21 January 2016
EMA/CVMP/EWP/374087/2015
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on the draft revised guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1)[1]

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

Stakeholder no.	Name of organisation or individual
1	VetCAST
2	Federation of Veterinarians of Europe (FVE)
3	European Coalition to End Animal Experiments (ECEAE)
4	Servei d'Anàlisi de Fàrmacs, Facultat de Veterinària, Universitat Auntònoma de Barcelona, Spain
5	Association of Veterinary Consultants (AVC)
6	IFAH-Europe

[1] Published with the reference number (EMA/CVMP/261180/2012).

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	The word “antimicrobial” is widely but wrongly used in the scientific literature as a noun. We suggest that it will be preferable for this word always to be followed by the word(s) “drug”, “veterinary medicinal product” or “treatment”, as appropriate.	Not agreed. It is acknowledged that the use of ´antimicrobial´ as a noun may not be fully correct from a grammatical point of view. However, the current use is widespread and would thus not be misunderstood.
1	We would draw to your attention the EUCAST approach in setting MIC breakpoints, as summarised in the paper by Mouton et al (2011). In Clinical Microbiology and Infection, 18, E37-E45. The abstract of this paper is as follows: *Clinical breakpoints are used in clinical microbiology laboratories to categorize microorganisms as clinically susceptible (S), intermediate (I), or resistant (R) dependent on the quantitative antimicrobial susceptibility as indicated by the MIC value determined in a well-defined standard test system. The laboratory report, with the designations of S, I or R for each antimicrobial agent, provides guidance to clinicians with respect to the potential use of agents in the treatment of patients, and clinical breakpoints should therefore distinguish between patients that are likely or unlikely to respond to antimicrobial treatment. In Europe, clinical breakpoints are set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), following a defined procedure. This includes evaluation of efficacy in experimental settings and clinical studies to derive pharmacodynamic targets such as the $f_{AUC/MIC}$ ratio or $\%f_T$ > MIC required for efficacy, the pharmacokinetic properties of the agent, Monte Carlo simulations to estimate exposures of the antimicrobial*	Noted. Additional text has been added to section 6.7 in regards to establishing clinical breakpoints.

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	agent in the target patient population and commonly used dosing regimens. The probability of target attainment is subsequently determined for a range of pharmacodynamic targets and the results from the Monte Carlo simulations. The breakpoints derived are subsequently evaluated with respect to the wild-type population of the target microorganisms, specific resistance mechanisms and other relevant data. In this paper, we provide an overview of the EUCAST process and considerations for setting pharmacokinetic / pharmacodynamic breakpoints. These are the breakpoints that in the EUCAST breakpoint tables are referred to as 'non-species-related breakpoints.	
2	FVE welcomes the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances and is satisfied with the concept of the paper. The attempts to reconcile clinical and epidemiological break points is done very well and well overdue, which we consider a real progress. FVE would like to draw the attention mainly on clarification of certain terms/definitions and the accuracy of the terms used in order to avoid confusion of the audience or even misinterpretation. Additionally we highlight the importance of ensuring that the work is now done by the European Union within VICH will ensure that these new guidelines are compatible with those within the VICH programme.	Noted.
3	**Language on animal welfare and the 3Rs** Although the guideline refers to animal welfare and the 3rs in places the location is not always appropriate and the text could be elaborated on. **We suggest the guideline clearly mentions**	Partly agreed. It is now mentioned in the beginning of the document, Section 5 (General consideration) that Directive 2010/63/EC

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	animal welfare, the obligations of Directive 2010/63/EC and the 3Rs at the beginning. We suggest language of this nature: *"Wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, should be used instead of an animal study in accordance with Directive 2010/63. Where this is not possible, studies should be selected that (a) use the minimum number of animals; (b) involve animals with the lowest capacity of experiencing pain, suffering, distress or lasting harm; (c) cause the least pain, suffering, distress or lasting harm; and are most likely to provide satisfactory results. If animals are to be used, numbers of studies, animals, dose levels and routes of administration should be kept to a minimum to generate the required information. Provision of social housing, enrichment and humane endpoints wherever possible should be made."*	and the 3R principles should be applied.
3	**Update of related pharmacokinetic guideline** The guideline also refers readers to EMEA/CVMP/133/99, which is the 'guideline on the conduct of pharmacokinetic studies in target animal species'. This guideline should also be updated to include animal welfare legal obligations (i.e. Directive 2010/63), the importance of the 3Rs and more up to date PK/PD approaches. According to a review, an update of this guideline should be a priority: "the main impediments to implementation of a PK/PD approach in drug development include poor understanding of PK/PD concepts by developers and, in veterinary medicine, the lack or inadequate recognition of its value by certain regulatory authorities (e.g. The European Agency for the Evaluation of Medicinal Products	Partly agreed. Although it may not be justified to open the pharmacokinetic guideline (EMEA/CVMP/133/99) solely for the introduction of a reference to the 3R principles, it is agreed that the pharmacokinetic guideline like all other guidelines should be revisited on regular basis to consider whether any revision is necessary. When this is done for the pharmacokinetic guideline, information on the 3R principles could be incorporated as appropriate.

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	(EMEA) guidelines for PK).” (Toutain, 2002).	
3	**Opportunities to reduce the number of animal tests** The opportunity should be taken with the revision to also highlight how animal tests can be reduced as the science has progressed. Currently, we do not feel the draft 1 Highlights these opportunities clearly enough, or draft 2 includes all opportunities. The guideline recommends PK/PD tests in animals, dose determination tests in animals, dose confirmation tests in animals and clinical field tests in animals. In the interests of reducing unnecessary testing in animals, opportunities to combine some of these tests or waive them based on the results of previous tests, *in vitro, ex vivo* or existing data **should be mentioned clearly at the beginning of each section**. In some cases, opportunities to avoid the test are mentioned, e.g. waiving of dose confirmation studies (line 346-), in these cases it would be preferable that these are presented at the start of the section.	Not agreed. The guideline contains information on how PK/PD information could be used to reduce the need for classical dose determination studies in animals. Furthermore, guidance is given on how to potentially waive dose confirmation studies in animals. Finally, it is requested that the guideline is read in conjunction with Directive 2010/63/EC implying that efforts should be made to omit animal studies wherever possible. Through these recommendations the reader is made aware that animal studies should only be used when necessary. This said, it has to be accepted that antimicrobials are evaluated in infected animals to ensure sufficient response to the treatment and safe use of the product. No further changes are regarded necessary.
3	Additional opportunities to avoid testing: **For example, PK/PD to avoid specific dose determination study:** For example, several studies have suggested that PK/PD studies can be used to determine appropriate dosage regimens for clinical trials, without the need for dose determination studies. (Toutain, 2002, Giraudel, 2005, McKellar, 2004, Lees, 2002). A study that compared a dose finding study in animals with a PK/PD study concluded that	The current version contains recommendations to use PK/PD analyses wherever applicable. The methods applied need to be validated for the intended purpose to ensure that the outcome is scientifically robust. Please note, section 6.7 advises: “…where the PK/PD relationship is well established using validated approaches, it may be possible to omit dose determination studies…”

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	the PK/PD trial was able to predict the recommended dose regimen for the drug nimesulide in dogs, which was later confirmed in clinical trials. (Toutain, 2001). These studies suggest that PK/PD studies can be combined with dose determination studies to reduce unnecessary testing. Furthermore, while dose finding studies traditionally require at least three doses to be tested in animals, the PK/PD approach only requires one single dose, which also leads to less suffering in the animals. According to one study, "the main impediments to implementation of a PK/PD approach in drug development include poor understanding of PK/PD concepts by developers and, in veterinary medicine, the lack or inadequate recognition of its value by certain regulatory authorities (e.g. The European Agency for the Evaluation of Medicinal Products (EMEA) guidelines for PK)." (Toutain, 2002).	
3	**For example, *in vitro*/*ex vivo* PK/PD studies:** Whilst the possibility to base Pk/PD on *in vitro* methods (alone) is mentioned in the guideline (confusingly under 6.3 dose confirmation studies) more detail on how this can be done is needed. - *In vitro* PK/PD studies are also often combined with *ex vivo* studies in biological fluids (e.g. serum, exudate) to predict dosage schedules in clinical trials. (Illambas et al., 2013). Computer-based methods have also been used for 'population PK/PD approaches', which are currently widely used for human drug development but not so much for veterinary medicine. According to a review, this approach "provides an opportunity to explain variation between animals in terms of breed, age, disease state, level of protection, and so forth. These models are capable of handling pooled	See response to previous question. Section 6.7 gives guidance to address this point. Although applicants are welcome to use alternative methods, they should be scientifically justified and it is beyond scope to provide guidance other than for well-established methods in this guideline.

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	data with allowance for fixed effects and random effects. Improving the power of PK and PD parameter estimation procedure will ultimately improve investigators' ability to develop optimal dosing regimens." (Toutain, 2002).	
3	**For example, use of existing information to predict dose determination** For example, a technique known as 'allometric scaling', was used to predict dose regimens and pharmacokinetic profiles of 85 veterinary drugs based on a database of existing information. The study concluded that "the analysis of available published pharmacokinetic data often helps to save time to estimate the first in-species dose regimen and important pharmacokinetic parameters for human and animal species during drug development and extra-label use in veterinary medicine." (Huang et al., 2014).	See response to previous question Although allometric scaling may be used as a tool in early development stages to predict drug dose regimens, we do not believe it can replace the studies currently required.
3	**Greater emphasis on need or not for experimental models of infection** In the interests of animal welfare and reduction in the use of experimental animals, greater emphasis on the need (or not) for experimentally infected animals to be used in the dose determination studies (line 275) and the preference for naturally infected animals in the dose confirmation studies (line 327) should be given.	Not agreed. It is currently mentioned that alternative methods to establish a dose could be used (PK/PD). Furthermore, under section 7.2 it is mentioned that the group size of negative controls should be the minimum required and in addition, that several parameters could be evaluated in the same study to reduce the need for study animals. This is regarded sufficient.
3	**Definition of 'clinical studies'** We are concerned that the guideline confuses the definitions of clinical studies/clinical trials/field trials. It is important that this is	Partly accepted It is now made clear in the heading of 7.4 that this section concerns clinical field trials and it would thus be clear that

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	rectified as “clinical trials” have a clear meaning under the veterinary products Directive. Furthermore, ‘veterinary clinical trials’ are except from the animal experiments Directive so this has bureaucratic and animal welfare implications. According to the current veterinary products Directive 2001/82/EC (chapter II Clinical requirements (1 .General principles), “the purposes of clinical trials are to demonstrate or substantiate the effect of the veterinary medicinal product **after administration of the recommended dosage**.” Furthermore the draft veterinary products regulation says under Article 4 (9) “‘clinical trial’ means a study which aims to examine **under field conditions** the safety or efficacy of a veterinary medicinal product or **both under normal conditions of animal husbandry or as part of normal veterinary practice** for the purpose of obtaining a marketing authorisation or a change thereof; “ Both definitions suggest to us that neither: PK/PD studies in animals, Dose determination studies in animals, Dose confirmation studies in animals, Nor any study where the animals are experimentally infected fall under the definition of a ‘clinical trial’. This is because 1. The recommended dosage is not (yet) known and/or the animals are not being treated as part of normal conditions of animal husbandry or as part of normal veterinary practice and /or	Directive 2010/63 does not apply to these studies. From the current wording of section 7.2 it is regarded to be sufficiently clear that Directive 2010/63 could be applicable to dose-determination studies. Dose-confirmation studies (section 7.3) could be made by use of experimental models or naturally infected animals kept under controlled clinical conditions. This implies that whether Directive 2010/63 is applicable or not for this type of studies would have to be a case-by-case judgement. No change to section 7.2 and 7.3 is proposed.

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	are not under field conditions (i.e. if experimentally infected animals are used). It is extremely important that the distinction between a clinical study and preclinical study is made as Directive 2010/63 on the protection of animals used for scientific purposes, Article 1 (5) states that the Directive does not apply to; "(c) veterinary clinical trials required for the marketing authorisation of a veterinary medicinal product;" Given that this Directive has recently been updated to afford greater protection for animals we do not support the use of language that could deliberately or inadvertently remove some tests from the auspices of this Directive. We suggest that section 6 is amended to make it clear what is meant by 'clinical studies' and 'field trial'. Under the draft as its stands any *in vivo* studies falling under 5.7 PK/PD, 6.2 dose determination and 6.3 dose confirmation are NOT 'clinical trials' as defined in the veterinary nor animal experiments Directive.	
3	**Definition of negative and positive controls** The use of a negative control is mentioned in several places in the document. In this guideline, negative controls are animals that have not been given the treatment (i.e. antibacterial) and are left to (potentially) develop an infection. It is rather confusing given that both naturally infected (field trials) and experimentally infected animals are included in this guideline so the infection status of the 'control' animal can vary.	Accepted. Definitions of negative and positive control have been added to the glossary.

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	Furthermore, In other scientific practices, a negative control refers to a group of animals that are not given the infection and not treated while a positive control group refers to animals that are given the infection and not treated. To prevent any misunderstanding, it would therefore be beneficial to include the definitions of a positive and negative control in the guideline glossary.	
4	After revising the document, there are some considerations that, in our opinion, must be taken in account when the efficacy of a VAM drug has to be evaluated. First of all, it is well known that the illness of the animals can affect to the pharmacokinetic behaviour of drugs. In the old guidelines this fact is not deeply taken in account and in all PK/PD analysis guides no recommendations are suggested in order to investigate the effects of the infection pathology in the pharmacokinetic behaviour of the drug. In this new guideline there are a reference (line 214-217, "It is acknowledged that the PK/PD analyses will be based on PK data obtained from healthy or experimentally infected animals. Nevertheless, the sponsor is encouraged to collect PK data from naturally diseased animals using population kinetic models. Knowledge of kinetic variability considerably increases the value of the PK/PD analysis.") about the possibility to study the effect of the pathology in the PK and PK/PD analysis. In this scenario, there is an easy way to obtain very valuable information whether or not the disease can affect the PK behaviour of the drug and to select PK/PD clinical break-point more realistic. As the applicants must perform clinical studies (dose selection, dose confirmation, etc.), to take some plasma samples to the diseased animals, during one day of treatment, and analyze the	It is agreed that the collection of PK data from naturally diseased animals could be valuable to explore exposure-effect relationships by use of population kinetic models. This is currently mentioned in section 6.7. Thus no further changes are regarded necessary. It has to be respected that in some member states animal welfare legislation strictly controls the extent of blood sampling from animals enrolled in clinical (field) trials.

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	drug concentration, would be an easy way to know the effect of the disease in the PK. Also, in these kind studies, an identification, isolation and MIC calculation of the pathogen are done. So a simple correlation between the susceptibility of the bacteria and the real plasma concentrations can be done. This approach can be easily done, also, because the applicants have not to validate the analytical methodology, because they have validated it previously. In terms of costs, it is not a relevant increase in the costs of the studies to perform, and the amount of information that it can be obtained is very high. Studies in our laboratory have demonstrated that this methodology can be simply applied, and similar clinical break-points can be obtained compared to the epidemiological cut-off values and clinical break-points published.	
5	We welcome the offer by CVMP and its working parties on efficacy and antimicrobial agents for a second round of consultation on the 'Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances'. We appreciate, that CVMP have taken on board many of our and other stakeholders' comments, which in general result in a guideline which may better meet the objective to facilitate applicants to obtain marketing authorisation for products containing antimicrobial agents and intended for use in animals. We especially appreciate that CVMP appears to acknowledge that this guideline can never cover all eventualities and allows for alternative study designs to be applied, if justified. We also support the "definition" section. Therefore, we have only a few comments to make.	

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6	IFAH-Europe welcomes the opportunity to review and comment on the revised draft Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances. We appreciate that several of our previous comments, some of which were discussed during the focus group meeting in December 2013, have been taken into account by CVMP. Compared to the initial version, the revised draft is more comprehensive, several important aspects are clarified, some requirements are relaxed, and a glossary is added. Nevertheless, we want to re-iterate that, especially for products which, according to official guidance, should be reserved for certain situations only (i.e. for cases of treatment failures or expected failures of other substances due to resistance), the increased complexity and increased data requirements will make the investment in such molecules very unattractive from a business perspective. While we appreciate that the proposed two-tiered approach could potentially be feasible (although expensive!) when dealing with livestock, we want to flag the difficulties we are foreseeing when this would need to be applied to the companion animal setting. Overall, we have the impression that any potential development programs for such molecules would need to go through Scientific Advice, which implies another extension of timelines as well as additional costs. IFAH-Europe has been informed at the VetCAST Stakeholder meeting in Copenhagen (Monday 27th April 2015) that VetCAST has reached out to EMA AWP with a proposal for VetCAST to become the EU	The additional burden connected to the evaluation of substances which according to official guidance should be reserved for certain situations is acknowledged. This has to be put in perspective of the necessity to obtain conclusive data regarding efficacy and safety in the target population for such products. The two-tiered approach is regarded appropriate to gain necessary information without causing insuperable hurdles. Adequate data should be provided to enable determination of the ECOFF, if feasible (e.g. for rare pathogens it may be justified that this is not possible). It is not mandatory for an applicant to suggest a clinical breakpoint; however, we would like to encourage this approach. The current text has been amended to address this point. Discussions with VetCAST are on-going and the concerns raised by IFAH-EU are acknowledged. As the guideline will equally apply to applications through DCP and National routes, CVMP will not automatically be involved in all applications. Clinical breakpoints will be accepted if they can be transparently supported by data.

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	operational body of EMA CVMP for definition/approval of veterinary-specific breakpoints. In lines 151-159 of this draft Guideline, reference is being made to interpretive criteria but it is currently not clear what would happen if the Sponsor does not propose an epidemiological cut-off value and/or a clinical breakpoint at the time of submission. Would that preclude CVMP from providing a positive opinion on the dossier, in other words does this become mandatory? If the latter, and especially if mandated to an external body such as VetCAST or equivalent, it will be of utmost importance for EMA CVMP to ensure a science-based, transparent process where Sponsors have the opportunity to actively participate in the scientific discussion. Formal processes and procedures will be required and confidentiality will need to be guaranteed at all times. Please confirm that clinical breakpoints scientifically established by CLSI will also be accepted. Apart from these major concerns, specific comments are provided in the next section.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
27	2	Comments: Change 'PK/PD relationship' in 'PK/PD integration approach'	Partly accepted. This section has been expanded and includes guidance beyond PK/PD integration.
57	2	Comments: Change 'therapeutic regimen' to read 'dosage regimen', i.e. dose, interval and duration. Through the PK/PD integration approach can be established the dose and dose interval, but not the duration of treatment.	Not accepted. The current wording "therapeutic regimen" is regarded appropriate to cover all aspects of treatment (dose, dosing interval and duration of treatment).
59	2	Comments: Change the order pharmacokinetics, pharmacodynamics and clinical trials according to the layout of the document.	Accepted.
60	2	Comments: Please change as following Proposed change : …is defined as a *pharmacologically active* substance primarily acting…	Not accepted. It is regarded superfluous to say pharmacologically active substance, it is regarded self-evident that the substance is pharmacologically active.
79-80	3	Comments: "Directive 2010/63/EC regarding the protection of	Partly accepted. The heading of section 7.4 has been changed to read ´Clinical field trials´, to make it more clear that Directive 2010/63/EC

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		animals used for scientific purposes also applies." See general comments. More detailed explanation of where the Directive applies (clinical vs field trials) and its significance should be included.	is not applicable to these trials. See also comment to previous comment on this topic.
80	3	Comments: "Applicants should also refer to other relevant European and VICH guidelines, including those listed in the reference list of this document." Can you be more specific about which 'other' documents are relevant? Would the guidance on bioequivalence and biosimilars be relevant?	Not accepted. The reference list mentions several guidelines which may be applicable. Depending on the product under study and other conditions it may be that also other guidance documents are relevant but this cannot be specified in further detail. The bioequivalence guideline would not be applicable for antimicrobial VMPs where pre-clinical and clinical studies are needed. There is no CVMP guidance available for biosimilars.
86-87	6	Comment: Reference is made to VICH GL27, however, the draft GL on the assessment of the risk to public health from AMR (EMA/CVMP/AWP/7064422013) is not mentioned at all.	Accepted. The EMA/CVMP guideline is now referenced, although currently still in draft.
93	2	Comment: Please change as following: Proposed change: …through *appropriate* reference…	Accepted.
97	5	Comment: "to the best possible extent" was added to the	Not accepted.

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		sentence. It is not clear, what is meant by this. Proposed change : Delete the words or replace by "… for therapy under clinical conditions	This wording was added to acknowledge that in some specific situations deviance between the study population and the intended target population for treatment may be acceptable, if this could be justified.
104	2	Comment: delete 'relationship' to read 'PK/PD integration approach' Proposed change: … pharmacodynamic/pharmacokinetic (PK/PD) *integration approach,* if…	Not accepted. The text in section 6 has been amended. The term PK/PD relationship is used when referring to PK/PD in a general sense. We would like to keep the term relationship here as general reference is made to section 6.7 (The pharmacokinetic/pharmacodynamic (PK/PD) relationship). Amendments in section 6.7 have been made to include (PK/PD) *integration approach*.
113	2	Comment: The pharmacokinetic studies, i.e. absorption, distribution, metabolism and excretion, should be performed by the same route that the veterinary product is applying for marketing authorization.	Accepted. Text updated.
113-115	3	Comments: "Measures should be in place to ensure any negative impact on animal welfare is kept to a minimum." See general comment about the need for a general statement on animal welfare and clarity on where the Directive 2010/63 applies. As a minimum we suggest:	Partly accepted. The sentence addressing the 3 R-principles was moved from section 6.1 to section 3. Thus 3 R-principles should cover all studies mentioned in the guideline.

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		"Measures should be in place to ensure that testing on animals shall be undertaken only as a last resort and any negative impact on animal welfare is kept to a minimum."	
121	1	Comments: In appropriate circumstances, it might be helpful to add, "if appropriate, reference should be made to actions of the drug substance over and above its direct microbial killing actions, which might contribute to clinical efficacy, e.g. effects on organism pathogenicity or virulence, influence on anti-inflammatory and immunomodulatory pathways of the host etc."	Accepted. Amendment made.
122-123	6	Comment: "Naturally resistant bacterial species relevant to the intended use of the veterinary medicinal product should be reported". It is unclear what is meant by this. A "naturally resistant species" would by definition be an intrinsically resistant species and hence would not be part of the label indication. Proposed change: Delete this sentence.	Partly accepted. Amended to "intrinsically resistant." It is still helpful for veterinarians to have information on intrinsically resistant organisms in case of mixed infections or cascade use.
128	1	Comments: We would prefer if you could refer to EUCAST and ISO standard 20776-1 (2006) for MIC determinations (or VetCAST if we establish a working relationship) rather than CLSI, as this would promote future collaboration	Partly accepted. ISO standard is the MIC determination method used by EUCAST, thus not deemed necessary to be mentioned additionally.

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		and data exchange between VetCAST and pharmaceutical companies. Moreover, ISO standard 20776-1 (2006) is the international reference method for broth microdilution tests and not CLSI.	CLSI also retained as an option, if no EUCAST values are available.
138-141	6	Comment: For some pathologies e.g., mastitis, different types are not feasible. Proposed change: …..should include, where applicable, different types.	Accepted. Text amended.
139-141	6	Comment: Different terms are being used such as “animal subgroup”, “production type”, “farm type” and “condition”. Proposed change: Please simplify the text, e.g., by deletion of “condition” and replacing “farm type” by “production type”.	Partly accepted. “Condition” and “type” have been replaced by clinical condition and production type.
140-141	2	Comment: Please change as following: Proposed change : …investigated (animal species *and category of animal*, condition,…	 Partly accepted. Text modified.

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144-147	6	Comment: Most of the published data do not precisely describe the MIC distribution, testing methodology or interpretive criteria or the interpretive criteria may have changed. We suggest clarifying this a bit more. Proposed change: It is acknowledged that for historical data information of the full distribution may not be available or studies were not performed according to the same methodology or interpreted using current interpretive criteria."	Accepted. Text amended.
151-159	1	Comments: Regarding this section, we envisage that VetCAST will be involved in the process of cut-off and breakpoint determination. Companies can propose breakpoints and cut-off's. However, to standardize and optimize the approach used by different companies and the criteria produced by them, external advice to CVMP by experts in the area of veterinary microbiology and PK-PD, based on data provided by the company, would improve the quality and predictive value of the criteria produced. All data used by the company to determine the cut-offs and breakpoints should be made available for external consultation and advice by VetCAST.	Comment noted, although there is currently no official relationship with VetCAST.
151-159	6	Comment:	Accepted.

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		It is currently not clear what would happen if the Sponsor does not propose an epidemiological cut-off value and/or a clinical breakpoint. Would that preclude CVMP from providing a positive opinion on the dossier, in other words does this become mandatory? Proposed change: Although there is much flexibility incorporated in the current wording, it would be helpful to add guidance on the overall weight/need for these data.	The wording has been revised. ECOFFSs should be provided, if feasible, and ideally a clinical breakpoint should be suggested.
156	2	Comment: Please change as following: Proposed change: …dose *regime* is shown efficient) deviating from the epidemiological *breakpoint* value.	Partly accepted. *Regimen* has been inserted, but in this case we believe that "cut-off" is the relevant term.
158-160	2	Comment: Please change as following: Proposed change: In case reference is made to a clinical breakpoint established by an external institute or published in *literature from peer-reviewed journals* it should be demonstrated that this value is relevant for the ~~product~~ *active antimicrobial substance* under study. It is recommended to include also major *active* metabolites contributing significantly to the antimicrobial activity in the *in vitro* susceptibility	Partly accepted. The sentence is changed: "It should also be demonstrated that this value is relevant for the active substance in the formulation under study"

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		testing.	
166	1	Comments: We suggest a possible addition to the text here, as follows: Proposed change : “Data on the kinetics of bacterial killing should preferably include all raw data and should comprise data on static or dynamic killing. To compute a critical numerical value for a breakpoint of a selected PK/PD indicator (AUC/MIC or fT>MIC) from the killing curve, a static system is generally acceptable for AUC/MIC but a dynamic system is normally required to compute a T>MIC”.	Accepted. Proposed change included in section 6.4 and 6.7.
167	2	Comment: Please change as following: Proposed change : …antimicrobial *agent* against…	Partly accepted: “*antimicrobial substance*”.
181	6	Comment: The terms ‘co-resistance’ and ‘cross-resistance’ need to be defined. Proposed change: Add definitions of co-resistance and cross-resistance to the Glossary.	Accepted. The same definitions have been used as those included in the draft Risk Assessment Guideline.

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184-185	2	Comment: Please change as following: Proposed change: …information may come from literature *from peer-reviewed journals* or proprietary studies and may derive from related antimicrobial substances *of the same class* in the absence of data on the specific substance.	Partly accepted. "*from peer-reviewed journals"* was included. "*of the same class"* was not included as this is already covered by …derive from "related" antimicrobial substances…
186-188	6	Comment: Cross-reference has been made to VICH GL27. We noted the recently released draft Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals, and are wondering to what extent this new Guideline will ultimately replace VICH GL27 and would therefore need to be referenced instead/as well?	Accepted. See above.
189 - 193	2	Comment: Please change as following: Proposed change : 5.6. Additional *in-vitro susceptibility* studies Additional *in vitro susceptibility* studies should, whenever relevant, include an investigation of possible synergy or antagonism and may include, for example,	Accepted. Text supplemented.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		investigation of post-antibiotic effects and, for certain antibacterial agents, an estimate of the rate of selection of resistant mutants and how concentrations above the MIC may affect or prevent selection of mutants. The methods for additional *susceptibility* studies should be well described and the clinical relevance of the obtained results should be justified.	
195	1	Comments: The potency and activity of some antimicrobial drugs, as indicated by MIC, MBC and time-kill data may differ markedly, when potency and activity are measured in biological fluids, such as serum and inflammatory exudate, from values obtained in normal growth media. This is specifically known for some macrolides and for oxytetracycline to greatly influence antimicrobial activity. We suggest a possible addition (or amendment) here, to be a little more specific as follows: "*Notwithstanding the guidance on the conduct of MIC, MBC and time-kill studies presented in sections 5.3 and 5.4 of these guidelines, namely to use internationally recommended guidelines and methodology in in vitro studies, any differences between artificial growth matrices (as required for use in international guidelines) and biological fluids, such as serum and heat-treated serum, should be reported for at least a limited number of isolates".* We suggest that this guidance is absolutely essential	Accepted. Text included in section 6.6.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		for some drugs/some pathogens to establish optimal dose schedules.	
199	2	Comment: Change as following: Proposed change: 5.7. The pharmacokinetic/pharmacodynamic (PK/PD) integration approach	Not accepted. Please see earlier comment. PK/PD *relationship* is kept as a general term inter alia in the heading of 6.7.
200 -205	2	Comment: *"To be effective, the 'dose' of an antimicrobial agent…"* What is the term dose refer to? Is it dose and dose interval or dose regime? For PK/PD integration approach can be selected the dose and dose interval, but not the duration of treatment. Please, state dose regime selection (i.e. dose and dose interval). Please change 'compounds' by 'active substances'. In the statement below (lines 221-222), says "*In addition, the use of PK/PD to predict the optimal duration of treatment is not well established at present…..*". We suggest moving this paragraph to the line 205. Proposed change : To be effective, the dose *regime* of an antimicrobial agent must be selected considering the susceptibility of the target bacteria. Therefore, for all *active*	Partly accepted. Amendments have been made to text as considered necessary. It is not accepted to move the highlighted text. Instead the preceding text has been amended to indicate that the PK/PD integration is primarily supporting the dose and dose interval, rather than dosing regimen.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substances with systemic activity, the MIC data collected should be compared with the concentration of the *active substances* at the relevant biophase following administration at the assumed therapeutic dose as recorded in the pharmacokinetic studies. In addition, the use of PK/PD to predict the optimal duration of treatment is not well established at present and sponsors should consider whether preliminary regimen-finding studies are needed to identify a suitable duration of treatment for any one 223 indication.. Based on *in vitro* susceptibility data, and target animal PK data, an analysis for the PK/PD *integration approach* may be used to support dose regimen selection and interpretation criteria for a clinical breakpoint.	
210	2	Comment: Please change as following: Proposed change: The overall assessment of the PK/PD *integration approach* should be…	Accepted.
218	2	Comment: Please change as following: Proposed change: In some cases where the PK/PD *integration approach* is well…	Accepted.
218-220	3	Comments:	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"In some cases where the PK/PD relationship is well established using validated models, it may be possible to omit dose-determination studies and to evaluate in a clinical trial the efficacy of one or a very few regimens." As mentioned in general comments above, several scientific studies have shown that PK/PD trials can be used to determine a dose regimen for clinical trials and that dose finding studies are therefore not always necessary. This point should be emphasised and examples of "validated models" should be provided e.g. *in vitro, ex vivo* and *in vivo* models as a last resort.	We do not consider that it would be within scope to give examples in this guideline of validated models as these are mostly specific to the antibiotic/organism and are available in published literature.
219-220	2	Comment: The term 'PK/PD parameter' is confusing. It should be read as following: Proposed change: …of one or ~~a~~ very few *dose* regimens. However, to be acceptable the choice of the PK/PD parameter, *i.e. integrated PK/PD variables correlating with bacteriological effects,* considered as best…	Partly accepted. The text has been amended so that the term "PK/PD index" is used instead (Toutain et al, 2002).
221-224	1	Comments: For long-acting formulations the applicant should also determine both magnitude and duration of activity; here EMA addresses the case of multiple dose administration but a LA formulation can be viewed also	Partly accepted. The text in section 6.7 has been re-drafted and the main principles requested are included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(from the antimicrobial effect) as a multiple dose administration; VetCAST would need this information for the PK/PD analysis. We suggest an addition to the text here that might assist in clarification, as follows, "An extensive peer reviewed literature now exists to justify and validate the use of Monte Carlo simulations/computations incorporating: (1) pharmacokinetic data (from healthy and/or diseased animals) with administration at the recommended dose rate; (2) pharmacodynamic data establishing breakpoint values (for example AUC/MIC ratios for various levels of bacterial kill); (3) serum protein binding data and (4) epidemiological MIC data for target pathogens, to provide Target Attainment Rate dosages. Sponsors will wish to consider this approach to setting dose rates for single dose administration of long acting products and/or daily doses to be administered at PK steady state. Sponsors will wish to consider that the most sound approach will be to perform a meta analysis by pooling available raw data using a population modelling approach. Following prediction of dosage by Monte Carlo simulations, sponsors will further wish to consider apportioning the overall variability of dose distributions to PK or PD variables".	
221-224	2	Comment: Move sentence above. Please see the previous comments.	See earlier comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: In addition, the use of PK/PD to predict the optimal duration of treatment is not well established at present and sponsors should consider whether preliminary regimen-finding studies are needed to identify a suitable duration of treatment for any one indication.	
225	2	Comment: Please change as following: Proposed change: Currently the most commonly used parameters to express the PK/PD *integration approach* are Cmax/MIC…	Not accepted. See previous comments.
230	1	Comments: It might be helpful to add here, “sponsors may wish to make use of both PK/PD integration and PK/PD modelling approaches in establishing doses for evaluation in clinical trials”.	Accepted.
239 - 240	2	Comment: An over-reliance on negative controls throughout the clinical testing guidance might be contrary to the principles of 3R's. FVE would like to draw your attention to this issue and ask for potential reconsideration of this part of the sentence. Additionally reference to the Directive 2010/63/EU of The European Parliament and of the council of 22	Not accepted. The current wording is regarded sufficiently clear on the subject that the use of negative controls should be kept at minimum. A general reference to Directive 2010/63/EC is made in the beginning of the document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		September 2010 on the protection of animals used for scientific purposes should be included. Proposed change: …claims, one clinical study using a negative control group should be provided preferably as a minimum, 239 unless the superiority of the product is proven otherwise. The “3R-principles” (replacement, reduction, refinement) *and Directive 2010/63/EU of The European Parliament and of the council of 22 September 2010 on the protection of animals used for scientific purposes* should always be applied whenever possible.	
240 - 241	3	Comments: “The “3R principles” (replacement, reduction, refinement) should always be applied whenever possible.” See general comments. The 3Rs should be mentioned earlier than this (i.e. at the beginning of the document and certainly before PK/PD studies).	Accepted. The sentence is moved to section 5.
241	3	Comments: “Several controlled trials are generally required…” In the interests of avoiding unnecessary animal use, if possible it would be preferred if clearer indications for how many trials are needed and why, otherwise the guideline does not currently assist in this area at all.	Not accepted. It is not possible to give further details regarding how many studies would be needed since this depends on several factors. It is however regarded useful to indicate that a number of studies will normally be needed to support the posology and the clinical efficacy and safety.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
241	6	Comment: The word 'always' is inconsistent with the qualifier 'whenever possible'. Proposed change: The "3R-principles" (replacement, reduction, refinement) should ~~always~~ be applied whenever possible.	Accepted.
248	2	Comment: Please change as following: Proposed change: The *veterinary medicinal* product formulation used…	Accepted.
258-259	1	Comments: We propose inclusion of a statement to justify the duration of activity of long-action formulations.	Accepted.
268	1	Comments: It could be reasonable here to suggest a POSSIBLE alternative to several dose determination studies, by inserting after "support", *"the sponsor may consider, as an alternative to several dose determination studies, the use of Monte Carlo simulations (vide supra) to predict for each pathogen 90 and/or 50%Target Attainment Rate dosages for (a) single dose administration (b) daily administration at PK steady state and (c) different levels of kill e.g.*	Not accepted. In the current text it is mentioned that PK and PD characteristics could be used to support posology. However, it is regarded appropriate to leave to the investigator to decide on which specific method to apply when using PK/PD analysis to gain support for a certain dose and dosing interval.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		bacteriostatic and bactericidal actions".	
274	6	Comment: For clarity and brevity please amend the sentence as follows: Proposed change: activity may be used to support ~~the need for any certain duration of exposure to the active substance~~ the dosing regimen.	Partly accepted. The text has been slightly changed. However, since this text concerns specifically the duration of treatment (and not the dose and the dosing interval) the proposed change to ´dosing regimen´ is not accepted.
289	1	Comments: Clinical and bacteriological efficacy can be markedly affected by time elapsing between appearance of clinical signs and dosing, so that the sponsor should be advised to consider this carefully in study design by a possible addition here as follows. *"The sponsor will wish to consider carefully the time elapsing between inoculation then appearance of clinical signs then product administration, recognising that a well-established infection will be more difficult to treat than one in which early therapeutic intervention is made, as pathogen load in the biophase is likely to be markedly dependent on the interval between pathogen inoculation and dosing".*	Not accepted. It is acknowledged that the timing of treatment in relation to inoculation may have impact on treatment efficacy for the reasons highlighted by the stakeholder. The current text recommends that treatment should normally not be initiated before clinical signs occur, to avoid an overestimation of efficacy in the study. This said, it may be justified to deviate from this recommendation in case of per-acute disease when a valid model is available. The current text is considered well balanced to address these different situations and no changes are proposed.
295-296	1	Comments: For bovine and porcine respiratory infections THREE major pathogens for each animal species can be realistic indications for a veterinary medicinal product.	Not accepted. It is mentioned in the current text that PK/PD information could be used to support a dose and dosing interval and

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		If then three studies per pathogen are recommended as the norm, this will make 3x3x2 studies for one drug even if just one dose is tested; this is a total of 9x2 = 18 studies. On the other hand, if only one microbial species (the least susceptible - see line 281) is selected, BUT three levels of dosage are to be tested, this would still involve nine dose determination studies for each animal species. We do not consider this to be feasible or desirable given the workload, debatable scientific justification, costs and animal welfare issues involved. Surely this is what the PK/PD-population modelling approach with MC simulations is for. We suggest that EMA reconsiders this requirement.	consequently reduce the need for classical dose finding studies. In addition, in line 265 and onwards it is mentioned that several parameters could be incorporated into the same study. Furthermore, as mentioned by the stakeholder, in case of disease where several pathogens are involved the dose determination studies could focus on the least susceptible to reduce the need for studies. Through these measures the number of studies could be reduced to a minimum. No change is regarded necessary.
298	6	Comment: In certain situations, bacteriological response may be difficult to determine without significant impact on the physical condition of the individual animal due to the required sampling methods, *e.g.* broncho-alveolar lavage requiring anesthesia in pigs. Proposed change: Efficacy evaluation should be based on clinical and <u>if applicable</u> bacteriological response as determined by appropriate clinical and bacteriological assessment.	Not accepted. For dose determination studies typically made in a small number of animals under experimental conditions, it is regarded necessary to assess the effect of treatment based on both clinical and bacteriological response, whereas for clinical field studies it is often sufficient to evaluate response based on clinical cure.
299-301	3	Comments: "Mortality should be assessed and post mortem data should be added wherever meaningful. The endpoints (primary and secondary) and timing of the response	Not accepted. The need for taking the 3R principles into account is mentioned in the beginning of the document and would thus not have to be repeated in further sections.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		assessment used should be justified in relation to the disease and substance under study." Mention of humane endpoints should be made here taking the 3Rs into account. References: Giraudel, 2001. Development and validation of a new model of inflammation in the cat and selection of surrogate endpoints for testing anti-inflammatory drugs. J Vet. Pharmacol. Therap. 28: 275-285. Huang et al. 2014. Interspecies allometric meta-analysis of the comparative pharmacokinetics of 85 drugs across veterinary and laboratory animals species. (2014). J. Vet. Pharmacol. Therap., 38: 214-226. Lees et al. 2002. Rational dosing of antimicrobial drugs: animals vs humans. Int Journal of Antimicrobial Agents, 19: 269-284. McKellar 2004. Pharmacokinetic/pharmacodynamics integration in drug development and dosage-regimen optimization for veterinary medicine. AAPS PharmSci, 4 (4): Article 38. Toutain, 2002. Pharmacokinetic/pharmacodynamics integration in drug development and dosage-regimen optimization for veterinary medicine. (2002). AAPS PharmSci, 4 (4): Article 38. Toutin et al, 2001. A	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pharmacokinetic/pharmacodynamics approach vs. a dose titration for the determination of a dosage regimen: the case of nimesulide, a Cox-2 selective nonsteroidal anti-inflammatory drug in the dog. Therap. 24, 43-55.	
300	2	Comment: Please change 'endpoints' by 'efficacy endpoints' and include same examples to primary and secondary endpoints. Proposed change: The *efficacy* endpoints (primary and secondary)…	Accepted.
301	2	Comment: Please change 'substance' by 'veterinary medicinal product': Proposed change: …disease and *veterinary medicinal product* under study.	Accepted.
302	6	Comment: For clarity please amend as follows: Proposed change: Clinical ~~O~~observations should be collected repeatedly before, during and after treatment, as appropriate.	Not accepted. The request for data collection concerns both clinical and bacteriological data and thus a restriction to clinical observations only is inappropriate.
310-311	2	Comment:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please change 'dosage regimen' by 'dosage regime of veterinary medicinal product': Proposed change: …appropriate *dosage regime of veterinary medicinal product* which should be… The *efficacy* endpoints (primary and secondary)…	
327	1	Comments: It is important to include here a statement in the text to indicate that the MICs of the organisms involved in the naturally infected animals should be known.	Accepted.
328-329	5	Comment: Dose confirmation studies are often still using negative control groups, but in any case artificial or natural disease in order to measure the effect, especially in case of treatment claims, which are a pre-requisite for other claims. We therefore believe that it is not possible to "reduce any negative impact on animal welfare". Proposed change: "Appropriate measures should be applied to avoid any non-justified impact on animal welfare"	Not accepted. It is acknowledged that <u>all</u> negative impact may not be possible to avoid, but a reduction as far feasible should always be the goal. It is difficult to determine which impact on animal welfare could be justified and thus the proposed rewording is not regarded useful.
333	2	Comment: Please add examples of primary endpoint(s).	Not accepted. Since the most relevant primary endpoint could vary depending on several conditions it is regarded relevant to include flexibility in the text in this regard. The mentioning of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The primary endpoint(s) (e.g .....) should preferably be…	specific examples can often be interpreted as mandatory requests which should be avoided.
335-356	2	Comment: Please change as following: Proposed change: …is based on *in vitro susceptibility* PD data only.	Accepted.
343	1	Comments: It would be helpful to add here after “or in the” the words “biophase of” before “target tissue” as veterinary pharmacologists are all too conscious of the fact that “tissue” concentration is utterly unhelpful.	Accepted.
352	1	Comments: We suggest here to insert after “clear” the words “concentration-effect and”	Not accepted. Although it would be of value to always have PK data from dose finding studies to be able to assess the concentration-effect relationship, this is not a general request. Thus, such relationships are not always clarified. Convincing data from a classical dose-effect evaluation could be acceptable.
357-358	1	Comment: We appreciate the modification of this sentence. However, we believe that the wording should be adjusted. The term “as far as possible” would normally be interpreted to use as many animals and timepoints as possible, which may bias studies by multiple handling of animals and is not compliant with the 3Rs	Partly accepted. It is agreed that the current wording could be misinterpreted as mentioned by the stakeholder. A slight rewording has been made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		principles. Proposed change: “, the variability between animals in feed/water intake should be explored in a limited, but representative number of samplings, with the purpose of ensuring ….”	
357	5	Comments: We suggest here to clarify insertion after “variability”, the words “in dose received and response obtained”	Not accepted. The text mean to say that variability in feed/water intake should be evaluated to indirectly clarify if the treated animals will be provided the dose needed to obtain a treatment effect.
359	2	Comment: Please change ‘Population PK/PD models’ by ‘PK/PD modelling approaches’. Proposed change: *PK/PD modelling approaches* (such as…	Partly accepted. The expression *PK/PD integration approach* is regarded relevant here.
370	5	Comment: The preparation of “dummy treatments” and its application is a relevant source of increased costs, both for manufacturing those under “GMP” as well as for the generally increasing number of treatments needed to be applied. Multiple injections are also adding unnecessary animal welfare concerns. Propose to delete the words “such as dummy treatment, if necessary and use the terminology of the previous version. No doubt that appropriate blinding is needed, but adding these terms will lead to many studies using	Partly accepted. The text is slightly reworded with the intention to make clear that dummy treatment is not always necessary to ensure blinding of the study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dummy treatments unnecessarily. Proposed change: “Blinding of the study needs to be ensured through appropriate study design and conduct measures.”	
375	2	Comment: Please change approved ‘product’ by approved ‘veterinary medicinal product’. Proposed change: …no approved *veterinary medicinal* products for the indication…	Accepted.
382	2	Comment: Please change approved ‘product’ by approved ‘veterinary medicinal product’. Proposed change: … should be a *veterinary medicinal* product authorised …	Accepted.
383-384	6	Comment: Amended to improve readability Proposed Change: The applicant should pay attention ~~to~~ that the chosen control product ~~needs to be~~ is sufficiently effective for the target indication at the time the study is	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		conducted.	
385	2	Comment: Please change approved 'product' by approved 'veterinary medicinal product'. Proposed change: *Veterinary medicinal* products for which …	Not accepted. The change is not necessary since it is mentioned first in this paragraph that the positive control should be a product authorized under Directive 2001/82/EU which implies that it is a veterinary medicinal product.
390	2	Comment: Please change approved 'product' by approved 'veterinary medicinal product'. Proposed change: .. proposed control *veterinary medicinal* product would be …	Not accepted. See response to previous comment.
388	2	Comment: Please change approved 'product' by approved 'veterinary medicinal product'. Proposed change: … an authorised *veterinary medicinal* product it has to …	Not accepted. See comment above.
398-401	6	Comment: In case of a superiority trial, it is not understood why the positive control would have to be a "relevant alternative for the current indication". In the extreme case, this positive control would be completely	Partly accepted. A superiority trial could be appropriate if a company would like to demonstrate that a product is more effective (due to e.g. a quicker onset of effect and higher response rate depending possibly on the pharmacological activity) for a

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ineffective and behave as a negative control. This is indirectly acknowledged in lines 402-404. Proposed Change: Delete the paragraph.	certain condition/subgroup of animals as compared to a product authorised for the same indication. E.g. a product may be claimed to provide higher efficacy against severe cases of Actinobacillus pneumonia as compared to a product authorised for the treatment of SRD (including Actinobacillus). In this situation it has to be taken into account that the positive control is effective at time of the study on basis of e.g. recent susceptibility data. The text has been slightly changed to clarify this.
408	1	Comments: We suggest to delete “where applicable”. We consider that information on antimicrobial susceptibility is crucial.	Accepted.
412-416	1	Comments: We propose to include “determination of MICs” to bacterial testing. As we stated above, information on susceptibility of the organisms involved in infections in clinical trials is of the utmost importance to assess the efficacy.	Partly accepted. It is already mentioned that susceptibility of the isolated bacteria to the test product should be tested in vitro. To clarify that susceptibility tests should always be performed the text has been slightly reworded.
423-450	6	Comment: Requirements for substances to which certain restrictions apply should preferably be listed under a separate heading in order to make clear that the requirements do not apply to all new antimicrobial developments.	Not accepted. It is regarded sufficiently clear in the text which recommendations relates to substances which are to be used under restriction.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
429-431	6	Comment: It is currently not clear if the sentence 'This study would have to include an effective positive control, implying the bacterium(a) under study is (are) fully susceptible to the chosen control' refers to the first or second study proposed below. Does this sentence refer to the study referenced in lines 435-438 (which we presume), or to the study referenced in lines 438-444, or both? Proposed change: Please clarify, perhaps by moving the sentence further down, e.g. place it at the end of line 436. Comment: There might be occasions where such effective positive control product is not available, i.e. the bacterium(a) under study is (are) resistant to all currently registered molecules that fulfil the requirements specified in Section 6.4.2. We therefore suggest to modify this sentence as follows: Proposed change: 'This study would have to include an effective positive control, implying the bacterium(a) under study is (are) fully susceptible to the chosen control, if available'. Note that this comment is linked to the request above to delete lines 398-401. It is difficult to understand why is would not be acceptable to demonstrate	Partly accepted. It is now mentioned that a negative control should be included if there are no products available that could suite as positive control (e.g. multiresistance). It is not regarded relevant to include as control a product containing a substance which due to resistance towards the bacterium(a) under study is expected to be ineffective. In that situation it is appropriate to include a negative control.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		superiority to an authorised product which is no longer efficacious due to the emergence of resistance. This is exactly the concept of a product that should be reserved for certain situations only!	
465-467	2	Comment: Please give definitions for “clinical endpoint”, “primary endpoint for efficacy”, “secondary endpoints”, etc.	Not accepted. The meaning of these expressions is considered to be well known and would thus not need further clarification.
482	2	Comment: Please change ‘target tissue’ by ‘specific/target tissue’ where the active substance is distributed. Target-tissue is used for residues of VMP. Proposed change (if any): …plasma or *specific/* target tissue.	Not accepted. “target tissue” is not exclusively used for residues of VMP but is regarded to be well understood from a distribution/clinical effect perspective.
531-533	6	Comment: The factors listed here are not definable and vague, at which level immunity is developed, how can the limitation of resistance development be assessed? Proposed Change: Please delete this paragraph	Not accepted. This bullet point means to indicate that the treatment duration should be justified in relation to the epidemiology of the disease which includes duration of shedding and development of immunity with the overall aim to accommodate treatment to the goal of obtaining sufficient response without unnecessary exposure.
534	6	Comment: Please note that some non-antimicrobial supportive treatment such as NSAIDS or steroids might interfere with certain primary efficacy variables such as rectal	Accepted. Accepted with a slight rewording of the proposed new text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		temperature. Proposed change: Non-antimicrobial supportive treatment, if not interfering with the primary endpoint(s), should be allowed in the treatment and the placebo group.	