the costs of data collection. With the limited resources putting effort on supervision and guidance/training of prudent use may be more important.	Not accepted. A recommendation on collection of data including label use would be out of scope of this paper. Recommendations to raise awareness of vets was included in point 4.
	7	**Data collection**. BEVA supports the statement that organised data collection on off-label	Thank you for your comment.

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		AM use is needed. The current lack of data makes it difficult to address the questions about the impact of veterinary use of AMs, and of off-label use of AMs, on AMR. It also makes it difficult to assess the impact of responsible use campaigns such as *Protect ME*. BEVA would strongly support joint initiatives to collect meaningful data (i.e. data beyond simple tonnage figures) from veterinary practice. The absence of data about off-label prescribing creates real challenges in understanding the impact that off-label prescribing of AMs is having on AMR.	It has been included in the recommendations that the research initiative should be " … sufficient to investigate the major off-label uses in the different species, …
56-57	5	Full diagnostic investigations including culture and sensitivity can be very expensive and time consuming, e.g. in the cases of diseases caused by *Mycoplasma* and *Ornithobacterium rhinotracheale* infections. The caveat "where possible" should be retained or expanded to reflect the above – 'if feasible' or 'if practically possible'	Accepted. No changes necessary, "where possible" will be kept in the recommendation.
57-58	5	In the majority of cases of disease in poultry group treatment is required in order to treat sick birds and those at risk of infection through close contact, and are likely to be incubating disease. The caveat "if feasible" should be retained.	Accepted. No changes necessary, "if feasible" will be kept in the recommendation.

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56-58	4	Comment: In case of fish limiting treatment to individual animals is not an option. Again, the prudent off-label use causes no more risks than prudent label use. Proposed change (if any): If feasible~~ it should be limited to~~ treatment should be limited to ~~of~~ individual animals although it is recognised that, for instance in case of fish, this is not possible.	Accepted with slight amendments.
	7	**Cascade prescribing must be supported by a diagnosis.** BEVA supports the principle of this and encourages its members to follow this approach wherever possible. The reality of clinical practice, however, is that the inevitable delay between sample collection and obtaining culture & sensitivity results can result in patient risk and clinicians may be compelled to prescribe before results are obtained. **Proposed change:** "Prescribing under the cascade should be supported by a full diagnostic investigation including bacterial culture and antimicrobial susceptibility testing, where possible ***or where delay would not result in unacceptable patient risk***."	Not accepted. Even if treatments have to be initiated immediately AST can be initiated at the same time. Treatment can be changed following AST results, if necessary.
56-59	2	Comment: RUMA agrees that ideally it is reasonable to try to isolate the organism and carry our sensitivity testing. But we have concerns that such a requirement may be impractical and uneconomic and could lead	Partially accepted. The recommendation has now been focused on critically important antimicrobials with

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		to difficulties treating minor species leading to increased animal health and welfare concerns. Do we know if there are sufficient laboratories able to do this testing at a reasonable cost? It seems premature to require antimicrobial "prescribing under the cascade to be supported by full diagnostic investigation including bacterial culture and antimicrobial sensitivity testing" as, until there is data on the amount of antibiotics used under the cascade, there is little justification for introducing such a requirement even with the "where possible" caveat. In particular, the paper recognises in lines 17-19 that "the cost of development of veterinary medicinal products inevitably leads to limited availability of products authorised for species and indications representing smaller market sectors." This means that for some species there are very few or no authorised antimicrobial products so nearly all use will be under the cascade. The volume of use is, by definition, likely to be very small and it is unreasonable to expect each use to be supported by full diagnostic investigation. Proposed change (if any): Ideally, prescribing under the cascade should be supported by full diagnostic investigation including bacterial culture and antimicrobial sensitivity testing, where possible. If feasible it should be limited to the treatment of individual animals.	higher importance to human and animal health:
56-59	6	Comment:	Accepted with amendments:

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		The reflection paper recognises that the cost of development of VMPs for some species with particularly small market sectors undoubtedly leads to limited availability of products (Lines 17-19). It therefore seems overly restrictive to suggest that prescription and treatment of conditions in these animal species under cascade principle should be supported by "full diagnostic investigation including bacterial culture and antimicrobial sensitivity testing". Proposed change (if any): … testing, where possible**, especially for CIAs**.	Off-label use, in particular that of antimicrobial substances/classes categorised as high important with regard to their use in human and animal health (WHO, AMEG) should be supported by a full diagnostic investigation including bacterial culture and antimicrobial susceptibility testing (AST), where possible.
58	1	Comment: Suggests off label use only applicable to individual animals; ignores the concept of population medicine and essential group treatments in many species (pigs poultry fish calves etc) Proposed change (if any):remove ref to individuals only	Partially agreed. Not agreed to delete reference to individual animals. Included that individual treatments may not possible with regard to the husbandry type e.g. fish, poultry, food rabbits.
60-68	2	Comment: RUMA agrees this recommendation but we would like it made clear in lines 63-64 that antimicrobials that are currently only authorised for human use may not be used legally under the cascade in food producing animals unless there is a MRL for the active ingredient. Proposed change (if any): line 63 – ".. assessment before prescribing for	Accepted with amendments. To address the point a footnote is included: "… assessment before prescribing ~~for use in~~

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		use in companion animals* antimicrobials that are presently only authorised for use in humans ....” * antimicrobials that are currently only authorised for human use may not be used legally under the cascade in food producing animals unless there is a Maximum Residue Limit for the active ingredient”	~~companion animals~~ antimicrobials that are presently only authorised for use in humans***** ....”
70-81	4	Comment: As already pointed out in general comments, in case of old VMPs the dosage is not always up-to-date with the scientific knowledge. Proposed change (if any): This should be better taken into account in the text.	Partially accepted. The concern on potential “not-up to date” dosing regimen is discussed further down in the document in chapter 5. No amendments necessary under recommendations.
70-82	7	**Treatment guidelines must be followed**. BEVA supports this and continues to promote this approach through AMU guidelines (*Protect ME*).	Thank you for your comment.
72	6	Comment: Proposed change (if any): … product availability in the Member State**, the region or the EU,** in addition…	Partially accepted. No need seen to additionally address the region. Sentence amended to: … product availability in the Member State(s) in addition…
77	6	Comment: A veterinary degree is only given after a 5 or 6 year study which includes the teaching of pharmacology and toxicology, and veterinary legislation. In addition, in many countries, veterinarians already have the obligation to follow life-long learning. Therefore it is not necessary to extra train	Not accepted. To further raise awareness on AMR related issues with regard to public health and to promote the responsible use OLU of antimicrobials should be communicated in

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		veterinarians about the use of guidelines, instead it has to be ensured that all veterinarians are made aware of the existence of the guidelines. Proposed change (if any): … and veterinarians ~~**trained in**~~ **informed about** their use…	trainings.
77-82	7	**Guidelines and stewardship programmes need to be further developed.** BEVA agrees with this and promotes both concepts through AM guidelines and via the AM stewardship requirements of its scientific journals Equine Veterinary Journal and Equine Veterinary Education. BEVA would welcome joint initiatives to enhance current guidelines and stewardship programmes across all species, and would support projects to produce targeted materials relevant for each species group.	Thank you for your comment. It has been included in the recommendations that the research initiative should be " … sufficient to investigate the major off-label uses in the different species, …."
78-79	6	Comment: Proposed change (if any): … published in press and **peer-reviewed** scientific journals…	Not accepted. Not included because not only "peer reviewed" journals are influential.
83-86	4	Comment: Antimicrobials should not be used for prevention (prophylaxis) unless, in exceptional cases for the treatment of individual animals. This principle should apply also to other use in order to use antimicrobials prudently as it makes no difference for bacteria if exposure is due to label or off-label use.	Comment noted. The concern is acknowledged and is considered in the CVMP strategy on antimicrobials and in the RONAFA report.
87-90	8	Comment: In the past the indications for antimicrobials were given for their antimicrobial spectrum. In the recent years the referrals have considerably reduced the spectrum of indications. Although when the	Comment noted. No changes necessary.

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		antibiotics are not used for a certain period of time, the microorganisms may get sensitive again. But following the referral, the pathogen microorganisms are no longer on the list of indications – the use is then Off-Label. So EGGVP supports recommendations as in lines 87 – 90 to save indications, e.g. for tetracyclines and penicillins, if they are only based on actual antimicrobial resistance data, but not when they are based on non-reachability of the infection site (pharmacokinetics). Comment: New indications: Sometimes research is done on antimicrobial susceptibility of newly detected microorganisms to "old" antibiotics, or a substance used is also effective in another disease or indication (often published in human medicine for e.g. tropical diseases for which no development of a new medicament is initiated, for veterinary medicine see also line 455 - 465). The off-label use should therefore be further allowed to use this new developments, as regulatory processes are too long (time) and too costful to bring these indications on a regular product information.	It is noted that in CVMP referral procedures all relevant preclinical and clinical data will be considered. There is no recommendation to disallow prescribing under the cascade. In future, the importance of the antimicrobial with regard to its use in human medicine and the risk for transmission of AMR from treated animals to humans should be further taken into account, which is outlined in the recommendations.
87-91	7	**Older' AMs should be protected commercially**. BEVA welcomes this proposal but recognises that this issue is largely commercially driven with pharmaceutical companies having to carry the financial burden of licensing. Protecting currently-licensed AMs is clearly highly important in maintaining an appropriate range of AMs to treat horses.	Comment noted. No changes necessary. The issue of data protection is outside direct scope.
	4	This point is very important. Every effort should be made to keep old antimicrobial substances available on the market. However, not all old indications should be kept. Use of antimicrobial treatment for salmonella should not be accepted.	Comment noted. No changes necessary.

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70-90	2	Comment: RUMA agrees with these recommendations	Comment noted.
92, 99	5	mis-numbered	Thank you, numbering is corrected.
92-96	2	Comment: RUMA welcomes the encouragement of the pharmaceutical industry to develop and market VMPs containing antimicrobials of low risk to public health to address therapeutic gaps and broaden their indications. However, we would question whether this is either economically or politically realistic especially after colistin became a drug of last resort for human use after decades of animal only use.	The concern is acknowledged. The need for new antimicrobials/re-introduction of old antimicrobials is dependent on the existing resistance situation which is a dynamic process.
	4	Comment: This point is strongly supported. Losing old, still efficacious substances from the market will lead to use of newer substances and even to the use of CIAs.	Thank you for your comment.
92-98	7	**Therapeutic gaps should be filled by 'older' or non-critical AMs.** Identifying and closing therapeutic gaps is an important principle in safeguarding equine health and BEVA agrees that, wherever possible and clinically acceptable, this recommendation should be followed. Again, BEVA recognises that this burden falls on the pharmaceutical industry although the medicines regulators can assist by streamlining licensing procedures.	Comment noted. No changes necessary.
92-99	4	Comment: Points 6 and 7 should be 7 and 8, respectively.	Thank you, numbering is corrected.
99-101	2	Comment: RUMA has regularly called for decisions on the use of antimicrobials to be based on evidence so we welcome this recommendation.	Thank you for your comment.

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99-102	7	**Research is needed to establish the impact of off-label AM use.** BEVA supports this recommendation (see also comments about Recommendation 1) and believes that filling the evidence gap is important to properly inform this debate.	Thank you for your comment.
103	6	Comment: Recommendations should also consider actions to increase the availability of the currently authorised medicines as well as the update and harmonisation of SPCs throughout the EU. Such actions will reduce at large extend the need for using of veterinary medicines off-label. Proposed change (if any): - Add additional paragraphs with actions on how to increase availability of veterinary medicines, antibiotics, alternative to antibiotics in feed, vaccines, among others. - Add additional paragraphs with actions on update and harmonisation of SPCs	Not accepted. The concern is acknowledged and is part of the CVMP's strategy on antimicrobials. Harmonisation of SPCs is envisaged in the new regulation.
137	6	Comment: Proposed change (if any): … the wide diversity of animal species, age-categories and disorders, results in the necessity for veterinarians using veterinary medicinal products…	No change necessary. The introduction is high level and draws attention to specific issues of the veterinary market.
145-148	6	Comment: The paper is only focused on the off-label use of antimicrobials. It should also deal with off-label use of other VMPs or vaccines in relation to AMR	See general comments to this party above.

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		risk. For example, alternatives to antimicrobials in feed and preventive vaccines are also used off-label, some of which use reduce the risks of AMR. Also the use off-label of older or lower EMA-AMEG classification of WHO critically important antimicrobials (CIAs) based on degree of risk to humans due to antimicrobial resistance development following use in animals should be acknowledged and considered.	
162-184	6	Comment: Steps of the cascade should be aligned to the new European regulation on veterinary medicinal products.	The new regulation has not yet been adopted into legislation and therefore the background to the paper is the existing Directive 2001/82/EC.
185	1	Comment: was the main drive for introduction of MRLs really AMR ?- what evidence	No. This sentence highlights the aspects of MRL evaluation that are specifically relevant for antimicrobials.
186	6	Comment: Include the reference to the CVMP document. Proposed change (if any): … mitigated by specific warnings and/or restrictions in the SPC **(---)**.	Accepted.
196-202	6	Comment: Veterinarians have been trained to follow science and evidence-based information and has an ethical and professional obligation to prevent and relief animal suffering (see veterinary Oath and Code of Conducts). Veterinarians have been trained on how to use veterinary medicinal products in the interest of animal health, animal welfare and public health. This is why veterinarians have ranked "training/literature as well	Accepted with some amendment:

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		as their own experience higher than SPC" (see De Briyne et al. (2013) report). In the same report is mentioned that veterinarians "viewed the SPC only occasionally and/or seldom before treatment", however it has to be acknowledged that veterinarians have usually access only to the Product Information Leaflet (PIL) included in the package of the product and not to the detailed SPC approved by the authorities. Proposed change (if any): 'While much off-label use is to address the absence of authorised products (for a specific species **or age categories** or **clinical** indication), there are other factors that may result in off-label use of VMPs. For example, De Briyne et 197 al. (2013) reported the results of a voluntary survey of veterinary practitioners on factors that influence antimicrobial prescribing habits. In this survey, which included 3004 responses from 25 European countries, respondents ranked training/literature as well as their own experience higher than SPCs as important sources of information influencing their prescribing behaviour. Furthermore, approximately 50% of the same respondents stated that they viewed the SPC only occasionally and/or seldom before treatment. ~~**Thus, off-label use may occur unintentionally since other sources of information on product use are utilised more commonly than the authorised SPC.**~~ The survey results suggest practitioners generally refer to the label and PIL rather than the SPC, that the term SPC is not universally understood and that SPCs are not always publicly available.	"While much off-label use is to address the absence of authorised products (for a specific species ~~or age categories~~ or clinical indication), there are other factors that may result in off-label use of VMPs. For example, De Briyne et al. (2013) reported the results of a voluntary survey of veterinary practitioners on factors that influence antimicrobial prescribing habits. In this survey, which included 3004 responses from 25 European countries, respondents ranked training/literature as well as their own experience higher than SPCs as important sources of information influencing their prescribing behaviour. <u>Of the respondents, 56%</u> stated that they viewed the SPC only occasionally and/or seldom before treatment; <u>a higher importance was associated with product labels and package</u>

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			leaflets, which should be consistent with the SPC although containing less detail.”
204	1	Comment: wording very restrictive on SPCs – agree leads to more off label use	Comment noted.
207	6	Proposed change (if any): … authorised target species **and age categories** would have classified as off-label. Where ‘older’ lower risk antimicrobials have been the subject of a recent review, specific narrow **clinical** indications against named target **animal** pathogens have been introduced …	Not accepted. This section relates to the situation where previously specific target pathogens were not named in the SPC, whereas after review, the indications are amended to include named target pathogens only. This is not a situation that would be specifically applicable to different age-categories of animal. Also, it relates to the target pathogens named in the indication, rather than the ‘clinical’ indication.
213-225	6	Comment: By looking only into associated risks the reflection paper is not holistic and misses to present an overall risk-benefit analysis. The benefits from off-label use should be also acknowledged and presented in this document. Off-label use of veterinary medicines is many times in line with responsible use practices, for example in case of (i) off-label use of an older or narrow spectrum antibiotic that is authorised in another Member State *vs* a CIA authorised in the home country, (ii) off-label use of a vaccine to prevent from disease, (iii) off-	See general comments to this party above.

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		label use of the right antibiotic for the underlined disease as indicated by the sensitivity tests, (iv) etc. Practical reasons, such as package sizes, strength, convenience of application, are correctly acknowledged in this reflection paper as they are very important in veterinary practice and should be considered in decision making for the right medicine.	
224	6	Comment: An indication on the extend of off-label use is provided in the publication 'Veterinary pharmacovigilance in Europe: a survey of veterinary practitioners by De Briyne N, Gopal R, Diesel G, Iatridou D and O Rourke DI'. '*Of the 2975 veterinarians who provided information on off-label use, 45 per cent replied that between 1 per cent and 10 per cent of their prescriptions were off-label, 25 per cent reported more than 10 per cent, and 30 per cent less than 1 per cent. Between the types of practice, off-label use was seen mostly in equine practice and the least in mixed practice. Large variations were observed between the different countries, with off-label use most frequently reported in the UK and the least in Croatia.*' Proposal Insert this reference in this reflection paper	Thank you for this reference. The proposed text has been included but abbreviated as the survey was not specific to antimicrobial prescribing: In a web-based survey conducted by the FVE and EMA to explore the reporting of adverse events (De Briyne 2017), of the 2975 self-selected veterinarians who provided information on off-label use, 25 per cent reported that more than 10 per cent of their prescriptions related to off-label use, although this related to all types of veterinary medicines, not just to antimicrobials. Between the types of practice, off-label use in this survey was seen mostly in equine practice and the least in mixed practice and large variations were observed between the different countries.
230	1	What evidence is there that off label use carries additional risks of AMR Remove or support claim	Not accepted. It is clearly stated in the document that owing to the limited data on off-label use, it is only possible to speculate

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			about the risks based on general principles and that off-label use 'might' be associated with additional risk.
237	1	Presumption that under-dosing increases AMR Provide evidence	This is not a presumption. Under-dosing can lead to sub-therapeutic concentrations thereby selecting for AMR and has been described e.g. by Gulberg et al: PLoS Pathog. 2011 Jul; 7(7)
247	6	Proposed change (if any): …exceed the microbiological ADI **value.**	Not accepted. The term ADI is general used without the suffix "value".
248-250	6	Comment: With regard to adverse events, the survey on veterinary pharmacovigilance in Europe (De Briyne et al., 2017) indicates that adverse events following off-label use were said to be observed less frequently (14 per cent) than with recommended use of medicines (37 per cent). Although this survey was referring to off-label use of veterinary medicinal products, it may provide also an indication about the extent of adverse events observed after off-label use of antibiotics. Proposed change (if any): Include in this reflection paper reference the publication on pharmacovigilance reporting in Europe with adverse events seen less frequently in off-label use than with normal use (De Briyne et al., 2017).	Although the survey is not specifically focussed on antimicrobials it is agreed to include the reference and to mention general aspects of this publication in the chapter of data collection on OLU. It is not agreed to include specific information on observed frequency of adverse events because the data basis of the survey is not sufficient to draw firm conclusions in this respect.
254-255	6	Comment: Proposed change (if any):	Partly accepted. The scope of this RP is on antimicrobials.

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		Clinical practice is a dynamic environment, where far from all **clinical** indications are covered by authorised ~~**antimicrobial**~~ medicines.	The unmet medical need is expressed by "… not all bacterial indications are covered by …"
260	6	Comment: Proposed change (if any): … accompanied by **identification of infecting organisms and** antimicrobial susceptibility testing,…	Accepted with slight amendment: … accompanied by isolation of the causative pathogen(s) and antimicrobial susceptibility …
263-264	3	Comment: Could be the place to include captive wild species in that list Proposed change (if any):	Accepted. Information included.
264	6	Comment: Proposed change (if any): … such as rabbits, **turkeys,** game and minor…	Not accepted. The AMEG report does not explicitly list "turkeys" as example of minor species. Turkeys are mentioned as minor species elsewhere in the document (line 760).
267	6	Comment: Proposed change (if any): … by differences in species **and age categories** pharmacokinetics…	Not accepted. The focus in this sentence is on the limitations of extrapolating PK data from major species to minor species rather than between age categories.
296-298 &	6	Comment: It is unclear with many of the examples presented in the annex whether	Comment noted. No changes necessary.

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annex		they are anecdotal or common practice (e.g. line 736-737). The annex show the great need for more availability of more authorised VMPs and the existence of outdated information on SPC.	In the annex it is mentioned that off-label antimicrobial treatments are thought to be relatively uncommon in modern poultry production. Lines 736-737 are clearly related to anecdotal practice.
299	6	Comment: Proposed change (if any): … glycopeptides (vancomycin), **oxazolidinones (**linezolid**)**, …	Accepted.
307	1	Carbopenems & Glycopeptides n/a for food producing animals in EU (can be used off label in companion /non food animals Clarify this point otherwise it is superfluous	No further clarification necessary as the concern is already explained in the preceding sentences.
314-330	6	Comment: FVE agrees that systematic (on-label or off-label) preventive use of antimicrobials in groups of animals is not any more considered an acceptable practice. FVE has been promoting best practices, such as biosecurity, proper hygiene and husbandry, good nutrition, holistic health plans through regular veterinary visits and prevention from disease through proper vaccination programmes, etc. FVE is pleased to see that these recommendations have been taken into consideration and included in the proposal for a new European regulation on veterinary medicinal products. Proposed change (if any):	Comment noted.
320-321	6	Comment:	Accepted.

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		Proposed change (if any): … improving **biosecurity,** hygiene and nutrition, minimizing transport and **increasing availability and** use of vaccination…	
332-334	6	Comment: Proposed change (if any): … Persoons et al., 333 2012; Timmerman et al., 2006 **; De Briyne et al.,2013**).	Not accepted. In the reference **of De Briyne et al., 2013** reasons for oral group medications are not reported.
340	6	Comment: Proposed change (if any): … In ~~**broilers**~~ **chickens**, dysbacteriosis …	Accepted with slight amendment, the reference relates to broilers, only: In chickens (broilers), dysbacteriosis …
352	3	Comment: Other alternative routes could be in situ slow release device of antibiotics such as PMMA beads (e.g with gentamycin) used in osteomyelitis or bumble foot treatments.	Comment noted. The list in line 352 is not exhaustive and provides only some examples.
368-370	6	Comment: Proposed change (if any): … differences in distribution of **low, moderate and high** lipophilic and **polar (**hydrophilic**) physicochemical properties of** antimicrobials and differences in metabolism and elimination (Baggot and Giguère, 2013). These variations can make the prediction of dose and dosage …	Acknowledged. The proposed change is in line with the text of the reference. It is not included as the left out information is not considered essential and the sentence would lose readability.
373 &/or 466	3	Comment: Regarding patient characteristics and evidence-based uses of VMPs,	General information on unmet medical need in zoo/wild animals has been taken up

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		pharmacokinetics published studies of antibiotic drugs in wild species should be listed as essential resources to avoid mis-use of these VMPs.	including the recommendation to share knowledge through professional bodies (section 5.1). Listing of references on PK studies in wild species would be beyond the scope of this paper.
388	6	Comment: Proposed change (if any): … colistin, **sulphate,** amoxicillin and…	Not accepted. The suffix "sulphate" is not necessary.
392	1	Combinations often needed where complex and multiple infections occur eg swine dysentery + salmonellosis in growing pigs. Complex respiratory diseases Remove 'limited' ref and replace with occasional	Not accepted. Several authorised products for treatment of swine respiratory disease (comprising multiple target bacteria including Mycoplasma spp.) are on the market. Although concomitant infections caused by Brachyspira and Salmonella do occur, the occurrence is variable in different European countries. To clarify that use of combinations may justified after a proper diagnosis the paragraph has been revised: "Without proper diagnosis including culture and AST circumstances where the use of combinations may be justified are limited

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			(e.g. in an emergency situation with known risk factors)"
392-395	6	Comment: The veterinarian has been trained to follow science based information and has an ethical obligation and responsibility on how to use each veterinary medicinal product in the interest of animal health, animal welfare and public health. It is wrong that the use of two or more antimicrobials in combination is considered as off-label use. Additionally, the existing combination products are not available throughout the EU. Therefore lines 392-393 is misleading and should be deleted. Proposed change (if any): ~~**Circumstances where the use of combinations (beyond authorised 'fixed combination' products) may be justified are limited.**~~ **The use of antimicrobials in combination should be justified by science-based evidence.** Except in an emergency situation with known risk factors, use of combinations should be based on culture and susceptibility testing.	Not accepted. The concern "*It is wrong that the use of two or more antimicrobials in combination is considered as off-label use"* is respected in the paragraph above, where it is stated: "Treatment with two or more different antimicrobials administered concomitantly may not be clearly regarded as off-label use …" To clarify that use of combinations may justified after a proper diagnosis the paragraph has been revised: "Without proper diagnosis including culture and AST circumstances where the use of combinations may be justified are limited (e.g. in an emergency situation with known risk factors)"
396-410	6	Comment: Practical reasons, such as package sizes, strength, convenience of application, are correctly acknowledged in this reflection paper as they are very important in veterinary practice and should be considered in decision making for the right veterinary medicine.	Accepted. Lines 401-403 amended: "A European survey investigating the

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		It should be highlighted that lines 401-403 may be misleading as the provided reference which indicates that "costs, treatment frequency and shorter withdrawal periods were important considerations" is not referring to preference of off-label use of products, rather indicates the selection among authorised products. Reference provided in lines 403-406 shows the importance of the off-label use in practice. The veterinarian should maintain the flexibility to use any available option and make responsible, science and evidence-based decisions on a case by case basis. For example, (i) veterinarians visiting remote areas must be able to treat the animals under their care using the available on spot tools, according to their training and professional knowledge, ethics and liability or (ii) veterinarians must be able to select the appropriate package/product for the animal species/ age category/size of the animal under their care.	general antimicrobial prescribing behaviour …". Comment noted.
409-410	6	Proposed change (if any): Although treatment compliance is an important consideration when prescribing antimicrobials, practical or economic reasons ~~**alone**~~ cannot be seen as **un**acceptable justification for off-label use.	Not accepted. The proposal changes the message of the sentence to a different direction without proper justification.
416	6	Proposed change (if any): … Pharmacokinetic **parameters** variability. …	Not accepted. In the context of dose optimisation "pharmacokinetic variability" relates not only to parameters but also to differences in

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			pharmacokinetics of species/subspecies.
416-418	5	Comment: providing the species to be treated, and the dose rate and duration remain unchanged, treatment of an infection which is not included on the SPC should not incur an increased withdrawal period. Proposed change (if any): If the dosing regimen remains unchanged, no change to the withdrawal period is required provided the indicated species is to be treated.	Not accepted. The concern is sufficiently addressed as the sentence implies that " … changing the dosing regimen may impact on the withdrawal period …"
420	6	Proposed change (if any): …the margin of safety **which is wide**.	Not accepted. "..where there are limited concerns regarding the margin of safety" suggests that the margin is wide.
434	1	Poor science to quote speculation without supportive evidence Remove reference	Accepted.
437-438	5	Dosing should be based on animal bodyweight in order to account for variations in food/water intake relative to bodyweight which can lead to under or over-dosing	Comment noted.
440-453	1	Erratic dosing is a feature of all mass treatment -depends on water/feed intake so risks errors. How accurately are farm animals dosed by individual injection? Weight usually guessed Weighing in the field (often literally) is impossible (human dosing is even more erratic with a single dose applied for all	Not accepted. No rewriting necessary. Acknowledged that "*erratic dosing is a feature of all mass treatment*". This section gives examples for under- or over-dosing of antimicrobials and points to the fact that

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		adults (LW 40-150kg) Rewrite this section	incorrect dosing is commonly caused unintentionally. Compared to other pharmaceuticals under-dosing of antimicrobials carries the risk of AMR for public health which needs to be considered in the context of this paper.
449-453	5	Comment: Where the dosing regimen remains unchanged, and the species is indicated on the SPC, the existing withdrawal periods should be observed. Proposed change (if any): as above.	Not accepted. The concern is sufficiently addressed as the sentence implies that " … changing the dosing regimen may impact on the withdrawal period …"
474	6	Comment: Proposed change (if any): … antimicrobial resistance **giving an epidemiological feature of the veterinarian activity region**.	No change necessary. "Well researched treatment guidelines have a role to assist veterinarians, if they take into account modern research findings (e.g. systematic reviews) as well as results of national or regional surveillance of antimicrobial resistance" implies that the epidemiological situation and prescribing behaviour of veterinarians is considered.
491	6	Comment: Proposed change (if any): … target species **or age categories** for an…	No change necessary. The section reflections and conclusions is high level.
501	6	Comment:	Not accepted.

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		Proposed change (if any): …pharmacokinetics **profile** and application…	The more general term pharmacokinetics is preferred here.
506	6	Comment: Proposed change (if any): … exchange of **Multi Drug Resistance (**MDR**)** organisms.	Accepted.
507	1	Heavy reliance on sens testing which is very old out of date technology, can give misleading or incorrect results, is slow and impractical (many bacterial pathogens are difficult to grow). MICs slow and expensive Call for better pen side diagnostic tests	Not accepted. Acknowledged. As long as pen side test are not established for veterinary medicine bacterial culture/AST is still the only diagnostic method available.
507-513	5	Peer-reviewed journals should apply normal editorial judgements for acceptance of manuscripts: publication of studies where off-label use is involved should not be censured. Such sources are invaluable in the decision making process for practitioners facing a lack of approved products and/or indications.	Comment noted. The intention outlined in the reflections/conclusions is not to censure peer reviewed articles but to raise awareness in editors and promote responsible off-label use of antimicrobials.
510-513	2	Comment: The potential market is often seen as being too small for pharmaceutical companies to spend a lot of money developing a claim, especially if it is a generic compound. Usually, the claim or indication is an extension of use to an existing product, which may even be approved in the same species, so the dose, duration of use, species safety and withdrawal period have already been established. The risks of doing any harm to the animal or of unusual residues in the meat are minimal. Even when a different dose or a new species of animal is involved the	Not accepted. The concerns raised by RUMA are acknowledged. The paper aims to give a balanced view of both responsible OLU and other practices that could lead to unjustified AMR risk.

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		withdrawal period is extended to protect the consumer. The alternative is disease and often damage to the health and welfare of the animal(s) that are being treated. RUMA feels the comments addressed to editors in this section are over-prescriptive and could unnecessarily restrict future veterinary medical developments and advancements. It is important to publish data on the use of compounds off-label, often for disease eradication purposes or on newly discovered infections to increase awareness and help. This can then lead to open debate and discussion and help the pharmaceutical industry to consider new indications and try to develop compounds, if the market is significant enough e.g. blackhead in turkeys, intestinal spirochaetosis in layers (Burch et al, 2006). Proposed change (if any): Delete "*Given that peer-reviewed scientific literature or veterinary conferences can be quoted as evidence for some off-label practices, editors could be encouraged to carefully consider the concepts of appropriate and inappropriate off-label antimicrobial uses in their journal scientific policy for the acceptance of manuscripts*" in lines 510-513.	Deletion not accepted. The key message of the recommendation to editors is to raise their awareness to promote a responsible off-label use of antimicrobials.
514-518	6	Comment: See comment above (lines 37-38 and lines 314 – 330). Proposed change (if any): These include **~~use of antimicrobials for practical or economic~~**	Partly accepted - see comment above. Sentence changed to: These include use of antimicrobials for practical or economic reasons alone, systematic preventive use in

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		~~reasons,~~ ~~systematic~~ preventive use in groups of animals, **~~unintentional~~** under- or over-dosing and concomitant use of two or more antimicrobials without proper diagnosis **and scientific evidence**.	groups of animals, ~~un~~ intentional under~~- or over-~~dosing and concomitant use of two or more antimicrobials without proper diagnosis.
520-874	6	Comment: Many of the examples presented in the Annex of the document do not demonstrate that off-label was against best-practice. On the contrary it may be an important indication of lack of necessary products or outdated information on SPC With regard to adverse events, the survey on veterinary pharmacovigilance in Europe (De Briyne et al., 2017) indicates that adverse events following off-label use were said to be observed less frequently (14 per cent) than with recommended use of medicines (37 per cent). Although this survey was referring to off-label use of veterinary medicinal products, it may provide also an indication about the extent of adverse events observed after off-label use of antibiotics.	See comment above. The reference De Briyne et al., 2017 is included and general aspects of this publication are mention in the chapter of data collection on OLU. Information on observed frequency of adverse events after OLU of antimicrobials is not included because the data basis of the survey is not sufficient to draw firm conclusions in this respect.
591	1	Ref treatments at birth in pigs This has a major lasting damaging effect on microbiome development and should NEVER be done beyond immediate clinical problem period (long term prophylaxis)	Comment noted.
601	1	Good point – the attitude should be medicate the animals (by weight) through the feed or water rather than medicate the feed or the water	Thank you for your comment.
621	1	Medicating wet fed pigs is challenging and if biofilms occur AMR reservoirs can develop. Action to remove biofilms is part of good management in wet fed systems.	Comment noted.

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644-662	7	**Unmet Medical Need**. BEVA supports the concept that preventive treatment with AMs, and with off-label use of AM's in particular, should be properly and carefully justified. Peri-operative use of AMs by equine practitioners is singled out in this section of the document. BEVA believes that equine use of AM's in this way has decreased significantly in the last five years and continues to decrease following guidance from BEVA and as practitioners, especially opinion leaders in referral hospitals, translate evidence-based principles from human and small animal surgical practice. In the absence of data is not possible quantify the scale of off-label AM use peri-operatively in equine practice, or to confirm that use is decreasing. However, the quantities used in this way are likely to represent a small proportion of the total AM use in equine practice. **Proposed change:** Add new line after line 662: **There are some indications that in the UK the peri-operative use of AMs by equine practitioners has decreased significantly since guidance was issued following the *Hughes et al* study.**	Not accepted. The proposed change cannot be accepted unless substantiated a reference/data.
757	5	Comment: The UK poultry industries now require that these products are not used in the breeding supply chain. Proposed change (if any): Add wording as above.	Not accepted. Not clear to what is referred to by " add wording as above". It is sufficient to note that use of 3rd and 4th gen cephalosporins in poultry is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			contraindicated in the EU as a result of the referral, rather than including measures taken in individual MSs.
761	5	Comment: where off-label use involves the indicated species, and the approved posology is used, there is no requirement to amend the withdrawal period. This advice is in compliance with EC Directive 2001/82/EC, Article 11(2). Proposed change (if any): as above	No changes necessary. There is no general requirement to amend the withdrawal period. This is considered in chapter alternative dosing regimen (5.7) "… changing the dosing regimen may impact on the withdrawal period …"
763-765	5	Comment: Although not specifically indicated for treatment of *Brachyspira pilosicoli* in laying hens, tiamulin is approved for use in laying birds, and has a zero egg withdrawal period and may be used to treat *B. pilosicoli* infection provided the approved posology is not altered. Proposed change (if any): as above.	No changes necessary. Information in lines 763 -765 is correct. Tiamulin is not authorised for treatment of *Brachyspira pilosicoli* in laying hens.
784-786	6	Comment: A comprehensive gap analysis on lack of availability of VMPs and vaccines has been done by the FishMedPlus Coalition. See http://www.fve.org/uploads/publications/docs/fishmed_plus_gap_analysis_outcome_final.pdf Proposal: 'there is a lack of authorised medicines for the variety of diseases seen in the minor and newer species to aquaculture (Alderman and Hastings,	Partly accepted. Reference added. First part of the proposal included.

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		1998, **FishMedPlus 2017**). Cited examples include bacterial infections **e.g. with Aeromonas in all species, Flavobacterium infection in trout and carp,** hatchery infections in seabass and streptococcal infections in sturgeon and tilapia (FVE, 2017, **FishMedPlus, 2017**). **Also it is important to recognise while parasite infections are a main cause of concern in all the fish species examined, secondary bacterial infection often occur between parasitic and bacterial diseases. To prevent bacterial diseases occurring (and the need to treat with antibiotics) it is necessary to be able to effectively treat parasitic infection and to increase the availability of authorised VMPs.** ’	It is acknowledged that there is concern on the availability of antiparasitics in fish but this is out of scope of this paper.
798	3	Comment: Use of Antimicrobial drugs in exhibit aquarium could be also included here, with the usual recommendations of 1. Limited and focal use (always first consider changes in husbandry and environmental issues that are mostly the source of bacterial infection); 2. activated carbon use before releasing waste water	Not accepted. Not included as these recommendations are not directly related to OLU rather than to good veterinary practice and responsible use principles.
875	3	Comment: Would be great to end with 1.7 Wild captive animals this would include zoo, circus and also non-domestic lab animals (e.g. non-human primates)	Thank you for your comment. The main scope of this RP encompasses companion animals and food-producing animals.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
References	3	Comment: Reference of wild species concerns could be added. Examples below : Proposed change (if any): Could be added: Pereira N, David H, Albuquerque T, Balyna N (2017). Antimicrobial bacterial resistance in public aquaria: should we be concerned? Preliminary report concerning six years of bacterial cultures and resistance to antimicrobials in fish, sea birds and amphibians. Proc Zoo Wildlife Health conf 2017. Berlin. P10. Lodwick, L.J., Dubach, J.M., Phillips, L.G., Brown, C.S. and Jandreski, M.A. 1994. Pharmacokinetics of amikacin in African elephants (Loxodonta africana).]Zoo Wildl Med 25(3):367-375 Melissa R. Nau, James W. Carpenter, Butch KuKanich, and Matt Warner (2017) Pharmacokinetics of a single dose of oral and subcutaneous enrofloxacin in caribbean flamingos (Phoenicopterus ruber ruber).).] Zoo Wildl Med, 48(1), 72-79	Thank you for your comment and the references provided. General information on unmet medical need in zoo/wild animals has been included as well as the recommendation to share knowledge through professional bodies. Listing of references on PK studies in wild species and on occurrence of resistance in fish, sea birds and amphibians would be beyond the scope of this paper.