14 November 2011
EMA/CVMP/SAGAM/358728/2011
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on Reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/SAGAM/741087/2009)

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

Stakeholder no.	Name of organisation or individual
1	IFAH-Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1.	IFAH-Europe would like to thank CVMP/SAGAM for the opportunity to comment on this reflection paper. In our view the paper is overall balanced and well written, however, we feel that it expands somewhat too much on mechanisms of action, resistance mechanisms and in vitro gene transfer and perhaps not enough on pathogen resistance prevalence and MLS resistance impact on animal and human health. The recommendations to align product use directions with improved responsible use conditions of use are very appropriate as a matter of principle. However, specific products, indications, target species, doses and durations were not detailed in any way, thus providing no guidance to regulatory authorities or drug sponsors on what exactly is to be proposed. This is particularly true for combinations which should be evaluated individually for risk and benefits as relates to antibiotic resistance. Lastly, more consideration of the existing risks assessments, of carcass contamination data and of human clinical data may have indicated some paths for effective risk mitigation strategies for zoonotic bacteria.	We thank IFAH-Europe for their comprehensive review of the reflection paper. We have considered all comments and suggestions made, and made changes accordingly or given justification where we could not agree. As to the details on different products, the data are so wide that it is impossible to describe here. However, proposal for a table on examples of combination products has been added. The chapter on risk assessment studies has been expanded. We think that more carcass contamination data or human clinical data are not relevant for the purposes of this paper.

2. Specific comments on text

Line no.	Comment and rationale; proposed changes	Outcome
18	Comments: Please replace “mass” by “group”. We suggest amending to read: “for medication of ~~large~~ groups of animals (~~mass~~ group medication) typically via feed or water”.	Agreed and amended accordingly.
22	We suggest to add “and vice versa” at the end of the sentence so it would read “….spread of resistance of animals to humans and vice versa.”	For the meaning of the sentence the present wording is correct.
23	Comments: Please replace “ group” by “herd”	Not always the whole herd was medicated but groups only. The word “herd” has been added.
39	Comments: We suggest “effective” is introduced in the sentence so it would read “Duration of treatment should be limited to the minimum required time for effective ~~treatment~~ cure of diseases.”	Changed: ...for cure of diseases.
51	Comments: Combinations are mentioned for action; however, the text does not address this to any extent. It is difficult to understand how an action can be recommended without having fundamental information available that provides some indication of the scope of the perceived issue.	The number of combinations is over 60, mostly with very long lists of indications etc. It is difficult to give even a short overview of them in the text. A table with examples has been proposed.
124	Comments: We suggest the following sentence is introduced: “Lincosamides are categorised as important in human medicine (WHO 2007)”	Changed accordingly
130	Comments: There is a lack of reference for the indicated “increase”. In particular, we feel that resistance to *Campylobacter jejuni*, the major pathogen in humans, is stable.	This is introduction, and use of references is thus limited. The wording is correct as resistance has emerged.
240, 745	Comments: Macrolide label use indications in human medicine are not documented or described, as for example by a reference to the Sanford Guide (Gilbert et al., 2009) or other physician references. Citing the WHO	Textbook references have been used later (Treatment guide by Finch et al. 2003). Taking into account the comment we have added further references.

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	Critically Important Antibiotic list does not substitute for a clinical practice guideline used by infectious disease physicians, since the purpose of the WHO list is entirely different (i.e. prioritization of risk assessment work to guide risk management interventions). Moreover, there is no information given on the estimated number of campylobacteriosis cases that might be treated with a macrolide, although some papers have provided this information (Hurd, 2004: Belanger, 2006; Buzby, 1996). We suggest this information is provided in Section 7.1.1.1 Campylobacter. Potential references are : Gilbert, D.N. et al. 2009. The Sanford guide to antimicrobial therapy, 39th edition Antimicrobial Therapy, Inc., Hyde Park, VT. Hurd, H.S., S. Doores, D. Hayes, et al., 2004, Public Health Consequences of Macrolide Use in Food Animals: A Deterministic Risk Assessment J. Food Protection 67:980-992. Belanger, A.E., and T.R. Shryock. 2007. Macrolide-resistant *Campylobacter*: the meat of the matter. Journal of Antimicrobial Chemotherapy 60: 715-723 Buzby, J. et al. 1996. Bacterial Foodborne Disease: Medical Costs and Productivity Losses. Food and Consumer Economics Division, Economic Research Service, U.S. Department of Agriculture. Agricultural Economic Report No. 741. Page 25.	Some of the references provided point out that how rarely macrolides are used to treat human campylobacteriosis and that the treatment does not affect the outcome very much in uncomplicated cases The CVMP/SAGAM preferred not to go to details in numbers of human cases treated etc. These estimates differ from country to country. We have stated in several places that most human cases do not need antimicrobials and that macrolides are not the sole alternative. In a separate chapter risk assessments have been shortly dealt with.
267, Table 2	Comments: We suggest two columns are added indicating respectively the target pathogens and indications.	Although we agree with the comment it would expand the table too much. Lists of older products in particular are very long.
318	Comments: We suggest a new table is introduced listing all combinations of MLs with compounds of other classes approved in the EU, similar as has been performed for the single MLs in Table 2. Any information as to host species, indications, target species, doses and durations, route of	Not possible for space reasons. A table including some examples of the combination products has been added, to indicate the problems.

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	administration should be added. This paragraph should also include scientifically-based information why the choice of the included components cannot be justified and their combination lacks scientific rational, as mentioned above (line 51) in the reflection paper.	
373	Comments: The horizontally transferable resistance section concentrates on the possibility of transfer, but does not include any substantial discussion on the probability or extent of such transfer in vivo. There is no discussion of the continuum of acquisition, selection, amplification and dispersion of newly acquired resistance genes. It would have been of value to construct a table listing prevalence of transferable genes, bacterial host, animal species, etc. to provide the reader with a sense of what the main mechanisms and genes are that will be addressed in later sections and by the recommended risk management actions. There is no discussion on the barriers to horizontal gene transfer in Enterococci, such as pheromones, plasmid compatibility groups, restriction enzymes, etc. For that reason, we chose to focus our comment on resistance transfer from animal to human via Enterococcus at this point. Studies have shown that Enterococci of animal origins do not carry the same virulence factors as Enterococci of human origin. This greatly contributes to how long the animal Enterococci will be able to colonize and/or persist in the human gut. Absence of common virulence factors also contributes to a limited 'resident' time in the human gut and thus further limits the possibility of gene transfer between animal and human Enterococci. (Simjee S, White DG, Carter PJ, Zervos MJ, Donabedian SM, Qaiyumi S, Zhao S, Wagner DD, Meng J and McDermott PF. Prevalence of enterococcal virulence genes in streptogramin-resistant E. faecium isolated from retail poultry and humans and gelE expression in a streptogramin resistant E.	I doubt if enough would be known on topics which are listed in this comment. Furthermore it would lengthen the document The prevalence of transferable genes is highly dependent of goals and sampling methodology, so this information probably would be of limited interest. The barriers for HGT are the same than in previous reflection papers and, to the best of our knowledge never have been mentioned. Enterococci are a special bacterial genus regarding this topic and probably more the exception than the rule. The Gram negative bacteria, like *E. coli* and Salmonella spp. are more likely to exchange genetic material. It is acknowledged that the probability and extent of transfer of resistance determinants between species is largely unknown. Some text has been added to point out this, as well as one reference.

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	faecium isolate. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, 2002. (abstract C2-114)). Studies of the antibiotic-resistant Enterococcus reservoirs that might occur in the human gastrointestinal tract offer little evidence of resistance determinant persistence or transfer. For example, vancomycin-resistant Enterococci from animals, when consumed by human volunteers, failed to colonize or persist. (Sørensen TL, Blom M, Monnet DL, Frimodt-Møller N, Poulsen RL and Espersen F. 2001. Transient intestinal carriage after ingestion of antibiotic-resistant Enterococcus faecium from chicken and pork. New England Journal of Medicine, 345:1161-1166); (Werner et al. 2011. Host range of enterococcal vanA plasmids among Gram-positive intestinal bacteria. Journal of Antimicrobial Chemotherapy, 66: 273-282). Transfer of resistance from poultry to human Enterococci was unsuccessful in favourable in vitro mating experiments (Borgen K, Sorum M, Wasteson Y, Kruse H, and Oppegaard H. 2002. Genetic linkage between erm(B) and van A in Enterococcus hirae of poultry origin. Microbial Drug Resistance, 8:363-368).	
479	Comments: Classifying a food animal isolate as resistant or susceptible is based on either clinical breakpoints, such as those established by CLSI, or by using an ECV, based on a value that separates the wild-type population from the non-wild type. Thus, it is not readily apparent upon what basis the “resistance” emergence was based. We suggest that it would be of more value to construct a table showing an MIC histogram, in particular for these antibiotics without any clinical breakpoint. Please replace “cut-off values” (line 485) by “breakpoints” because for target pathogens usually clinical (CLSI) breakpoints are used, e.g., in MARAN and DANMAP. It would also avoid disconnects, such as in lines 524-	We consider producing that kind of table not feasible, due to the high number of bacteria. We now use the term “interpretation criteria” to avoid using cut-offs or breakpoints. The point on tilmicosin has been clarified.

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	525, where similar percentages of resistance for tylosin and tilmicosin should be found, but are not.	
489	Comments: Please delete the sentence “For animal pathogens, uniform data are so far not available” and add the following. “Regarding pan-European data, the CEESA VetPath programs have collected first intent isolates from 1999-2006. Irrespective of the interpretive criteria, the prevalence of ‘resistant’ isolates in the case of tilmicosin, and ‘non-wild type in the case of tylosin, have remained consistently low throughout the EU over the 7-year collection period. It can be concluded that in target pathogens no new resistant mechanisms have emerged nor have the existing ones propagated to an extent to cause any concern.” VetPath I collection period 1999-2004:GR Micro Ltd., Study IV246/20/05: A Report to CEESA AISBL (Brussels, Belgium) - Determination of the antimicrobial susceptibility of the VETPATH-1 collection of bacterial pathogens (2006) VetPath II collection period 2004-2006: Quotient Bioresearch Ltd., Study number IV257-31-05; A report to CEESA AISBL (Brussels, Belgium). Determination of the antimicrobial susceptibility of VetPath II (2004-2006) collection of bacterial pathogens (2009)	We are aware of the pan-European data which is referred to. However, data available are not uniform, thus the sentence is kept. It is true that resistance to tilmicosin is still quite low, but as regards new mechanisms the situation little is known. However, a new study on genetics of macrolide, triamilide, and lincosamide resistance in P. multocida was recently published (Kadlec et al. 2011). This reference has been added to the reflection paper.
492 - 493	Comments: The text mentions that “certain trends for MLS resistance among animal pathogens and zoonotic bacteria are apparent”. We suggest introducing references here	References follow in the next chapters dealing with each pathogen group.
517 and 531	Comments: Please replace “cutoff” by “breakpoint”	Please see the answer above.
525	Comments: Please add “Mannheimia” before “haemolytica”. The abnormal discrepancy between the tylosin and tilmicosin resistance rates has been	Corrected.

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	commented on above and the quotation should be deleted.	
530	Comments: We suggest adding the sentence after "….as 35%". : "In the European survey VetPath (2002-2006), neither P.multocida nor M. haemolytica bovine strains were found to be resistant to tilmicosin; in pigs, 2.1 % of P. multocida isolates showed resistance (Thomas et al. 2009)" Thomas, V., A. de Jong, P. Butty, D. Felmingham, K. Godinho, U. Klein, H. Marion, D. Rigaut, B. Schiessl, S. Simjee, T. Shryock, M. Valle. Antimicrobial susceptibility of respiratory tract pathogens isolated from diseased cattle and swine across Europe. J. vet. Pharmacol. Therap., 32 (Suppl. 1):230-231, 2009.	The reference (Thomas et al.) is a poster abstract, with limited details. Breakpoint used is 32 µg/ml, which is higher than used in national monitoring programmes. For these reasons is preferred not to cite this reference.
586	Comments: We suggest bringing the following modifications to the paragraph: "For Lawsonia intracellularis there are no standards for susceptibility testing. In one study, MIC90 values of Lawsonia intracellularis were higher for tylosin (64µg/ml) as compared to those of tilmicosin (2µg/ml) or erythromycin (0,5µg/ml) (Giguère 2006a). A new study (Wattanaphansak 2009) tested tylosin and lincomycin among other antimicrobials. Tylosin and lincomycin showed the following activity (tylosin : intracellular MIC ranging from 0.25 to 32 µg/ml; extracellular MIC ranging from 1 to >128 µg/ml, lincomycin : intracellular MIC range 8 to >128 µg/ml; extracellular range 32 to >128 µg/ml). The clinical relevance of these results remains difficult to appreciate." S. Wattanaphansak, R. S. Singer and C. J. Gebhart, 2009. In vitro antimicrobial activity against 10 North American and European Lawsonia intracellularis isolates. Veterinary Microbiology 134: 305–310.	The reference and information presented in it has been added.
614	Comments: After "meat." we suggest inserting the following sentence: "Clinical resistance based on CLSI breakpoint of 32 mg/L amounted to 2%"	The statement reflects the EFSA report, and we prefer not to

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		reanalyse the EFSA conclusions.
619	Comments: Since the ECDC data is quoted, it would be good to quote from ECDC the repartition of cases among the different species of *Campylobacter* in order to underline that an overwhelming majority of cases is due to *C. jejuni*	This has been stated later, but added also here.
624, Table 5	Comments: We suggest mentioning here the value of the harmonised Epidemiological Cut-off Value that has been used	Done.
682	Comments: Please add a sentence "This observation cannot easily be explained"	An explanatory sentence has been added.
745	Comments: We have some reservations concerning this part. We think that the critiques of the various risk assessments have been given somewhat too much weight (e.g. Collignon et al in line 773) or have been misunderstood (as for the Kelly paper). Indeed, the value of the risk assessment approach is that it is iterative and welcomes new data and links in the food chain. This is the point made in the Kelly paper, which we think has not been reflected adequately in this reflection paper. As for Collignon's comments, the Reflection Paper authors have omitted Hurd's detailed response, which is cited below. In it, Hurd provides additional calculations that address the suggestions made by Collignon and others. This section of the Reflection Paper is too important to be declared as "equivocal" as in line 908. We would suggest the deletion of the last sentence starting line 772. We ask the reflection paper authors also to give consideration to the following papers: Ternhag, A., T. Asikainen, J. Giesecke, and K. Ekdahl. 2007. A Meta-Analysis on the Effects of Antibiotic Treatment on Duration of Symptoms Caused by Infection with Campylobacter Species. Clin Infect Dis 44:696-	The text has been reviewed.

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	700. Hurd, H. S. 2004. Letter to the Editor (response). J. Food Protection. 67; 2370-2374.	
749	Comments: The paper quotes a poultry meat contamination rate in the EU of 26%. Because the focus is on resistance, please quote papers mentioning the proportion of MLS resistant *Campylobacter* on poultry meat and other meats. For example, DANMAP 2009 and 2008 clearly indicate an absence of macrolide resistant *C. jejuni* recovered from domestic poultry meat. In the 2007 DANMAP, 1.8% of the *C. jejuni* recovered from poultry meat were resistant to erythromycin. It should be noted that CIPARS and NARMS have now discontinued campylobacter isolation from beef and pork meat due to the low recovery frequency. The Australian resistance monitoring program in 2008 reported 5% erythromycin resistance in *C. coli* (n=60) and 3.3% erythromycin resistance in *C. jejuni* (n=60) from poultry retail meats. (Pilot survey for antimicrobial resistant (AMR) bacteria in Australian food, Prepared for the Australian Government Department of Health and Aging by Food Science Australia, Queensland, November 2008) In Ireland, A total of 39 strains of *Campylobacter jejuni* and 36 of *C. coli* isolated from poultry skin samples were tested for antimicrobial susceptibility. The samples were collected as part of official monitoring at slaughtering from 8 poultry plants and were mainly from broilers, with a few hens, turkey and duck carcasses also sampled. No erythromycin resistance was seen in *C. jejuni* and 5.6% (2/36) *C. coli* were erythromycin resistant (Ireland - NATIONAL REFERENCE LABORATORY ANTIMICROBIAL RESISTANCE (Food, Feed and Animal Health) Annual Report 2009)	A sentence has been added here. Australian and US references preferably not added as focus is on European situation. No more references on meat campylobacters have been added as the current ones are considered sufficient. That reflects the situation in samples from animals.

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	In the US NARMS program, Retail meat samples (*n* _ 24,566) from 10 U.S. states collected between 2002 and 2007, consisting of 6,138 chicken breast, 6,109 ground turkey, 6,171 ground beef, and 6,148 pork chop samples, were analyzed. A total of 2,258 *Campylobacter jejuni*, 925 *Campylobacter coli*, and 7 *Campylobacter lari* isolates were identified. Chicken breast samples showed the highest contamination rate (49.9%), followed by ground turkey (1.6%), whereas both pork chops and ground beef had <0.5% contamination. Erythromycin susceptibility against 2194 *C. jejuni* and 867 *C. coli* isolated from chicken breast showed <1% ERY resistance in *C. jejuni* and <10% ERY resistance in *C. coli*. (Zhao *et al*. 2010. Antimicrobial resistance of *Campylobacter* isolates from retail meat in the United States between 2002 and 2007**.** Antimicrobial Agents and Chemotherapy, **76**: 7949-7956).	
781	Comments: We suggest "introduced" is replaced by " used off label"	Accepted and changed
787	Comments: The references Capoor, Rawat et al. 2007 and Gunell, Kotilainen et al. 2010 show very low incidence of higher MICs with no indication that susceptibility has declined i.e. resistance has developed, over time. Further, since a clinical breakpoint has not been established for azithromycin against *Salmonella* it is impossible to determine if resistant populations actually exist. Therefore, we propose the sentence is changed slightly, so the sentence would read : "Susceptibility testing of *Salmonella* strains is advisable before treatment, as resistance against azithromycin may be developing ~~can develop~~ (Capoor, Rawat et al. 2007; Gunell, Kotilainen et al. 2010)" Capoor MR, Rawat D, Nair D, Hasan AS, Deb M, Aggarwal P, Pillai P. In vitro activity of azithromycin, newer quinolones and cephalosporins in ciprofloxacin-resistant *Salmonella* causing enteric fever. J Med Microbiol.	Changed to: "may develop"

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	2007 Nov., 56(Pt 11), 1490-4. Gunell M, Kotilainen P, Jalava J, Huovinen P, Siitonen A, Hakanen AJ. In vitro activity of azithromycin against nontyphoidal *Salmonella* enterica. Antimicrob Agents Chemother. 2010 Aug., 54(8), 3498-501.	
789-790	Comments: Please delete this statement as it is an assumption and there is no data to support it.	The statement stays (slightly changed), it now states that the new macrolides might have an influence. In the reference cited, the authors refer to their earlier study "… we detected an identical sequence for a 540-bp fragment of the ermB gene in a limited number of porcine (*S. suis*) and human (*S. pneumoniae* and *S. pyogenes*) streptococcal strains (Martel et al., 2001). This can be added if necessary.
818	Comments: Please add fluoroquinolones so that it would read. " but macrolides and fluoroquinolones are also used."	Added.
821	Comments: This paragraph refers to an order of antibiotic preference in national treatment guidelines and textbooks, but does not provide specific citations or documentation. It is difficult to understand how policy can be made without supporting documentation.	References added.
829	Comments: Macrolide treatment of mastitis may offer the advantage of intracellular penetration to reach *Staphylococcus* spp. and *Streptococcus* spp., a treatment feature that beta-lactams cannot duplicate. Therefore we suggest the removal of the sentence.	Clinical relevance of the intracellular penetration is lacking. Cure rates with macrolides are not better than with beta-lactams, maybe on the contrary. E.g. in the documentation of pirlimycin it is stated that intracellular penetration has been documented but not intracellular killing. A new reference showed that protein binding lowered antimicrobial activity of clindamycin by reducing intra-bacterial concentrations (Burian et al. 2011). In fact penethamate (is hydrolyzed to benzylpenicillin) can penetrate into cells (Almeida et al 2007). Mastitis bacteria are in general not intracellular, except mycoplasma and *S. aureus*. The target

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		compartment for streptococci is milk (Erskine 2003). The word "any" deleted.
848	Comments: We suggest that the paragraph is a bit pessimistic. Clinical success and MIC of the macrolides may not necessarily correlate with each other. Also, other effects like immunomodulation which indicate limitations to the topic of resistance in terms of efficacy are not discussed at all. We suggest the sentence starting line 848, which is somewhat of an oxymoron anyway, be deleted.	
853	Comments: It is incumbent upon SAGAM to compile a list of MLS products, label indications, doses, durations and related information that is summarized in the first 4 bullet points. Since this is the first appearance for some of this information, it is surprising to find it in a "summary". Until this information is provided, it is difficult to precisely understand the CVMP recommendations that are on lines 16-57.	A new table has been added to the document.
861	Comments: Add " Streptogramins are no longer used in animals in the European Union"	Added
892	Comments: We suggest a sentence is added to balance the paragraph. We would suggest inserting. "A majority of mastitis and respiratory pathogens remain highly susceptible to macrolides"	Added.
905	Comments: Please remove the word "certain" as the two animal pathogens implicated i.e. *Brachyspira* and *S. hyicus* are mentioned.	Agreed