12 February 2015
EMA/CVMP/EWP/737951/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances' (EMA/CVMP/261180/2012)

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

Stakeholder no.	Name of organisation or individual
1	European Group for Generic Veterinary products (EGGVP)
2	Association of Veterinary Consultants (AVC)
3	International Federation for Animal Health Europe (IFAH-Europe)
4	ECO Animal Health Ltd
5	European Coalition to End Animal Experiments (ECEAE)
6	Professor Peter Silley, MB Consult Limited & University of Bradford
7	Federation of Veterinarians of Europe (FVE)

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1. General comments – overview

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1	EGGVP welcomes and fully supports the initiatives and efforts of the Agency to minimize the risk of developing antimicrobial resistance. In this context, transparent and pragmatic guidance for the demonstration of efficacy of antimicrobial substances is necessary.	
1	Although the scientific background of new requirements is not put into question, its high complexity raises concern and it jeopardizes the availability of veterinary antimicrobials. If the efforts to comply with these requirements are not proportionate with the value of the product on the market, many antimicrobials (specially 'old' ones) will disappear since the intention of industry to invest in such products will not be very high. Experience also shows that, when requirements are too complex and cannot be met by industry, there are less indications and pathogen combinations approved for the same target species. This leads to serious availability problems and to the promotion of off-label use, putting veterinarians in a very uncomfortable and unpractical situation. EGGVP fears that the opportunity to help keeping a broad arsenal of antimicrobial veterinary products available has been left out in this proposal.	Comments regarding increased complexity of requirements in the draft guideline are not substantiated and could thus not be further commented on. The guideline does not concern old VMPs currently on the market and would thus not affect availability of these products.
1	The current text does not distinguish between the well-established (older) antimicrobials and the newer ones. EGGVP believes that separate guidance is necessary for these products (ref. comment above for 'old antimicrobials'), and would like the Agency to consider other approaches and practical solutions for this most important category of veterinary medicinal products.	Not agreed. The same scientific principles for efficacy assessment are applicable for old and new products.
1	One of the main objectives of this guideline is to provide more	Answers to specific comments is given below in this

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	precision on the indications for the design of clinical trials in order to build a more predictable regulatory system. However, the current text still contains ambiguous and unspecific terms related to requirements, and it lacks some necessary references (please see 'specific comments' for further details). More specificity of requirements, methods and references would be desirable.	document.
2	We appreciate the drafting of the revision of this guideline and appreciate the efforts taken to try to balance the risks associated with the use of antimicrobials for the treatment of animal infectious disease caused by bacteria and their benefits. Within the current political environment and the ongoing discussions regarding the prudent use of antimicrobials in both, human and animal medicine, the revision was hoped to balance the requirements for efficacy testing of antimicrobials within the prudent use limitations as outlined by EPRUMA and similar national and international organisations.	Noted.
2	We appreciate the efforts to define treatment, metaphylaxis and prevention. However, we believe that the current proposals in the revision add significant complexity to the development of antimicrobials for veterinary use.	See above. Comments regarding increased complexity of requirements in the draft guideline are not substantiated, and could thus not be further commented on.
2	As many products are destined to be applied locally, specific reference would be appreciated separately from the parenteral and oral use product development requirements.	Some specific recommendations for locally active products are are given for dose determination (section 6.3). In other respects the guideline is applicable also for locally active products. Reference to the intramammary guideline is given for the efficacy evaluation of such product.
2	The current text of this guideline leaves still a lot of space and	The wording of the guideline has been improved, and more

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	options for interpretation for both, the applicant, as well as the competent authorities evaluating a marketing authorisation. We have strong doubts that in the current climate the requirements stipulated in this guideline will motivate industry to invest in the development of innovative new products. The investment into a dossier will grow significantly while there is even less assurance in the success of any such investment in a marketing authorisation so introducing the spectre of regulatory uncertainty.	clarity added to concerns addressed below.
2	The requirement implemented for intramammary products to consider both this guideline and the "guideline for intramammary products for use in cattle" is seen as critical. We believe that intramammary products should be covered in a specific guideline without making reference to the oral and parenteral use. This will increase costs for a marketing authorisation of intramammary products in an area, where antimicrobials have been used prudently for many decades and resistance development is low.	Agreed. For intramammary products recommendations for the design of clinical trials are provided in the Guideline for the conduct of efficacy studies for intramammary products for use in cattle (EMEA/CVMP/344/99-FINAL-Rev.1).Only the pharmacology section of the current guideline applies for intramammary products. This has been clarified in the text.
2	In summary we believe that the requirements as stipulated in this guideline will further discourage innovation for the development of veterinary medicinal antimicrobial products.	Noted.
2	The animal welfare aspects of treating animals with infectious disease, ranging from moderate morbidity to high mortality, in addition to the potential for infecting other animals as well as recrudescence in individual animals or groups of animals are likely to be severe. As both *in-vitro* and *in-vivo* data are requested in the guideline this should give sufficient evidence about the efficacy of a product and specific treatment strategies should be left with the	Not agreed. *In-vitro* and experimental data will not provide a reliable estimate of the efficacy level under clinical use. Thus, the efficacy of the product needs to be confirmed in field studies sufficiently dimensioned to confirm statistically a clinically relevant effect level. However, for substances reserved for use only under particular circumstances, such as 3rd and 4th

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	prescribing veterinarian. Field clinical studies are the best means of proving efficacy under "real life" conditions; therefore, it should be sufficient to confirm the efficacy under field conditions in a limited number of representative locations.	generation cephalosporins and fluoroquinolones, it may be acceptable to confirm efficacy in the intended target population through efficacy evaluation in a smaller number of animals that fully corresponds to the target population, provided sufficient field data is also generated in other animals (see section 6.4.3 of the revised draft).
3	IFAH-Europe welcomes the opportunity to comment on the draft revision of the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances. The proposed revised guideline responds to a public health concern, but also raises a number of serious issues for animal health and the animal health industry: **1. Impact on innovation** Whilst the European Council, Commission, Parliament, CVMP and HMA have all expressed the desire and support for development of new antibiotics, there is a significant probability that this revised guideline will actually be a disincentive and discourage new veterinary antibiotic development. Classifying a substance as a second line choice immediately limits the market size. The development of a new antibiotic regarded as a second line substance may not be economically viable because of substantially increased development costs due to the new requirements combined with a restricted market. Thus, by implementing the provisions as described here, there would be very little incentive for sponsors to develop new products. While there is a common goal of all stakeholders in veterinary medicine to ensure the efficacy of the antimicrobials long-	1 and 2. The guideline does not refer to any classification of substances as first or second line but only advices that any official guidance on preferred choices of antimicrobials should be taken into consideration. Currently such guidelines are established e.g. for 3rd and 4th generation cephalosporins and fluoroquinolones. Suggestions have been added to the guideline (section 6.4.3) regarding how to confirm efficacy in clinical trials for such products. It is agreed that a restriction put on a substance saying it should be used only under particular circumstances will have consequences on the market. However, this issue is out of scope for the guideline.

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	term and to minimize the emergence and spread of resistance, some requests of the guideline seem not to be appropriate to achieve this goal. In contrast, highly demanding requests may lead to the use of few antibiotics which will exert a constant selection pressure and thus could select for resistance and become obsolete.	
3	**2. Early Classification is a disincentive** Classification of a product as a *de-facto* second line treatment is a risk management measure which is not appropriate during new product development and the investigation of efficacy. From a scientific point of view, the intrinsic efficacy of an antimicrobial for a specific indication/pathogen(s) needs to be established, regardless of whether another antimicrobial would be regarded as the first line choice. The study design will be focused on the disease, disease-specific inclusion- and exclusion criteria and cure or clinical outcome. Preferably, a comparative design comparing efficacy to a positive or negative control will be applied. Only after proper evaluation should risk management options and recommendations be introduced in the relevant sections of the SPC if necessary. The OIE responsible use principles should be specified as a guiding outline, rather than the proposed uniform and unbalanced restriction on use. In the current proposal, certain classes of antimicrobials will be classified as second line by default, regardless of the indication. However, they may be indicated for conditions for which no antimicrobial listed as a first line treatment is approved. Furthermore,	See above.

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	the classification of novel molecules will not be clear. Flexibility, rather than specific direction, is needed to ensure that novel interventions can be appropriately evaluated and that the infected animal receives the best and most appropriate treatment to manage the disease.	
3	**3. Generics** This Guideline is applicable for new antimicrobial substances as well as for variations and extensions to previously authorised products, but does not apply to generics. The described requirements for variations and extensions will discourage sponsors from developing new claims for old substances already established in the market. Why should sponsors engage in expensive studies according to the revised guideline, if generics can then obtain the same claim within a short period of time without submitting any data? We would suggest that in the future legislation for variations and extensions of existing products data exclusivity should be granted for at least three years. A company producing a generic product is not required to reconfirm the efficacy of the reference product; similarly there should be no requirement for a company producing an original product to reconfirm the efficacy of a product used as a positive control in an efficacy trial.	3. Concerns raised regarding regulatory requirements for generics are not commented as these are not within the scope of this guideline. Data exclusivity rules are addressed in the proposed new Regulation but this is out of scope for the current guideline. The concerns raised regarding the justification of positive controls are commented further down in this document.
3	**4. Align with the OIE Terrestrial Code** The OIE Terrestrial Animal Health Code Chapters 6.9 and 6.10 have recommendations regarding animal disease studies, target pathogens and potential AMR effect on animal health and it is felt that CVMP should take these into consideration whilst revising the current GLs	4. The recommendations and requirements put down in this document are regarded to be in correspondence with the OIE Terrestrial Animal Health Code Chapters 6.9 and 6.10.

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	so as to maintain alignment between CVMP and OIE expectations. Specifically: Chapter 6.9. - Responsible and prudent use of antimicrobial agents in veterinary medicine Chapter 6.10. - Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals	
3	**5. Exclude intramammaries** The proposed revised GL applies to antimicrobial substances used in veterinary medicines for all routes of administration and to all pharmaceutical forms. This is a tremendous shift in scope compared to the current guideline where antimicrobials for intramammary administration are excluded and for which only the pharmacodynamic section of the GL applies. It is recommended that the separation of intramammaries is retained in order to avoid any ambiguities in guidance and that the specific guideline for antimicrobials intended for intramammary administration (EMEA/CVMP/344/99) is updated as appropriate.	5. For intramammary products recommendations for the design of clinical trials are provided in the CVMP "Guideline for the conduct of efficacy studies for intramammary products for use in cattle" (EMEA/CVMP/344/99-FINAL-Rev.1), which is currently under revision. Only the pharmacology section of the current guideline applies for intramammary products. This is now clarified in the text.
3	**6. Clear definitions are needed** For clarity a glossary should be added to the guideline with clear definitions of the key terms used within the guideline (antimicrobial, treatment claim, prevention claim, metaphylaxis claim, relapse *etc.*). We strongly recommend the use of the EPRUMA document on veterinary medicinal product terminology which contains the following definitions:	6. A glossary has been added to the guideline to clarify key terms. The definitions do however not comply fully with the suggestions given by the stakeholder since the proposed definitions (EPRUMA) do not fulfil regulatory needs in all aspects.

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	• **Antimicrobials:** a general term for any compound with a direct action on micro-organisms used for treatment or prevention of infections. Antimicrobials include anti-bacterials, anti-virals, anti-fungals and anti-protozoals. • **Anti-bacterials:** compound with a direct action on bacteria used for treatment or prevention of infections. • **Antibiotics:** synonymous with anti-bacterials. • **Curative (therapeutic) treatment:** Treatment of an ill animal or group of animals, when the diagnosis of disease or infection has been made. • **Control treatment (metaphylaxis)**: treatment of a group of animals after the diagnosis of clinical disease in part of the group, with the aim of treating the clinically sick animals and controlling the spread of disease to animals in close contact and at risk which may already be (subclinically) infected. • **Preventive treatment (Prophylaxis)**: treatment of an animal or a group of animals before clinical signs of disease, in order to prevent the occurrence of disease or infection. Prophylaxis with antibiotics is only applied to animals at high risk of bacterial disease under prescription by a veterinarian on the basis of epidemiological and clinical knowledge.	
3	**7. Additional clarification is needed on assessment of second line antibiotics** The Concept Paper EMA/CVMP/760764/2010 announced that *more guidance is needed for products that are 'reserved for the treatment of clinical conditions which have responded poorly, or are expected to*	7. It is not regarded possible to classify substances as first, second or higher lines as this will be dependent on several factors that will vary case by case. The guideline only recommends that official guidance on preferred choices of antimicrobials should be taken into consideration (see

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	respond poorly, to more narrow spectrum antimicrobials'. It should be defined which or on which criteria active substances or product types must be considered as 'second line', and how this should be reflected in the indication(s) and/or other sections of the SPC. In addition, recommendations should *be* given as *to the design of efficacy studies in support* of *these claims.* It is therefore surprising to see that none of these aspects are covered in the draft revised Guideline EMA/CVMP/261180/2012. This implies that pharmaceutical companies remain in a vacuum and are lacking clarity on how such new antimicrobials would be assessed. This clearly hampers and discourages any investments in this area.	previous comment). Recommendations are given how to support efficacy for products which according to official guidance should be reserved for certain purposes (3rd and 4th generation cephalosporins and fluoroquinolones). Section 6.4.3 has been expanded in this respect.
3	**8. Uncertainty is a disincentive** The fact that the guideline will substantially change, but not before the end of 2013, puts products ready to enter or already in the development stage in a vacuum. In theory, guidance currently in place should be followed, but any study following that guidance will no longer be considered acceptable by the time the application for marketing authorisation will be submitted. Until the draft GL is approved, precise information on future requirements cannot be deduced. This is a serious and immediate hurdle to the development of new antimicrobials in the short and medium term. It should be clearly stated that studies that have been started before the new guideline will have come into effect, will be assessed by the authorities according to the requirements of the current guideline. Apart from these major concerns, specific comments are provided in	8. In principle, for all guidelines subject to revision, any study designed and conducted before the revised guideline has been made public will be assessed according to the recommendations given in the previous version. Hence, a new guideline will only be applied for submissions made after a certain period of time after publication. In case of uncertainty regarding which guideline to comply to applicants are advised to consult the regulatory authority.

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	the next section.	
5	The European Coalition to End Animal Experiments (ECEAE) is the pan-European member of the International Council on Animal Protection in Pharmaceutical Programmes (ICAPPP). We are an umbrella organisation representing animal protection organisations across 22 member states who campaign peacefully to end animal experiments. ECEAE welcomes the inclusion of statements relating to 3Rs principles and animal welfare in sections of the guideline relating to clinical studies and field trials. However, we urge CVMP to extend such considerations to cover all areas of animal use detailed in the guideline, including the generation of data required for PK/PD relationship analyses.	PK/PD data is considered to potentially reduce the need for experimental animal data and has thus potential benefits from an animal welfare perspective. In addition, reference to Directive 2010/63/EC regarding the protection of animals used for scientific purposes has been added to the text (see below).
6	At the stakeholder meeting it was agreed that a definitions section would be of value in the guideline. I agree but it is important that any definitions used are internationally accepted by the scientific community. At the stakeholder meeting there were terms being discussed that do not have universal acceptance in the scientific community. The issue “Second line” antimicrobials was discussed at length at the Stakeholder Meeting and how this impacts development of new antimicrobials. One potential way forward would be to consider a risk assessment in terms of impact on public health as a separate exercise to be conducted outside the current guidance documents, perhaps in the same way as MRLs are currently handled. This would give sponsors the opportunity to submit a risk analysis before	It is agreed that the risk assessment relating to public health is done separate from the clinical evaluation of the product. According to current legislation it would not be possible to submit a public health risk assessment separately but it would have to be included in a complete dossier.

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	embarking on a full development programme, if they so wished. Such a risk assessment is already carried out by many sponsors with respect to US submissions.	
7	The Federation of Veterinarians wants to thank the EMA and CVMP, for the possibility to provide comments on this guideline both in written and through the physical meeting on 8 December. Overall FVE welcomes the new guidelines and only have minor comments. It is important for the profession to have a good arsenal of licensed antimicrobial products available to use responsibly for treating the many different bacterial diseases in all the different species of animals. Since it will become more and more difficult to bring new molecules on the market in the future, it is important to ensure as much as possible the availability of the currently existing products. FVE believes the new guideline to demonstrate efficacy is well-balanced. FVE recognises and shares the opinion of the industry that more efforts are needed to encourage investing in the development of new veterinary products. Health of animals interlinks with human health. Therefore in the concept of the 'One Health' funding and incentives for the development of new veterinary products should be equally ensured for both sectors. Parallel to this guideline, regulators should try to take actions to encourage the development of new innovative products e.g. ensuring	The text has been scrutinized with regard to the use of the terms "recommendations" and "request", to ensure that these are used properly throughout the guideline. A list of definitions has been added. Consistency with definitions taken by other EU bodies for the same terms has been considered. The terms" first line" and "second line" are not used in the guideline.

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	that for extensions and variations no review of the original data is needed. Overall, it needs to be ensured that enough data are collected but also that the requirements are not too high considering the regulatory difficulties and the related animal welfare concerns involved with this data collection. A risk-benefit analysis should also be done. In the text, it should also be more clear which aspects are more a possible recommendation/suggestion than a requirement (differentiate between 'need to know' and 'nice to know'). FVE supports the suggestion that a list of definitions should be added in an annex (break-points, Co/X-resistance, etc) consistent with those from other EU bodies: EFSA, CLSI, UCAS, EPRUMA, etc. One of the agenda topics of the 8 December meeting was "'Second line' antimicrobials". FVE recommends staying away from the term of first and second line antimicrobials as these are unclear terms.	

2. Specific comments on text

Line no.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
049	3	Comment: This document is a guideline but experience has shown that “advice” in guidelines is often interpreted as “law”. Proposed change: Please add the following sentence to the end of line 51: “Alternative study designs may be applied if justified.”	Accepted.
050	1	Comments: Metaphylaxis is considered as a standalone label claim (see line 244), implying the simultaneous treatment of sick animals and healthy in-contact animals. Proposed change (if any): “… the intended claim could be treatment, metaphylaxis, or prevention”.	Not accepted. Metaphylaxis is in this guideline defined as the group-treatment of in contact animals (but not the treatment of clinically diseased animal in the same group). Regarding formulations for individual administration, this will allow for the approval of either a treatment claim or a treatment and metaphylaxis claim.
051	1	Comments: As stated in the text, the spirit of this guideline is to provide recommendations. However, experience shows that advice provided in guidelines is often interpreted as mandatory requirements or law. This message should be reinforced in the text. Proposed change (if any): The following sentence should be added at the end of line 51: “Alternative study designs may be applied if justified.”	Accepted.

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051	1	Comments: The Agency should note that preventive use is not allowed in all Member States.	Noted. National regulations are not taken into consideration in this guideline.
057-58	3	Comment: The need to provide a clear definition of what is considered as an antimicrobial substance in the current guideline is acknowledged. However, as stated in our comment on line 46, it could be even clearer to state “antibacterials” as defined by the HMA. A substance may have a primary antibacterial action and be intended for use as such; alternately a product may have a primary or major antibacterial action but not be marketed as such; i.e. marketing is based around a secondary physiological activity. In these latter cases it can be hard to define what is the primary and what is the secondary activity. Proposed change: Please amend the sentence as follows: “In the context of this guideline an antimicrobial is defined as a substance to be presented as an antibacterial *i.e.* a substance primarily acting against bacteria.” This would reinforce the message in lines 70-72.	Not accepted. The definition of antimicrobial agent which is given as a footnote in the guideline is regarded sufficient.
057-58	3	Comment: The need to provide a clear definition of what is considered as an antimicrobial substance in the current guideline is acknowledged. However, as stated in our comment on line 46, it could be even clearer to state “antibacterials” as defined by the HMA. A substance may have a primary antibacterial action	Not accepted. The definition of antimicrobial agent which is given as a footnote in the guideline is regarded sufficient.

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		and be intended for use as such; alternately a product may have a primary or major antibacterial action but not be marketed as such; i.e. marketing is based around a secondary physiological activity. In these latter cases it can be hard to define what is the primary and what is the secondary activity. Proposed change: Please amend the sentence as follows: "In the context of this guideline an antimicrobial is defined as **a substance to be presented as an antibacterial *i.e.*** a substance primarily acting against bacteria." This would reinforce the message in lines 70-72.	
061-63	2	Comment: this guidance should not be applicable to intramammary products, as a separate guideline is established. Proposed change (if any): Replace second sentence of paragraph by: this guideline does not apply to intramammary products use in cattle	Partly accepted. It is clarified that only part of the pharmacology section is applicable to intramammary products, whereas regarding clinical data the CVMP guideline on the "Conduct of efficacy studies for intramammary products for use in cattle has to be considered.
068-69	1	Comments: In order to take into account particular applications where efficacy studies may be waived, it is proposed to amend the scope as follows. Proposed change (if any): "The guideline does not address applications for generic products and applications relying on well-established use, when according to current legislation efficacy studies for those applications are not required."	Not accepted. It is agreed that new data would not have to be generated to support well established use application. However, in such application published clinical data would have to be presented to support the well established use. It may thus be confusing to include a reference to this application form in this section. The text has been simplified to avoid misinterpretation.

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074-77	5	Comment: A significant proportion of this guideline relates to animal studies. Hence reference should be made to legislation relating to the protection of animals used for scientific purposes. Proposed change (if any): This Guideline replaces the current CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/2001) and should be read in conjunction with Directive 2001/82/EC as amended. **Directive 2010/63/EC regarding the protection of animals used for scientific purposes also applies**. Applicants should also refer to other relevant European and VICH guidelines, including those listed in the reference list of this document.	Accepted.
079	3	Comment**:** "However, all use will inevitably select for resistance". Resistance selection happens provided there is a resistant population already present. In the absence of a resistant population antimicrobial use will not select for a resistant population. Therefore this statement is not correct. "Inadequate use" is an odd phrase to use if the implication is of under-dosing by intention and does not cover poor prescribing practices. The term "inappropriate use" would be better and more inclusive of poor use scenarios. Proposed change: Please amend as follows: "However,	Not accepted. Resistant bacteria will always occur due to e.g. mutations. Thus, when a selection pressure is put on a population there will be a risk for selection of bacteria which have required mutations which promotes survival and thus the risk for resistance is always present. The term "inadequate" is meant to reflect the use of an insufficient dosing strategy. Inappropriate use which depends on non-compliance to dosing recommendations is out of scope of this guideline.

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		all use ~~will~~ may select for resistance. Thus it is vital that all unnecessary or ~~inadequate~~ inappropriate use is avoided,"	
082	1	Comments: This guideline deals with the efficacy of veterinary medicines for the treatment of animals. Public health aspects are covered in other guidelines. Proposed change (if any): Delete the sentence: "In addition, potential risks to public health need to be considered"	Partly accepted. All risk aspects are important to take into account in order to maintain effective antibiotics on the market. From that perspective it is regarded relevant to include a reminder in this general part of the guideline that also public health aspects have to be considered. Reference to separate guidelines has been added.
082	2	Comment: The "potential risks to public health" is a new requirement. Further there is no guidance as to how this should be addressed, or the information to be included. Proposed change (if any): Take out the term "Public health" or clarify regarding resistance development etc.	Partly accepted. All risk aspects are important to take into account in order to maintain effective antibiotics on the market. From that perspective it is regarded relevant to include a reminder in this general part of the guideline that also public health aspects have to be considered. Reference to separate guidelines has been added.
082	3	**New requirement** Comment: "In addition, potential risks to public health need to be considered". It is unclear what is meant by this. This guideline deals with the efficacy of veterinary medicines for the treatment of animals, it has no bearing on public health. Public health aspects are covered in GL644. Proposed change**:** please delete the sentence	Partly accepted. All risk aspects are important to take into account in order to maintain effective antibiotics on the market. From that perspective it is regarded relevant to include a reminder in this general part of the guideline that also public health aspects have to be considered. Reference to separate guidelines has been added.

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085	1	Comments: The decision on the need of treatment is a clinical decision and lies with the veterinarian. Proposed change (if any): delete the sentence.	Not accepted. It is regarded necessary to justify the indication when to clinically evaluate effect of a certain treatment.
085-89	1	Comments: The use of antimicrobials for several diseases has been well described in the literature. Literature references as possible source for justification of use of antimicrobials should be included.	Not accepted. The potential use of literature data to support different aspects of clinical efficacy is detailed further on in the guideline, e.g. the dose determination section. It is not regarded necessary to mention this opportunity also here.
085-89	2	Comment: This is a very broad comment on multifactorial diseases. Under clinical field conditions, we mostly find more than one pathogen in a problem herd and not infrequently involving sub-optimal management/housing. However, the presence of inflammation (e.g. rectal temperature, oedema) associated with the involvement of a relevant pathogen must be sufficient to justify antimicrobial treatment. In enteric disease (e.g. *Brachyspira* spp., *Lawsonia* spp.) the presence of clinical signs and the pathogen should be sufficient, although there may be other associated factors (e.g. poor hygienic conditions). We have serious concerns that the current text will have a serious impact on study design leading to the fact that many studies are impossible to implement under field conditions. How for instance is it expected to carry out studies on a “reserved” antimicrobial in previously treated non-	Not accepted. It is regarded relevant to emphasize under this general heading that for multifactorial diseases the contribution of the antimicrobial treatment should be clarified. This is done by describing the dynamic of the disease and the different factors that could affect the occurrence, and clinical course. In addition, well designed clinical studies where contributing factors are controlled to the best possible extent can bring relevant information regarding the contribution of antimicrobial treatment. The bullet point does not address specifically “reserved” substances. Which data could be used to support clinical efficacy is detailed further on in the document and would not have to be repeated under this section. Thus the proposed change is not endorsed.

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		responders? It is a statistical impossibility!! In any event, the disease in such animals will, due to the delay in effective treatment, be well advanced or chronic with little likelihood of a clinical response to ANY treatment. Proposed change (if any): In- case of multi-factorial diseases, both, the presence of clinical signs and the target pathogen should be evident, although in some cases, the statistically proven effect may be limited to one, either the bacteriological or the clinical parameter.	
085-86	3	Comment: "Use of antimicrobials for treatment of mild and transient infections that will resolve independent of treatment will be questioned." The decision on the need to treat is a clinical decision by the Veterinarian and as such lies outside the scope of this guideline. Proposed change: Please delete the sentence (see also our comments to lines 346-347).	Not accepted. Given that non-inferiority data is often provided where it is difficult to conclude on efficacy, in particular for infections with high tendency to self-heal, it is considered that the sentence could stay.
086-89	3	Comment: For some multifactorial diseases, the use of antimicrobials and the timing of that use have been well described in the literature. Proposed change: Please include literature references as possible source for justification of use of antimicrobials in multifactorial diseases. Studies would then follow the requirements of the guideline.	Accepted.

Line no.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
093-98	3	**Focus Group discussion topic** Comment**:** This paragraph seems to imply that the categorization as 'second-line' antibiotics should be incorporated in clinical trials, and in particular field trials raises several significant issues: - From an animal welfare standpoint, animals that have already been treated unsuccessfully are in very bad health and the chance for therapeutic success even with a powerful antibiotic is very low. It can be doubted that such trials are technically feasible for this reason. - From a practical standpoint, the restrictions to the use of such substances to animals actually correspond to risk mitigation measures. The field trials aim to demonstrate the product efficacy and such development constraints are not sustainable with regard to the number of subjects having to be included as per the proposed field restricted use. - In addition, the relevance of this section on the longer term is questionable: o it does not consider the aspects of co and cross-resistance. Older antibiotics from the same class might select for resistance that will not be able to be treated by the newer generation of antibiotics. o the reason for the mitigation measures as regards to those antimicrobials of critical	Partly accepted. To ensure a proper evaluation of substances which according of official guidance documents are considered to be reserved for specific condition, it is regarded necessary to evaluate the effect of treatment in what according to these documents is the relevant target population for treatment. It is however acknowledged that it may not be possible for practical reasons to implement this for every situation. The text has been modified to indicate this. Furthermore, examples on how to design studies to support efficacy in these situations, is given further down in the document.

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		importance – again, once marketed - relies mainly on their impact on digestive flora and the potential transfer of resistance. An innovative development might be to prevent the impact of antimicrobials of critical importance on the gut flora, but the paragraph closes the door to any development based on third or fourth generation cephalosporin and fluoroquinolone based products. Since the list of critically important antibiotics may be expanded to include other classes, the risk taken by the industry when initiating development of a product is very high and hardly sustainable. The proposal is a major disincentive to new innovative developments. Proposed change**:** Delete this paragraph or at least amend as follows: **"**Official guidance on preferred choices of antimicrobials to be used and those to be reserved for certain conditions such as CVMP recommendations (when available) e.g. for fluoroquinolones and third and fourth generation cephalosporins **should be reflected in the SPC** ~~should be considered when taking decisions on which populations to include in the studies. For example, fluoroquinolones and third and fourth generation cephalosporins are recommended to be used only in cases that have responded poorly or~~	

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		~~are expected to respond poorly to other antimicrobials and this limits the target population for these classes.~~"	
099	2	Comment: PK/PD cannot always be used to determine the duration of treatment as far as we understand. Also some compounds do not obey conventional PK/PD	Not accepted. It is agreed that PK/PD data may not be useful to determine the duration of treatment. However, the bullet point comments on dose and dosing interval in addition to the number of treatment. It is mentioned that these parameters can be supported by considering PK/PD data, if established, as well as by taking into account the severity of the disease and the desired outcome (i.e. clinical or bacteriological cure). More detailed information on which data is relevant for which parameter is given further on in the document and for that reason no further clarifications are regarded necessary in this section.
099-101 and 195-196	1	Comment: These sentences are contradictive: *"…should always be justified by…*" versus *"…may be used to support*". The terms used in sentences 195-195 ("may be used to support") are preferred. EGGVP believes that PK/PD may be a useful tool, but experience shows that efficacy may sometimes be assured at dosages far below those based on PK/PD analysis. There are some areas in PK/PD modelling that still need to be resolved; therefore, some flexibility and considerations need to be taken into account when implementing it.	Accepted. The bullet point has been re-worded in accordance with the following comment.
099-101	3	Comment: The PK/PD approach can allow setting the dose and the dosing interval but not the number of administrations. Additionally the PK/PD approach is not applicable for topical treatments; and even for	Accepted.

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		systemic treatments experience has shown that it is not always fully applicable for some classes of compound (*e.g*. Macrolides) and some uses (*e.g*. compounds active in the rumen or GI Tract). Proposed change: amend the sentence "The dose **and** the dosing interval ~~and the number of administrations~~ of the antimicrobial product ~~should always~~ **can** be justified by considering the pharmacodynamic/pharmacokinetic (PK/PD) relationship, if established, as well as the severity of the disease, **whereas the number of administrations should be in line with the severity of the disease."**	
099-103	3	Comment: PK/PD criteria are not available for all antibiotics but when available could be used in substitution to the dose determination It is also undesirable for the duration of exposure to be shorter than necessary. Proposed change: please amend the sentence as follows: "exposure should not be longer **or shorter** than necessary to accomplish the desired outcome."	Partly accepted. The text regarding PK/PD has been slightly re-worded. It is regarded relevant to emphasize that unnecessary long treatment durations should be avoided from a risk perspective. A clinical study would not necessarily reveal if the treatment period was too long, but a too short treatment duration would result in insufficient efficacy results. From that perspective it is not regarded necessary to mention that the treatment duration should not be too short.
102	1	Comment: Duration should be defined more clearly. Ideally duration should be until 2 days after clinical and/or bacteriological cure, however that is not accepted in SPCs and it would lead to problems with establishment of the withdrawal period.	Not accepted. The dose finding section of the document emphasizes the importance of defining a relevant treatment duration. However, as mentioned by the stakeholder himself it would not be appropriate to indicate that treatment should be maintained for 2 days after resolution of clinical signs/bacteriological cure.

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107-110	5	Comment: PK/PD analyses detailed in Section 5 will be based on PK data obtained from animals. Applicants are directed to Guideline EMEA/CVMP/133/99 which details methods involving animals but makes no reference to animal welfare. Hence it is appropriate to remind applicants of the need to consider animal welfare with generating PK data. Proposed change (if any): For the conduct of pharmacokinetic studies please see the CVMP Guideline on conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99). Studies on pharmacodynamics should be performed according to validated and internationally accepted methods, and according to Good Laboratory Practice (GLP), where applicable. **Measures should be in place to ensure any negative impact on animal welfare is kept to a minimum**. Data requirements are detailed below.	The guideline does address the need to take animal welfare into account, especially for negative controls in different place. However the comment from the stakeholder is accepted.
109	4	Comment: There are no accepted methods for assessing PK-PD properties of macrolides in general and in respiratory tissues in particular Proposed change (if any): Studies…accepted methods when applicable, and according to GLP.	Acknowledged. Accepted.
110	2	Comment: GLP is an appropriate standard, but most diagnostic laboratory work is carried out to the international standard ISO 17025. The *in-vivo* phase of pharmacodynamic studies should be carried out	Partly accepted. This paragraph has not been modified as proposed, but reference to both, GCP and GLP standards is now included in

Line no.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
		according to VICH GL9 (GCP) or GLP. Proposed change: Studies on pharmacodynamics should be performed according to validated and internationally accepted methods, and according to Good Laboratory Practice (GLP)~~, when applicable~~. Alternatively the in-vivo phase may be done according to VICH GL9 (GCP).	the first section under 6. Clinical studies (also referring to "preclinical studies).
118	4	Comment: there is undue emphasis on MICs. The clinical response is far more important that MIC data. Selection of an antibiotic should consider other factors such as apoptosis, effect on the inflammatory response. Proposed change (if any): Harmonisation across the main regions would be useful.	Not accepted. Both MIC and clinical data have value.The guideline has been revised to indicate that standardised methodology, such as those described by CLSI, should be used when available.
121	1	Comment: Reference should be made to specify the methodology.	Partly accepted. See above.
121	4	Comment: There are no validated standardised methods for determining MICs for many animal pathogens. Proposed change (if any):	Accepted. This is recognised in the text.
121-123	3	Comment**:** The guideline needs to specify that the most current CLSI documents should be used and in the absence of approved methods, a widely accepted published method should be used *e.g.* for mycoplasma the methods proposed by Peter Hannan.	Partly accepted. The text has been revised to reference CLSI methods.

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		Proposed change**:** (a) Please reference the CLSI-VAST documents for the standard methodologies and (b) please add the following sentence to the end of line 123: **"In the absence of standardised methodologies a widely accepted published method should be used."**	
124-135	1	Comment: Some more detailed information regarding "representative number of clinical isolates of each target bacteria" and "a lower number of isolates" may be beneficial. It may be difficult to provide in-depth guidance to be universally applicable, but some more discussion about requirements on representative/minimum number of samples from companion and food producing animals would be needed.	Text has been revised to indicate that the number of isolates should be "scientifically justified". This needs to be done on a case-by-case basis, therefore detailed guidance is not given.
124-126	5	Comment: The phrase "representative number" lends itself to a variety of interpretations. Alternative wording would improve clarity. Proposed change (if any): MIC data should be provided for all target bacteria. A **scientifically justified** ~~representative~~ number of clinical isolates of each target bacteria, **representative of the EU area**, should be collected, to allow detection of isolates with MICs deviating from the normal distribution of strains without any acquired resistance (wild type).	Accepted.
124-134	6	Comment: Whilst this section makes a lot of sense, I believe it is not practically feasible and could lead to	Partly accepted.

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		problems. Clearly MIC data should be provided for all target bacteria but the issue comes with the following text where it states that a representative number of clinical isolates of each target bacteria should be collected, to allow detection of isolates with MICs deviating from the normal distribution of strains without any acquired resistance (wild type). This is good science; however you are asking that this should be done by taking into consideration, “selection of livestock farms including units of different type, size and production intensity. The tested isolates should come from the animal subgroup(s) or production type(s) that are targeted in view of the indication (e.g., weaning piglets, veal calves etc.)”. The problem here is that it will not be possible to collect enough isolates within respective production types/countries and so the data will not be able to be analysed with sufficient power. I welcome the intention but the reality is that because of relatively low numbers of isolates there will be no opportunity to draw any conclusions from the respective data sets as they will be too small; it will only be when all data is pooled that conclusions can be drawn on wild type distributions Proposed change: Consider removing the need to select for isolates from different production types as it is of limited value to generate data that cannot be analysed	Isolates should come from different production types that reflect the diversity of the target population; however, the requirements have been somewhat relaxed.
128-129	3	Comment: It would also be advisable to remove the	Not accepted.

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		<5year restriction on isolates for rare pathogens. Proposed change**:** "within five years (excluding historical isolates of rare pathogens of the same species) prior to the submission of the application."	It is already stated that a lower number of isolates is needed for rare pathogens. This is general guidance and it is always possible to provide a justification for deviations in exceptional circumstances.
131-132	3	**New requirement** Comment: "…units of different type, size and production intensity." These criteria may make it difficult to satisfy the proposed GL depending on the geographical spread of the condition and the target species and subgroup. The laboratories and farmers providing the isolate frequently refuse to provide this information for confidentiality reasons and stigmatization. This is the experience gained from the CEESA Vetpath programme. Proposed change: delete this request or at least it should be amended to read "…should include**, where feasible,** units of different type, size and production intensity."	Partly accepted. Requirements modified in revised text.
131-132	7	Comment: for the selection it is suggested to include units of different type, size and production intensity Proposed change (if any): delete 'production intensity' as this is unclear	See above.
132	2	Comment: It can be difficult to obtain isolates from	See above.

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		animals living in units of a different type, size and production intensity. Proposed change: ….. size and production intensity, if possible.	
139-143	3	Comment: The susceptibility trends of the target bacteria against antimicrobials may be extremely difficult to determine because most of the published data do not precisely describe the MIC distribution. Moreover, the epidemiological cut-off values, set to define the wild type population, may vary between the monitoring systems and also over time. In such a context, comparisons are complex and may lead to erroneous conclusions. Proposed change**:** "these should be further discussed and compared with already available (historical) data, **when available**; to allow conclusions to be drawn on acquired resistance. (…)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.**"	The requirements have been modified so that only higher level conclusions are expected. The text clearly acknowledges that for historical data, full information may not be available.
140-142	3	Comment**:** "reduced susceptibility" and "less susceptible", please be consistent in terminology. Proposed change**:** "…subpopulation of ~~less susceptible~~ bacteria showing **reduced susceptibility** needs to be further characterized…"	Accepted.

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142	3	**New requirement** Comment**:** It is unclear what "subpopulation of less susceptible bacteria needs to be further characterized" means, as this word implies 'testing'. Please clarify the extent of further characterisation required. Is it intended that sponsors should carry out studies to determine every resistance gene for a given antibiotic? For example there are a vast number of the resistance genes; would a sponsor be expected to check for the presence or determine the absence of each one of them? Inclusion of information from published literature should be sufficient. Proposed change**:** what "subpopulation of less susceptible bacteria needs to be further ~~characterized~~ documented"	Accepted. The requirement for further characterisation of bacteria with reduced susceptibility has been removed.
146-156	2	Comment: It may be useful to include in the Appendix a definition of "epidemiological cut-off" and "clinical breakpoint" to prevent any misunderstanding. ► Resistance monitoring utilises epidemiological cut-off values which separate the naïve, susceptible wild-type bacterial populations from isolates that have developed reduced susceptibility to a given antimicrobial agent. The wild-type susceptible population is assumed to have no acquired or mutational resistance and commonly shows a normal distribution. This cut-off value will not be altered by changing circumstances (such as alterations in frequency of antimicrobial administration).	These definitions are provided by bodies such as EUCAST.

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		► Clinical breakpoint is a pharmacodynamic parameter that describes the threshold MIC under which the organism is likely to respond *in vivo.* Clinical breakpoint determination is based on a number of parameters that are by nature dependent on formulation (pharmacokinetic properties), animal species, disease, site of infection, etc. Epidemiological cut-off values (a fixed value) and clinical breakpoints (variable) therefore represent two independent entities that should not be confused. Proposed change: The data on MIC distribution should be interpreted using adequate interpretation criteria. The epidemiological cut-off value should be determined, if feasible, to define the population without any acquired resistance. The applicant should suggest a clinical breakpoint (i.e. a MIC value under which the selected dose is shown efficient). Any such clinical breakpoint must be supported by microbiological, clinical and available PK/PD data and the dose should be selected accordingly (see dose finding below). In case reference is made to a clinical breakpoint established by an external institute or published in literature it should be demonstrated that this value is relevant for the product and the indication under study.	
146-154	3	Comment: Epidemiological cut-off values (ECOFFs) and clinical breakpoint (CBP) are independent values. Clinical breakpoints always have to be supported by	Partly accepted. The text has been clarified.

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		microbiological, clinical and PK/PD data. In some cases epidemiological cut-off values and clinical breakpoints may be the same but this can only be decided once MICs, PK/PD and clinical parameters have been considered for the determination of the clinical breakpoint. Proposed change: “The epidemiological cut-off value can be proposed as the clinical breakpoint. In case a population with reduced susceptibility is identified Alternatively the applicant can suggest a clinical breakpoint” Reference should be made to the well-established CLSI guidance document VET-02 (formerly M37-A3).	
146-148	4	Comment: It might be possible to estimate epidemiological cut-off values. Clinical breakpoints can only be set after a large number of animals or groups of animals have been treated, which may take several years to accumulate—usually post approval. Using EC values as proposed clinical breakpoints will for some antimicrobials restrict their use to cases where MICs are several dilutions below the clinical breakpoint, and may rule out treatment with a potentially useful antimicrobial (AM). This may place undue selection pressure on alternative AMs. This situation would be therapeutically (and commercially) untenable. Proposed change (if any): The data on MIC distribution should be interpreted using adequate interpretation	Not accepted. Text allows an alternative clinical breakpoint to be proposed where supported by clinical and PK/PD data.

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		criteria. The epidemiological cut-off value should be determined, if feasible, to define the population without any acquired resistance. Where no acquired resistance is present the epidemiological cut-off value can be proposed as the clinical breakpoint.	
146-154	6	Comment: I support the view that the epidemiological cut-off value should be determined, to define the population without any acquired resistance, however the epidemiological cut-off value cannot be proposed as the clinical breakpoint without provision of additional data as this is not scientifically justified. A clinical breakpoint is a function of three types of data, microbiological susceptibility data in the form of susceptibility distributions, clinical data and PK/PD data. Epidemiological cut-off values represent only one strand of data and make no reference in isolation to clinical data and as such cannot be used to set clinical breakpoints without any clinical data. This is fully outlined in the relevant CLSI documentation. It may be that the epidemiological cut-off value is the same as the clinical breakpoint for some drug/bug combinations but this has to be established by considering all the available data Proposed change: Delete: The epidemiological cut-off value can be proposed as the clinical breakpoint and emphasise and modify lines 151-152 to read “Any clinical breakpoint must be supported by microbiological, clinical and available PK/PD data.	Partly accepted. The text has been clarified.

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148	1	Comment: It should be noted that there are divergent opinions on cut-off values for MICs.	Noted.
157	3	Comment: The title of section 5.4 is incorrect Proposed change: Please correct to: "5.4. Minimum ~~Bacterial~~ **Bactericidal** Concentration (MBC)…."	Accepted. This has been corrected.
163-165	3	Comment**:** It is doubtful whether MBC values can be used to determine whether a molecule is time- or concentration dependent. Data on kinetics of bacterial killing should only be used to demonstrate whether a molecule is bacteriostatic or bactericidal. Proposed change**:** please delete "and whether it is time-dependent (i.e. dependent upon the period of time, during which the concentration of the antimicrobial substance exceeds the MIC, but for which concentrations of several magnitudes of the MIC do not increase efficacy), concentration dependent (i.e. efficacy increases when administered at doses which confer concentrations several times the MIC) or co-dependent (i.e. which depends both upon concentrations above the MIC and the period of time during which the concentration of the antimicrobial substance exceeds the MIC)."	Not accepted. The title of this section covers MBC and kinetics of bacterial killing.
171	2	Comment: Concern has been expressed regarding the use of the word 'validated' as it has special implications in this context. Proposed change: Remove 'validated and'.	Not accepted. The methods should be validated.

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172	1	Comment: Reference to these methods should be specified.	Not accepted.
172-173	2	Comment: What would be defined as a clinical relevance of claimed bactericidal activity against a certain bacteria? Proposed change: Examples should be given	Not accepted. Not considered necessary.
174-176	1	Comment: Consider removing this requirement. In order to test cross-resistance, MAH will search in literature to find out which antimicrobials should be included in the studies. Sometimes there are so many antimicrobials that not all can be tested. If cross-resistance is well documented in literature, to state immediately on the SPC that there is a possible cross-resistance with a particular product could be considered.	Not accepted. The information could come from literature or studies conducted by the applicant. This is a requirement also of VICH GL 27.
181	3	Comment: It is not clear if the additional in vitro studies described in this paragraph are obligatory or not. Proposed change: Please amend the title as follows: "5.6. ~~Additional~~ **Optional** in-vitro studies"	Not accepted. These studies should be provided where they are relevant to the claim or any AMR risk associated with the product.
183	3	Comment: The antimicrobial concentrations do not prevent mutations, as these will occur at all	Accepted. Correction has been made.

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		concentrations. But the antimicrobial concentrations may have a role in preventing the selection of mutants. Proposed change: **"**… and how concentrations above the MIC may affect or prevent **selection of mutants** ~~mutations~~"	
190-221	3	Comment**:** As already stated in the comments for lines 99-100 the PK/PD approach is not always possible (e.g. topical treatments). This should be optional. Proposed change**: "**Therefore, for all compounds with systemic activity**, and when feasible**, the MIC data collected should"	This is general guidance. The applicant can provide a scientific justification when the PK/PD approach is not applicable. New approaches are under development for situations where plasma PK is not directly relevant. In addition this section is not applicable for topical treatment.
192-194	3	Comment**:** The terminology "the relevant biophase" needs clarification. What is a relevant biophase? Which are the possible relevant biophases? The PK/PD approach relies on plasma concentrations for compounds with a systemic action and it should be underlined that tissue concentrations are not relevant for a PK/PD approach that is valid and reliable only for systemic diseases.	See above. The applicant should justify the relevant biophase according to the antibiotic/pathogen and site of infection. We do not want to preclude development of new approaches.
193	4	Comment: The biophase for some AMs, e.g. tylvalosin, is the lysosome in epithelial cells, and in circulating leukocytes. Analysis of the drug molecule in these matrices would require a lengthy and difficult development and validation programme. It is generally	See comments above.

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		agreed that efficacy of macrolides is best evaluated in clinical trials. Proposed change (if any): suggest insert "If or where possible".	
195	4	Comment: The PK/PD relationship is not established for macrolides, particularly those for oral administration. Proposed change (if any): Add "if established" after "PK/PD relationship".	See comments, above.
195-196	3	Comment: Please correct the grammar. Proposed change: "an analysis for the PK/PD relationship can be use**d** to determine or to support dose regimen selection".	Corrected.
199	3	Comment**: "**likely" is incorrect in this context. Proposed change**:** please amend as follows: "supportive information on the ~~likely~~ **potential** efficacy".	Accepted.
201	4	Comment: PK/PD not relevant for macrolides and usual recommendation is for clinical studies to determine posology.	See comments, above.

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205-208	3	**New requirement** Comment: "encouraged to collect PK data from naturally diseased animals" While the scientific value of this is not disputed, the reality of achieving this is extremely challenging, and will only become more challenging with current reviews and changes to national animal welfare policies. Additionally there may be serious methodological limitations (*e.g.* privately owned small animals and handling of livestock animals) and analytical feasibility (analytical lab not in the proximity of the farm, sample storage). There is a significant risk of negative impact from the over implementation of this proposed requirement. Proposed change: delete or at least amend to read "naturally diseased animals using population kinetic models, **where feasible**."	Not accepted. This is not a strict requirement.
206-207	2	Comment: The collection of PK data from naturally diseased animals is an additional workload under field conditions that is often not justified in client owned animals. The frequency of sampling necessary may give rise to welfare considerations. Also in some EU Member States e.g. UK such procedures will invoke regulations under animal protection law with which it may not be possible to comply "under field conditions". According to Directive 2010/63 EC multiple blood sampling in an animal may cause such studies to be submitted to an ethical committee review, while field	Not accepted. Depending on study factors, it may still be possible to collect valuable information from limited sampling. We prefer not to make reference to national regulations in this EU guidance as it is known that national legislation differs on a number of issues that might be relevant to the guideline.

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		studies are routinely exempted. Proposed change: …, the sponsor is encouraged to collect PK data from artificially infected animals to do population kinetics. They may be added by a limited number of samples taken from naturally diseased animals, if justified, based on animal welfare and national regulatory considerations. Knowledge of kinetic variability …	
206-207	4	Comment: PK/PD data may be used to support dose regimen selection. To "encourage" collection of PK data from naturally diseased animals and the use of non-validated population models would therefore appear excessive for non-pivotal data. Obtaining serial blood samples from diseased animals for non-pivotal data may also be questioned on animal welfare grounds. Proposed change (if any): Remove sentence.	Not accepted. See comments, above.
212	1	Comment: It should be clarified what is meant by independent data.	See below. Deleted.
212	3	Comment**:** "prospectively justified by independent data". Does that mean that only published data could be used and that data could not be generated by studies performed or sponsored by the applicant? Proposed change**:** "prospectively justified ~~by~~	Accepted.

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		~~independent data~~".	
216-221	2	Definitions for commonly used parameters are imprecise. For example, no references to steady-state conditions nor to the time interval over which %T>MIC and AUC/MIC are usually calculated.	Partly accepted. The paragraph has been amended to indicate that further characterisation of PK/PD parameters should be specified according to the antimicrobial and microorganism under investigation.
216-220	3	**Focus Group discussion topic** Comment: The PK/PD parameters indicated are not adapted to long acting products of particular interest in the veterinary field. The PK/PD rational for such products is not reliable. How should such cases be managed?	This is general guidance. The applicant can provide a scientific justification when the PK/PD approach is not applicable or when taking a non-standard approach.
218-219	2	The leading A in AUIC is misleading because dividing the AUC by the target strain's MIC value does not give birth to an area, a term generally thought as two-dimension parameter. In fact, AUC/MIC may be expressed as a one-dimension parameter (time) or considered a dimensionless factor/ratio (see Toutain et al 2007, Mouton et al 2005). Mouton et al 2005 identified at least three different definitions corresponding to three different calculation mode for AUIC! The same authors recommend that statements such as "AUIC (AUC/MIC)" should be avoided. Our recommendation: delete "by convention referred to as AUIC (area under the inhibitory concentration time curve)"	Partly accepted. Text modified.

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224-227	2	Comment: Dose determination, dose confirmation and field studies should be compliant with GCP standards, being the standard for efficacy testing. GLP may also be acceptable where data are collected in efficacy studies that require GLP accreditation (PK data). GLP is the standard for safety studies, which is not the primary objective of Dose Determination, Dose Confirmation and field studies. Proposed change: It is recommended to conduct preclinical and clinical studies according to GCP; GLP may also be acceptable. (rest deleted!). In exceptional cases non-GCP or non-GLP studies may also be acceptable, but only if traceability, integrity and validity of the data is guaranteed by appropriate means.	Not accepted. The text in the draft document is considered to provide appropriate information regarding which quality standard to apply for different studies.
228-229	1	Comment: This is in contradiction with the proposed designs for field trials and dose determination studies.	Not accepted. It is regarded relevant to remind that this principle should be applied whenever possible. It is mentioned that PK/PD data may allow for the omission of traditional dose finding studies which is in line with the 3R principles.
228-229	2	Comment: why does the 3R principles (replacement, reduction, refinement) apply only to pre-clinical studies?	Accepted. The text has been changed to indicate that the 3R principles are applicable for both pre-clinical and clinical studies.

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		Proposed change: The 3R-principles should always be applied; for pre-clinical studies, methodologies other than clinical studies should be applied, where appropriate models are available.	
228-229	4	Comment: Although the 3R principles should be followed wherever possible, the OECD / FDA guidelines will take precedence over this regarding animal numbers. As pre-clinical studies are done with the active ingredient a reduction in animal usage can be achieved if all regions, in particular those within VICH (EU, USA, JAPAN) agree to accept pre-clinical data from one source—e.g. Japan used to insist on doing its own tox studies and would not accept EU or US derived data. Proposed change (if any): Should this sentence be here as you are discussing pre—clinical in the clinical section. Is this a mistake and should it be clinical and not pre-clinical?	Accepted. It is acknowledged that other guidelines may restrict the possibility to apply these principles. The text has been changed to include both clinical and pre-clinical studies but to mention that the principles should be applied to the extent possible.
228-229	5	Comment: ECEAE welcomes the inclusion of a statement relating to the principles of the 3Rs. We suggest the following expansion in the text. Proposed change (if any): When conducting pre-clinical studies, the “3R-principles” (replacement, reduction, refinement) should be considered. **Particular attention should be given to study design, selection of group sizes, environmental**	Not accepted. It is not regarded necessary to include further details regarding these principles. It will be up to the applicant to take every relevant aspect into consideration.

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		enrichment, methods of experimental infection, sampling techniques, frequency of inspection at the peak of the expected effect, and use of humane endpoints and / or agreed therapeutics to reduce suffering.	
230	3	Comment**:** How can this be applicable in case of multi-bacterial infections or when there are bacteria and *Malassezia* involved for example?	Not accepted. This is a general statement. Detailed recommendations on how to provide relevant clinical data in case of multi-bacterial infections are given in section 6.4.3.
230-233	1	Comment: Some guidance regarding the number of studies is provided in sub-sections for dose-determination and dose-confirmation studies, and field trials. It may be beneficial to insert the reference to these sub-sections. The studies should be designed as appropriate for the product type and the disease. The studies should be of appropriate quality and performed according GLP and/or GCP. The guideline applies to all new applications for marketing authorisation as well as for variations and extensions of existing marketing authorisations; with the exception of generic products. In sub-sections, it may be beneficial to provide some guidance regarding the number of controlled trials, especially for dose-confirmation studies and field trials for various types of applications, including hybrid applications	Not accepted. It would not be possible to include more explicit recommendations regarding the number of studies necessary to support different aspects of the clinical evaluation, or different type of applications since this will vary depending on disease, type of product and size and quality of the data. This is already mentioned in the text.
232-233	2	Comment: It should be clarified, what is meant by “several controlled studies”.	Not accepted. It would not be possible to include more explicit recommendations regarding the number of studies necessary

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		Proposed change: Several controlled trials (e.g. Dose determination, dose confirmation and multicentric field studies) are generally required dependent on the size and the quality of studies conducted.	to support different aspects of the clinical evaluation, or different type of applications since this will vary depending on disease, type of product and size and quality of the data. This is already mentioned in the text.
241	4	Comment: Definitions could do with harmonising between EU and US. For example Treatment is equivalent to Control in the US. The availability of many veterinary CROs in the USA with expertise in challenge studies (for production animals) with specific pathogens means that many EU dossiers will contain studies done in the US that will also be used for US approval. Why does the EU retain “prevention” when this is increasingly being discouraged by CVM. Is this judicious use of an antimicrobial to administer it to healthy animals to prevent infection? “Targeted treatment” where the decision to treat is based on previous or current diagnostics seems a more acceptable justification for the use of an antibiotic.	Partly accepted. A list of definitions is added to the document. It would not be possible to harmonise all definitions between EU and the US since the expressions have long tradition and is used with a common understanding by several parties dealing with medical treatment of animals.
242	7	….after the onset of clinical signs of the disease….	Accepted.
242-247	2	Comment: We appreciate the introduction of a clear definition of the different claims.	Noted.
244	4	Comment: metaphylaxis is the norm where products are used to treat groups of animals. In this case group medication is initiated when some animals in the group e.g. 10-15% exhibit clinical signs and it is not possible	Accepted. The text on metaphylaxis has been slightly amended to make it more clear that for formulations intended for group treatment such as oral powder to be mixed in drinking water,

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		under commercial farming circumstances to separate clinically affected animals from others in the group. The apparently normal animals in such a group may be non-infected but exposed to challenge, or may be incubating the disease in question. Furthermore in such circumstances medication will be delivered via the food or water to the group as a whole. Proposed change (if any): differentiate treatment of individual animals from treatment of groups of animals.	a metaphylaxis claim will be accepted when sufficient efficacy has been demonstrated on group level by use of relevant endpoints and the necessity to apply metaphylaxis for the particular disease is in principle supported from an epidemiological perspective. It is agreed that for such formulation the separate evaluation of the treatment effect among in-contact animals is generally not feasible, and thus a treatment and metaphylaxis claim will be given on basis of evaluation on group level. This implies that efficacy for clinically diseased animals and the healthy in-contact animals is evaluated in combination. For individual treatment formulations specific efficacy data from in-contact animals may be waived on the condition that reliable support from other sources can be presented, confirming that metaphylaxis can effectively control outbreak of the particular disease and furthermore, that the product under study can be assumed to be effective in these situations. When sufficient support from other sources cannot be presented, clinical data for the particular product would have to be presented. It is also mentioned in section 6.4.7 that independent of formulation metaphylaxis can possibly be justified only for highly contagious and/or severe diseases.
249-252	3	Comment: It is not sustainable to encompass through the dose determination studies the dose level (3 dosages should be tested), dosing interval and the number of administrations. Indeed too many variables would need to be taken into account to support all the	Accepted.

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		questions raised in the current sentence. It should be accepted that several parameters can be set in order to test only a limited number of possibilities. The current proposal is a major disincentive to the development of any antimicrobial-based product. Proposed change: move lines 274 to 281 up so that they follow the statement in lines 249 to 252, so that this statement is put into context.	
250-252	5	Comment: If the pathogen used in dose determination studies causes acute disease that progresses rapidly then animals used as negative controls may suffer significantly, regardless of measures taken to ensure welfare. Hence the number of studies requiring the use of negative controls should be minimised. Rather than investigating dose level, dosing interval and number of administrations separately, applicants should be encouraged to adopt study designs allowing more than one parameter to be investigated at a time if this will reduce the number of animals likely to suffer significant distress. Proposed change (if any): Dose determination studies encompass dose level, dosing interval and number of administrations. They are important to ensure efficacy of the product without unnecessary exposure to the compound. **Consideration should be given to study designs that incorporate more than one of these parameters so as to reduce the number of**	Accepted.

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		negative control groups used overall in dose-determination studies.	
253	1	Comment: In case of naturally infected animals the use of a negative control may not be possible for ethical or economic reasons. Proposed change: "Dose determination studies with experimentally infected animals should always include a negative control."	Not accepted. The difference between experimental and natural infections when regard ethics, is not understood. It is already mentioned that animal welfare should be taken into account. This text has been expanded according to the comment below.
253-254	5	Comment: ECEAE welcomes the inclusion of a statement relating to animal welfare concerns. However, even with measures in place to reduce the negative impact of infection on animals, welfare cannot always be ensured, particularly if using pathogens that produce acute disease. Hence the drafted wording is misleading. Additionally it would be helpful to applicants if they were reminded of measures that could be applied to improve the welfare of negative control animals. Proposed change (if any): Dose determination studies should always include a negative control. Appropriate measures should be applied to **minimise any negative impact on** ~~ensure~~ ~~animals~~ **animal** welfare. **Group sizes of negative controls should be the minimum required to produce meaningful data. If acute clinical signs of disease are expected, frequency of monitoring should be increased**	Partly accepted. The proposed text has been added, with some minor adjustments.

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		around the peak expected effect to ensure timely application of humane endpoints.	
257	2	It is stated: “the susceptibility..to be effective”. Please clarify, what is meant by this.	Accepted. It is clarified that a strain representative of the wild-type population could be used in a challenge study.
257	3	Comment: It is unclear what “representative of the bacterial population” means. Is that the median, the MIC50, or the geometric mean MIC? Proposed change: Clearly specify that “representative” means the geometric mean MIC in order to be truly representative of the complete bacterial population.	Accepted. It is clarified that a strain representative of the wild-type population could be used in a challenge study.
257	4	Comment: “representative” should be defined. It is accepted practice to run challenge studies with a fully sensitive strain of the pathogen in question. This is normally the type strain because this has been used to validate the challenge method. Where there is wide variation in field susceptibility field trials may be carried out against less susceptible strains. The eventual claim would be for treatment of organisms sensitive to <name of antimicrobial>. Should the challenge strain be the modal/geometric mean/MIC50/MIC90 value? In which case the MIC survey would be carried out prior to any clinical work in order to arrive at these values. Perhaps select a dose from the dose determination study (with fully susceptible strain) and use strains with differing MICs	Accepted. It is clarified that a strain representative of the wild-type population could be used in a challenge study.

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		in dose confirmation study. However, selection of a representative strain is not possible unless there is a validated harmonised MIC method.	
266-267	2	Comment: As there is the requirement to have always a treatment claim proven before granting a metaphylactic claim, this is not always possible in the case of acute/peracute diseases (e.g. *Actinobacillus pleuropneumoniae (APP)*, necrotic enteritis caused by *Clostridium perfringens*) associated with the production of bacterial toxins resulting in severe clinical signs including death, this is a requirement that is not always practically feasible. As a model should be as similar as possible to the naturally occurring disease, it is necessary in some cases, as illustrated above, to start treatment prior to the occurrence of clinical signs, as long as there is sufficient data available (validation of the model) and clinical signs are clearly evident in the control group. Proposed change: Unless a validated model is available in an acute or peracute disease, that justifies initiation of treatment prior to the appearance of clinical signs, in case of therapeutic treatment claims, drug administration should not be initiated before the clinical signs relating to bacterial infection are observed.	Partly accepted. The possibility to initiate treatment before clinical signs have been noted is now mentioned. A slight rewording of the proposed text has been made.
270	4	Comment: The PK/PD relationship is not established for macrolides, particularly those for oral administration.	Accepted.

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		Proposed change (if any): Add "when appropriate" after "PK data"	
274	3	**Focus Group discussion topic** Comment**:** If different dosing intervals and a different number of administrations need to be tested, the number of groups becomes extremely high and so does the number of animals to be included.	Accepted. This comment was given previously (for line 249-252). The stakeholder proposed to move line 274-281 to follow immediately after these lines. This would suggest more clearly alternative approaches to support the dosing strategy. This was accepted.
277-279	3	Comment: For many classes PK/PD parameters related to resistance development have not been established. Hence, it is unclear what data are expected from sponsors. Proposed change**:** The final sentence should be amended to read as follows: "In addition, the PK and PD characteristics of the active substance should be considered, including considerations ~~of the balance between~~ **on** sufficient efficacy for the target bacteria species ~~and the risk for resistance development~~. **If validated methods have been published in the scientific literature, the risk for resistance development in relation to PK/PD should also be considered".**	Partly accepted. The sentence regarding PK/PD has been changed to clarify that this kind of data could support a dosing strategy that provide relevant exposure and thus sufficient clinical efficacy and lowest possible risk for contributing to resistance development.
277-279	4	Comment: The PK/PD relationship is not established for macrolides, particularly those for oral administration. In addition, do we have sufficient	Partly accepted. The sentence has been reworded to clarify the intention with

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		scientific knowledge to enable an informed "consideration" of the risk of resistance development to be made? Proposed change (if any): Remove sentence.	PK/PD data in this respect.
282-284	2	Comment: The current text calls for multiple endpoints, which appears strange according to statistical methodology and may also not be appropriate for all diseases. Proposed change: "Efficacy evaluation should be based on clinical and bacteriological response as determined by appropriate clinical and bacteriological assessments; post mortem data should be added, wherever meaningful and mortality should be assessed."	Partly accepted. A slight rewording has been made to the proposed change.
282	3	Comment**:** It is stated that, for dose determination studies, "efficacy endpoints should include the clinical and bacteriological response". For some multifactorial and/or polybacterial diseases (*e.g.* respiratory disease or skin infections), bacteriological endpoints are not deemed to be suitable because it would be impossible (and undesirable) to achieve a complete bacteriological cure. Proposed change**:** Please add the same language as in lines 420-422: "**Depending on the epidemiology and pathogenicity of the disease, microbiological**	Not accepted. This chapter concerns dose determination meaning that the recommendations relates to the conduct of experimental infections which would include one single bacterium species. In that context it would be important to explore bacteriological response. A slight rewording of this section is suggested on basis of a previous comment.

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		cure rate may also be relevant. “	
285-287	2	Comment: The requirement stated that “observations should be collected repeatedly before treatment is considered questionable for certain models and may also not be appropriate for certain procedures. It should be clarified what is meant. As any model shall include a negative control group, the natural course of disease should be already integrated in any model and can be seen in the control group. Proposed change: Clinical observations should be carried out before and after treatment. During the treatment period, assessments should be done as frequently as possible (e.g. daily). The time of response assessment should be selected so as to show the effect of treatment in a relevant matter as compared to the negative control group, thereby taking into account the natural course of the disease.	Partly accepted. “as appropriate” has been added to open up for a justification of the recording schedule used in each particular case. The change proposed in the second paragraph of this comment is accepted.
290	4	Proposed change (if any): Consider changing “dimensioned” to “designed”	Accepted.
295-304	3	Comment**:** This paragraph refers to locally acting products and states “In other cases, such as e.g. locally active products for the gastro-intestinal tract, clinical dose finding studies should be performed as detailed above. …. Regarding systemically administered products intended to combat a localised	Accepted. A clarification has been added.

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		infection (e.g. metritis) the dose should be established according to recommendations given in the previous section." Proposed change**:** In both cases, it should be clarified as to which section is referenced: to lines 295-298 about formulations applied directly to the infection site or to 249-293 about systemic administrations?	
310	2	Proposed change: "A" study should ….	Accepted.
311	2	Comment: There should be at least one of the clinical studies where a negative control group is used, either dose determination or dose confirmation and the effect is clearly shown. Only in this case, a positive control group is usually acceptable, unless other data are available to prove the superiority of the Investigational Veterinary Product as compared to a negative control group. Proposed change: For treatment claims, one clinical study using a negative control group should be provided preferably as a minimum, unless the superiority of the product is proven otherwise. In certain cases, especially under field conditions in acute to peracute disease, a negative control group may not be justified on animal welfare grounds and therefore an appropriate positive control may be acceptable, provided internal validity and sensitivity of the study is ensured.	Partly accepted. The proposed text indicating that at least one clinical study should include a negative control to confirm superiority of the product, has been introduced under general principles in section 6.1. Regarding section 6.3, the fact that that the current text mentions that a negative control should preferably be included and furthermore, that a positive control is acceptable in case a negative control cannot be used, is regarded sufficient to cover the specific cases mentioned in this comment.

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310-311	5	Comment: It is not clear what is meant by “rescue protocols” at this point in the Guideline. At other points in the text we assume it refers to therapeutic intervention. However, during the conduct of dose-confirmation studies the application of “humane endpoints” would also seem appropriate. It is not clear if this is what is meant. As this statement has direct bearing on animal welfare the term should be defined in the text and / or examples given for clarity.	Accepted. A clarification has been inserted.
312-313	3	Comment**:** The terminology “internal validity and sensitivity of the study is ensured” is unclear. Proposed change**:** please amend as follows: “For treatment claims, in case the use of a negative control is not possible an appropriate positive control may be acceptable ~~provided internal validity and sensitivity of the study is ensured~~.”	Partly accepted. A reference to the statistical guideline has been added, where these basic concepts are explained.
317-321	3	**Focus Group discussion topic** **More detailed requirements** Comment: the relapse rate needs to be assessed at a time point which could be difficult to justify, and there is a risk of confusion between reinfection and relapse. The distinction may be very subtle in practice and not necessarily representative of real-life conditions. Proposed change: please clarify the expectations on the sponsor (in focus group meeting).	Partly accepted. It is acknowledged that it is difficult to define a time point when to assess relapse rate to avoid to the best possible extent that relapse and re-infection do not overlap. Nevertheless, it is regarded important to evaluate in addition to the short term efficacy, to what extent the effect is sustained. A higher frequency of disease cases within the first weeks after treatment termination as compared to e.g. a positive comparator could indicate that the infection was not combated to a sufficient extent. Furthermore, it would have

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			to be assumed that dose confirmation studies are performed under good hygienic standards which would reduce the risk for new infections in case the treatment was sufficient to combat the infection in treated animals. The text has been changed for clarity.
334-335	4	Comment: Dose confirmation studies would usually be done before field trials (if required). In addition, to suggest an alternative having stated in the previous sentence that feed/water intake should be considered when confirming the dose is contradictory. Proposed change (if any): Remove sentence.	Partly accepted. The sentence proceeding the commented sentence has been change to increase clarity. In case the dose confirmation study could not provide sufficient information regarding intake variability, e.g. due to few animals included, it would be possible to explore this in the field study. This would bring additional support for the selected dose.
336	4	Comment: It is not stated whether field trials are mandatory, or whether dose determination/confirmation studies using representative strains are sufficient. Field trials may be not be possible on commercial farms, so bringing field infected animals to a CRO for dose confirmation studies may be preferable.	Not accepted. The omission of field data may under exceptional circumstances be accepted, e. g. possibly in case of MUMS application. This is however a rare situation and thus not regarded necessary to mention in the guideline.
338 and 351	4	Proposed change (if any): Consider substituting "masked" for "blinded"—the latter term is not acceptable nowadays	Not accepted. The term "blinded" is regarded to be well known. Both terms are used in the VICH GCP GL.
341	4	Proposed change (if any): Consider substituting "production forms" for "production types"	Accepted.

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346-347	3	Comment: the language in these sentences is incongruous when lines 85-86 discourage such situations? Please delete lines 85-86 and let the data from a control group determine if treatment is necessary. Proposed change: delete lines 85-86	Partly accepted. The sentence has been amended to indicate that a placebo group is useful in situations where the self cure rate is suspected to be high. It is agreed that according to what is said in line 85-86, for conditions where the self cure rate is known to be high it will be questioned whether antimicrobial treatment is prudent.
352-353	1	Comment: This is contradictive. For certain diseases use of placebo treatment by definition poses animal welfare problems.	Not accepted. When the use of placebo is suggested in the document the need to ensure animal welfare is always mentioned. However, the referred sentence has been slightly amended and moved to section 6.4.1.
356	2	Comment: the language in these sentences is incongruous when lines 85-86 discourage such situations? Please delete lines 85-86 and let the data from a control group determine if treatment is necessary. Proposed change: delete lines 85-86	Partly accepted. It is assumed that this comment regards lines 346-347. See previous comment to these lines.
356-365	1	Comment: All the criteria mentioned for the positive control make it very hard to find a suitable product. It cannot be expected from companies that they re-establish the clinical efficacy of already registered products. This may result in a significant increase in the number of negatively controlled studies, which has animal welfare implications.	Partly accepted. The text is not intended to suggest that efficacy of the control product should be re-confirmed. However susceptibility pattern may change over time and possibly for that reason different dosing strategies may have been approved in different member states. To ensure that the control can be

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		Proposed change: "The control product should be authorised for the same indication and the applicant should justify that the chosen control can be considered as an effective treatment for the target indication."	expected to be effective for the target indication it would be necessary to avoid products where the posology varies and recent susceptibility data could question the effectiveness. One sentence that could be interpreted as if the effectiveness of the control product should be re-confirmed through clinical studies, has been deleted.
357-359	2	Comment: If a control product is used that has got the same indication and route of administration as the intended indication according to an authorisation under Directive 2001/82 as amended, there should not be any need to justify its use as the control product. There is no doubt that the control product should be active against the infectious agent that is used. However, it must be noted that the SPCs and label claims may vary between Member States, especially of older products. Proposed change: Remove the second sentence of the paragraph. Third sentence to be: The active ingredient of the positive control product should be effective against the target pathogen on each farm, where applied in the study.	Partly accepted. See comment above.
356-363	3	**New requirement** Comment**:** This paragraph brings a lot of restrictions regarding the selection of positive control products: - *control product should be authorised under Council Directive 2011/82/EU for the same*	Partly accepted. See comment above.

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		indication - *the applicant should justify that the chosen control can be considered as an effective treatment for the target indication* - *use of the chosen control product should be justified based on information about the susceptibility of the target pathogens for the compound* - *products for which recent susceptibility data suggest that posology may be inadequate for the infection under study, or products where posology differs between member states should be avoided* - *a comparator should always be used according to the label instructions* All these criteria make it very challenging to find a suitable comparator product and, as a result, pharmaceutical companies may frequently have no suitable positive control. It is unacceptable to expect that companies are re-investigating and re-confirming the clinical efficacy of previously registered products. This may result in a significant increase in the number of negatively controlled studies, which has animal welfare implications. Lines 360-361 imply that "recent susceptibility data" (disclosed by whom and how robust?) trump/question existing approvals. This cannot be in the interest of either authorities or industry. Proposed change**:** This paragraph should become more flexible and limited to for example: "The control	

Line no.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
		product should be authorised for the same indication and the applicant should justify that the chosen control can be considered as an effective treatment for the target indication (e.g. based on scientific literature)."	
357	7	The applicant should justify that the chosen product can be justified for effective treatment for the target indication…	Accepted.
362	7	A comparator …(of..? not clear to me)….	The comment is not understood.
364	3	**Focus Group discussion topic** Comment: Please clarify "advice is sought from the authorities". Which authority? Using which procedure? Would that advice be binding on the authority?	Not accepted. In case the company finds it difficult to decide what could be an acceptable comparator it is recommended that the issue is discussed with the authority, to avoid the inclusion of a comparator which is later deemed irrelevant. Advice can be sought from national authorities or from CVMP, depending on which market is aspired. Scientific advice is not legally binding. It is no regarded necessary to further elaborate on the possibility to obtain scientific advice.
369-371	3	**Focus Group discussion topic** Comment: It may not be possible to reliably expect a recognized level of efficacy of the chosen control product under all study conditions. Whilst the control product was registered for the indication under study, it may not show the same level of efficacy under the specific study conditions selected for a modern class of antibacterial, i.e. specific endpoints that are intended to demonstrate specific features of that new class. This	The applicant should pay attention to that the chosen control product needs to be sufficiently effective for the target indication at the time the study is conducted.. In case efficacy level is uncertain it may be necessary to include a negative control to confirm internal validity. In case the applicant expect that a new test product will have better effect than previously authorised products, a superiority trial could be performed (see comment below).

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		would particularly hold true if only old products are available as control products. It must be ensured that study data for a new product are not questioned because a control product fails to show the same efficacy as reported at the time of approval under less stringent test conditions.	
374-375	3	**Focus Group discussion topic** Comment: It is not clear why "susceptibility" is excluded from any superiority calculation. What is the justification and if taken out, what would be left? See also Lines 376-378, lack of efficacy might be partially caused by reduced susceptibility and/or resistance, why should that be removed? Proposed change: please delete this sentence.	Not accepted. It would not be appropriate to select a comparator which is known to be ineffective due to high resistance. That would create the same situation as comparison to placebo, and a placebo group would then be more appropriate. The text intends to indicate that a superiority design would be acceptable in case the company expects that the test product for any particular reason (other than resistance) would be superior to a previously authorized product with the same indication. A better effect could be related to the PD characteristics of the antimicrobial; e.g. a bactericidal substance may show quicker onset of effect for severely diseased animals as compared to a bacteriostatic substance.
383	1	Comment: Isolation of the target pathogens prior to inclusion will be difficult to obtain. Waiting for lab data prior to study inclusion will minimize the possibilities for inclusion. Clinical signs and disease history of a farm may be adequate to set a diagnosis of clinical disease. The presence of the target bacteria can be confirmed after inclusion. Proposed change: “When the aim is to confirm efficacy against one or several specified bacteria, isolation of	Partly accepted. The text has been slightly reworded to clarify that sampling should be performed at time of inclusion, which indicates that laboratory results may not yet be available at time of treatment initiation.

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		the target pathogen(s) from the animals or a representative proportion of them should be confirmed prior to, during, or post treatment."	
383-385	3	Comment: This is too idealistic, especially for a natural infection study. Waiting for lab data prior to study inclusion will dismiss the window of opportunity for treatment of the animals. Enrolment criteria based on clinical signs used to support a diagnosis of clinical disease is adequate and should be followed by confirmatory bacteriologic data….similar to lines 388-390. Proposed change: please amend as follows: "When the aim is to confirm efficacy against one or several specified bacteria, isolation of the target pathogen(s) from ~~the animals or a representative proportion of them is required at the time of inclusion~~.**sentinel or enrolled animals should be confirmed prior to, during, or post treatment. Confirmation of bacterial presence does not need to occur prior to study enrolment so long as clinical signs of disease support the decision to prescribe antimicrobial treatment."**	Partly accepted. The text has been slightly reworded to clarify that sampling should be performed at time of inclusion, which indicates that laboratory results may not yet be available at time of treatment initiation. In line 380-381 it is mentioned that appropriate clinical (and microbiological) inclusion criteria should be used and thus it is not regarded necessary to repeat this as proposed by the stakeholder.
388	7	…on basis of clinical signs of the disease only,….	Accepted.
412	3	Comment: As commented above, microbiological criteria are not always relevant. Proposed change: "…. clinical response criteria and**/or** microbiological criteria"	Accepted.

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419-422	4	Comment: In cases where clinical signs are mild, reduction in lesion score may be used as the primary efficacy parameter. For group housed animals and certain infections reductions in mortalities, improved feed intake and growth rate relative to unmedicated animals is another measure of the effectiveness if treatment. Because AGP have been used in the past to improve performance, presentation of feed intake and growth rate data seems to be ignored now yet, as mentioned above, it is an important measure of effective treatment.	Comment acknowledged. However, it would not be useful to mention different endpoints since which are the relevant endpoints will have to be decided by the company case by case. The choice needs to be justified.
423	2	Proposed change - add: such as in claims for chicken, swine, bees, fish …. Where appropriate in case of mortality, post-mortem examinations including bacteriological sampling may be necessary to explore any treatment effect in these situations.	Partly accepted. Regarding swine it would be possible to make individual efficacy assessment and thus this species is not included among the examples.
430-432	2	Comments: The timing of follow-up measurement should be appropriate to allow the detection of relapses (reoccurrence of clinical disease in initially clinically cured animals) related to insufficient effect of treatment but avoiding the inclusion of re-infected animals. Re-infection is usual and difficult to avoid in herds with highly infectious diseases, especially when only a few animals are treated based on individual inclusion criteria among other “reservoir” animals. Therefore the document should not put too much emphasis on relapse rates.	Partly accepted. The text has been slightly changed for clarity.

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436-483	3	**Focus Group discussion topic** Comment: The section on Special considerations for metaphylaxis claims contains a lot of details specific for individual animal treatment. Only lines 448-453 refer to group treatment while, in our opinion, many of the principles mentioned under 'products intended for individual treatment' (lines 454-483) also apply for group/flock administrations. It is currently not clear which approach should be followed to obtain a metaphylactic label claim for group treatments. By default, any herds included will be "well managed herds" given the need to perform studies to GCP. The relevant management conditions to the targeted indications will also be recorded as per GCP. Also by default, treatment will be administered to the entire group of animals, but more details on what to analyse and how are required. The focus group meeting should discuss the following examples of questions on different approaches: - Examine the overall efficacy on a group level, not distinguishing between sick and in-contact animals? Would this result in a 'Treatment and metaphylaxis' label claim or a standalone 'metaphylaxis' claim? - Perform two separate statistical analyses within one study, one for the sick animals and another one for the healthy in-contact animals? This would bring many practical concerns, because the sick animals could be	Partly accepted. The section on metaphylaxis has been reworded to increase clarity on which information is necessary for different formulations to support a metaphylaxis claim, and how to perform a clinical study when that is regarded necessary for individual treatment formulations. See also comments below and comment to line 244.

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		compared against a positive control while the healthy in-contact animals should be compared against a negative control, but one cannot attribute different treatments within a pen. To ensure sufficient statistical power, this would become a huge study. - Perform two separate clinical trials, one for treatment against a positive control (if available) and one for metaphylaxis against a negative control? This will significantly increase cost. Proposed change: This paragraph needs more guidance on how to obtain a metaphylactic label claim for group/flock treatments and the differences with individual treatment (if any) should be clarified. The bullet point on "Well managed herds…" can be deleted.	
436	4	Comment: How is metaphylaxis claim described on the SPC? Treatment and prevention? Treatment and control?	Metaphylaxis can never occur as a separate claim but would always be connected to a treatment claim. Thus, the claim would be "Treatment and metaphylaxis".
438	7	Comment: bring definition metaphylaxis in line with EPRUMA agreed definition Proposed change (if any): We suggest changing the sentence to: '*In outbreaks of infections in a herd/unit where the causative agent is known to spread quickly and causes clinical disease in a large proportion of the stock within a short time span, metaphylactic treatment of clinically diseased animals and possibly infected animals likely to be in the incubation phase due to close contact with*	Not accepted. It is necessary to define metaphylaxis as the group-treatment of in-contact animals and not also include the treatment of clinically diseased animals in the definition. This will enable the approval of either a treatment claim or a treatment and metaphylaxis claim for a formulation intended for individual administration, dependent on what data is presented. For formulations intended for mass medication via food and water, a metaphylaxis claim will be granted in conjunction with a treatment claim when sufficient efficacy data is

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		diseased animals may be justified from an epidemiological point of view. '	presented on group level, and the need for metaphylaxis in principle for the disease under study is supported.
443	1	Comment: This is not in line with the definition of a metaphylactic claim (lines 244-246). It is not clear which approach should be followed to obtain a metaphylactic label claim for group treatments. Treatment is administered to the entire group of animals and the overall efficacy on a group level is examined. After group treatment it is not possible to distinguishing efficacy between sick and in-contact animals.	For formulations intended for mass medication via food and water, a metaphylaxis claim will be granted in conjunction with a treatment claim if sufficient efficacy data is presented on group level, and the need for metaphylaxis for the disease under study can in principle be justified by e.g. epidemiological information.
444	4	Proposed change (if any): Add in-feed route of administering medicines as well as via the drinking water—for group treatments	Accepted.
452	3	Comment**:** Typo – delete one of the two commas after 'fish'.	Accepted. The line has been deleted.
465-468	1	Comment: The threshold for the initiation of metaphylactic treatment can be discussed. For the reason of efficacy and to prevent/reduce the resistance of target pathogens agent the tested antimicrobial, it can be beneficial to initiate the treatment and metaphylaxis as early as feasible from the clinical (diagnostical) standpoint (when antimicrobial burden is still low in affected animals). This may differ between the indications (pathogens) and should be reflected in the clinical trial protocol.	It is agreed that the criteria used to define the appropriate time to initiate metaphylaxis treatment varies between diseases. For that reason the guideline text is general on this point.
465-468	2	Comment: In certain diseases, e.g. caused by *Mycoplasma gallisepticum* in chicks, from infected	Not accepted.

Line no.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
		parent flocks a proportion of them will be carrying the infection hence they are treated metaphylactically on arrival as day old chicks. However they may not actually be showing clinical signs or be diseased. Proposed change: Add (e.g. the proportion of *infected* or clinically diseased animals at a certain time point within a group)	The example given would rather be classified as prevention. Study recommendations given in 6.4.8 would thus apply.
472 and 477	3	Comment**:** Placebo group appears here as a "must" whereas in 345-352 it is just recommended Proposed change**:** add in 477 […] negatively controlled, where appropriate.	Not accepted. There is no contradiction as in line 349-350 that a negative control is necessary in some situations to support a metaphylaxis claim. This situation is further clarified in line 462-464 (there is not enough literature data to support the metaphylaxis claim).
475 - 476	3	Comment**:** there is no common sense on well managed herds and there is no definition on such a term. In addition a positive reaction to a poor management is more unlikely than a positive reaction to a good management. Proposed change**:** delete 475 and 476	Partly accepted. This bullet point has been re-worded according to previous comments.
475-476 and 495-496	1	Comment: It may be beneficial to insert the possibility to perform positive controlled study. In some indications (e.g. perioperative prophylaxis) the use of established positive therapy may be beneficial for animal welfare.	Party accepted. It is mentioned that alternative study designs may exceptionally be accepted provided the efficacy of the preventive treatment can be determined with sufficient certainly.

Line no.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
475-476	2	Comment: In order to avoid the influence of poor management conditions, any study is requested to be a controlled study, preferable negative controlled. Randomisation to treatment should also reduce any potential bias by external parameters. Therefore this sentence is not conclusive and should be replaced. Proposed change: The study design, and selected herds and houses used where any such studies are performed should assure that management or housing do not add unacceptable bias to the study results.	Accepted.
477	4	Proposed change (if any): Consider changing text from " Studies should be negatively controlled " to " Studies should have an unmedicated group "	Partly accepted. The recommendations regarding control have been slightly reworded.
485-488	7	Comment: bring definition prevention in line with EPRUMA agreed definition Proposed change (if any): We suggest changing the sentence to: '*Preventive claims refer to the administration of a VMP to treat an animal or group of animals before clinical signs of disease, in order to prevent the occurrence of disease or infection. Such claims should only be considered in those situations when the risk for infection is very high and the consequences are severe. This should never be done routinely or to compensate for poor hygiene and for inadequate*	Not accepted. It is considered that the EPRUMA definition overlaps the definition of metaphylaxis The last sentences in the proposed text relates to prudent use and is thus not relevant for this guideline.

Line no.	Stakeholder No.	Comment and rationale; proposed changes	Outcome
		husbandry or housing conditions. It should only occur under prescription by a veterinarian on the basis of epidemiological and clinical knowledge. ‘ FVE also wants to remark that in some countries preventive claims are prohibited eg. The Netherlands.	
489	3	Comment: The use of a negative control whilst scientifically justifiable is not always possible ethically or economically in field trials. Proposed change: please amend as follows “To support a preventive claim a negatively controlled study should be used **unless otherwise justified** and animal welfare…”	Party accepted. It is mentioned that alternative study designs may exceptionally be accepted provided the efficacy of the preventive treatment can be determined with sufficient certainly.
502-505	3	Comment: The "strongly suspected" seems to contradict what is requested earlier, i.e., establishment of MIC data and PK/PD relationship. Additionally there is also a specific guideline on SPC for antimicrobials, and the added value of the specifics here is not clear. Proposed change: please delete lines 502-505	Accepted.
518	2	Up-to-date definitions for terms used in the guidelines including those of PK/PD interest should be given in an Appendix to be created	Partly accepted. The definitions have been slightly reworded. PK parameters are not defined.