31 January 2010
EMA/CVMP/SAGAM/779301/2010
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on Reflection paper on meticillin-resistant *Staphylococcus pseudintermedius* (EMA/CVMP/SAGAM/736964/2009)

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

Stakeholder no.	Name of organisation or individual
1	Quotient Bioresearch Ltd.
2	AVC
3	IFAH-Europe

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
2.	AVC appreciates the initiative of CVMP/SAGAM for this reflection paper, that we consider to be well balanced and very comprehensive as it covers the majority of aspects to be related to the specific questions related to the emergence and presence of MRSP	
3.	IFAH-Europe would like to thank CVMP/SAGAM for the opportunities for stakeholders to contribute to this reflection paper and to complement CVMP/SAGAM for the initiative. In our opinion this is a well written, accurate and balanced reflection paper with a good summary and recommendations. However we also feel that the recommendations for actions (pages 2-3) are not always precise. It is clear that there are still substantial gaps in the knowledge of certain areas and it is to be hoped that unwarranted or disproportionate action will not be taken on the basis of the paper's contents. Although the paper suggests possible ways forward which avoid the need for antibacterial therapy, even if promising and worthy of developing, we anticipate that it will still be some time before these entities become available as commercial products.	

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	It has been demonstrated in various studies that MRSP isolates are susceptible to human-use compounds of valuable classes such as glycopeptides, lipopeptides, oxazolidinones, streptogramins. The current version of the Critically Important Antibiotics list of WHO (3rd edition, 2009) is listing at least 9 different classes of antibiotics for MRSA treatment. IFAH-Europe fully supports that reserve antibiotics should be principally reserved to exceptional cases. Only in serious selected cases might the application of such drugs to companion animals be considered. It should be noted, however, that the usage of these compounds in human medicine is relatively frequent and it is difficult to understand that the rare usage in companion animals might limit the therapeutic options in man. IFAH-Europe encourages experimental work to determine the risks of emergence of resistance to these compounds, in order to determine a decent base for evidence-based risk management measures. IFAH-Europe, however, also feels there is a strong disbalance between human medicine and companion animal medicine and is convinced that for animal welfare reasons vets should have sufficient tools available to avoid unnecessary suffering of pain by dogs and cats. IFAH-Europe considers the almost exclusive application of these classes in human medicine is inappropriate and is an over cautious approach. IFAH-Europe proposes to prepare a scheme, which will allow veterinarians legally, and including documentation, to use in serious cases selected drugs of the nine classes. We would be grateful whether SAGAM would consider our proposal.	CVMP remains of the opinion that the use of last resort medicines (such as those listed) should be avoided to the extent possible. The Committee does not know whether the use in animals today is rare and if this is the case finds it important to keep it that way. The CVMP is reluctant to express preference for any of these molecules or suggest posologies as neither the risks nor the benefits from such treatment has been assessed by CVMP. Any use of these molecules must be based on benefit/risk assessment in each case as performed by the prescribing veterinarian. We strongly recommend the veterinarian to consider AMR risks in this assessment.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 5.2.1 lines13-20, Section 9 point 7a	1.	Comment: The paper states that *S. aureus* MIC breakpoints for oxacillin should be used for *S. pseudintermedius*. However, the breakpoint of ≥0.5 mg/L stated in the next paragraph is for coagulase negative staphylococci (CNS) Proposed change: The paper should state that CNS breakpoints for oxacillin rather than *S. aureus* breakpoints should be used.	We agree that CNS breakpoints should be used and this is now stated more clearly.
CVMP recommend ations: Page 2, line 26	2.	Comment: AVC believes that further warnings on the responsible use should be added on all SPCs throughout the EU for all antimicrobials, as all of them may apply a selection pressure to the bacteria and therefore be associated with an increased incidence of MRSP/MRSA and ESBLs in gram negative bacteria. Careful consideration and justification prior to the use of these compounds regarding their suitability for each case is required. This includes in any case sensitivity testing, wherever possible prior to the use of these active ingredients, in any case when therapeutic agents are changed due to non-efficacy and the need for scientific justification in any case when applying the cascade system that such active ingredient will be efficacious at the site of infection. Proposed change: Specific recommendations for the SPC of antimicrobial products should be implemented throughout the EU	CVMP agrees in principle with the comment. Non-prudent use of antimicrobials of any kind constitutes a risk factor for selection of MRSP. However, the Committee does not believe that adding warning sentences to all antimicrobials would

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			decrease this risk. The Committee prefers to restrict the use warning sentences to focus on products where specific risks have been identified.
Suggested Action: page 3	2.	Comment: as mentioned above, such action should be added here, appropriately stressing that such warnings have to be implemented throughout the EU, for all products containing such active ingredients independent on their licensing procedure. It is expressively important to handle originator products exactly the same as generic products and vice versa.	It is agreed that risk mitigation measures should be handled equally for originator products and generics.
Suggested Action: page 3	2.	Comment: Diagnostic Laboratories should be encouraged/forced to state on their diagnostic reports in any case of suspicion of multi-resistance the term: "CARE: suspected to be multi-resistant (MRSP, MRSA, ESBL where appropriate), handle and treat animals carefully and inform owner to potentially consult their physician" Proposed change: Add as appropriate in the different parts of the reflection paper	Agreed. The following text will be added to the recommendations (focussing on MRSP): Diagnostic Laboratories are recommended to state on their diagnostic reports in any case of a confirmed case of MRSP: Due to the specific resistance pattern of the most common variant it is recommended to handle and treat animals with caution and explain to the owner that MRSP might be difficult to treat and constitute a risk for colonisation/infection of other dogs and cats.
Suggested Action / Responsible Body 1st line	2.	Comment: We feel that there may be more and more other specialised professions involved as responsible body in appropriate hygiene. Proposed change: propose to add: professionals, especially those responsible for veterinary premises, kennels and places where animals are kept	Agreed. We changed the sentence accordingly: Animal owners and keepers, veterinarians and related professionals including people responsible for kennels and other premises where dogs are kept.

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Suggested Action / Responsible Body 2nd line	2.	Comment: We feel that there are more organisations needed to have detailed guidelines for the appropriate use of antimicrobials Proposed change: propose to add: Veterinary associations, Marketing authorisation holders, national animal health trade associations, state veterinary services and laboratories, animal trade associations, farmers associations	In treatment guidelines veterinarians are the most obvious responsible persons. Laboratories, trade and farmers associations etc are normally not involved in drafting treatment guidelines for companion animals.
Suggested Action / Responsible Body 3rd line	2.	Comment: We feel that there are more organisations needed to generate more information on the efficacy of therapeutic strategies for the treatment of animals infected with MRSP/MRSA Proposed change: propose to add: Marketing authorisation holders	Agreed, although marketing authorisation holders might not be the correct expression as the issue is not limited to approved products.
Suggested Action / Responsible Body 4th line	2.	Comment: We feel that there are more organisations involved in the development of vaccines Proposed change: propose to add: veterinarians	We find this unnecessary as it would be difficult for a veterinarian to develop a vaccine without being liaised with either a research institute or the pharmaceutical industry.
Suggested Action / Responsible Body 6th line	2.	Comment: We feel that there are more organisations involved in the development of better diagnostic tools Proposed change: propose to add: State and private laboratories	Agreed, although it is limited to laboratories with research capacity. Add Community Reference Laboratory Antimicrobial Resistance (CRL AMR) and other laboratories, universities, research institutions

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Suggested Action / Responsible Body NEW line	2.	Proposed change: Add a line: Suggested Action Increase awareness of veterinarians on the need for hygienic precautions and careful consider the need for antimicrobial therapy to reduce the presence of MRSP/MRSA Responsible Body: HMA, National ministries, Veterinary associations, universities, laboratories and others	Agreed in principle but we note that this is covered in previous lines.
NEW line	2.	Comment: Surveillance of the occurrence of MRSP/MRSA possibly including notification to a central register may be a useful tool to get a closer idea of the current situation and the development of it in the future. We do not have a clear idea of the prevalence in companion animals. Proposed change: Diagnostic laboratories	Agreed
Page 2, paragraph 3	3.	The order of sentences in paragraph 3 should be reversed. Currently the first sentence announces the bullet list of recommendations, but in-between are two sentences on risk factors. Please move the first sentence to the end of the paragraph. Last sentence: unclear English: we suggest "load" is replaced by "usage".	Agreed
Page 2, line 4	3.	For improved precision please amend as follows; "for which there are few, if any, effective veterinary approved antimicrobials"	Agreed
Page 2, 2nd para	3.	Data on the frequency of MRSP infections in dogs and cats co-infected with *S. aureus* would be useful. Co-	As MRSA is getting more and more common in the human population it will be more and more common in companion

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		infections are rare.	animals as well. It might not be common today but unfortunately the prevalence of such cases is likely to increase.
Page 2, bullet point 2	3.	*'Other strategies':* Chapter 7.1.2.1 indicates that the efficacy of several 'other strategies' is not proven even if sometimes reported (disinfectants, debridement) or the alternative do not exist yet (phages, vaccines). Perhaps then it would be better to write. "More research is required into alternative strategies so that their use can be recommended to reduce the use of antimicrobials."	"Other strategies" could be a number of different things, some of them well established (such as adequate wound treatment), others less so. We believe that the former should replace antimicrobial therapy to the extent possible already today, and the latter should urgently be assessed.
Page 2, bullet point 3	3.	'*Internationally agreed guidance'* - the guidance referred to on spread (chapter 8.1) is from the British Small Animal Veterinary Association. Although Britain is made of several nations, it is not customary to refer to British guidance as "international". Perhaps "internationally agreed guidance" would be more precise.	The principles of prudent use of antimicrobials are discussed and agreed internationally e.g. in the OIE terrestrial code.
Page 8, first paragraph	3.	The statement "infections with MRSP are common in dogs and to a lesser extent cats" seems conflicting with the occurrence on page 10. Please change to "Infections with MRSP are more frequent in dogs than in cats (Morris *et al*. 2006). The true incidence of MRSP is unknown, but may be more common among patients seen at referral institutions."	Partly accepted. We changed the sentence "Infections with MRSP are common in dogs and to a lesser extent cats" into "Infections with MRSP are more frequent in dogs than in cats (Morris *et al*. 2006)." We agree that MRSP might be more common in referral institutes, but there is no scientific evidence for this as yet.
Pages 9-10, Section 5.2.1	3.	*"Phenotypic methods"* This section is slightly unclear. The changes of the breakpoints are not well presented. A small table with the past and future oxacillin breakpoints would help.	The section on the MIC breakpoints has been adjusted. We added i.e. ≥4 mg/l. This paragraph now reads: In 2008, the Clinical and Laboratory Standards Institute (CLSI) published a document M31-A3 for the determination of in vitro

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		After the first sentence on page 10, for clarity "i.e., ≥4 mg/L" should be added. Because of recent findings, it is proposed to re-introduce the oxacillin breakpoints of 2004 (CLSI-link: http://data.memberclicks.com/site/aavld/Letter to the Editor.pdf). We think that more work should be done to validate the proposed breakpoints. For instance, Norström *et al.*/NORM-VET 2004 present a MIC distribution with 82% of the isolates with oxacillin MICs ≥0.5 mg/L. Is it really expected that these isolates are carriers of the *mecA* gene? It is unclear whether an intermediate category has been foreseen. Note that all isolates are susceptible to cephalothin and enrofloxacin. Similarly, isolates recovered in BfT-GermVet have oxacillin MICs of 0.5 and 1 mg/L, but were not reported to be MRSPs (Schwarz *et al.*, 2007). In cases of MRSP detection, susceptibility testing should be mandatory.	antimicrobial susceptibility of MRSP for isolates from animals to replace those from 2004. These guidelines advise that oxacillin susceptibility of *S. pseudintermedius* should be determined using clinical breakpoints equivalent to those recommended for human and veterinary isolates of *S. aureus* (i.e., ≥4 mg/L for broth dilution and ≤10 mm for disk diffusion). It must be noted that these interpretive criteria fail to detect meticillin resistance in some *mec*A-positive isolates of *S. pseudintermedius* (Schissler, Hillier et al. 2009). Oxacillin minimum inhibitory concentrations (MIC) of ≥ 0.5 mg/L (agar and broth dilution) and a zone diameter of ≤17 mm around a 1 µg oxacillin disc (disk diffusion) used for coagulase negative staphylococci (CNS) are highly correlated with the detection of *mec*A in *S. pseudintermedius* (Bemis et al., 2009). Therefore, the 2004 CLSI criteria for oxacillin disk diffusion and oxacillin broth microdilution tests can assist in the interpretation of meticillin resistance in *S. pseudintermedius* isolates (Bemis et al., 2009, Schissler et al., 2009). Breakpoints only help to distinguish between phenotypically susceptible and resistant isolates. Additional test are needed to categorize isolates as MRSP. Phenotypical tests are influenced by pH, temperature, salt concentration and in addition there is always a difference between the presence of a gene and the expression of the gene. Therefore, whatever breakpoint is established, no breakpoint will distinguish MRSP from non-MRSP in 100% of the cases. In diagnostic laboratories, MRSP are only detected after

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			susceptibility testing. If *S. pseudintermedius* with an unusual resistance pattern is detected, additional tests like mecA PCR are performed. Therefore it is unnecessary to make susceptibility testing mandatory in cases of MRSP detection, because this was already done.
Section 6.1; page 10	3.	'*Occurrence'*: The prevalence may have been overestimated. It is very true that MRSP has been increasingly reported, but it is also true that prevalence of MRSP is not clearly known. In this respect it should be recognized that many studies are probably biased toward a higher prevalence and higher levels of resistance, as clinics usually submit samples from dogs that have been recurrently infected or from cases with therapeutic failures. Repetitive samples from the same subject may not have been excluded. This may apply to the German studies (Ruscher *et al.* 2010), where routine samples from diagnostic laboratories have been investigated; hence, usually from animals which were already exposed to one or more antibiotics. Similarly, the figures of Sasaki *et al.* (2007a) are based on pre-treated dogs of a referral clinic. Please also note that the latter study refers to only one clinic and may not reflect the MRSP occurrence for untreated dogs in Japan. In future prevalence studies only samples from untreated, first-time cases should be included. Consequently, the current prevalence figures (6.1; page 10) may have been overestimated.	It is correct that the prevalence of MRSP depends on the population studied and that there are still gaps in our current knowledge. However, we clearly state this in the document and therefore we do not feel that this paragraph should be changed. Companion animals colonized with MRSP are important in the view of epidemiology and are a potential source of MRSP for other animals and therefore it is important to mention prevalences of healthy animals as well as diseased animals. Prevalences of 0 % are also mentioned so we feel that this paragraph reflects the current knowledge.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>The structure of this section could be improved. One part of the references refers to healthy subjects (colonization and contamination); another part of the studies refers to diseased animals. Only the latter category is relevant for therapeutic issues.</td><td></td></tr>
<tr><td>Section 6.2</td><td>3.</td><td>The multi-resistance character of most MRSP is important and could be more focused. Would it be possible to insert a second example, e.g. findings of Ruscher et al. (2010):

<table><tr><td>Antimicrobial</td><td>Resistance (%)</td></tr><tr><td>Clindamycin</td><td>99</td></tr><tr><td>Ciprofloxacin</td><td>96</td></tr><tr><td>Erythromycin</td><td>99</td></tr><tr><td>Fusidic acid</td><td>0</td></tr><tr><td>Gentamicin</td><td>99</td></tr><tr><td>Linezolid</td><td>0</td></tr><tr><td>Rifampin</td><td>0</td></tr><tr><td>Teicoplanin</td><td>0</td></tr><tr><td>Tetracycline</td><td>62</td></tr><tr><td>Trim./sulfamethoxazole</td><td>100</td></tr><tr><td>Vancomycin</td><td>0</td></tr></table>
On the other hand, we have frequently observed oxacillin-resistant S. pseudintermedius (MICs ≥ 0.5 mg/L) which were susceptible to clindamycin, fluoroquinolones, 3rd gen. cephalosporins or other veterinary-licensed antimicrobial compounds relevant for the therapy of staphylococci infections in companion</td><td>The manuscript by Ruscher et al. (2010) is already mentioned in this paragraph and we do not feel that a second table adds new information to the document.
The resistance pattern of the MRSP depends on the origin of the isolates. There is a difference between isolates from the US and Europe and also within European countries there are differences. Therefore we agree that susceptibility testing is important, although the results have to be interpreted with care. Isolates containing mecA should be reported as resistant to 3rd generation cephalosporins irrespective of the results of phenotypic susceptibility testing. Isolates susceptible to clindamycin but resistant to erythromycin should be tested for inducible clindamycin resistance. Inducible clindamycin resistance of S. (pseud)intermedius has been described by Boerlin et al. (2001), Vet. Microbiol. Mar 20;79(2):155-69.</td></tr>
</table>

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		animals. IFAH-Europe, therefore, strongly proposes always determining the antimicrobial susceptibility of oxacillin-resistant staphylococci in order to ensure selection of an appropriate therapeutic drug.	
Page 2 Last paragraph	3.	Please check the spelling of *glycylcyclines*. Because of the next sentence "Treatment of MRSP with products…..", it is appropriate to replace "avoided" by "minimized".	The spelling was corrected. Avoided was replaced by "avoided to the extent possible"
Page 3, fifth point	3.	EC and EFSA are also (very) competent! Please delete "competent".	But they are not national authorities. National Competent Authorities (NCA) is a commonly used designation for national authorities which have at national level the responsibility for a certain matter. Not all national agencies/ authorities are competent (responsible) with regard to antimicrobial resistance surveillance.
Page 6, last paragraphs	3.	Please replace MRSP by "*S. pseudintermedius*" because context is not limited to MRSP. MRSP is defined in point 3.4. Delete ,. after the reference Talan et al., 1989a.	Accepted. MRSP was replaced by *S. pseudintermedius*
Page 8, last paragraph	3.	Why is the occurrence of *S. pseudintermedius* in humans underestimated? It is largely unknown because usually only the prevalence of coagulase-positive staphylococci is reported. Delete Goldstein from Talan *et al*., 1989a.	The occurrence of S. pseudintermedius is **probably** underestimated because in many laboratories all coagulase-positive staphylococci are grouped together as *S. aureus.*
Page 9, 2nd para	3.	The time sequence is unclear; please delete "since then".	Accepted.
Page 11	3.	Please delete MSSP in line 8 of the second paragraph. Replace in the last paragraph "eleven" by nine (Table 1 comprises only 9 compounds) or preferably add other	We deleted meticillin susceptible *S. pseudintermedius.* Rifampicin and streptothricin are not in the table because these are not licensed for dogs. However they were tested and

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		compounds from the paper as well.	therefore eleven is correct.
Page 12	3.	Please replace ciprofloxacin by enrofloxacin, because dogs (animals in general) are treated with enrofloxacin, not ciprofloxacin. Ciprofloxacin is only licensed in human medicine. Please include other compounds of Perretin *et al.*, 2010 in the list, particularly linezolid, vancomycin, quinupristin/dalfopristin, rifampicin, fusidic acid, mupirocin. It might be valuable to include some tables from other papers as well. BPs seems not accurate for trimetoprim/sulfamethoxazole.	We agree that enrofloxacin, not ciprofloxacin is used in dogs, however ciprofloxacin was tested and we cannot change this because the reference (Perreten et al.) would be inappropriate. We do not want to include compounds that are not licensed in dogs and in addition the table is on resistance and therefore compounds to which no resistance was detected were excluded. The row with trimethoprim refers to trimethoprim without sulfametoxazole and the source of break-points is described in the paper quoted.
Page 15	3.	Please delete "Lamport" from the reference Curtis *et al.*	The references have been checked.
Page 16, point 3b	3.	Please replace "is probably underestimated" by "is largely undetermined" or by "could have been underestimated", because the statement is slightly speculative.	Is largely underestimated would not be correct because we do not know. Could have been underestimated is not correct because this implies that this is not the case at present.
Page 17, point 7a	3.	Application of this breakpoint may overestimate the phenotypic prevalence of MRSP. Please see above. Does this breakpoint only apply for broth dilution and for example not for agar dilution method?	Application of this breakpoint is the breakpoint accepted by experts in the field. This also applies to agar dilution. We added this.
Page 17, point 8	3.	Point 8 does not properly reflect the current situation. Please add in the second sentence "…antimicrobials licensed for companion animals is common; resistance to critically important classes applied in human medicine is usually absent."	Partly agreed. We do not agree to add text on critically important antimicrobials being susceptible as this will change over time. Furthermore, resistance is already evident for instance for rifampicin.
Page 18, point 18	3.	Please add "….needed and adherence to the guidelines should be mandatory."	Not agreed. Although the Committee agrees that compliance with guidelines is very important it is not possible to make it

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			mandatory to adhere to them.
Page 18, point 23	3.	Please replace the second part by “and to determine the susceptibility to a wide spectrum of compounds of classes other than the beta-lactams”.	Not agreed but find the point 23 of the summary assessment well reflecting the content of the main body of the text.
Page 19	3.	Please check AGISAR reference and add “3rd edition”.	Agreed