15 January 2015
EMA/CVMP/89283/2014
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Reflection paper on the risk of antimicrobial resistance transfer from companion animals' (EMA/CVMP/AWP/401740/2013)

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

Stakeholder no.	Name of organisation or individual
1	European Centre for Disease Prevention and Control (ECDC)
2	Joint comments by the Federation of Veterinarians on Europe (FVE), Federation of European Companion Animal Veterinary Associations (FECAVA) Union of European Veterinary practitioners (UEVP)
3	Swissmedic, Swiss Agency for Therapeutic Products
4	British Small Animal Veterinary Association (BSAVA)
5	IFAH-Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The following reference is important, is currently not cited and should be taken into account in the Reflection Paper. Thank you. Pet animals and foreign travel are risk factors for colonisation with extended-spectrum β-lactamase-producing Escherichia coli. Meyer E, Gastmeier P, Kola A, Schwab F. Infection. 2012 Dec;40(6):685-7. doi: 10.1007/s15010-012-0324-8. Epub 2012 Sep 13. Abstract OBJECTIVE: The purpose of this study was to determine the prevalence of extended-spectrum β-lactamase (ESBL) and vancomycin-resistant enterococci (VRE) colonisation among healthy infection control personnel and to determine risk factors for ESBL or VRE colonisation within this group. METHODS: Participants were recruited at an infection control symposium in 2011. Volunteers were asked to perform a rectal swab and to fill in questionnaires on risk factors of ESBL or VRE carriage (report on diet, contact with domestic or production animals, travel, hospital stay and antibiotic use all within the last 12 months). Rectal swabs were inoculated onto ESBL and VRE chromogenic agar; species identification and susceptibility testing was done by using a VITEK 2 system. In the multivariable analysis, a logistic regression with stepwise forward variable selection was performed. RESULTS: Two hundred and thirty people participated in the study, i.e. 36 % of the symposium attendees (231/639). No VRE faecium or faecalis were isolated, whereas ESBL were isolated from 8 out of 231 individuals, i.e. 3.5 % (95 % confidence interval 1.5-6.7). In the	Accepted. Line 443 sentence and reference were introduced.

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	multivariable analysis, travel to Greece or Africa and contact with pets were independently associated with ESBL positivity. The odds ratios were as follows: travel to Greece 15.2, travel to Africa 14.8 and for having a pet animal 6.7. CONCLUSION: This is the first report showing that contact with pets increases by almost seven-fold the chance to be colonised with ESBL Escherichia coli. A colonisation rate of 3.5 % with ESBL-producing enterobacteriaceae among infection control personnel is of concern and reflects probably less an occupational health risk but the reservoir of and the expansion into the community, especially in persons with pet animals and travel history to high-endemicity countries.	
2	FECAVA, FVE and UEVP welcome the efforts of EMA, CVMP, to prepare a reflection paper on this important topic. Companion animals are often part of the family and due to this close contact with humans special attention needs to be paid to prevent the risk of transfer of resistance between animals and humans. Another aspect is that companion animals might also be in contact with farm animals e.g. farm dogs. Callisto, an EU funded research project which FVE coordinate's, also investigates this topic. CALLISTO's mission is to provide an overview of the current situation with regard to the role of companion animals, as a source of infectious diseases for people and food animals, to identify knowledge and technology gaps for the most important zoonoses and propose targeted actions to reduce the risk of zoonotic diseases transferred via companion animals. More info can be found on www.callistoproject.eu In the text it is unclear what is meant by the term 'companion	This comment is addressed at Line 89 - In this document

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	animals'; is it only dogs and cats or also horses, or also reptiles or other exotic animals kept as companion animals. FVE believes this last group, some of which derived from the wild, need special attention. We propose to insert the following definition (agreed by Callisto) 'Companion animals are any domesticated, domestic-bred or wild-caught animals, permanently living in a community or kept by people for company, enjoyment, work (e.g. dogs supporting blind people) or for psychological support, including – but not limited too – dogs, cats, rabbits, guinea pigs, ferrets, reptiles, birds and ornamental fish. '	the term companion animals apply primarily to dogs, cats, and horses not intended for human consumption. From a regulatory point-of-view, horses are classified as a food-producing species and data requirements of products for horses are covered by GL27. Horses are included herewith because they are commonly kept in close contact with people.
	Proposed action 1 The abbreviated risk assessment guidelines mentioned as CVMP action 1 is difficult to assess in the absence of further information. Codex (Codex Alimentarius, 2011) and VICH GL27 (EMEA, 2004) needs to be studied to determine how they could be usefully applied to small animal products. (see line 51)	As noted in recommendation 1, other guidance already available should be taken into consideration. The CVMP is currently working on a risk assessment guideline for food-producing species. Once this is completed, guidance for companion animals will then be addressed more specifically based on the experience gained.
	Proposed action 3 to record cascade use: The veterinary profession is principally in favour of the recording of all antimicrobials used for animals. Nevertheless, the practical challenges and also the financial aspects should be considered; who will pay to develop the system and for the data input and analysis?	The cost implications are acknowledged. Systems are currently being investigated in several member states. It is recognised that the costs would probably ultimately be borne by the veterinary profession and companion animal owners.
	Proposed action 4' to extend AMR surveillance programmes to include organisms of public health significance isolated from companion animals: This is a worthy proposal for an action but might be challenging in practice especially if samples want to include a normal population of companion animals (not only those seen at veterinary practices). It	This is just a recommendation. The development of such surveillance would be complex and is outside the scope of this document.

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	would be interesting to see some further reflections on how to practically organise and finance this. (see line 85) Line 88 – Knowledge gaps The paper rightly identifies several knowledge gaps in this area. It would be good to have EU funding available to gain more knowledge on these. It would be good in the reflection paper to make more distinction between topical treatment and systemic treatment (eg line 415).	We do agree. Yet susceptibility testing does not categorize bacteria based on topical vs systemic use of antimicrobials.
3	Thank you for the opportunity to comment on a subject of increasingly high importance. The draft is very-well written and describes the major bacterial zoonotic organisms which have acquired antibiotic resistance and may thus cause a serious threat to human health.	Thank you for this comment.
4	The aim of the document is stated as “to discuss the possible need for data in applications for new veterinary medicinal products for companion animals”, although the paper is restricted to discussion of antimicrobial resistance. The paper provides a good overview of the literature regarding organisms which may be transmitted between companion animals and man with emphasis on methicillin-resistant Staphylococcus aureus, methicillin-34 resistant Staphylococcus pseudintermedius, vancomycin-resistant enterococci, extended-spectrum 35 beta-lactamase producing Enterobacteriaceae and carbapenem-resistant Gram-negative bacteria. While this makes sense in terms of	Thank you for this comment. Thank you for this comment. We do agree that antimicrobial resistance may be transferred by bacteria dissemination, and also genes and genetic material. Data existing on the latter is available on this reflection paper.

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	reviewing the literature in terms of considering the risks of antimicrobial resistance it may be more appropriate to consider the transfer of genes and genetic material.	
	The paper does not really discuss the risk of antibacterial resistance developing in and being transferred from companion animals to humans but rather discusses the possibility. While we acknowledge that this is an important subject it would be helpful to put these discussions in the context of discussing risks from other sources including other humans, foods and the environment. Contamination of food in particular has the potential to disseminate resistant bacteria much more widely than companion animals. The paper states that "A unique and critical aspect related to antimicrobial resistance in companion animals is their close contact with humans." While we acknowledge that some companion animals may have significant contact with humans others, especially some cats, may not. It is also important to realise that this contact is not unique and dairy cows in particular will have close contact with humans.	Thank you for this comment. We do agree that humans, foods and the environment are risks but this reflection paper focus on companion animals rather than on the previous.
	Throughout the paper the emphasis is on the transmission of resistant bacteria from companion animals to humans, with the exception of the reference to MRSA (line 241). We think that it is important to acknowledge that the interaction of microorganisms, hosts, antimicrobials and the environment is highly complex and that antibacterial resistance is a “One Health” issue therefore the transfer of resistant bacteria (or their genes) between companion animals and humans in both directions should be considered. It is important be aware that in some cases pets may be acquiring the infection from humans.	Thank you for this comment. This reflection paper focus on companion animals as a reservoir for humans rather than the opposite but transmission on both directions is assumed to be possible.

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	While acknowledging the importance of responsible use of antibacterials it is important to ensure that veterinary surgeons have access to a range of effective products licensed for the conditions that they treat in order to protect both animal welfare and public health.	Thank you for this comment.
	The BSAVA acknowledges the importance of surveillance in monitoring the development of resistant organisms and will be supporting this through its funding of the Small Animal Veterinary Surveillance Network (SAVSNET http://www.savsnet.co.uk/).	Thank you for this comment.
5	IFAH-Europe welcomes the opportunity to comment on this Reflection Paper. The document provides a good review of the current situation with regards to multidrug resistant (MDR) organisms in companion animals in Europe. However, apart from methicillin-resistant Staphlococcus pseudintermedius in dogs and cats and MRSA ST398 in equines, based on the references cited it could be seen as a review of the outcome of numerous occasions of spill-over of human-associated (MDR) pathogens into the companion animal reservoir. There is evidence of a shared microbiome between pet owners and their pets (though, surprisingly, this is not discussed in much detail and should be expanded as this is critical to the future development of the situation in the companion animal reservoir for existing and future human MDR pathogens and genes): bidirectional transfer of resistant bacteria is also possible, realistic and a challenge that companion animal vets and owners are going to increasingly face in the future. Indeed, one could speculate that the future medical challenge in companion animal medicine is going to be much harder than that in livestock medicine because of this shared microbiome. There should	Thank you for this comment.

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	be acknowledgement that the likelihood of transfer in either direction is not well-established and there are many data gaps. We agree that new compounds will be needed to treat infections in companion animals in the future; this will include infections with MDR bacteria of human origin, which pose some challenging dilemmas. Neither of these points receives the focus they merit. The recommendations regarding risk assessment of potential spread of resistant organisms are extremely vague, and at present not encouraging investment in new compounds for veterinary medicine, with the risk that antibiotics authorised only for human use may find their way into veterinary medicine, which is highly undesirable. Indeed a number of countries / ideas circulating around Europe are proposing a restriction of the existing cascade to ban use of certain vital human antibiotics in animals: one is not sure how spill over infections of MDR human infections in animals will be treated in the future – the CVMP needs to cut this 'Gordian knot' and propose a way forward as the alternative of euthanasia of diseased or colonised (i.e. asymptomatic, but a risk for human health) companion animals is unlikely to be accepted by society as a whole. One point which has come up in various papers by the CVMP is the potential for the future use of any new veterinary compound or class in human medicine: would this also be part of the risk assessment? Given the fact that pathogens might be shared, this is a particular challenge. In view of the above, we believe that more reflection is needed on a realistic path forward, with due attention to risk mitigation options including hygiene at household levels when dealing with and treating companion animal infectious diseases. The latter should be a component of responsible use as well.	The CVMP is currently working on a risk assessment guideline for food-producing species. Once this is completed, guidance for companion animals will then be addressed more specifically based on the experience gained. Current EU legislation does not allow exclusion of the use of certain human-only antibiotics in animals, although this option has come forward in the proposals for the new legislation. Any decisions in this respect would require close collaboration between the human and veterinary sectors in order to characterise the risks to both human and animal health, and it is recognised that societal factors would also be a consideration.

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	The text also rightfully mentions the importance of hygiene and infection control in veterinary clinical settings, but fails to make that recommendation. It is clear that an integrated, one health approach will be required. As with many other documents of this type, clarifying what is meant / covered by 'antibiotics critical for use in human health' would be helpful. Does this mean the current WHO list? Or is the CVMP looking at creating its own list as hinted at in the recent questions of the European Commission to DG Sanco An alternative human CIA list has also recently been published in France which appears to have merits – see: http://ansm.sante.fr/var/ansm_site/storage/original/application/f26feefbd544911eb24fe45324c361b5.pdf The Canadian list is also useful http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr_ram_hum-med_intro-eng.php	The need for a "One Health" and otherwise holistic approach to controlling AMR is now addressed further in the recommendations, although further discussion of some of these aspects is not within scope of this paper. Indication is given in lines 161 – 163.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 104, 123, 251, and throughout the manuscript	1	**Comments**: In human medicine, the abbreviation "MRSP" is commonly used for "macrolide-resistant *Streptococcus pneumoniae*" **Proposed change**: It would be better to use another abbreviation. Please correct.	In veterinary medicine *S. pneumoniae* is not a companion animal pathogen. So in this context the abbreviation may not lead to confusion. Additionally, MRSP is the abbreviation for meticillin-resistant S. *pseudintermedius*.
138	1	**Comments**: When did the CVMP mandate the SAGAM to draft this reflection paper? **Proposed change**: Please mention the date of the mandate.	CVMP mandated SAGAIM in January 2011. The date is mentioned.
181	1	**Comments**: It would be interesting if the reason that horses need combination therapy was included in this statement. Is for the purposes of resistance? Is there more resistance in horses that you are trying to make sure is covered? Is it just common practice? **Proposed change**: Please include a reason why	Accepted. Changes were introduced in Line 181 used in "empiric antimicrobial therapy".
216-217	1	**Comments**: MRSA is one of the most significant [what do you mean by "significant"? frequent?] bacteria causing hospital-acquired [in 2014, it is better to say "healthcare-associated infections"]. However, at least in Europe, MRSA is not one of the most significant [what do you mean by "significant"?	Accepted.

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		frequent?] bacteria causing community-acquired infections in humans (e.g. see: http://www.eurosurveillance.org/images/dynamic/EE/V15N41/art19688.pdf) **Proposed change**: Please re-formulate.	
224	1	**Comment**: I suppose that this sentence applies to both food-producing and companion animals, but this reflection paper addresses companion animals **Proposed change**: "…a variety of conditions in companion animals…"	Accepted.
229-240	1	**Comments**: somewhat confusing as to which ST you are referring. Previously you had mentioned hospital-acquired strains (l. 229), but you don't clarify further down that you are still only talk about such strains. **Proposed change**: please elaborate more and describe.	Partly accepted. Line 227- sentence was moved in order to avoid confusion.
241-250	1	**Comment**: " in the veterinary context transmission of MRSA….. human-to-animal". What do you mean by the veterinary context? Do you mean that the this is the opinion of the veterinarians? I also feel the lack of description of what ST398 really is as well as the lack of mention of LA-MRSA in this context. **Proposed change**: please elaborate and create a	Partly accepted. In companion animals the MRSA strains are evolutionary related to different typical human-associated MRSA clones (except for horses). We do not feel ST398 and LA-MRSA is relevant in this context.

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		separate paragraph on ST398 (please see Witte et al. EID. 2007. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725865/).	
284-291	1	**Comment**: Slightly confusing paragraph: you mention that colonisation among veterinarians is rare, but then you mention a 4% carriage rate (colonisation that is) in dermatologists (still veterinarian dermatologist however) and then you mention again that MRSP colonization of humans (I assume here you mean non veterinarian humans?? Are they owners? Random people?) **Proposed change**: please re-formulate and make sure you give a clear description of what you are mentioning. Also please keep in mind that usually colonisation can lead to infection	Partly accepted. Line 294- changed to “they are generally considered to be harmless commensals but are capable…”
294-296	1	**Comment**: What do you mean by “They are generally considered to be of a relatively low virulence but are capable of causing a wide range but are capable of causing a wide of infections including sepsis”? Do you mean that they are opportunistic commensals? I’d suggest that you check a text book or the EARS-Net report for a short description. **Proposed change**: Please re-formulate.	Accepted. The sentence was reformulated accordingly.
350	1	**Comment**: Was this the first time from any animal	Not accepted. This is implied in the subsequent test that is

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		(food-producing, companion, etc.), or only from companion animals? Probably the latter. **Proposed change**: If the above is correct, then "…of companion animal origin" (NOT "… of animal origin").	from companion animals. Additionally, it was the first description in animals (food-producing and companion).
329-331	1	**Comment**: you state that ESBL producing bacteria in veterinary patients is limited. I am not quite sure what "limited" means. Please see some surveillance stats: http://www.ncbi.nlm.nih.gov/pubmed/23177909 perhaps worth mentioning. **Proposed change**: please include some figures and whether these were infections or screening.	Partly accepted. Line 328. Limited was deleted and "there are few reports…" was introduced. Figures were not included because the aim of the reflection paper is not to be an extensive review.
335-362 (*Escherichia coli*)	1	**Comment**: See the recently published article: http://jac.oxfordjournals.org/content/early/2014/01/06/jac.dkt518.full.pdf+html on "Carbapenemase-producing bacteria in companion animals". This article cites two references on carbapenemase-producing *E. coli* in companion animals (Stolle et al. *J Antimicrob Chemother* 2013; Shaheen et al. *Antimicrob Agents Chemother* 2013), which must be analysed and reported in this paragraph. **Proposed change**: Carbapenemase-producing *E. coli* must be mentioned in this paragraph.	Accepted. New text and references were introduced.
380-381	1	**Comment**: Why is *E. coli* here?	*E. coli* was deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: delete the mention of *E. coli* in this sentence that should only address *K. pneumoniae*.	
Lines 46 and throughout (including line 215	1	**Comments**: Please spell out "meticillin-resistant *Staphylococcus aureus* (MRSA)" and then use "MRSA" throughout the document. Please note the spelling of "meticillin" as recommended by WHO (NOT "methicillin").	Corrected.
Line 48 and throughout	1	**Comment**: Please use "multidrug-resistant" instead of "multi-drug resistant" here, but also throughout the document	Corrections were made in lines 32, 48, 149, 208 and 457.
110-111	1	**Comment**: "*Campylobacter*", *Pseudomonas*" and "*Acinetobacter*", and "*Clostridium difficile*" must be in italics. **Proposed change**: Please correct.	Corrections were made.
167	1	**Comment**: Correction needed **Proposed change**: "beta-lactams" (NOT "beta lactams").	Correction was made.
169	1	**Comment**: Correction needed **Proposed change**: "First-generation" (NOT "First generation")	Correction was made.

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171	1	**Comment**: Correction needed **Proposed change**: “third-generation” (NOT “third generation”).	Correction was made.
184	1	**Comment**: Correction needed **Proposed change**: “third- and fourth-generation” (NOT “third and fourth generation”).	Corrections were made.
189	1	**Comment**: Correction needed **Proposed change**: “microbiological culture and antimicrobial susceptibility tests“ (NOT “culture and ASTs”)	Accepted.
190	1	**Comment**: Correction needed **Proposed change**: “Antimicrobial administration” (NOT “Antimicrobials administration”)	Correction was made.
194	1	**Comment**: Correction needed **Proposed change**: “university” (NOT “University”)	Correction was made.
218	1	**Comment**: Correction needed **Proposed change**: “causes” (NOT “cause”)	Correction was made.
220	1	**Comment**: Re-formulate	Correction was made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: “Since the first reported…”	
241	1	**Comment**: Re-formulate **Proposed change**: “from humans to animals” (NOT “human-to-animal”)	Correction was made.
255	1	**Comment**: Re-formulate **Proposed change**: “Methicillin resistance” OR “Resistance to methicillin” (NOT “The methicillin resistance”)	Correction was made.
279	1	**Comment**: “patients” could be interpreted by readers from human medicine as being human patients. Re-formulate **Proposed change**: “animal patients” (NOT “patients”)	Accepted.
294	1	**Comment**: Re-formulate **Proposed change**: “humans” (NOT “people”)	Accepted.
298-299	1	**Comment**: *vanA* and *vanB* are genes and should start with a small “v”. **Proposed change**: Please correct accordingly.	Corrections were made.
305	1	**Comment**: Re-formulate	Correction was made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "*vanA*-carrying VRE isolates" (NOT "*VanA*-type VRE")	
345	1	**Comment**: Typo **Proposed change**: "*Enterobacteriaceae*" (NOT "Enterobacteriacea")	Correction was made.
366	1	**Comment**: Re-formulate **Proposed change**: "in contact with animals" (NOT "contacted with animals")	Correction was made.
368	1	**Comment**: Re-formulate **Proposed change**: "… was responsible for some of these outbreaks." (NOT ""… has been described to be causative organism in some of these.")	Correction was made.
369	1	**Comment**: Re-formulate **Proposed change**: "between companion animals and…" (NOT "between animals and humans")	Correction was made.
422	1	**Comment**: Typo **Proposed change**: *A. baumannii*	Correction was made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(NOT "*A. baumanii*")	
490	1	**Comment**: unclear sentence: " … the use of antimicrobials in companion animals with the corresponding selection and potential spread…" **Proposed change**: please re-formulate	Accepted.
487	1	**Comment**: " emerge in the companion animals" **Proposed change**: please remove the "the"	Correction was made.
513 (Table 1)	1	**Comment**: Typo **Proposed changes**: "ESBL-producing" "*Enterobacteriaceae*" (NOT "Enterobacteria")	Corrections were made.
540-1047	1	**Comment**: The references as not cited in a consistent fashion (see, e.g., citation of the names of journals, use of capital letters in the titles of the cited articles, etc.) **Proposed change**: Please correct.	Corrections were made.
596-601	1	**Comment**: Double citation of this reference **Proposed change**: Please remove one citation occurrence in the reference list.	One citation was removed.

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828	1	**Comment**: Missing words “In E. Commission, editor” **Proposed change**: Please complete	Correction was made.
902-907	1	**Comment**: Double citation of this reference **Proposed change**: Please remove one citation occurrence in the reference list.	One citation was removed.
966-971	1	**Comment**: Double citation of this reference **Proposed change**: Please remove one citation occurrence in the reference list.	One citation was removed.
975-982	1	**Comment**: Double citation of this reference **Proposed change**: Please remove one citation occurrence in the reference list.	One citation was removed.
989	1	**Comment**: Typo **Proposed change**: *Emerging* (NOT “*Emergining*”)	Correction was made.
1022-1027	1	**Comment**: Double citation of this reference **Proposed change**: Please remove one citation occurrence in the reference list (and remove a/b after publication year).	One citation was removed.
29	2	**Comment**: The text says: ‘*Risk factors for colonisation*	By colonisation it is meant the presence of bacteria on a body

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		of companion animals with resistant bacteria.' It would be worth to clarify whether colonisation, i.e. persistence and proliferation, is meant or rather carriage. Same comment for line 141	surface (e.g. skin, intestine) without causing disease. Carriage in this sense is a synonymous. Colonization can be transient or persistent.
69-71	2	**Comment**: The text says '*In regards to prescribing, it is the responsibility of professional bodies, universities and veterinary practitioners to develop and apply responsible use guidelines.*' It would be worth noticing here that this point is already been taken up by the profession. FVE and FECAVA both already produced guidance notes on this issue. Eg FECAVA http://www.fecava.org/sites/default/files/files/FECAVA%20Advice%20on%20Responsible%20use%20of%20Antimicrobials.pdf http://www.fecava.org/sites/default/files/files/FECAVA%20Recommendations%20for%20Appropriate%20Antimicrobial%20Therapy.pdf FVE http://www.fve.org/veterinary/medicines.php#CA (in all EU languages)	Accepted. References were included.

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		An alternative location to mention this guidance would be line 187. **Proposed change**: include references in the reflection paper	
90	2	**Comment**: include food producing animals **Proposed change**: change sentence to: 1. Risk factors and transmission routes involved in the transfer of antimicrobial resistance between companion animals, food producing animals and humans and vice versa.	Correction was made.
154	2	**Comment**: Antibiotics in companion animals are mostly used therapeutically rather than for prophylactic purposes. Treatment is mostly individual via injection or tablets. In this aspect the use of antimicrobials in companion animals differs much from the use of antimicrobials in food producing animals. While it is correct that antimicrobial consumption data for companion animals is incomplete, it should be mentioned that the overall sales of antimicrobials for companion animals is only a fraction of the total amount of antimicrobials sold for animals (see ESVAC reports).	Partly accepted. Changes were introduced. Information on the ESVAC project was added.

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		It should also be noted that for some of the less common companion animals eg ornamental fish or reptiles, licensed antimicrobial are hardly available, therefore the cascade is the only option a veterinarian has to treat these animals.	
185-188	2	**Comment**: Frequency of ASTs Frequency of AST for companion animals can be seen in table 6 of the paper on 'Factors influencing antibiotic prescribing habits and use of sensitivity testing amongst veterinarians in Europe' from De Briyne N. (Veterinary Record, 2013) http://veterinaryrecord.bmj.com/content/early/2013/09/25/vr.101454.full AST frequency differs greatly between countries. **Proposed change**: include reference to above paper	Accepted.
413	2	**Comment**: Where is the reference to 'In veterinary medicine multidrug resistance is a common problem in *Pseudomonas.*' Is this correct? Also no reference to topical therapy and no differentiation between antimicrobials used for topical and systemic therapy is made. **Proposed change**: include reference to paper on multidrug resistance on Pseudomonas and include reference to difference between topical and systemic treatment	Partly accepted. Reference *Buckly et al 2013* was introduced. Issue on topical therapy and AST susceptibility criteria was addressed previously.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
513	2	**Comment**: Table 1 lists selected microbiological hazards identified in this document. Should it not also include commensal organisms, such as coagulase-negative staphylococci – commonest cause of nosocomial infection in humans and commonly occur in animals?	It was accepted but in the literature revision references on CoNeg Staphylococci are still scarce in veterinary medicine.
254	3	**Comment**: Include the paper of Wettstein et al who presents case reports of methicillin-resistant Staphylococcus pseudintermedius infections in cats: Wettstein, K, S. Descloux, A. Rossano, and V. Perreten. 2008. Emergence of methicillin-resistant Staphylococcus pseudintermedius in Switzerland: Three cases of urinary tract infections in cats. Schweiz. Arch. Tierheilkd. 150: 339-343.	The revision cited is a valuable citation.
258	3	**Comment**: New MRSP clones have emerged in Asia and are also spreading. Please include the following reference: Perreten, V., P. Chanchaithong, N. Prapasarakul, A. Rossano, S.E. Blum, D. Elad, and S. Schwendener. 2013. Novel pseudo SCCmec element (ψSCCmec57395) in methicillin-resistant Staphylococcus pseudintermedius CC45. Antimicrob. Agents Chemother. 57(11):5509-5515.	It was considered that this would constitute very detailed information for the present reflection paper.
273	3	**Comment**: Only the SCCmecV cassette from MRSP ST68 spreading in the USA has been found to be	It was considered that this would constitute very detailed information for the present reflection paper.

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		closely related to S. aureus SCCmec cassette. The SCCmec cassette of MRSP ST71, which is the predominant clone spreading worldwide consists of a combination of two cassettes likely originating from S. epidermidis and S. aureus. Recently, a new pseudoSCCmec elements has been described and is related to SCCmec elements found in S. haemolyticus. Please include the following references: Perreten, V., P. Chanchaithong, N. Prapasarakul, A. Rossano, S.E. Blum, D. Elad, and S. Schwendener. 2013. Novel pseudo SCCmec element (ψSCCmec57395) in methicillin-resistant Staphylococcus pseudintermedius CC45. Antimicrob. Agents Chemother. 57(11):5509-5515. Descloux, S., A. Rossano, and V. Perreten. 2008. Characterization of new Staphylococcal Cassette Chromosome mec (SCCmec) and topoisomerase genes in fluoroquinolone and methicillin-resistant Staphylococcus pseudintermedius. J. Clin. Microbiol. 46:1818-1823. **Proposed change**: The text should be adapted appropriately like e.g. “Evidence suggests that the origin of the MRSP SCCmec elements is diverse and may be associated to S. aureus as well as coagulase-negative staphylococci such as S. epidermidis and S. haemolyticus (Kania et al., 2009; Descloux et al., 2008; Perreten et al., 2013).	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
433	3	**Comment**: Recently, a case of urinary tract infection caused by a carbapenem-resistant A. baumannii was reported in a cat (Pomba et al, 2013). The strains belonged to the same clonal lineages as those causing infections in humans. Cats may also play an important role in the spread of carbapenem-resistant. The manuscript should be modified appropriately and the reference should be included: Pomba, C., A. Endimiani, A. Rossano, D. Saial, N. Couto, and V. Perreten. First report of OXA-23-mediated carbapenem resistance in ST2 multidrug-resistant Acinetobacter baumannii associated with urinary tract infection in a cat. Antimicrob. Agents Chemother. AAC.02527-13; published ahead of print 2 December 2013 doi:10.1128/AAC.02527-13	Changes were introduced in the text.
513	3	**Comment**: Table 1. Please include cats as a source of carbapenem-resistant Gram-negative bacteria.	Correction was made.
51-52	4	**Comment**: We would agree with the statement but suggest that this should be considered from a one health perspective looking at the risk to both humans and animals	We do agree that AMR dissemination occurs in both directions human-to-animal and also animal-to-human. The latter being the object of this reflection paper.
64-66	4	**Comment**: We acknowledge the importance of restriction of certain antibacterials, especially those restricted in human medicine such as imipenem, linezolid, teicoplanin and vancomycin, as well as	This issue will be addressed in the scientific advice to the Commission on the impact on public and animal health of the use of antibiotics in animals. No proposals to amend text at present.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		careful consideration before the use of certain antibacterials (including 3rd and 4th generation cephalosporins and fluoroquinolones). However care should be taken in talking about restrictions relating to all antibacterials considered critically important in human medicine as this includes the penicillins http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf?ua=1 **Proposed change**: specific antibacterials or classes of antibacterials should be named	
83-83	4	**Comment**: The Cascade use of antibacterials is common in companion animal practice where many products are licensed for specific indications. In most cases the use relates to a product authorised for use in that species but not necessarily for that particular condition. **Proposed change**: That the requirement for recording and monitoring cascade use of antibacterials should be restricted to the use of antibacterials not licensed for use in that species and particularly for the use of antibacterials only licenced for use in humans.	Agreed. Currently there is very little data on the off-label use of antimicrobial VMPs. Although the greatest concern relates to use of human-only authorised substances, it would also be of concern if other human CIAs are being used extensively off-label for indications that do not align with responsible use, therefore further information in this regard would be of value. Amendment was made.
85-86	4	**Comment**: We strongly support this statement although we would suggest that surveillance has benefits not only to public health but also has the potential, through increasing knowledge of the sensitivity patterns of organisms, to support better and	Agreed. No amendments necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		more effective prescribing.	
145-146	4	**Comment**: We note that the paper applies primarily to dogs and cats; however, some exotic pets, notably reptiles, have been implicated in zoonotic diseases and should also be considered. This is especially important as the range of licensed antibacterials in “exotic” species is limited.	Agreed but it was not in the mandate of this reflection paper.
502-503	4	**Comment**: Again it is important to be clear that antibacterial resistance is not necessarily animal derived. **Proposed change**: Antimicrobial resistance transfer between humans and animals should be considered in both directions.	Agreed but it was not in the mandate of this reflection paper.
522-524	4	**Comments**: We agree that requesting resistance data for new antibacterial products appears reasonable however, there are unlikely to be many new antibacterials for veterinary medicine and care would need to be taken to ensure that these requirements did not discourage manufacturers seeking authorization for further indications, especially regarding older / narrow spectrum antibacterials which may enable more responsible prescribing.	Accepted.
527- 528	4	**Comments**: While we accept the need to follow the SPC this sentence suggests that the alternative to this is the use of human products when in most cases it is	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		more likely to be the use of products already licensed for use in the same species, but for a different indication, or licenced for other veterinary species. In certain species (rabbits and exotics) the licensed products are not always the most appropriate to use in terms of responsible antibacterial prescribing (e.g. fluoroquinolones)	
536-537	4	**Comments**: We would agree that it is important when licensing antibacterials to ensure that its intended use is in accord with principles of responsible use.	Agreed.
20-21	5	**Comment**: What antibiotics are meant by 'critically important for human health' – does this mean the current WHO list? Why would the companion animal use of antimicrobials that are critically important for human health be an additional risk factor for the emergence and transmission of antimicrobial resistance? To our knowledge, it has not been proven that these molecules would select more for resistance than the older compounds. This sentence seems to completely ignore the concept of co- and cross-resistance and appears to extrapolate from data in the human field which has been shown for ceftazidime but not for other 3rd generation cephalosporins such as cefotaxime, cefoperazone, and ceftriaxone (or other penicillins included in the CIA list).	This issue will be addressed in the scientific advice to the Commission on the impact on public and animal health of the use of antibiotics in animals. No proposals to amend text at present.
51-63	5	**Comment**: Realistically, the likelihood of exposure of pets and humans to each other's bacterial flora is	The specific microbiological hazards of concern are identified in Table 1 of the paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		probably 100% within a household (Song et al, 2013i; Johnson et al, 2008ii; Hanselman et al, 2009iii, Davis et al, 2012iv; Leite-Martins, 2012v; Morgan, 2008vi; Skurnik et al, 2006vii). Hence, there is a need for reflection on appropriate endpoints.	
53-54	5	**Comment**: in principle these could be adapted to companion animals; the zoonotic organisms of concern in companion animals are different from food borne pathogens. Vose is general to the risk analysis process; VICH GL27 is useful construct to the drug registration process, but would need to be changed to specifics for companion animals. For reasons of consistency, VICH GL27 would be the preferred guidance. CODEX Alimentarius was specifically designed to address food borne concerns.	See above. The CVMP is currently working on a risk assessment guideline for food-producing species which draws on OIE, CODEX and VICH GL 27. Once this is completed, guidance for companion animals will then be addressed more specifically based on the experience gained.
59	5	**Comment**: How does one make an abbreviated risk assessment based on the numbers of animals treated? This skips many aspects of risk analysis. Also, how can one predict numbers of animals treated when there is a data gap identified (line 92) as to extent and patterns of antibiotic use in animals currently.	Agreed. Revised text in relation to the exposure assessment has been added into the Discussion section of the paper, although it is still recognised that due to limited knowledge in this area, this is difficult to estimate.
90-94	5	**Comment**: The points identified as knowledge gaps seem indispensible for performing a proper risk assessment, although current scientific literature contains more information than what is currently included in the paper. Hence, the terminology of lines	Agreed. It is now highlighted that a qualitative risk assessment will be performed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		51-52 should be adapted to reflect that any assessment will be potentially be limited to a qualitative risk assessment at best, and identification of risk mitigation measures as appropriate.	
122-128	5	**Comment**: Transmission pathways are bi-directional; the origin of MRSA in pets is frequently human. Also, when healthy pets are found to carry ESBL-producing bacteria, source attribution is virtually impossible. The likelihood of pets carrying carbapenemase-producing strains is also high (see Stolle, 2013 quoted in the reflection paper (RP)). Given the complex interplay between the various reservoirs, sources can be multiple; e.g. there is increasing evidence that recreational and/or drinking water may play an important role in the dissemination of resistance genes/resistant bacteria.	It was agreed that AMR dissemination occurs in both directions human-to-animal and also animal-to-human. The latter being the object of this reflection paper.
154	5	**Comment**: To what extent are antimicrobials used in everyday practice for PROPHYLACTIC purposes in companion animals? Is this not minimal and limited to surgical prophylaxis, in analogy with common practice in human medicine?	The AWP is currently working on a reflection paper on off-label use that will specifically address this issue.
252	5	**Comment**: “The first reports of MRSP (identified at that time as Staphylococcus intermedius) in dogs and humans in North America and in cats in Brazil date back to 1999.” (Quote from Guardabassi et al, 2013viii)	It was agreed that AMR dissemination occurs in both directions human-to-animal and also animal-to-human. The later being the object of this reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		References quoted by the authors: Gortel et al, 1999ix; Lilenbaum, 1999x. Reference already mentioned in the RP: Gerstadt et al, 1999.xi	
292-321	5	**Comment**: We agree with the identification of the human host as a hazard for the dog population. From the text it is not clear how often clinical infections occurred in dogs or in the household members where VRE had been detected in the dog, nor if the household members were also carriers.	Data is scarce on the burden of disease transmitted by pets to their owners.
332	5	**Comment**: Hidalgo reports data on 7 strains in cats and dogs all referred from the same veterinary surgery, which may suggest a common source (and potentially human), but with no further data on origin, antibiotic treatments, and medical history and/or carriage by the members of the households these pets belonged to. For completeness, the isolates were found to coproduce DHA-1 and SHV-11 β-lactamases, as well as the QnrB4 resistance determinant. The authors performed only limited screening for resistance determinants; e.g. Carbapenemases were not included but these determinants may have been present as well. Reports such as these (and section 4.3) seem to suggest that we have to protect the companion animal reservoir from contamination with MDR human pathogens?	It was agreed that it could be an infection control measure in particular cases.
335-362	5	**Comment**: Once more an illustration of the need to protect the pet reservoir.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
358-360	5	**Comment**: References to substantiate this statement? Notwithstanding that, bacteria or genes found on processed food don't necessarily originate from the animal reservoir, but can be linked with (lack of) hygiene at processing.	Agreed.
380-381	5	**Comment**: Stolle 2013 (see RP reference list) in their discussion: "However, off-label usage of carbapenems is not common practice at the veterinary clinic where we obtained the OXA-48 producers, evidenced by the history of antimicrobial treatment of the dogs, which is documented in Table 1. Although we cannot rule out that carbapenems had been administered to the dogs once in their lifetime, it seems more likely that they had undergone nosocomial colonization rather than experienced in vivo selection of OXA-48-producers driven by antibiotic treatment. This is further supported by the fact that all dogs except for dog 2, which was, however, previously housed together with dog 1, were kept in the intensive care unit for at least 24 h during their stay in the veterinary clinic, hinting towards a common environmental source. Efforts are currently under way to determine whether the maintenance of multidrug-resistant enterobacterial isolates might be owing to an undetected hygiene problem or putative human carriers (veterinary personnel or surgeons). So far, OXA-48-producing isolates have mainly appeared as colonizers rather	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		than as primary or sole aetiological agents, almost always correlated with comorbidities in the patients." The authors cite the likelihood of human to pet transfer in their conclusions.	
404-407	5	**Comment**: note that the CVMP reflection acknowledges that C. difficile, Salmonella Campylobacter ,are not an urgent direct hazard (line 517) in the discussions. This makes sense, and publications that would support that approach include (but are not limited to): Procter et al, 2013xii, who studied the prevalence of zoonotic pathogens in pet dogs that visit dog parks, and looked at the risk factors for shedding of Campylobacter spp. And Parsons et al, 2010xiii, who's conclusions are very similar to what their Canadian colleagues found, namely a low prevalence of C. jejuni, the most common Campylobacter spp. associated with disease in humans (1.2%, 95% CI 0.3, 3).	Agreed.
507-509	5	**Comment**: This is a transfer that might occur with any bacteria	Agreed.
509-511	5	**Comment**: More correctly: transfer of ARG from bacteria from CA to bacteria in humans potentially including pathogenic bacteria which eventually may cause disease in (presumably) the owner of the pet?	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 529-	5	**Comment**: We would support the use of VICH GL 27, tailored to companion animals.	The CVMP is currently working on a risk assessment guideline for food-producing species which draws on OIE, CODEX and VICH GL 27. Once this is completed, guidance for companion animals will then be addressed more specifically based on the experience gained.
533-536	5	**Comment**: Any transfer would occur primarily in the household setting and how to extrapolate this or estimate any risk to public health in the broader context is not clear. Would there be a threshold for numbers of animals potentially treated with the compound?	See amendments.
536-538	5	**Comment**: It would be useful to define more precisely what is meant by “responsible use principles” in this context, since this is subject to interpretation.	Different organisations have produced responsible use recommendations, many of those are at national or species level. A more specific definition cannot be provided here.

References cited in the comments

[i] Song et al, 2013. Cohabiting family members share microbiota with one another and with their dogs. eLife 2013;2:e00458. DOI: 10.7554/eLife.00458.

[ii] Johnson et al, 2008. Multiple-Host Sharing, Long-Term Persistence, and Virulence of Escherichia coli Clones from Human and Animal Household Members. JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2008, p. 4078–4082.

[iii] Already quoted in paper: Hanselman et al, 2009. Coagulase positive staphylococcal colonization of humans and their household pets. Can Vet J 2009;50:954–958.

[iv] Davis, M. F., Iverson, S. A., Baron, P., Vasse, A., Silbergeld, E. K., Lautenbach, E., & Morris, D. O. (2012). Household transmission of meticillin-resistant Staphylococcus aureus and other staphylococci. The Lancet infectious diseases, 12(9), 703–16. doi:10.1016/S1473-3099(12)70156-1.

[v] Leite-Martins, L., Beça, N., Lopes, E., Frias, C., Matos, A. de, & Costa, P. M. da. (2012). In-home and through-home transmission of antimicrobial resistance between human and pets. In ICAR 2012 (p. 2012).

[vi] Morgan, M. (2008). Methicillin-resistant Staphylococcus aureus and animals: zoonosis or humanosis? Journal of antimicrobial chemotherapy, 62(September), 1181–1187. doi:10.1093/jac/dkn405

[vii] Skurnik, D., Ruimy, R., Andremont, A., Amorin, C., Rouquet, P., Picard, B., & Denamur, E. (2006). Effect of human vicinity on antimicrobial resistance and integrons in animal faecal Escherichia coli. The Journal of antimicrobial chemotherapy, 57(6), 1215–9. doi:10.1093/jac/dkl122

[viii] Guardabassi et al, 2013. Public health impact and antimicrobial selection of meticillin-resistant staphylococci in animals. Journal of Global Antimicrobial Resistance 1 (2013) 55–62.

[ix] Gortel et al, 1999. Methicillin resistance among staphylococci isolated from dogs. American Journal of Veterinary Research, Volume 60, Issue 12, December 1999, Pages 1526-1530.

[x] Lilenbaum, 1999. Prevalence and antimicrobial susceptibility of staphylococci isolated from saliva of clinically normal cats. Letters in Applied Microbiology Volume 28, Issue 6, pages 448–452, June 1999

[xi] Gerstadt et al, 1999. Methicillin-resistant Staphylococcus intermedius pneumonia following coronary artery bypass grafting. Clinical Infectious Diseases, Volume 29, Issue 1, 1999, Pages 218-219.

[xii] Procter TD, Pearl DL, Finley RL, Leonard EK, Janecko N, Reid-Smith RJ, Weese JS, Peregrine AS, Sargeant JM. A Cross-Sectional Study Examining Campylobacter and Other Zoonotic Enteric Pathogens in Dogs that Frequent Dog Parks in Three Cities in South-Western Ontario and Risk Factors for Shedding of Campylobacter spp. Zoonoses Public Health. 2013 Jun 26. doi: 10.1111/zph.12062.

[xiii] Parsons BN, Porter CJ, Ryvar R, Stavisky J, Williams NJ, Pinchbeck GL, Birtles RJ, Christley RM, German AJ, Radford AD, Hart CA, Gaskell RM, Dawson S. Prevalence of Campylobacter spp. in a cross-sectional study of dogs attending veterinary practices in the UK and risk indicators associated with shedding. Vet J. 2010 Apr;184(1):66-70. doi: 10.1016/j.tvjl.2009.01.009.