10 May 2010
EMA/CVMP/561927/2009…
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Draft Guideline on the conduct of bioequivalence studies for veterinary medicinal products'(EMA/CVMP/016/00-REV.1-CONSULTATION)

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

Stakeholder no.	Name of organisation or individual
1	Association of Veterinary Consultants (AVC)
2	European Group for Generic Veterinary Products (EGGVP)
3	Farma Research Animal Health BV
4	Food and Drug Administration (FDA), USA
5	National Agency for Medicines Finland
6	International Council on Animal Protection in Pharmaceutical Programmes – (ICAPPP)
7	Veterinary Drugs Directorate (VDD), Canada
8	IFAH-Europe (International Federation for Animal Health Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AVC considered that this guideline covers a large body of relevant science and brings it together in a coherent and systematic manner.	
2	One of the major product groups posing problems when demonstrating bioequivalence are local applications. As these are important guidance is needed to obtain a harmonised approach. It is felt that these should be part of this guideline. In the human guideline and in the FDA guidance exemptions wavers for clinical endpoint comparison for topical products are included. This guidance should be included on the vet side as well. In the old guideline, exemptions were included for products which were identical (manufactured according to the same part II by the same manufacturer). This situation, although not excluded, is no longer included in the guidance. The guideline is mainly relating to plasmakinetics. Guidance on the cases in which to use other biological fluids and some study specific guidance related to that would give a more complete picture.	Locally applied products with systemic exposure are considered covered by the proposed guideline. However, locally applied locally acting products are outside the scope. Details on study design for studies using pharmacodynamic or clinical endpoints will be dependent on therapeutic area and indication claimed. Therefore no general guidance is given within this guideline. A waiver for identical products is not considered necessary to detail as this is obvious. Regarding other biological fluids, no guidance is included as this a rare scenario.
3	We disagree with the statements in lines 336 to 338 in the Draft Veterinary BE Guideline: "The bioanalytical part of bioequivalence trials should be conducted according to the principles GLP. However, as such studies fall outside the formal scope of GLP, the sites conducting the studies are not required to be certified as part of the GLP compliance certification scheme." for the following reasons: A: This is a complete reversal of the original guidelines. B: The statement itself is unclear, i.e. Which studies fall outside the formal scope of GLP, clinical studies, bioequivalence trials or bioanalytical parts of such studies? C: BE studies for veterinary product are comparative Pharmacokinetic (i.e. pharmacological) studies which can waiver the need for consumer safety data (normally acquired via Residue depletion studies), animals safety data (normally acquired via Target animal safety studies) and efficacy data (normally acquired via clinical studies). According to the current EEC directives and Guidelines,	Please note that BE-studies (for the purpose of this guideline) are defined as PK-studies. The principles for GLP apply but formally this is not safety studies.

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	Pharmacological (incl. Pharmacokinetic), Residue depletion and Target animal safety studies should be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) and Clinical studies in conformity with Good Clinical Practice. With BE data "replacing" GLP based safety data it is not allowed to waiver GLP-compliance for the bioanalytical part of BE studies. One should realize that not only the "scientific" integrity of the analytical method (covered by adequate validation) but also the integrity in sample handling and data analysis can influence or determine the outcome of a BE study. Claiming to conduct studies according to the principles GLP, is claiming GLP over a study or part of it. This means the "site" performing the study or parts of it is eligible for inspection and "certification".	
4	For two products, pharmacokinetic equivalence (i.e. bioequivalence) is established if the rate and extent of absorption of the active substance investigated under identical and appropriate experimental conditions only differ within acceptable predefined limits. Rate and extent of absorption are typically measured by Cmax (peak concentration) and AUC (total exposure over time), respectively, in plasma or serum to ensure that plasma/serum versus time profiles are similar. Suggested changes: Valid use of AUC and Cmax to evaluate product bioequivalence parameters is founded upon an assumption that the drug clearance (CL) drug volume of distribution (Vd) is not biased by the study design. Comment: Be aware that some of the newer formulations within human drugs (e.g., liposomal preparations, especially stealth liposomes) may be administered via intravenous injection but that formulation effects (altered Vd, CL and rate and extent of exposure at the target site) CAN nevertheless be influenced by formulation and manufacturing method. The original bioequivalence paradigm, with time, will not be applicable to some dosage forms.	Agreed. However, there is never the case that a guideline covers each and every possible situation. The example with stealth liposomes for intravenous administration seems superfluous to include in a guideline for veterinary medicine.
5	In some parts the guideline is somewhat vague, which leaves the interpretation of the guideline to an individual assessor and this may lead to different interpretations and disharmony (see two examples	We have tried to be as precise as necessary in the guideline.

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	below). All requirements should be stated as clearly as possible to avoid misinterpretation and, in the worst case, referrals.	
6	Since this guideline includes reference to the conduct of animal studies, we feel it is appropriate for a small section on '3Rs considerations' to be included. This might include text such as: "The 3Rs should be adhered to in any animal study that is conducted; that is efforts should be made to replace, reduce and refine the use of animals wherever scientifically and practically possible. *In vitro* or *in silico* methods should be employed where possible; if these are of sufficient quality to mitigate *in vivo* studies these should be used and scientific justification provided. If animals are to be used, numbers of studies, animals, dose levels and routes of administration should be kept to a minimum to generate the required information. Provision of social housing, enrichment and humane endpoints should be made. Applicants are referred to Directive 86/609/EEC regarding the protection of animals used for experimental and other scientific purposes. Council of Europe Treaty ETS 123 European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes CPMP/SWP/728/95 Replacement of animal studies by *in-vitro* models "	This is addressed where appropriate in the detailed comments. Please note that several parts of this guideline (the BCS-system, detailed information on study design etc) aim at reducing the number of animals needed. *In silico* methods have never been proposed for bioequivalence.
7	1. Overall the document is well written and contains important information on how to conduct blood-level studies and *in vitro* dissolution studies for generic products but also for other comparative applications in the course of the development/manufacturing of a reference product. 2. There are several novel issues raised in this document compared to other international veterinary bioequivalence guidelines which include the use of BCS, alternative study designs, two-stage designs and the analysis of enantiomers. 3. The guideline does not however include information on	The comment is appreciated and has been considered when revising the guideline. In cases where the guideline applies to generics only, this is stated. Else, the text is applicable for all products independent of legal base for the application

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	pharmacological (pharmacodynamic) and clinical end point studies for the demonstration of bioequivalence, nor does it include any information on human safety requirements. 4. This guideline puts a strong emphasis on the Biopharmaceutics Classification System (BCS) (based on human data for confirmation of an *in vitro-in vivo* correlation) as a basis for granting biowaivers to several different dosage forms of veterinary drug products. However, very few studies (none published) have been conducted in animals using this system, making it difficult to validate this method in animals. 5. Although it is mentioned on lines 111-113 that some parts are applicable to generic products only, in general, it is unclear throughout the document when particular situations are acceptable for generics or not (e.g. variations and extensions – lines 126-130; strengths to be tested – lines 257-267; dose to be tested – lines 275-288; comparisons between formulations – lines 466-468). 6. Repeated information is found in both the main document and the Annex (e.g. BCS, *in vitro* dissolution studies and biowaivers for medicated feeding stuffs/drinking water).	

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8	IFAH-Europe is very pleased with the opportunity to comment on the proposed revision of the EMEA/CVMP Guideline (GL) on the conduct of bioequivalence studies for veterinary medicinal products. This is a very critical document and the objective of the revision should be to provide industry with greater clarity and appropriate guidance when comparing or bridging formulations and products. In general, many parts of the draft guideline seem to be taken from the human bioequivalence GL (EMEA/CHMP/1401/98-Rev. 1). As a result, the GL lacks flexibility and consideration of veterinary specificities such as the use of premixes or the species-dependant anatomy and physiology of the gastro-intestinal tract. Furthermore the GL does not cover the situation of hardly soluble substances, which are not intended to act systemically but locally (e.g. many anthelmintics). Further general comments include: - The use of the term "*pharmaceutical form*" instead of "*dosage form*" throughout the document; - The exclusion of clinical and pharmacodynamic endpoints; thus clear guidance on the use of such endpoints is now lacking; - The lack of references to (non)-linearity of pharmacokinetics; however, it can have consequences on the bioequivalence testing, especially in the case of over-dosing or in dissolution testing. IFAH Europe would in general like to draw attention to the four following points, as also raised at the Focus Group meeting on 6th May 2009, which was a great opportunity for exchange with CVMP experts. They are: - The appropriateness of biowaivers and the use of the Biopharmaceutical Classification System (BCS) and dissolution testing; - The statistics; - The study design and - The evaluation of enantiomers. Overall, we must ensure that the revised GL will be consistent with other existing guidelines issued by the European Competent	Premixes are covered. Species differences are considered both in the main guideline text and in the BCS appendix. "*dosage form*" has been changed to "*pharmaceutical form*" Locally applied products with systemic exposure are considered covered by the proposed guideline. However, locally applied locally acting products are outside the scope as they cannot be studied by means of PK. After consideration, references to non-linear kinetics have been removed in all cases except for when different doses are used in the same study. In the old guideline, linearity was to be considered when extrapolating results between strengths and when designing the study where multiple dose studies were recommended in case of non-linearity. On the other hand, data on linearity in vet medicine are most often poor and seldom request have been made to study additional strengths or present multiple dose data due to lack of data on linearity. Consequently, as we now are removing the requirement, we are actually not changing practice. There may be very rare situations where a non-linearity would affect the possibility to extrapolate the result from a strength to others but we are willing to take that risk given that if linearity/non-linearity was to be considered, a lot of additional studies would have to be performed due to missing data on linearity. Regarding the request for steady state studies, such studies would be more sensitive to detect differences in the amount of absorbed drug in case of dose- or time dependent pharmacokinetics where the exposure is markedly higher at steady state than expected based on single dose PK data. A steady state study would, however, be less sensitive than a single dose study to detect differences in Cmax. The situation where a multiple dose study would be more sensitive than a single dose study is therefore rare and single

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	Authorities, such as the "2.9.3 Ph. Eur. Dissolution test for solid dosage form" or the VICH GL 39 on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products (EMEA/CVMP/VICH/810/04-corrigendum).	dose studies are in general are sufficient. Hence, in order not to complicate the guideline, the request for multiple dose studies due to non-linearity has been removed.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
081	7	**Comments:** **INTRODUCTION (background)** i. Although the term "blood-level study" has been used internationally for many years, this guideline uses the words "bioequivalence study" to refer to the blood-level study only (i.e. pharmacokinetic equivalence).	The term bioequivalence study is widely used for studies where it is demonstrated that the rate and extent of absorption (i.e. absorption pharmacokinetics) of two formulations is similar.
081 to 85	1	**Comments:** Rate and extent of absorption are described as typically represented by AUC and Cmax. It is true that extent of absorption is represented by AUC but Cmax is not enough to describe the rate of absorption. Either Tmax or T1/2 absorption (except in case of flip-flop effect), mean absorption time, etc. are required in addition to Cmax to describe rate of absorption. Tmax is linked to Cmax by the equation $Cmax = F.D/V\ e^{(-Kel \times tmax)}$ but volume of distribution and Kel are usually unknown when performing bioequivalence studies. **Proposed change (if any):** Consider removing "rate" in the sentence or adding another parameter to Cmax to describe rate of absorption (e.g. Tmax).	Acknowledged. However, in most cases AUC and Cmax together give a sufficiently detailed estimation of the pharmacokinetic profile resulting from a certain rate and amount of absorption. We feel the text is sufficiently correct for its purpose.
092	1	**Comments:** It is clear that this guideline refers to what might be termed conventional bioequivalence i.e. measuring values in plasma and serum of a veterinary medicine following administration. To us the potential scope of bioequivalence is far wider e.g. extending to possibly tissue fluid for an anti-inflammatory, levels of a non-systemic insecticide on skin or hair over time. These ideas also capture the sense of the word bioavailability that is used in the Directive. **Proposed change (if any):** We suggest the word "systemic" is added before bioequivalence to convey that this is just one aspect of pharmacokinetics as these other possibilities will be areas of interest in future.	Acknowledged, however we believe this is covered by the definition of bioequivalence. Rate and amount of absorption refers to systemic availability.
092-95	8	**Comments**: the GL reads that the cases when pharmacokinetics (PK) parameters cannot be used are *"beyond the concept of bioequivalence and this*	We acknowledge that there might be situations where hybrid applications

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		GL does not cover these aspects". We question this statement since there are cases where non-PK parameters or other PK parameters than Cmax and AUC are scientifically justified and can be used. Also the current EMEA/CVMP GL already considers these cases. **Proposed change**: please add a sentence in line 94, such as: *"In these cases, pharmacodynamic parameters, PK-PD parameters or other PK parameters than Cmax and AUC may be used if scientifically justified"* and amend line 94-95 as follows: *"This is however not detailed in ~~beyond the concept of bioequivalence and~~ this guideline ~~does not cover these aspects~~."*	are approved without data on rate and extent of absorption but other PK parameters. It might also be found more appropriate to use PD or clinical data. However, this guideline covers bioequivalence (i.e. rate and amount of absorption) only. A minor change to the text is made.
094 and 101	1	**Comments:** The use of endpoints may be confusing: usually pharmacokinetic plasma levels are collected over time, rather than at a single endpoint. Does the use of endpoint here refer to the plasma sample being a useful endpoint for measurement? **Proposed change (if any):** Please clarify.	Noted. The text has been amended
094-95	7	**Comments:** It is unclear why pharmacological (PD) and clinical end-point studies are "beyond the concept of bioequivalence" as implied in this document. The indirect demonstration of bioequivalence between test and reference products, using these alternative studies to the blood-level study, has been confirmed internationally for several years for many veterinary and human drug products. Since many veterinary drug products do not have systemic exposure, an alternative to the blood-level study should be included in a bioequivalence guideline for veterinary medicinal products	The scope of this guidance has been restricted to PK as PK is the most sensitive way, in comparison with PD and clinical endpoints, to demonstrate similar product performance. Of course, therapeutic equivalence may be demonstrated by means of PD or clinical endpoints but as these approaches are quite different in methodology, we do not cover them in this guidance. Of note is that products being documented as equivalent by PD or clinical endpoints are referred to the hybrid application route.
095	1	**Comments:** "This guideline does not cover these aspects" **Proposed change (if any):** We suggest changing to "clinical equivalence or other appropriate equivalence	Please see comment to stakeholder 8 above.

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		studies should be performed in this case".	
101-104	8	**Comments**: the GL reads: "...*pharmacodynamic or clinical endpoints may be used under exceptional circumstances, to demonstrate similar efficacy and safety"* - Clarification would be welcomed on the meaning of "*exceptional circumstances*"; the GL currently in application explicitly allows the use of pharmacodynamic endpoints in cases where the direct measurement of the rate and extent of absorption is inappropriate; it specifies that in such cases "*it may be necessary to demonstrate bioequivalence on the basis of a pharmacological end-point study*"; and that "*the pharmacological parameter should be relevant (related to the drug activity)"*. - Also does "*similar"* efficacy and safety mean "*equivalent"* safety and efficacy? **Proposed changes**: - Please amend the text as follows: "~~*If bioequivalence cannot be demonstrated using pharmacokinetic endpoints, pharmacodynamic or clinical endpoints may be used under exceptional circumstances, to demonstrate similar efficacy and safety*~~. *The pharmacological parameter should be relevant and related to the drug activity. For a veterinary medicinal product where PK/PD is uncoupled and the PK profile does not correlate to the onset and duration of main PD action, especially if the parent compound is metabolised into its active component, it makes more sense and is justified to use a PD endpoint study instead of a PK."* - Also to clarify that once bioequivalence has been demonstrated, it will be considered suitable for safety & efficacy, please add: "*If bioequivalence cannot be demonstrated using pharmacokinetic endpoints, pharmacodynamic or clinical endpoints may be used to demonstrate similar efficacy and safety."*	If PK is possible to use, this is the preferred way. The reason is that we are interested in the similarity of product performance and this is indirectly observed via PK with a higher sensitivity than in a PD or clinical study.
103-104	7	**Comments:** **SCOPE** As mentioned above, it is unclear why pharmacological (PD) and clinical endpoint studies are beyond the scope of these guidelines. They are an alternative to the blood-level studies and are considered by other international regulatory authorities as being able to indirectly demonstrate bioequivalence between two products without systemic exposure.	See above.

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		Proposed change (if any):	
108	8	**Comment**: a reference to the FDA "Guidance for industry: Dissolution testing of immediate release solid oral dosage forms" in lines 587-588 should also appear here. **Proposed change**: please reword line 108 as follows: *"...refer to other relevant European, VICH or international guidelines…"*	Lines 587-589 are deleted because of unnecessary reference to FDA guidance.
119-120	8	**Comment**: examples of suitable *in vitro* studies used for bridging may need specifying.	The sentence is removed. Information on *in-vitro* studies is found elsewhere in the guideline.
121-125	8	**Comment**: the end of this paragraph, i.e. "...*the rate and extent of absorption from this formulation is at least as high as that for the formulation intended to be marketed*" is unclear. Thus clarification is expected on the following: - What kind of study can be used (*in vitro*)? - Does this section concern oral and parenteral products?	1. Any kind of *in vivo* comparative pharmacokinetic study could be used dependent on area of concern. 2. Yes
122	1	**Proposed change (if any):** We suggest replacing "in case a tolerance study" with "where a tolerance study"	Accepted.
138-140	1	**Comments:** We understand from this sentence that new residue studies should be performed for generic injectable forms but it is not clear whether this includes only residues at the injection sites (usually the limiting factor to establish withdrawal periods in that case) or a complete residue study including liver, kidneys, fat (or skin/fat) and muscle outside injection sites. **Proposed change (if any):** Please clarify this point.	The intension here is to indicate that bioequivalence alone is not sufficient. Details on study design for residue depletion studies is to be found in Note for guidance, approach toward harmonisation of withdrawal periods (EMEA/CVMP/036/95)
138-140	8	**Comment**: the sentence reads: *"It should be noted that bioequivalence cannot be used for extrapolation of withdrawal periods between injectable products for intramuscular and/or subcutaneous injection in food producing animals".* However, Article 13 of Directive 2001/82 as amended reads: "*1. By way of derogation from point (j) of the first subparagraph of Article 12(3), […], the applicant shall not be required to provide the results of the*	See comment above. It is agreed that neither bioequivalence nor residue depletion data are needed in case of identical products.

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		*safety and **residue tests** or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product" […].* *2. "For the purposes of this Article: […] (b) 'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose **bioequivalence** with the reference medicinal product has been demonstrated by appropriate bioavailability studies."* Finally Title III of Annex I to Directive 2001/82 as amended reads: […] "*For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:* - *Evidence to demonstrate equivalent or differing depletion of residues from the administration site, which **may be** substantiated by appropriate residue depletion studies,* […]." This aspect was further addressed at the focus group meeting when it was correctly noted that since bioequivalence only relates to the rate and extent of absorption, there cannot be a conclusion from the bioequivalence data per se on the elimination part of PK. Though we acknowledge that residues must be addressed, further clarification on this matter is expected. Furthermore, in cases where the test and reference products are identical, the residue depletion study should be waived.	
147	2	**Comments:** The draft guideline states that the dose, expressed as amount of test substance should be the same in both phase of a cross-over study. Although the guideline could be interpreted in different ways, Dr. Törneke (CVMP) explained that this is a must. Moreover, it was stated that in fast growing animals a cross-over design is not appropriate and a parallel design should be applied to BE studies. In general, the dose for farm animals is expressed as mg or ml per kg of body weight. Not adjusting the dose in bi-phasic studies in fast growing animals will result in incorrect dosing and a bias in the study results. Moreover, a parallel study design will result in the necessity of increasing the number of experimental animals. It is our experience that a bi-phasic cross-over BE study can surely be applied in fast growing animals, provided that the study is accurate implemented and conducted. The new guideline should clearly explain	It is assumed that this comment refers to line 282-283. It is not a "must" but it says that the dose should be the same *unless the change in body weight is considerable*. We believe this is sufficiently clear. Regarding choice of design, we agree that it is the responsibility and freedom of the applicant. The guideline state that we allow different designs if it is scientifically justified.

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		that it is the responsibility and freedom of the applicant which design is used for BE studies.	
148	8	**Comment**: a study can either be GLP or GCPv as appropriate, not both. Thus the '*and*' should be deleted. **Proposed change**: please amend as follows: "*Bioequivalence studies should be conducted under GLP ~~and/~~ or GCPv, as appropriate…*"	It may indeed be both. The in-life phase may be GCPv and the analytical part GLP.
148-149	1	**Comments:** GLP/GCP **Proposed change (if any):** As stated at lines 336-338, GLP apply to the bioanalytical part (not GCP). We suggest "Bioequivalence studies should be conducted under Good Laboratory Practice (GLP) and/or Good Clinical Practice (GCP) for the in vivo phase and GLP for the bioanalytical phase."	Agreed. However, we believe the text is clear without this high level of detail and thus no changes are proposed.
148-149	1	**Comments:** GLP/GCP: GCP as described in relevant guideline apply to clinical studies and in-use safety studies in target animal species. Although Bioequivalence studies have indirectly consequences in terms of clinical efficacy and target animal safety, the relevance of GCP is questionable as BEq studies are usually conducted in experimental farms (not field studies) and using healthy animals (not clinical conditions). Nevertheless, GCP studies may be requested in case field studies are required. As stated at lines 336-338, GLP apply to the bioanalytical part, but definitely not GCP. **Proposed change (if any):** We suggest "Bioequivalence studies should be conducted under Good Laboratory Practice (GLP) for the bioanalytical phase and according to GLP for the animal phase in case of laboratory studies (experimental farm or laboratory animal facilities) or Good Clinical Practice (GCP) in case of field studies".	See above.
149	7	**Comments:** Since blood-level studies are the only ones discussed here, GLP only would be expected, not GCP?	It's agreed that GCP is not expected but it would be accepted. See above.

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153	8	**Comment**: it is not clear what a *"sufficiently long"* wash-out period is. The current GL is more detailed and refers to a "*wash-out period of at least ten-times the terminal half-life of the active or its metabolites*". Though it is assumed that applicants are familiar with pharmacokinetic principles, it also seems reasonable to provide some indication (e.g. at least seven-times the half life or ten-times the terminal half-life of the active or its metabolites) while allowing to deviate, where justified. **Proposed change**: please add at the end of the sentence (line 154): "*A wash-out period of at least seven times the terminal half-life is generally thought sufficient; any deviation will have to be justified.*"	Agreed, we have now changed the text to state that a normal wash out period last at least 5 elimination half-lives, which is a commonly used cut off point.
157, 163, 202	1	**Comments:** Ask for scientific advice **Proposed change (if any):** The fees for scientific advice (12,100 Euros) should be taken into account every time "ask for scientific advice" is mentioned in the Guideline. A more detailed examination of each concerned paragraph should be considered in the final guideline.	We have referred to Sci Adv in situations where we feel general guidance cannot be given.
159	8	**Comment**: a criterion for '*long half-life*' would be useful e.g. >24h.	It is only a recommendation to consider a parallel design due to practical reasons. The choice between a cross over design and a parallel design due to long half life has to be taken by the sponsor. There is no need for a criterion.
162-164	8	**Comments** We recommend considering a scaled approach to bioequivalence criteria (Cmax and AUC) as described in Haidar SH, Makhlouf F, Schuirmann DJ, Hyslop T,We, Davit B, Conner D, Yu LX, Evaluation of a Scaling Approach for the Bioequivalence of Highly Variable Drugs. AAPS J. 2008 Aug 26. This method avoids unnecessary exposures to subjects in bioequivalence studies who receive no therapeutic benefit while adequately ensuring acceptable product	The comment is acknowledged. However, we do not consider that we need more additional information on HVD as widening of the acceptance range for Cmax based on efficacy and safety arguments will still be an option. Regarding references, we are reluctant

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		performance. We further recommend adding a reference to e.g. "Design and Analysis of Bioavailability and Bioequivalence Studies 2000 Shein-Chung Chow and Jen-Pei Liu (chapter 2, 9 and 10) Second edition, Marcel Dekker, Inc." or other references. Also high inter individual variability must be defined. It is important that this is not only linked to an arbitrary figure but also to practical constraints, in particular the number of animals raises different considerations depending on the animal species (this is a specificity of the vet sector). **Proposed change**: please amend line 162 as follows: "*In case of substances with highly variable disposition where it is difficult to show bioequivalence due to high intra individual variability, different alternative designs, such as scaling, have been suggested in literature. In general, a drug product is called highly variable when the within-subject variability is greater than 30%. However, whenever the within-subject variability requires that a number of animals that would raise practical and/or ethical issues in the species considered for a traditional cross-over design, alternative designs may be used. In such case, it is recommended to seek Scientific Advice.*"	to include specific publications as this is an evolving field.
165-168	8	**Comment**: the rational for single dose vs. multiple dose studies is less clear than in the current GL. The reason given "*e.g. problems of sensitivity of analytical method…"* is not unique and the rationale behind choosing multiple dose study design should also clearly relate to the PK properties of the product and the intended use means requirement for steady state conditions. The lack of an appropriate lower limit of quantification (LLOQ) only does not qualify as a justification. **Proposed change**: please replace "*Multiple dose designs should be justified and could be considered if e.g. problems of sensitivity of analytical method preclude sufficiently precise plasma concentration measurements after single dose administration*" with: *A multiple dose study should be considered when there is excessive intra-subject variability in bioavailability, or when the concentration of the active substance resulting from single dose is too low for accurate determination by the analytical method. In any case, a multiple dose study can be performed where justified.*	Not agreed. The section is considered to be sufficiently precise. Further, it is not a general rule that intra-subject variability decreases in a multiple dose study and the suggested text on this issue is considered potentially misleading.
166	1	**Comments:**	See comment on line 80-85 above.

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		"a difference in rate of absorption" **Proposed change (if any):** Rate of absorption cannot be described using only AUC and Cmax parameters.	
169-176	8	**Comment**: this paragraph addresses the oral route, especially feeding; it assumes that excipients can influence the bioavailability when the treatment is administered fed or fasted. This seems however contradictory to section 7.1 of the annex (page 22/22). Furthermore, for immediate release products, bioequivalence demonstrated under fasting conditions is more sensitive to differences in pharmacokinetics. Thus it is unclear if bioequivalence in unfed animals only can be proposed for a product which can be administered fed or fasted (if the SPC leaves this choice) or if both types of administration need to be tested. **Proposed change**: we propose adding the following sentence: "*For a product which can be administered fed or fasted, the choice to conduct the bioequivalence either way should be left to the applicant and justified accordingly*."	Accepted. Fasting conditions are recommended unless the SPC of the reference product recommends administration only in the fed state in which case the bioequivalence study should be conducted accordingly. Consequently, there is no need for both types of administration (fed fasting) to be tested for an immediate release formulation. We don't find the texts contradictory. For details on excipients in case of possible biowaivers (including medicated feed) please see 5.2 in the Annex.
172-174	6	**Comments:** The draft guideline states: *The rationale for conducting **each** bioequivalence study under fasting or fed conditions should be provided in the protocol.* This could be interpreted as meaning that two studies (under fed and fasting conditions) have to be conducted. If this is not the intention then it may be better to replace the word 'each' with 'a'. **Proposed change (if any):** The rationale for conducting **a** bioequivalence study either under fasting or fed conditions should be provided in the protocol.	Accepted.
177 – 178	4	**Comments:** The number of test animals must be appropriate for statistical analyses and should be carefully estimated and justified in the protocol. **Proposed change (if any):** **2.** Considerations should include such factors as:	We do not consider it necessary to detail more information on sample size calculations.

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		a. The estimated within-subject error (Crossover Study Design) or the between-subject error (Parallel Study Design) associated with the pivotal bioequivalence parameters. b. The magnitude of difference between the test and reference products. c. The delta (acceptance criteria) being applied to the bioequivalence assessment.	
177-178	6	**Comments:** The draft guideline states: *The number of test animals must be appropriate for statistical analyses and should be carefully estimated and justified in the protocol.* In light of 3Rs considerations it would be preferable within this sentence to show that the minimum number of animals required should be used. **Proposed change (if any):** The minimum number of test animals must be kept as appropriate for statistical analyses and should be carefully estimated and justified in the protocol.	The number of animals should be carefully estimated based on power calculations. A request for a minimum number of test animals may influence applicants to under power their study and that would be against 3R.
177-178	8	**Comment**: depending on the data available at the time of the study, the number of animals necessary to demonstrate bioequivalence cannot always be precisely estimated. In this case, a two-stage approach can be chosen as stated in 5.15.3 (p. 11/22). Also literature references could be added. **Proposed changes**: - Please add at the end of line 178: "*Where the number of animals necessary to demonstrate bioequivalence cannot be precisely estimated, a two-stage approach can be chosen (see section 5.15.3)*". - Also add the following references: → E. Diletti, D. Hauschke and V. W. Steinijans, Sample size determination for bioequivalence assessment by means of confidence intervals. International J. of Clinical Pharmacology, Therapy and Toxicology, V29, No1 1991 page 1-8; → D. Hauschke, A note on Sample Size Calculation in Bioequivalence Trials, J. of pharmacokinetics and pharmacodynamics V29, N° 1 February 2002 page 89-94;	Agreed. However, it is felt that adding the references would bring a too high level of detail into the text. After all, the number of animals is for the sponsor to decide.

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		→ E. Diletti, D. Hauschke and V. W. Steinijans Sample Size determination: Extended tables for the multiplicative model and bioequivalence ranges of 0.9 to 1.11 and 0.7 to 1.43. International J. of Clinical Pharmacology Therapy and Toxicology V30 Suppl No 1 1992 (pp 59-62).	
179	4	**Comments:** Generic versions of formulations designed to modify rate or site of absorption need special consideration. In veterinary medicine there are numerous different types of modified release formulations. These could be for oral use such as prolonged release tablets for companion animals (similar to formulations for human use), pastes for horses **(COMMENT: ARE THERE REALLY SUSTAINED RELEASE PASTE FORMULATIONS?)** or intraruminal boluses for cattle. Many modified release formulations are parenteral **(COMMENT: THE WORD PARENTERAL IS BEING USED INAPPROPRIATELY. SEE DEFINITION BELOW)** such as spot-ons and pour-ons, which are absorbed through the skin, or prolonged release injectables. In most cases such products are intended for single use and no accumulation between doses is expected. If so, single dose bioequivalence data is normally sufficient to demonstrate similarity between products. **MEDICAL DICTIONARY DEFINITION OF PARENTERAL:** Not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc. Origin: Gr. Enteron = intestine (11 Mar 2008).	Agreed.
182-185	8	**Comment**: the two sentences starting from "*These could be for oral…*" are misleading for the following reasons: 1. First of all, this list appears to be inaccurate, e.g.: a. "*paste for horses*" are included in this section on "*modified release formulations*". However, it is not the case for all pastes, e.g. anthelmintic pastes are not designed to delay the absorption but to facilitate the administration; in such cases, the actives are quickly absorbed. b. Also 'intraruminal boluses' exist in sheep, not only cattle; 2. The added value of the comment "*similar to formulation for human use*" is questionable for the purpose of this CVMP GL; 3. Also pour-on/spot-on formulations are not considered as parenteral	The text has been revised taking the comment into consideration.

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		formulations even if systemic absorption may occur depending on the active substances. **Proposed change**: please amend as follows: "~~*These could be for oral use such as prolonged release tablets for companion animals (similar to formulations for human use)*~~, ~~pastes for horses or intraruminal boluses for cattle. Many modified release formulations are parenteral such as spot-ons and pour-ons, which are absorbed through the skin, or prolonged release injectables~~. *In veterinary medicines, there are several types of modified released formulations that use different routes of administration and may be adapted between the different animal species*".	
185-190	8	**Comment**: the GL reads: *"In most cases, such products are intended for single use":* such consideration may apply to "real" single use products and also to products whose administration is repeated e.g. each month or twice a year. **Proposed change**: for the sake of clarity, please amend the paragraph as follows: "~~In most cases such products are intended for single use~~ *Prolonged release formulations whose aim is to e.g. avoid repeated administration or to modify the PK parameters (such as to even out the plasma peak for safety reasons) are generally intended for discrete administration; thus* ~~*and*~~ *no accumulation is expected.* ~~*If so*~~ *In this case, single dose bioequivalence data is normally sufficient to demonstrate similarity between products. However, for prolonged release administration intended for repeated dosing, i.e. the aim of the modification is to reduce fluctuations during steady state therapy or to reduce the frequency of administration, where there is accumulation between doses, demonstration of bioequivalence should be based on multiple dose studies."*	We have clarified the section. Multiple dose studies for prolonged release formulations are only required if there is accumulation between doses.
187-191	4	**Comments:** For prolonged release formulations intended for repeated dosing, i.e. the aim of the modification is to reduce fluctuations during steady state therapy or to reduce the frequency of administration, where there is accumulation between doses, demonstration of bioequivalence should be based on multiple dose studies. For such products Cmin is an important parameter to consider, in addition to Cmax and AUC. COMMENT: Firstly, the guidance should describe how one can confirm the presence of steady state conditions (e.g., measuring 3-consecutive trough	The example of Type-1 error inflation is not agreed to as this equation assumes that the parameters, in this case AUC, Cmax and Cmin, are uncorrelated. This is not the case. However, we acknowledge that Cmin is a parameter where one might expect a large variability. Cmin is nevertheless considered a primary parameter when establishing

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		concentrations and confirming that there is a slope of zero). With regard to the inclusion of Cmin as a third pivotal metric in the bioequivalence assessment, I hope that the simulations and information provided below helps to illustrate my concerns about why such a decision will detract from the evaluation of product bioequivalence. 1) By requiring that equivalence be met with multiple parameters, you are inflating the risk of a Type 1 error. (For simplicity, the overall Type 1error can be estimated as approximately 1-(1-α)^n; where α = 0.05 (in our case) and n is the number of tests. So, with one species, AUC and Cmax, the overall type 1 error = 1- (1-0.05)^2 = .0975. If we now have 3 pivotal parameters, then the risk of the Type 1 error = 0.143. If we have 3 parameters and we are testing the product in 2 species, then the overall risk of Type 1 error impacting the approval of the generic formulation = 0.265. In other words, there is more than a 26% risk that we will reject the null hypothesis when it is in fact true! Further adjustments to this estimate are appropriate when we consider our 2-one-sided test procedure. 2) Cmin values are largely dependent upon the relationship between T½ and Ka. In some cases, trough concentrations may not occur immediately prior to the next dose (e.g., see figure below from Mazer et al., J. Sex Med, 2005, 2:213-226. In situations where Cmin does not occur immediately prior to the next dose, how will you adequately capture trough values?	bioequivalence for prolonged release formulations. The reason is that we want to see that the release characteristics are similar. As we allow a widening of Cmin to 70-143 % if adequately justified, we believe that a study may still be designed with a reasonable number of animals. Details on how the last sample within the dosing interval should be collected and how steady state should be verified are included in the guideline.

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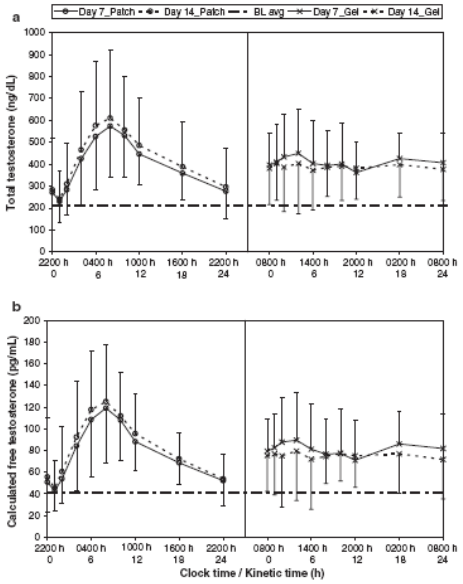

Figure 1 Mean (SD) steady-state pharmacokinetic profiles of (a) total testosterone (TT) and (b) calculated free testosterone (cFT) obtained on day 7 and day 14 during night-time applications (ca. 2200 hour) of Androderm® (left panels) and morning applications (ca 0800 hour) of AndroGel® (right panels). Time is expressed both in 24-hour clock time and in kinetic time, corresponding to the time after application of the patch or gel. Horizontal lines (dot-dash) denote the mean time-average baseline levels (BLavg) of the 28 subjects. Normal range for TT is 306–1031 ng/dL (Meikle et al. 1996). Normal range for cFT is assumed to be same as for free testosterone concentrations measured by equilibrium dialysis, i.e., 52–280 pg/mL (Esoterix Endocrine).

3) In cases where Cmin does coincide with a specific timepoint (predose), you will be facing the greater variability associated with comparisons at a particular timepoint (Cmin) versus parameters that can vary within each individual (Cmax, Tmax, AUC). Therefore, it is nearly always the case that the width of the confidence interval for Cmin will exceed that of AUC and Cmax. This is seen in the simulated cases below.
4) Because of the within-subject variability that is likely to occur, you may find that concentrations immediately prior to the steady state dose and concentrations at the conclusion of that profile result in differences in the confidence intervals. How will you ascertain which trough concentration is the most appropriate? This large variability is particularly likely in situations when dosing is in frequencies of greater than once per day (superimposition of circadian rhythms).

Most importantly, if we consider AUC and Cmax (with a qualitative evaluation of Tmax), you will find that Cmin provides no additional useful information to the bioequivalence assessment. Therefore, you will find that it serves only to

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detract from the ability to establish product bioequivalence.

To illustrate this point, I simulated two examples: one with a faster and the other with a slower absorption rate. The mean simulation inputs were as follows:

Dataset 1:Mean Parameter Values

	KA	VC	F	KEL
Test	1.41	1.00	0.46	0.08
Ref	1.50	1.03	0.50	0.08

Parameter CV

	KA	VC	F	KEL
Test	0.24	0.14	0.19	0.17
Ref	0.23	0.10	0.18	0.15

Dataset 2: Mean Parameter Values

	Ka	Vd	F	Kel
Test	1.60	0.97	0.55	0.11
Ref	1.53	1.01	0.48	0.11

Parameter CV

	Ka	Vd	F	Kel
Test	0.21	0.14	0.21	0.14
Ref	0.27	0.18	0.20	0.16

Note that in these simulations, I did not include the within-subject variability in T½ that leads to the normal fluctuations in trough concentrations. Inclusion of the latter source of error would only serve to further emphasize the impact that I am trying to show through these very simple simulations.

The dummy study was conducted as a 2-trt crossover and steady state values were achieved. The AUC was $AUC_{0-\tau}$, the Cmax was the peak at steady state, and Cmin was concentration immediately prior to the final dose. The resulting confidence intervals and confidence interval widths are provided below.

Dataset 1

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	LSMEAN					Width
	Test	Ref	T/R	UCL	UCL	
Cmin	4.05	4.48	0.90	0.75	1.09	0.34
Cmax	22.59	24.07	0.94	0.78	1.08	0.31
AUC	511.96	558.40	0.92	0.82	1.07	0.25

Dataset 2

	LCL	UCL	Width
Cmin	0.85	1.37	0.52
AUC	0.92	1.41	0.49
Cmax	1.01	1.40	0.39

Again, note that the width of the confidence interval for Cmin was wider than that of the other two parameters. Moreover, should one chose the Cmin prior to the last dose or at the end of the last dosing interval? Depending upon the magnitude of the within-subject variability, the test/reference ratios can be quite different for the two different timepoints.

That this can be a real problem in real life is exemplified in a study by van der Lee et al (Antivir Ther, 2006, 11: 439-445), where they estimated the %CV associated with AUC_{0-24}, Cmax and Cmin as 39%, 30% and 130%, respectively.

Therefore, unless there are specific pharmacodynamic reasons why Cmin is a critical parameter, it is strongly advised that Cmin be considered solely as a secondary parameter which is used primarily to confirm the presence of steady state conditions. The only two situations when Cmin may be of value during comparative bioavailability studies are:

- When a pioneer is wishing to use alternative dosing regimens and comparative profiles);
- When a drug exhibits effects associated with time above a specific concentration (e.g., the β-lactams) and there is either highly variable Tmax values or where the Tmax values may differ between the two formulations.

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192	7	**Comments:** Does this sentence imply that modified release products for ruminants only require fed studies to be conducted?	Fasted and fed state is not applicable to ruminants as their stomachs are never empty.
192-193	8	**Comment**: the purpose of bioequivalence study is to compare two formulations and not to evaluate the feed/fasting effect of a given formula that could be performed if necessary in another protocol using the tested product only. **Proposed change**: please remove the sentence: "*For orally administered modified release formulations to non ruminants, bioequivalence normally need to be established under both fed and fasting conditions*."	This is not agreed to. A bioequivalent product should be possible to use interchangeably with the originator in both fasting and fed state. For modified release formulations, it is common that food affects the release of the active substance in a formulation specific manner. Therefore, there are higher demands on such formulations in comparison to standard immediate release formulations. Nevertheless, according to the guideline, applicants may still perform only one study (fasting or fed) if adequately justified.
194	2	**Comments:** There are some pharmaceutical forms not commented (intramammary, topical)	Topical products for systemic use is mentioned (spot on/pour on). Topical products with locally active compounds are out of scope for this guideline. See introduction and scope above.
194-205	7	**Comments:** i. Lines 200-205 – There is an international concern that the BCS can not be extrapolated to all animal species (ruminants and non ruminants). ii. This information is repeated in the Annex under Section 7.	The BCS appendix has undergone a major revision. We now present a rather restrictive use of it which should address the comment made. Repetition will be minimised.
198	1	**Proposed change (if any):** Space between 6.1 and annex	Accepted.

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198-199	1	**Comments:** "For products to be administered in milk/milk replacer, special consideration should be applied": this statement does not help the applicants. **Proposed change (if any):** Requirements in Part II (Analytical Part) include solubility and stability in reconstituted milk. Providing the active substance is soluble in milk, milk or milk replacer supplemented by the test or reference products should be considered as equivalent as they represent equivalent solutions or stable suspensions of the same active substance at the same concentration.	Accepted with the provision that the active substance completely dissolves in the aqueous fraction.
199	2	**Comments:** Special considerations for products to be administered in milk/milk replacer, are not described. Additional information is required.	Accepted. Some additional information on solubility and stability in milk has been added.
200	2	**Comments:** For premixes the in vivo bioequivalence study is mandatory if not Class I or III. For this kind of products however, the variability in intake can be quite significant so one might question the usefulness of a bioequivalence study compared to this. Unless specific excipients may influence the intake, an in vivo bioequivalence study should not be required for this class of products.	If comparative PK studies are needed, this should be done according to a suitable study design. It's agreed that BE designs are not always appropriate but this doesn't automatically make a product a biowaiver.
200-205	8	**Comment***:* given the low bioavailability of class III compounds, a small absolute variation could lead to a significant variation in availability; therefore a waiver can generally not be granted for a class II or III that are characterized by a low bioavailability, either because of low solubility or because of low permeability. **Proposed change**: please amend as follows: *"Premixes and other dosage forms for use in-feed can only be eligible for a biowaiver if they belong to BCS (Biopharmaceutics Classification System)-class I ~~or III~~ (see Annex). In all other cases, i.e. classes II, III or IV, bioequivalence should be studied in-vivo, unless justified otherwise."*	This comment is not correct. A small absolute variation in content between two class III products would not translate into a significant variation in AUC as F is not dependent on the formulation.
201	2	**Comments:**	Acknowledged. However, the

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		Cross design studies in chicken and poultry when treatment duration is e.g. 7 days it is not possible due to production cycles	relevance of this comment for the text at line 201 is unfortunately not understood.
206-214 5.4 Parameters	1	**Proposed change (if any):** A definition should be given in appendix for each parameter (e.g. AUCt, AUCτ, etc.) as it has been done in the corresponding guideline for human drugs.	Accepted.
207-208	8	**Comment**: in single dose studies, the draft GL requires bioequivalence to be based on AUC and Cmax. However there are substances where Cmax is of no therapeutic relevance and efficacy is dependent on parameters like MRT or time above MIC90. Also Cmax cannot always be used for comparing IV with other routes of administration and AUC over the entire sampling time is not always a reliable parameter either. In such cases (where the absorption phase is not identical), AUCs may be determined from e.g. Tmax-Tlast, i.e. AUC may be analyzed by phases provided this is planned upfront in the protocol. **Proposed change**: in order to address that point, i.e. to allow basing bioequivalence on a different parameter than Cmax if justified, it is suggested that the following statement is added: "*In cases where the Cmax is inappropriate, other relevant parameters may be used instead e.g. partial AUCs, MRT or time above MIC90. In that case, adequate justification should be provided to support that the plasma curves are not changed except for the absorption phase*." This comment further applies to lines 409-410.	It seems like the comment primarily refers to situations where a similar concentration time curve is not expected (i.e. not generics). In other types of applications, such as hybrids and extension, we may allow more flexibility depending on the situation and other parameters may be useful. As these are case by case decisions, we do not want to include the text.
207-211	8	A short description of the abbreviated parameters would be helpful, as different terms are used in practice e.g. AUCt, AUClast.	Accepted.
212	8	**Comment**: even if the animals used in the bioequivalence studies are from a homogeneous group, in particular with regard to weight, variability can occur and have a significant impact on the results when comparing dose normalised and not normalised results. **Proposed change**: the possibility to present dose normalised results should be allowed where justified (and not only for the exemptions of section 5.9). Normalisation by dose should be described more accurately, i.e. in what	It is believed that it is sufficiently clear when you are allowed to use dose normalisation. A rather strict approach has been taken in order to standardise the EU view on dose normalisation.

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		situations is dose normalisation allowed?	
216-218	1	**Comments:** "the reference product must be a veterinary medicinal product authorised in a Member State or the Community on the basis of a complete dossier in accordance with the provisions in Directive 2001/82": Does "a complete dossier" refer only to Article 12 authorised products, or can well-established use (Article 13.a) products also be reference products? **Proposed change (if any):** Suggest that this should be harmonised with the wording of Article 13.2(a) which gives a definition of a reference medicinal product.	According to NtA a reference product may be authorised in accordance with Art. 12(3), 13a, 13b or 13c. The text has been updated for clarity.
221	7	**Comments:** Are there occasions when a generic product would not be of the corresponding pharmaceutical form as the reference product, as seen in the USA with "hybrid generics"? If not, the word "normally" should be removed as it may imply that different pharmaceutical forms may be compared between a generic and reference products.	Agreed. The text has been detailed for clarity.
221-222	8	**Comment**: this sentence does not provide any helpful information and should either be deleted or at least clarified. We understand that *"the corresponding"* means *"the same"* pharmaceutical form in the case of pure generics (Article 13(1) of Directive 2001/82 as amended); thus *"corresponding"* should be replaced with *"same"*. Also hybrid generics (Article 13(3) of Directive 2001/82 as amended) where the pharmaceutical form of the hybrid differs from that of the reference product, are not mentioned at all. **Proposed change**: please delete the sentence and replace with: "*For a generic application according to Article 13(1), the generic is normally compared with the same pharmaceutical form of a reference product (various immediate-release oral pharmaceutical forms shall be considered to be one and the same, Article 13(2)b). In the case of an application under Article 13(3), the hybrid generic may be compared with a pharmaceutical form differing from that of the reference product*."	Accepted.

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224	8	**Comment**: for consistency, the term *"pharmaceutical form"* should be used throughout the document, instead of "*dosage form"* and *"formulation"*.	Accepted.
227-229	7	**Comments:** This paragraph is confusing. Does this sentence imply that the generic product may have a variation or an extension beyond the conditions of use of the reference product, pre or post market? Would a generic product be allowed to provide safety, efficacy and residue data for the proposed new target animal species even though the reference product does not have it approved on its label? If yes, would a manufacturer of another generic product be able to add the new target species (which is not on the reference product) on its label by conducting a bioequivalence study with the previously approved generic product? What if the reference product then wanted to include that new target species on its label, would a bioequivalence study compared to the generic product be sufficient for approval? Would this also be the case for a change in dosage form, route of administration or different strengths?	Yes, in principle this would be acceptable.
227-229	8	**Comment**: this section is unclear: do extensions only relate to generic products? The sentence should be re-worded to bring clarity.	Accepted.
230-235	8	**Comment**: batch control results might be available for bridging studies, but not for generic applications. Indeed batch control results for the reference product will normally not be available to the generic applicant. The draft GL reads that the assayed content of the batches of the test and reference product should not differ by more than 5%, thus various batches would have to be screened. If the batch control result of a reference product is not available a method has to be developed to perform the required analysis. In addition it is not the responsibility of the applicant for a generic product to re-test the dissolution profiles & assayed content of at least 3 batches of the reference product. What about hybrid generics (different strengths)? This case, again, is not considered. **Proposed change**: pleased amend as follows: *"Batch control results of the test and reference products should be reported and the tested product should meet the specifications of the finished product that will be used for release. ~~The assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product determined with the test~~*	Not accepted. The proposed change allows for a 10% difference in assayed content between test and reference product. Suggested change in line with human BE GL: "Unless otherwise justified" covers the case of hybrid generics. In human GL it is "advisable to investigate more than one single batch…."

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		~~*procedure proposed for routine quality testing of the test product. In order to demonstrate that a representative batch of the reference product with regards to dissolution and assay content has been selected, the applicant should present dissolution profiles and content analysis of at least 3 batches of the reference product, unless otherwise justified.*~~*"*	
230-235 (whole paragraph) + 751	1	**Comments:** "should not differ more than 5%" **Proposed change (if any):** As each product may vary by ± 10% (considering a 95-105% validity at batch release), it may be difficult to comply with this requirement as this would exclude studies performed with perfectly valid batches. We suggest "should not differ by more than 10%" instead.	Not accepted. See lines 230-235 (Stakeholder No. 8).*)*
230-235 (whole paragraph) + 751		**Comments:** "at least 3 batches of the reference product" **Proposed change (if any):** We have examples of reference products which it would be almost impossible to buy by more than one batch at a time, which would make impossible any study where three valid batches (not expired) are tested simultaneously. This requirement is probably applicable for human drugs but with more difficulties for some veterinary medicines. We suggest removing this requirement. Line 751 states "more than one single batch" and should also be revised.	Not accepted. It doesn't say that a company must investigate two or three batches of the test and the reference product. Only, investigation of more batches gives more assurance that the test and reference batch used are representative.
233 – 235	4	**Comments:** **Reference and test product.** In order to demonstrate that a representative batch of the reference product with regards to dissolution and assay content has been selected, the applicant should present dissolution profiles and content analysis of at least 3 batches of the reference product, unless otherwise justified. COMMENT: How will the generic sponsor determine an appropriate in vitro dissolution test method?	Test methods should be developed product related based on general and/or specific pharmacopoeial requirements in order to reflect the in vivo dissolution.
235	2	**Comments:**	Not accepted. See lines 230-235

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		The requirement to collect and analyse 3 batches of the reference product is very impractical. Batches are released sequential and for some products this could imply quite a long period which would be needed to be able to collect three batches. Also the need is not understood. Each reference batch should be within the authorised limits and when authorities have any doubt they could check the reference products dossier whether or not the collected batch is a fair representative of the reference product . **Proposed change (if any):** Change 3 batches to 1 batch.	+751 (Stakeholder No. 8).
237-238	8	**Comment**: this paragraph refers to "*pilot batches*"; however bioequivalence studies do not have to be conducted with pilot batches. This sentence is thus irrelevant. **Proposed change**: please remove the sentence: "*The production of pilot batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale*" or reword it further explaining how the applicant can justify that the product tested is representative of the commercial product.	Partly accepted, se revised guideline text.
240- 247	8	**Comment**: *"... and preferably from a homogeneous group (age, breed, gender, weight...)"*: does this mean that the study should preferably be restricted to one gender? If the case, we do not support such definition of 'homogenous group' that is further defined as an essential pre-requisite to parallel design studies. **Proposed change**: please delete the sentence: "~~*This is an essential pre-requisite to give validity to the study results.*~~"	You need only to consider prognostic variables that affect the pharmacokinetics of active substance in question. If there are no gender differences, you do not have to consider gender.
240 ff Par. 5.6	2	**Comments:** in the first sentence (sentence 240 and 241) "target population" is used, in sentence 245 is stated that parallel design studies should be homogeneous in all prognostic variables. Question: what is the minimum border in kg BW for milk producing animals (depending on race) in general; is this the weight when an animal reaches	We can't see that there would be a lowest acceptable body weight for milk producing animals. "Target population" could in this case be interpreted as any ruminating cattle. However, we don't see the need to detail this in the guideline.

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		maturity? Or is this at the age of first milking? This is a discussion point every time because it is not stated anywhere in the guidelines, but only defined by national authority.	
240-247	3	**Comments:** Inter animal variation does not affect BE analysis in cross-over design studies. **Proposed change (if any):** Animals used in bioequivalence studies should be clinically healthy representatives of the target population. In cross-over design studies the nutritional status of the animals should be well controlled and comparable between treatments and periods if applicable (i.e. fasted or fed in case of oral administration). In parallel design studies, the treatment groups should be homogeneous and comparable in all known prognostic variables that can affect the pharmacokinetics of the active substance e.g. age, breed, gender, weight, hormonal and nutritional status, level of production, etc. (if relevant). This is an essential pre-requisite to give validity to the study results.	Agreed. However, the proposed text already allows non-homogenous stock in cross over studies.
248	4	**Comments:** **Species to be studied.** The included animals should be of the target species. In case a product is intended for more than one species, bioequivalence studies should normally be performed in each species. Exemptions should be clearly justified. COMMENT: Are you also going to be considering class? For example, if lactating and beef cattle are included in the approval, will the generic sponsor be required to conduct two separate bioequivalence studies on each of these two classes of animals?	No this is not the intention
248-251	6	**Comments:** The draft guideline states: *5.7 Species to be studied* *The included animals should be of the target species. In case a product is*	Although we partly agree with this comment we have difficulties defining when such bridging could be accepted. Therefore studies should normally be performed in each species. However,

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		intended for more than one species, bioequivalence studies should normally be performed in each species. Exemptions should be clearly justified. In light of 3Rs considerations it is important to not encourage unnecessary use of animals. It may be scientifically justifiable to use the data from similar species. **Proposed change (if any):** 5.7 Species to be studied The included animals should be of the target species. In case a product is intended for more than one species, wherever possible scientific attempts should be made to use the data from one species for other related species (e.g., between ruminants, between birds, etc, wherever possible), bioequivalence studies in multiple species should be performed as a last resort. Exemptions and inclusion of multiple species should be clearly justified.	the guideline has been updated it indicate that there are circumstances where species bridging could be accepted.
249	2	**Comments:** The bioequivalence test is intended to demonstrate equivalence between two products. It should be sufficient to test this in one target species and extrapolate to others in most cases were formulations are comparable. Only in exceptional cases testing in each target species should be required.	See above
249-251	8	**Comment**: we would welcome some clarification on ways to deal with different production classes e.g. calves, dairy and meat cattle or broilers vs laying hens…. Also there should be no exemption from the requirement to perform bioequivalence studies for each target species.	See above. Notably, this comment totally opposes other comments received.
250	7	**Comments:** Does this also mean that minor species would also require bioequivalence studies?	The text has been clarified on this point.
251	1	**Comments:** "Exemption should be clearly justified" is vague **Proposed change (if any):** Suggest giving examples here, such as e.g. extrapolation from cattle to sheep or from chicken to turkey.	See above

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253	2	**Comments:** As with species, unless there is a specific reason, testing with one route of administration should suffice.	We don't agree. It is possible that two products are bioequivalent for one route of administration but not for another.
253-255	8	**Comments**: - Hybrid generics for which the route of administration may differ between test and reference product should also be considered; - For products for intramuscular and intravenous route, one can demonstrate bioequivalence for intramuscular route only as intravenous falls under the biowaiver clauses further down in the GL. **Proposed changes**: please consider: - Clarifying how to deal with hybrid generics; - Adding in line 255: *"…all different routes, except for intravenous, should be tested."*	The content of the comment is agreed to but we see no need to detail it in the guideline. It should be obvious from other parts of the guideline text.
256	4	**Comments:** **Strength to be tested.** If a new application concerns several strengths of the active substance, a bioequivalence study investigating only one strength may be acceptable (see section 6.2). In case the strength of the test product differs from the reference product's and this precludes equal doses in the two treatment groups, it is recommended to use different doses and then dose normalise (i.e. to divide AUC and Cmax with the amount administered) the pharmacokinetic parameters. COMMENT: You should specify that dose normalization is not appropriate if the formulation or API exhibits evidence of nonlinear kinetics. An example of a formulation-related lack of linearity is the failure of some oral dosage forms to not show dose proportional bioavailability due to differences in *in vivo* dissolution (rate and extent). Another example would be differences in injection volume influencing the rate of drug absorption.	Accepted.
256-267	7	**Comments:** i. Line 258-261 (different strengths) - It is unclear if this concerns innovative products only or generics too.	It refers to both. Further, see below.

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		ii. This should assume linear kinetics have been demonstrated.	
257-258	8	**Comment**: the GL acknowledges that for a new application with several strengths of the active substance, a bioequivalence study investigating only one strength may be acceptable (see section 6.2). In such cases, a reference to linearity of pharmacokinetics profile has to be included in the text. **Proposed change**: pleased add a reference to linearity of pharmacokinetics profile.	After consideration, references to non-linear kinetics have been removed in all cases except for when different doses are used in the same study. In the old guideline, linearity was to be considered when extrapolating results between strengths and when designing the study where multiple dose studies were recommended in case of non-linearity. On the other hand, data on linearity in vet medicine are most often poor and seldom request have been made to study additional strengths or present multiple dose data due to lack of data on linearity. Consequently, as we now are removing the requirement, we are actually not changing practice. There may be very rare situations where a non-linearity would affect the possibility to extrapolate the result from a strength to others but we are willing to take that risk given that if linearity/non-linearity was to be considered, a lot of additional studies would have to be performed due to missing data on linearity. Regarding the request for steady state studies, such studies would be more sensitive to detect differences in the amount of absorbed drug in case of dose- or time dependent pharmacokinetics where the exposure

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			is markedly higher at steady state than expected based on single dose PK data. A steady state study would, however, be less sensitive than a single dose study to detect differences in Cmax. The situation where a multiple dose study would be more sensitive than a single dose study is therefore rare and single dose studies are in general are sufficient. Hence, in order not to complicate the guideline, the request for multiple dose studies due to non-linearity has been removed.
268 - 288	7	**Comments:** There is no mention of which dose to use when multiple claims involving different pharmacological action (e.g. therapeutic and production) are made on the reference product's label.	Any approved dose is accepted. The text is changed for clarity
269	5	**Comments:** **5.10 Dose to be tested** In the previous guideline EMEA/CVMP/016/00-corr-final it was stated "When several doses are approved for the reference product, bioequivalence testing must be conducted with the highest dose" and this was applicable when the reference product had a dose range (e.g 10–20 mg/kg). In the new draft guideline on line 269 it is however said that the studies should be performed with **an approved dose**. Thus, it remains unclear what the approved dose is in case that the reference product has a dose range. It is absolutely mandatory to clarify how the bioequivalence study should be performed if the reference product has a dose range, i.e. is it done with the lowest or highest dose or some dose between them. **Proposed change (if any):** The old text should be maintained with minor modification: "When several doses **or dose ranges** are approved for the reference product, bioequivalence testing	See above.

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		must be conducted with the highest dose." Justification: The guidance is unambiguous and disharmony leading to possible referrals can be avoided.	
269	8	**Comment**: the concept of approved dose is only valid for bioequivalence studies referring to an approved product (generic or extension to a new route) and does not apply to development purposes. Also, it should be made clear that this refers to the approved dose, as relevant in practical conditions of use, and not normalized according to the assayed potency. **Proposed change**: please add: "*... should be performed with an approved dose, when demonstrating bioequivalence to an approved product*."	Not agreed. We state that it is the general rule and it will of course be ok to run BE-studies during development of an NCE even though it is not a formally approved dose.
269-272	4	**Comments:** The general rule is that bioequivalence studies should be performed with an approved dose. However, it is acknowledged that for some animal species e.g. the dog it could be difficult to find subjects suitable for investigation of high strength solid dosage forms. In this case overdose studies might be considered if tolerated. COMMENT: Within human drugs, the highest dose is not body weight dependent, and the requirement to test the highest dose was due to concerns of nonlinear elimination kinetics that could exaggerate differences in the rate and extent of absorption. This is not the case in veterinary medicine where the same mg/kg dose is being employed. In this case, regardless of tablet strength, the same "dose" is being administered. Moreover, by conducting an overdose study, you are risking nonlinear absorption kinetics (i.e., less than proportional increase in absorption due to low solubility, pump saturation, etc). In this case, you will reducing your ability to distinguish between inequivalent formulations. For this reason, it is highly desirable to dose as per the product label. The corresponding tablet strength is then administered, even if it is not the highest approved strength. Comparability in products across strengths is then confirmed by doing a comparative dissolution study. Comparisons either within product or between products (test versus reference) may be appropriate if the reference formulation shows a slower *in vitro* rate of dissolution for the large strength tablets.	Is case an in vivo study is needed for a high strength (e.g. due to considerably different composition as compared to lower strengths) it might be difficult to find experimental dogs of an appropriate size (as such dogs are normally Beagles). Then overdose studies would be accepted if tolerated. We are aware of risks related to saturable kinetics but see not better alternative than accepting studies in Beagle dogs in this specific case.

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279	8	**Comment**: it might be useful to add clarification on what is considered a tolerated deviation (whether higher or lower) from the approved dose. Normally the bioequivalence studies should be done with the approved dose, which already took into consideration the tolerated dose range under field condition. Generally (providing a safety margin) a deviation of 20% from the approved dose should be considered as acceptable. **Proposed change**: please amend indent a) as follows: *a) If there are no tolerance concerns, administration of ~~higher or lower~~ doses that deviate by no more than 20% from ~~than~~ the approved dose may be acceptable...".*	We would be ready to accept much higher deviation than this if tolerability is acceptable. See above.
279-281	3	**Comments:** The doses administered should be in accordance with the SPC of the reference product. Higher doses could results in product bioequivalence more easily in case of "saturated" pharmacokinetics at these unrealistic levels. **Proposed change (if any):** Deleted original statement.	See above.
282-283	8	**Comment**: a 'considerable change' in body weight is too subjective. **Proposed change**: the term *"considerable"* should be defined more clearly in % of bodyweight.	This will depend on the relationship between drug clearance and body weight, a relationship that might be more or less tight depending on molecule and species/age (do their organs get larger or do they only get fatter with time?). Therefore we prefer to leave this open for the sponsor to decide and justify.
284-285	3	**Comments:** Normally solid oral dosage forms such as tablets are prescribed for a relatively large range of bodyweights, so bioequivalence should be valid throughout the relative large dose range in mg/kg bw. In case of e.g. oral paste formulations (e.g. adjustable per 50 kg bw in case of horses) a weight restriction is also not applicable. Only the inter-animal variation of pivotal parameters will increase when not restricting the weight of the test animal.	Agreed. However, we believe this is what the text says if read in its context.

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		The intra-animal variation (i.e. the variation determining the power of analysis in a cross-over study) is not affected by variations in the test animal weight. The same holds true for administering 1 and 2 discrete dosage forms within 1 study. **Proposed change (if any):** If anything the restriction should be limited to: In case of different discrete dosage units, restrict the weight of animals in such a way that all animals receive the same discrete dosage units.	
284-285	6	**Comments:** The draft guideline states: *c) An attempt should be made to **restrict** the weight of the test animals to a narrow range in order to maintain the same dose across study animals.* The use of the word 'restrict' might imply that that the weight of the animals needs to be necessarily reduced, rather what is of importance is that the animals are of a similar, normal weight, i.e. the range of weights is restricted, not the weights themselves. **Proposed change (if any):** c) An attempt should be made to **ensure** the weight of the test animals **lies within** a narrow range in order to maintain the same dose across study animals.	Partly accepted. The text has been changed taking the comment into consideration.
289 - 309	7	**Comments:** i. It is unclear if the measurement of the active metabolite of a pro-drug is necessary instead or in addition to the parent drug (e.g. benazepril). ii. Lines 303-307 seem to contradict lines 298-302 for the analysis of enantiomers. An achiral bioanalytical method does not take into account the enantiomers, it measures the racemic mixture without differentiation, which makes it difficult to demonstrate BE for <u>both</u> enantiomers in the case of same PD with different PK. The demonstration of BE for both active enantiomers (including same PD) should require an enantiomeric bioanalytical method.	The guideline has been updated to reflect on metabolites and prodrugs. The section on enantiomers has been updated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
291-295	8	**Comment**: the GL should reflect all cases, i.e. measurement of the metabolite is also relevant when the parent compound is not active but the metabolite is. Each case should anyhow be justified. **Proposed change**: please amend line 295 as follows: "*Bioequivalence determinations based on parent compound and/or metabolites should be justified...*" A decision tree about parent vs. metabolite would also be useful as given in Appendix IV 'Decision tree on measurement of parent compound or metabolite' in draft EMEA/CPMP/EWP/QWP/1401/98-Rev.1 (p. 28/29) – see: http://www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf	The proposed decision tree is not considered needed. In most cases, BE should be based on parent compound (consider a prodrug a parent compound) as these data most closely reflects the products performance.
298-308	4	**Comments:** Regarding enantiomeric active substances, the use of achiral bio-analytical methods is possible when it is demonstrated that both enantiomers show at least one of the following characteristics: the same pharmacokinetics, the same pharmacodynamics, or the concentration ratio of enantiomers is not modified by a change in the rate of absorption. If none of these characteristics is fulfilled or can be asserted with confidence, enantiomeric bio-analytical methods are required. If one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer. If both enantiomers contribute significantly to activity, bioequivalence should be demonstrated for both enantiomers. The use of achiral bio-analytical methods is also possible when both products contain the same single enantiomer and there is no inter-conversion *in-vivo*. COMMENT: In addition, you need to confirm that neither the test nor reference formulations include an enatiomeric excipient that may selectively interact with one of the enatiomers of the API.	Not accepted. This would be a very rare case which do not qualify to be included in a guideline with general recommendations.
298-309	8	**Comment**: the purpose of bioequivalence is to compare one formulation to another. The aspect of stereoisomerims is quite large and the requirements are already extensively listed in the GL on chiral substances (EMEA/CVMP/128/95-	The text on chiral active substances is actually more allowing than in the guideline referred to.

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		Final). On page 6 of this GL, the requirement to develop bioanalytical method during the development of a product is limited to specific cases. Unless there are clear known, safety or efficacy issue with one of the enantiomer, the use of a chiral bioanalytical method is not justified in the demonstration of bioequivalence for veterinary medicine. **Proposed change**: please consider replacing lines 298-307 with a cross reference to EMEA/CVMP/128/95 as follows: "*For chiral substances, please refer to EMEA/CVMP/128/95 on 'Investigation of chiral active substances' to assess the use of an achiral or chiral bioanalytical method*".	
316	1	**Proposed change (if any):** Last sentence, suggest reword as "It should be noted that the generic route is not available to suprabioavailable products, but that the 'hybrid' generic route (Article 13.3) may be appropriate"	Accepted. A similar wording has been included.
316 Par. 5.12	2	**Comments:** Bioequivalence in case of formulations with different bioavailability; sentence 316 It should be noted that suprabioavailable products cannot be generics. Question: under which denominator will the product fall? Would this present a ´new´ product and what will the consequences be.	Accepted. Change of text. They will be hybrids or extensions.
320-321	8	**Comment**: the draft GL recommends to avoid Cmax as first point of concentration time curve; this is however not always possible and should be reflected in the text. **Proposed change**: please amend as follows: "*The sampling schedule should be planned to avoid, where possible, Cmax being the first point of a concentration time curve*".	There is no need to change. The proposed text is sufficiently vague as we only ask for the schedule to be planned for Cmax not being the first point.
327	8	**Comment**: what is meant by acceptable truncated AUC? E.g. 3 times T1/2?	The use of truncated AUC needs to be justified by showing that absorption is complete at the timepoint of truncation. Literature data would be relevant.
331	8	"*trough*" should be amended to read: "*through*"	Not accepted, it is intended to be

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			"trough".
333-334	4	**Comments:** To maximise sampling time efficiency, it may be necessary to run a pilot study to help identify COMMENT: This goes back to my previous comment regarding linear regression of Cmin values. At the very least, you need to provide some guidance with regard to how sponsors can confirm that steady state conditions have been achieved.	Accepted, some requirements on how to document steady state is included.
333-334	8	**Comment**: the decision on whether a pilot study is necessary should be left to the applicants. **Proposed change**: please delete the sentence: "*To maximise sampling time efficiency, it may be necessary to run a pilot study ... variability in the concentration values*."	Accepted
335 - 373	7	**Comments:** i. Lines 337-338 – How would you then ensure that the bioanalysis was done in compliance to GLP? What proof of compliance would be required to accompany the application?	This text is in accordance with present practice. No new requirements are introduced.
336	2	**Comments:** BE studies should be conducted under GLP according to reproducible and standardized conditions. These conditions cannot be fulfilled in practical farm situations. Although oral administration of products in a limited amount of food does not fully reflect the administration in practice, it remains an accurate and precise way to fulfil the demands for conducting BE studies.	Agreed. Most often studies are performed GLP but could also be performed according to the principles GCPv which would ne more applicable to farm conditions. The comment on limited amount of food is not understood in this context.
339-346	8	**Comment**: validation of bioanalytical method is well described in other guidance documents, which should be referred to. **Proposed change**: please add a reference to the US FDA GL # 145 'Bioanalytical Method Validation'.	We would prefer not to list references to guidelines outside EU and VICH.
344	8	**Comments**:	The section has been shortened and no longer specifically addresses the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- It is unclear if the stability of both stock solutions and analyte(s) or analyte only must be performed in the biological matrix; - Also do the stock solutions refer to spiked/working solutions? If not the case, the stability should only be assessed in the solvent. **Proposed change**: please amend the GL taking the above into consideration.	subject commented on.
347-350	8	**Comment**: we find the current wording misleading as it could lead to the understanding that the validation is a part of a given bioequivalence study. Indeed, it is unclear if once a bioanalytical method has been validated, it can be used for several bioequivalence studies or not. The validation of a bioanalytical method can be managed separately from the *in vivo* bioequivalence study (as a study itself). Then once validated in a matrix, a re-establishment of the method may be performed before using it for the assay (i.e. verification of performance of the method: linearity, accuracy, precision at LLOQ and extraction output). **Proposed change**: please amend as follows: "*The validation of a bioanalytical method should comprise two distinct phases: (1) ~~the pre-study~~ a phase in which compliance of the assay with the characteristics listed above is verified and (2) ~~the study~~ another phase ~~itself~~ in which the validated bioanalytical method is applied to the actual analysis of samples from the bioequivalence study in order to confirm the validity of the determinations.*"	The section has been shortened and no longer specifically addresses the subject commented on.
351-365	7	**Comments:** ii. This section is very detailed and information for this part could be referenced	Accepted, the section has been shortened.
353	1	**Proposed change (if any):** Suggest add "even" before "commercial kits"	The section has been shortened and no longer details commercial kits.
353	8	**Comment**: it is our understanding that this sentence aims to ensure that bioequivalence methods are valid; thus the terminology 'commercial kits' appears to be inappropriate. **Proposed change**: we propose replacing '*commercial kits*' with '*bioanalytical methods*'. It may be useful to also add a reference to the EMEA/CVMP GL on 'Conduct of pharmacokinetics studies in target animal species'	The section has been shortened and no longer details commercial kits.

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		(EMEA/CVPMP/133/99-Final).	
357	1	**Proposed change (if any):** Suggest delete "the" before "spiked" and add "that may be" after "samples"	The section has been shortened and no longer specifically addresses the subject commented on.
362-364	8	**Comment**: the meaning of "*separately prepared Quality Control samples*" is unclear. Does this mean that the QC for a given concentration should be prepared independently or that they even cannot be prepared from the same solution? Does "*prepared*" mean "*extracted*" or "*spiked*"? We would welcome further clarification on this point.	The section has been shortened and no longer specifically addresses the subject commented on.
384-385	8	**Comment**: the impossibility to use non-parametric analyses is surprising. Even if the applicant "knows" that a 2x2 works with the compound and the PK parameters are reasonably estimated, a non-parametric confidence interval usually gives interchangeable results with the parametric ones. If the parametric assumptions become compromised, the non-parametric approach could still be expected to give accurate results. Furthermore**,** what if equal variance test fails for ANOVA in case of high variability in bioavailability for instance? **Proposed change**: please amend the sentence as follows: "~~*A non-parametric analysis is not acceptable*~~. *As a general principle, non-parametric analysis is not permitted. However, it may be accepted on a case-by-case basis, provided adequate argumentation is given*".	One objective of the new guidance was to completely standardise the method of analysis. Non-parametric analyses are useful in general but not considered appropriate or necessary in bioequivalence as the influence of outliers tend to be reduced.
390-401	8	**Comments**: - The testing and reporting of p-values and confidence intervals for sequence effects are contrary to the statement "*A test for carry-over should not be performed …*" because the 2x2 crossover design test for sequence effect is the test for carry-over. - Also the rationale on the handling of potential carry-over in a 2x2 crossover (i.e. dropping out individual animals with potential carry-overs and re-computing of confidence intervals) is not clear. Is this approach supposed to provide higher power than using only period 1 data? Also why is 5% of the Cmax value stated as a threshold for excluding animals? **Proposed changes**: - Please keep the requirements for confidence intervals for 'treatment effect'	The guideline now contains recommendations on carry over and how to present descriptive data on effects from the ANOVA. We believe that the guidance given is clear. Yes, the rationale is to provide higher power. 5 % is a commonly accepted threshold on the human side. In order of harmonisation it is also included here.

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		only (not for period and sequence) as follows: "*In addition, tests for difference and the respective confidence intervals for the treatment effect ~~the period effect, and the sequence effect~~ should be reported for descriptive assessment*." - In order to get a better understanding, we recommend using both approaches i.e. one analysis discarding potential carry-overs and one analysis on period 1 data only, or to leave it to the applicant's discretion.	
392-394	1	**Comments:** We understand that tests for differences for the period effect, sequence effect should be reported for descriptive assessment. However, the consequences in case of significant period and/or sequence effect are not described in the guideline. In addition, a test for carry-over is not requested. **Proposed change (if any):** We suggest adding confirmation in the guideline that period/sequence effects will not be considered as limiting factors in the determination of bioequivalence, providing the confidence interval of the considered surrogate (AUC) remains within the acceptance range (80-125%)	We prefer to not generalise but we agree that in most cases, a significant effect will not be considered a limiting factor. Significance in itself is not very interesting but togheter with data on the magnitude, there may still be scenarios where we might ask questions.
394 – 401	4	**Comments:** A test for carry-over should not be performed and no decisions regarding the analysis (e.g. analysis of the first period, only) should be made on the basis of such a test. The potential for carry-over of the analyte can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 (and beyond if applicable). If there are any animals for which the pre-dose concentration is greater than 5 percent of the Cmax value for the animal in that period, the statistical analysis should be repeated with those animals excluded. Results from both analyses should be presented, but the analysis with the animals excluded should be considered as primary. COMMENT: I strongly disagree with the recommendation that a carry-over effect not be statistically evaluated and that if present, it can be determined solely by examination of the period 2 pre-treatment samples. Such a statement insinuates that the sole source of carryover effect is residual drug. This is not the case. There can by physiological carryover effects that influence drug metabolism and distribution that can influence the blood levels in subsequent periods. Potential stress effects can influence absorption. Therefore, it is	We agree. Equal carry over should not be a problem. Unequal carryover, could be an issue but its occurrence is not likely in a well controlled study. We request descriptive data which still makes it possible to raise questions on effects, if warranted.

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		imperative that carryover effects be evaluated. In this regard, I refer to the following set of equations to support this position: In a 2-sequence,2-period, 2 treatment crossover, we subtract Group 1 (GP 1) from Group 2 (GP 2) to determine the treatment effect. Therefore: Grp 1 = Per 2 – Per 1 + (Trt B – Trt A) + Co A and Grp 2 = Per 2 – Per 1 + (Trt A – Trt B) + Co B Subtract the effects associated with the two groups: Grp 1 – Grp 2 = { (Per 2 – Per 1) + (Trt B – Trt A) + Co A} – {(Per 2 – Per 1) + (Trt A – Trt B) + Co B} = [(Per 2 – Per 1) – (Per 2 – Per 1)] + [(Trt B – Trt A) – (Trt A – Trt B] + (CoA – CoB) Note that the period effects cancel out, leaving treatment and carryover effects. This is why period effects do not, in and of themselves, disqualify the bioequivalence assessment. A difference in the period effects in Grp 1 and Gp 2 would be translated as a carryover effect. For example, let's say that as an animal matures, the bioavailability of the parenteral formulation is more greatly affected for product A versus B. For a 2-period, 2-seuqence, 2-treatment crossover study, this would statistically appear as a "carryover" effect (period-by-sequence interaction). Moving forward with our mathematical manipulation, the equation for the difference between Grp 1 and Grp 2 can now be re-written as: [(Trt B – Trt A) - (Trt B – Trt A)] + (Co A - Co B)	

	Per 1	Per 2
Gp 1	Trt A (y11)	Trt B (y12)
Gp 2	Trt B (y21)	Trt A (y22)

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		The relationship between Trt B and A can be rewritten as: (Trt B) – (-Trt B) = 2* Trt B (-Trt A – Trt A = -2* Trt A Grp 1 – Grp 2= 2(Trt B – Trt A) + (Co A - Co B) Therefore, we see that the difference between Grp 1 and Grp 2 is a function of Trt effects and carryover effects. Thus, we have a valid bioequivalence comparison (estimation of the difference between treatments A and B) only under the condition that: CoA = CoB OR CoA and CoB = 0.	
396	1	**Proposed change (if any):** Suggest add "Instead" or "Or rather" before "the potential"	The comment has been considered when changing the text.
406-407	8	**Comment**: with regard to the length of the wash-out period, the current GL states at least ten-times the terminal half-life of the active or metabolite. This should remain applicable. **Proposed change**: please add: *The wash-out period should be at least ten times the terminal half-life.*	The text is revised but we believe 10 half-lives might be unnecessarily in many cases. A washout period of at least 5 half lives is now recommended. This is considered a standard cut-off in BE-studies..
408 - 417	7	**Comments:** i. The acceptance limits do not mention (as in previous EMEA guideline) that a widening of the 90% confidence bounds for Cmax and exceptionally for AUC may be acceptable in some cases. Why has this changed from the previous guidelines? ii. For veterinary drug products with wide intra-individual variability, several suggestions are dispersed throughout the document e.g. alternative design (lines 161-164), increase the number of animals for adequate study power (lines 414-415) and two-stage designs (lines 418-427). The use of these studies is controversial among human and veterinary regulatory agencies.	The strict approach suggested in the draft guidance has revised. The final conclusion is that we do not need to raise unnecessary high requirements. We now allow a maximal widening of the Cmax and Cmin (if applicable) limits to 70% to 143% if it has been prospectively defined in the protocol together with a justification from efficacy and safety perspectives. This is quite in line with the old guideline. Bullet 2 is not understood. We have given options for the applicants to consider which are scientifically

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			correct.
409	2	**Comments:** Cmax is an indirect parameter in BE studies because it is influenced and determined by both absorption and elimination and is strongly dependant on the sampling scheme. This is why this parameter may exhibit a greater variation. Confidence interval limits of 70% to 143% as accepted in the current guideline should be maintained in the new guideline, especially in the case that this is clinically justified (not a narrow efficacy window).	See above.
410	2	**Comments:** Acceptance limits within 80% to 125% are too short. This principle could be right for human medicines but not for veterinary ones. In order to meet this limit, a very high amount of animals could be required for the studies, and it is not affordable for food production animals. Special problem could raise for medicated premixes and products for use in drinking water. Therefore, it is recommended to keep the limit existing at present (70-143%) in the previous Guideline EMEA/CVMP/016/00-corr-FINAL.	See above.
410	5	**Comments:** **5.15.2 Acceptance limits** It is not totally clear if the accepted limits are restricted only to 80% to 125% and wider limits are no longer accepted as in the old guideline ("… limits of 70% to 143% could be acceptable, when based…"). Does the sentence "Normally, in such cases, the number of included animals should be increase to ensure sufficient statistical power" refer to the fact that wider limits are no longer allowed? The need for tighter acceptance interval in exceptional cases is on the contrary mentioned. **Proposed change (if any):** It should be clearly stated if wider limits are acceptable or not.	See above.
412-415	8	**Comment**: for the bioequivalence of AUC, we support the recommendation to increase the number of animals to ensure sufficient statistical power where it might be difficult to show bioequivalence within the 80% to 125% limits due to	See above.

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		large intraindividual variability. However for Cmax, we would recommend the possibility to use wider acceptance limits (70% to 143%), if justified. Increasing the number of animals does not necessarily tighten the confidence interval in case of large intraindividual variability, or the number of animals required to tighten the confidence interval is beyond practical limits. **Proposed change**: please keep the Cmax section of the current GL (section 9.2) as follows: "*For Cmax, the generally acceptable limits for the 90% confidence interval are 80% to 125%. However, as the parameter may exhibit a greater variation and is strongly dependent on the sampling scheme, limits of 70% to 143% could be acceptable, when based on clinical evidence and when specified in the protocol.*"	
414-415	2	Par. 5.15.2 Acceptance limits; **Comments:** ´ the number of included animals should be increased to ensure sufficient statistical power`. Question: with what formula is this number to be calculated, is there some guidance that could be given. In our experience even for a statistician it is difficult to determine.	Sample size calculations according to standard practice are considered well known and not needed to be detailed in the guideline. See also comment to stakeholder 8 on line 177.
415-416	1	**Proposed change (if any):** We suggest adding a sentence: "Exceptionally, a broader acceptance interval (e.g. 70-143%) could be accepted when clinically relevant and stated in the study protocol." To increase the number of animals in this particular case would be unethical considering animal welfare.	The strict approach suggested in the draft guidance has revised. The final conclusion is that we do not need to raise unnecessary high requirements. We now allow a maximal widening of the Cmax and Cmin (if applicable) limits to 70% to 143% if it has been prospectively defined in the protocol together with a justification from efficacy and safety perspectives. This is quite in line with the old guideline.
416	8	**Comment**: '*Narrow therapeutic index*' is not defined, nor to which extent a tighter acceptance interval would be acceptable. This would be useful. **Proposed change**: please define '*Narrow Therapeutic Index*'.	It is not possible to define a set of criteria to define a narrow therapeutic window and it must be decided on a case by case basis.

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			The request for tighter confidence interval for substances with a narrow therapeutic window has been removed as this requirement was deemed to rigorous. Narrow therapeutic windows needs only to be considered when applying for a biowaiver. This is a precautionary approach as the application of BCS to animals is new.
418 - 427	7	**Comments:** i. Lines 418-427 - In what situation would a two-stage design be acceptable? ii. Wouldn't all protocol then pre- specify the use of a two-stage design in case it was needed?	A two stage design is acceptable in all situations as long as it is prospectively defined.
418-427	8	**Comment**: the flexibility for acceptance of a two-stage approach is appreciated. It would also be useful to delineate under which circumstances such approach would be acceptable. It is mentioned that the adjusted significance levels should be pre-specified in the protocol. It is unclear whether these can be established arbitrarily or if they can be determined according to the results of the first stage. **Proposed change**: please define the conditions where a two-stage approach may be accepted; literature references could be added for that purpose.	See above
429-431	4	**Comments:** All treated animals should be included in the statistical analysis, with the exception of animals in a crossover trial who do not complete at least one period receiving each of the test and reference products (or who fail to complete the single period in a parallel group trial). COMMENT: Inclusion or deletion of subjects completing only one period will have no impact on the size and direction of the confidence intervals, but you will be discarding important information. For example, let's say that we have a dataset where 3 subjects, administered the test product in period 1, had a very high concentration due to a subject-by-formulation interaction. These subjects	The comment is acknowledged. However, we base our decision on the confidence intervals and do not follow up on outliers except for in rare cases where one would suspect fraud. In order to fully investigate a potential animal by formulation interaction, as presented in the example, you would need replicate administrations of both test and reference product.

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		ended up dropping out of the study. We now have 21 subjects in the study that completed the crossover. Based upon your guidance, you recommend dropping those 3 subjects from the analysis. The following analysis of the dataset provides an example of the consequences of your recommendations: DUMMY DATASET:	

	TRT	PARAM	PER	SEQ
1	TEST	200	1	1
2	TEST	245	1	1
3	TEST	215	1	1
4	TEST	92.47332	1	1
5	TEST	173.7108	1	1
6	TEST	63.55186	1	1
7	TEST	149.2184	1	1
8	TEST	193.0685	1	1
9	TEST	84.43499	1	1
10	TEST	133.3547	1	1
11	TEST	109.5613	1	1
12	TEST	45.0642	1	1
13	TEST	68.64439	2	2
14	TEST	66.18945	2	2
15	TEST	146.6594	2	2
16	TEST	105.1146	2	2
17	TEST	149.295	2	2

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		18	TEST	158.1212	2	2	
		19	TEST	157.7501	2	2	
		20	TEST	120.9703	2	2	
		21	TEST	99.25596	2	2	
		22	TEST	60.91908	2	2	
		23	TEST	44.38601	2	2	
		24	TEST	66.61595	2	2	
		4	REF	93.66079	2	1	
		5	REF	156.1677	2	1	
		6	REF	67.9103	2	1	
		7	REF	138.5398	2	1	
		8	REF	169.5054	2	1	
		9	REF	86.73593	2	1	
		10	REF	126.615	2	1	
		11	REF	107.8647	2	1	
		12	REF	50.06419	2	1	
		13	REF	72.62097	1	2	
		14	REF	70.36036	1	2	
		15	REF	136.6448	1	2	
		16	REF	104.232	1	2	

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		3		
17	REF	138.5963	1	2
18	REF	145.0516	1	2
19	REF	144.7826	1	2
20	REF	116.9939	1	2
21	REF	99.37933	1	2
22	REF	65.44216	1	2
23	REF	49.38526	1	2
24	REF	70.75446	1	2

Analysis 1: EXCLUDING SUBJECTS 1-3 (as per EMEA Guidance) FROM THE STATISTICAL ANALYSIS: Analysis 2: INCLUDING ALL SUBJECTS

The confidence intervals estimated with or without those 3 subjects are identical

	Least Square Geometric mean		Arithmetic mean		90% confidence interval	
	Ref	Test	Ref	Test	Lower	Upper
Analysis #1	99.41	100.35	105.30	108.90	0.96	1.02
Analysis #2	108.91	109.94	105.30	122.80	0.96	1.02

Therefore, as you see, there is no reason for excluding these subjects from the analysis as the confidence intervals will be the same with or without these subjects. However, their exclusion does influence the assessment of the arithmetic and least square geometric means. You loose a great deal of information that could clue you into a potential problem that warrants further investigation.

432	1	**Comments:**	The approach of excluding outliers

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		We'd suggest that there is a case to "eye ball" or similar data before analysis, and to possibly exclude individuals if they are clearly outliers and a logical explanation can be found. The example is of an in-feed medication. One animal might have been sick or off-food for an un-related reason during the study and thus have had a very reduced feed intake. While this is something that is relevant for consideration, it would be a pity if the failure to exclude the data from this one animal led to the data from a large number of animals failing to sit within the approved criteria. The knock on of this could be that the study would have to be repeated and hence more animals would be used (not consistent with implementation of 3Rs). **Proposed change (if any):** We agree that where possible these types of eventualities should be included in the protocol.	after the data are seen is in general not accepted. We have amended the guideline to allow for two scenarios of *post hoc* exclusion of data.
433-435	8	**Comment**: excluding an animal from the statistical analysis before bioanalysis is not always feasible. For instance, concentrations > LLOQ are observed prior to dosing; an implausible shape of profile, implausibly high concentrations suggesting interference or errors in handling are only revealed after obtaining the bioanalytical results. Where outliers are observed in bioanalytical results, it should be possible to exclude the results post-study, following investigation and identification of an assignable cause. **Proposed change**: please delete the sentence: "*In consequence, the decision to exclude an animal from the statistical analysis must be made before bioanalysis*."	Not agreed. This approach of excluding outliers after the data are seen is exactly what we wish to avoid. Such an approach creates bias.
450 – 451	4	**Comments:** For single dose studies, the percentage of AUC∞ that is covered by AUCt should be reported for each animal in each period. COMMENT: There are many cases where λ_Z cannot be accurately defined for each study subject. What can a sponsor do in these situations?	This request is made in order to get a picture of if the sampling schedule is sufficient. A low number of animals lacking λ_Z is acceptable and will not influence this assessment.
458-460	8	**Comment**: the number of presented chromatograms should be reconsidered. The total number of chromatograms for study samples, calibrators and QC samples for 5 subjects (2 x cross-over, 15 sampling times) equals to ~180-200. The size of the study report will thus be significantly increased. **Proposed change**: it appears preferable and more practicable to list calibrator	Not accepted. The text has been updated in line with the human bioequivalence guideline where chromatograms from at least 20% of the animals should be

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		and QC results together with descriptive statistics in the study report and have the raw data (chromatograms, MS traces, etc) available on file.	included. This is in accordance with the Crystal City III White Paper from the AAPS/FDA Workshop in May 2006.
460-461	8	**Comment**: it is unclear if the sentence about manual and automatic integration still refers to the analytical report. Does this mean that details about integration must be provided in the report or is it sufficient in the raw data? Anyhow each chromatogram re-integrated by either changing of the automated procedure or manually will be documented in the raw data. Thus this last sentence should be deleted. **Proposed change**: please delete: "*Any manual integration of chromatograms should be justified and listed together with values from the automatic integration*."	Accepted.
462 - 504	7	**Comments:** The terms "exemptions" and "biowaivers" are used in this document.	"biowaiver" is now used.
464 ff Chapter 6 (and after)	1	**Comments:** Bioequivalence waivers such as those concerning identical products, changes in colours, flavour or preservatives, non-absorbed compounds have not been included in the guideline. **Proposed change (if any):** Types of products listed in EMEA/CVMP/016/00-corr-Final, chapter 4., items c, d, f should be also be included in the revised guideline.	Partly accepted. This guideline focuses on recommendations for bioequivalence studies for immediate release formulations with systemic action. Item c = regards to identical product = superfluous. Item d = out of scope (See line 488 (Stakeholder No. 2). Item f = OK = low concentrations = recognised as having no influence.
464-489	8	**Comment**: - b) 'Topical route' should be added as part of 'other parenteral routes'; - Also the exemptions from the GL currently in application should be kept.	Partly accepted. See lines 464 ff (Stakeholder No. 1).

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		Proposed change: please amend b) as follows and add f) and g): *b) In the case of other parenteral routes, e.g. intramuscular or subcutaneous* *s and topical routes and when the product is of the same type of solution (aqueous or oily), contains the same concentration of the active substance and the same excipients in similar amounts as the reference product, bioequivalence studies are not required.* *f) The product is a reformulated product by the manufacturer that is identical to the original product except for colouring agent or preservatives, which are recognised as having no influence upon bioavailability*). *g) The product is an oral dosage form which is not intended to be absorbed.*	
476-477	1	**Comments:** "In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the product is of the same type of solution (aqueous or oily), contains the same concentration of the active substance and the same excipients in similar amounts as the reference product, bioequivalence studies are not required." **Proposed change (if any):** Proposal: "In the case of other solutions of the same type (aqueous or oily) and containing the same concentration of the active substance and the same excipients in similar amounts as the reference product, bioequivalence studies are not required for the same route of administration, whichever the route (enteral, parenteral)."	Not accepted. See lines 464 ff (Stakeholder No. 1).
476-479	4	**Comments:** In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the product is 476 of the same type of solution (aqueous or oily), contains the same concentration of the active substance and the same excipients in similar amounts as the reference product, bioequivalence studies are not required. COMMENT: In addition to formulation, sterilization procedures can also influence product bioavailability. Please keep this in mind as you render your decisions regarding biowaivers.	This is considered a more or less theoretical issue. Sterilization is performed before release. A biowaiver may be applied to a finished product on the basis of its composition but certainly also on its release specifications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
480	2	**Comments:** Clarification is required to confirm whether neither "in vitro" nor "in vivo" bioequivalence study is required in these cases.	It must be clear that in this case no comparative in vitro dissolution studies are needed, since the active substance is completely dissolved and ready to be absorbed. Because the composition of the solution is such that the absorption of the active substance is not influenced by the excipients, no in vivo BE study is considered required.
480-481	1	**Comments:** "An aqueous oral solution at time of administration … as an approved oral solution" would limit bioequivalence vs. Oral solutions and would thus exclude soluble powders. **Proposed change (if any):** Replace sentence by "…an aqueous oral solution at time of administration and contains an active substance in the same concentration as approved reference products which presents as a aqueous oral solution at time of administration …" This would be in accordance with the statement of lines 804-806.	Accepted
488	2	**Comments:** It is not included "The product is an oral dosage form which is not intended to be absorbed"	Not acceptable. These are not automatic biowaivers: formulation may affect bioavailability at locale site of action, therefore clinical end-point studies or detailed justification ± in vitro studies would be required. Furthermore, the scope of this guideline is limited to systemically active compounds only.
488	7	**Comments:** As mentioned above, the BCS has not been studied in animals yet. Extrapolation from *in vitro* to *in vivo* situations in ruminants and non-ruminants must be done with caution.	The text has been updated to create a worst case scenario.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
489	1	**Proposed change (if any):** Suggest adding item f) The product is a reformulated product by the manufacturer that is identical to the original product except for excipients which are recognised as having the same functional characteristics, colouring agents, flavouring agents or preservatives, which are recognised as having no influence upon bioavailability.	Agreed, except see comment above (464 ff).
490 - 504	7	**Comments:** i. There is no mention on how non proportional strengths could be handled – All strengths should have a bioequivalence study conducted or the lowest and the highest strengths. ii. This should assume linear kinetics have been demonstrated.	This will depend on the situation. No general guidance can be given.
496	2	**Comments:** "The ratio between amounts of active substance **and** excipients is the same": this implicates that if there are different strengths from one tablet, not all the strengths can have the same weight. Different strengths of one oral tablet will have different shape and weight which has consequences for the production.	It is normally the case that the tablets differ in size. So, in the case of preparations containing more than 5% of the active substance and where the ratio between the amounts of excipients is similar, a waiver for additional strengths can normally not be claimed.
500	8	**Comment**: the GL only addresses immediate release generic products. Re-formulation of a modified release or of an additional strength of a modified release formulation are particularly not discussed. However, they should also be considered for such products for which a comparative dissolution study is also relevant; PK of the reference product should be well described, pertinent criteria should be defined in the protocol and selected based on the performance (safety/efficacy/PK profile) of the product. **Proposed change**: please add consideration for other cases above.	Reference is made to Quality of Modified Release Dosage Forms for Veterinary Use (EMEA/CVMP/680/02)
505 - 589	7	**Comments:** i. Line 506 – The following words should not be in italic "**of a vete**rinary". ii. Some of the information in this section has been repeated in the Annex,	The texts have been updated. However, there are differences between dissolution studies that might

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Section 5 – perhaps these two sections should be combined and summarized.	be used to justify a biowaiver under BCS, and those used for quality purposes, or to support additional strengths after an in vivo BE study has been conducted with one strength.
505 ff	8	**Comments**: - Line 506: the GL should specify '*for oral use';* - It is critically important that dissolution tests are performed using conditions that are validated for the species concerned. This requirement should be incorporated in the guideline; - Also, the "*number of units to be tested*" is missing. **Proposed changes**: - Line 506: please amend as follows: "*During the development of a veterinary medicinal product for oral use, a dissolution test...*" - Please specify that dissolution tests must be performed using conditions that are validated for the species concerned; - Number of units to be tested: in our experience, twelve (12) units would be recommended to reduce influence from variation among individual dose units; please add to the GL.	Not accepted. It is a general introduction of dissolution testing and this might also be applicable to e.g. rectal preparations. It doesn't add something specific since it is clear that dissolution testing here are related to oral dosage forms. Accepted. The relevant section will be amended. Agreed, but it is already mentioned as a condition for the evaluation of the similarity factor.
541	2	**Comments:** Specifications on type of buffer and dissolution volume for different animal species is required	The text has been amended. There is no longer any need for mentioning different volumes.
541	8	**Comment**: the third pH has been changed from 6.8 to 7.5; a justification would be welcomed.	This change had been made to extend highest pH to cover intestinal pH range regarding all target species.
541 (and 714, 747)	1	**Comments:** pH 1.2, 4.5 and 7.5 is based on the human guideline. We suggest considering the situation in veterinary medicine where stomach pH conditions may be different from one species to another. A weak basic substance with pKb of 5 may be highly soluble at pH 1.5 and 3 (average gastric pH) but insoluble at pH 7, making the study meaningless for dogs. The situation may be opposite in cattle.	Partly accepted. The in vitro study must be a validated predictor of the in vivo dissolution of the product; that is, the in vitro test conditions should be closely related to in vivo conditions of the target animal. Dissolution should not only be determined at gastric pH,

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): We suggest replacing by "three different buffers with pH corresponding to average gastric pH in the target species of concern ± 1.5 pH units".	but also at enteric pHs.
552	8	**Comment**: clarification would be welcomed on whether the '*10% average difference*' refers to an absolute difference (e.g. 80 ± 10%) or a relative difference (e.g. 80 ± 8%).	It refers to an absolute difference. If it were to refer to a relative difference, the margins at the early dissolution time points would be disproportionate.
555-556	8	**Comment**: the GL reads: "*…comparison at 15 min is essential to know if complete dissolution is reached before gastric emptying*". This threshold may be appropriate in humans with rapid gastric emptying, but is not representative of the wide range of animal species dealt with in the veterinary sector. For example, gastric emptying in dogs differs depending on the breed and weight and can last several hours as supported by the following literature references: http://jn.nutrition.org/cgi/content/full/134/8/2039S; http://www3.interscience.wiley.com/journal/119501189/abstract; http://www3.interscience.wiley.com/journal/119535876/abstract?CRETRY=1&SRETRY=0. This is again different for cats, pigs, horses and of course ruminants. **Proposed change**: please rephrase as follows: *"For immediate release dosage forms, comparison at a early time point should be performed to know if complete dissolution is reached before gastric emptying of the target species. The selection of the time point should also be defined to address the absorption phase well before the Tmax."*	Due to the variability in gastric emptying times, 15 minutes should be regarded as the "worst case scenario".
555-558	1	**Comments:** More than 85% should be dissolved within 15 minutes to know if complete dissolution is reached before gastric emptying. This is based on human data but the situation in animals may be very different as gastric emptying time may be as high as 80 min in dogs and almost infinite in ruminants **Proposed change (if any):** We suggest revising the parameters in the light of actual gastric withdrawal times in target animals. AVC remains at the disposal of EMEA to discuss this more in details.	See above
587-589	1	**Comments:**	Accepted. See line 108 (Stakeholder

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Reference to FDA guidance **Proposed change (if any):** We are pleased that other international regions are being considered, but do not think it is good to refer specifically to a non-EU guideline, which could change and may introduce ambiguity. We suggest instead that the "same principles" referred to should be written into this guideline, if the principles are considered to be in line with EU legislation.	No. 8).
591	1	**Proposed change (if any):** ANOVA should be in bold	Accepted.
591-618	8	**Comment**: as already suggested at the time of consultation on the concept paper, we propose adding definitions for "*strength*" and "*dose*" as follows: **Proposed change***:* please add the following definitions: - *Strength: Amount of active substance(s) included in the VMP.* - *Dose: Amount of active substance(s), as included in the VMP, to be given to an animal; it is often expressed in mg/kg body weight.*	Accepted.
592 – 618:	4	**Comments:** **DEFINITIONS.** ANOVA model**:** Analysis of variance model **BCS:** Biopharmaceutics Classification System, see Annex **Bioavailability**: The proportion of an administered compound that is absorbed from a pharmaceutical form and becomes systemic available. **Bioequivalence**: The similarity between two products that contain the same active substance(s) or the same therapeutic moiety and that show similar rate and amount/extent of absorption of the compound. In most cases the rate and amount/extent of absorption is expressed as Cmax and AUC. The aim is to show that two medicinal products are similar to such degree that their systemic effects, with respect to both efficacy and safety, will be essentially the same.	Partly accepted. The definitions has been revised. Definitions on specific pharmaceutical forms has been taken from the European Pharmacopeia.

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		Biowaiver: The possibility of waiving *in-vivo* demonstration of product bioequivalence ~~studies in favour of specific~~ based upon such information as comparative *in-vitro* testing, API physico-chemical characteristics, and comparative formulation. ~~in order to conclude bioequivalence of oral immediate release products with systemic action.~~ COMMENT: Your statement that you will grant biowaivers for oily solutions not only demonstrates that biowaivers are NOT restricted to oral dosage forms but that you are also willing to grant biowaiver to some sustained release formulations (oily depot injections are considered sustained release formulations. See Martinez et al., J Control Release. 2008 Jul 14;129(2):79-87 **Generic medicinal product:** A product approved or intended for approval according to Article 13 of the Directive 2001/82/EG (as amended 2004/28/EG), defined by Article 13.2b. **Immediate release formulations**: Formulations showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing method. ~~In the case of a solid dosage form, the dissolution profile of the active substance depends essentially on its intrinsic properties.~~ Comment: This is not a correct statement. Two immediate release formulations can have markedly different in vivo and in vitro dissolution characteristics for a variety of reasons, including the milliling of the API, its crystalline habit, tablet hardness, blending time, addition of disintegrants, grade of CMC, etc. **Modified release formulations:** Formulations where the rate and/or place of release of the active substance(s) is different from that of a conventional-release dosage form administered by the same route. This deliberate modification is achieved by a special formulation design and/or manufacturing method. Modified-release dosage forms include prolonged-release, delayed-release and pulsatile-release dosage forms. **NCE:** New Chemical Entity **Therapeutic moiety:** The molecule or ion, excluding those appended portions	

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		of the molecule that cause the active substance to be an ester, salt or other non-covalent derivative (e.g., hydrate, complex, chelate) of the molecule, responsible for the physiological or pharmacological action of the active substance. **ANNEX BCS BASED BIOWAIVERS:** COMMENT: You include information on buffer volumes for horses, cattle, swine, chickens, turkeys and pre-ruminating calves. However, since your guidance also clearly describes the use of biowaivers for solid oral dosage forms (which are administered largely to dogs and cats), you need to also include a volume estimate for these species. You should also indicate that the BCS-based biowaiver does not apply to bridging between drugs administered in Feed versus water. These two methods of dosing are largely dependent upon animal behavior, and drinking and eating behavior can differ markedly. Therefore, drug input will likewise differ. Biowaivers cannot account for such differences in input.	
594	8	**Comment**: "systemic" should read "systemically"	Accepted.
619 - 636	7	**Comments:** There is no reference for BCS	Accepted. Also (although human-based): A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in vitro Drug Product Dissolution and in Vivo Bioavailability: Amidon et al. 1995 (Pharmaceutical Research 12:413-419)
632	8	Other suggested references: - US FDA GL on 'Bioanalytical method validation (GL 145, May 2001) - US FDA GL on 'Dissolution testing of immediate release solid oral dosage	Not accepted. No need to refer to these non-EU GL's.

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		forms'	
638 - 814	7	**Comments:** i. Here the word "biowaivers" is used, whereas the word "exemptions" is used in the document. ii. How is *in vitro-in vivo* correlation demonstrated in animals since this BCS is based on human data? iii. There is a lot of detail in this section that could be concisely summarized.	Accepted. 'Exemption' is replaced by '(bio)waiver'.
648	1	**Comments:** "The concept is applicable to pharmaceutically equivalent immediate release, solid pharmaceutical forms for oral administration and systemic action." **Proposed change (if any):** Suggest changing to "The concept is applicable to pharmaceutically equivalent immediate release, liquid, semi-solid and solid pharmaceutical forms for systemic action.	Not accepted. The BCS system is only applicable to oral dosage forms. Oral solutions may be waived for in vivo BE demonstration according to other principles.
648	8	**Comment**: oral forms in veterinary medicines are not only solid or liquid (which are in fact quite rare) but also semi-solid (e.g. oral paste for horse). The concept of BCS-based biowaiver should also apply to these forms and the wording should be less restrictive. **Proposed change**: please amend as follows: "*The concept is applicable to pharmaceutically equivalent immediate release, solid and semi-solid pharmaceutical forms for oral administration and systemic action*."	Accepted. The BCS system can also apply to semi-solid preparations for oral use.
690	2	**Comments:** ***Annex – BCS-bases biowaivers, Chapter 3, sentence 690*** To apply for a biowaiver for a BSC-Class III active substance it is stated that all excipients must be qualitatively the same and quantitatively very similar. In our opinion excipients should be interchangeable instead of qualitatively the same. For instance, because of the following reasons. If the concerned reference product may be administered along with food, then food will regularly have more influence on the bioavailability of the product then interchangeable excipients will have. Furthermore, excipient X which is qualitative conform the British Pharmacopeia could not be interchangeable with excipient X which is qualitatively conform the European Pharmacopeia according to the adopted guideline. Even while both excipients X exhibit the same properties.	With a "qualitative the same" excipient an identical excipient is meant. Well-established excipients mongraphed in different pharmacopoeias are usually considered identical. In general, the use of the same well-established excipients in similar amounts is preferred.

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695-697	7	**Comments:** What are the criteria for species specific BCS studies? How are these going to be validated to show *in vitro-in vivo* correlation?	Investigations on active substance solubility and intestinal permeability with an understanding of the interrelationship between pH, medicinal product solubility and the species specific intestinal physiology may result in granting a biowaiver for that medicinal product related to that target animal. An in vitro/in vivo correlation may be established. We cannot offer detailed guidance here.
707	1	**Comments:** "The active substance should not belong to the group of "narrow therapeutic range" medicinal products." This group of products should either be clearly defined, by reference to an appropriate source, or reword this sentence. WHO Working document QAS/04.109/Rev.1 gives some guidance, but not a consolidated list for veterinary medicine. **Proposed change (if any):** Unless a suitable source can be cited, reword as follows: "The active substance should not have a narrow therapeutic range".	The text has been changed to "non-critical in terms of efficacy and safety" .
708	2	**Comments:** Absorption-High permeability: In this paragraph it is mentioned "data from mass balance studies" .The requirements for classify the permeability in some cases will be imply new studies as bioavailability or mass balance studies that not always are published.	That is correct. Bioavailability data, own or literature, should be included in a biowaiver application.
711	1	**Comments:** "The active substance is considered highly soluble if the highest single amount administered as immediate release formulation(s) is completely dissolved in a volume of buffer corresponding to the gastric volume of the target species of	Solubility is now defined according to Ph. Eur criteria.

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		buffers within the range of possible physiological pH values (1 - 7.5) at 37±1." It is not realistic to perform a dissolution test in a volume of 18 or 200 l. We suggest scaling down to e.g. 1 litre using the same concentration as that expected under physiological conditions. **Proposed change (if any):** Suggest changing to: "The active substance is considered highly soluble if the highest single amount administered as immediate release formulation(s) is completely dissolved at a concentration corresponding to dissolution in a volume corresponding to the gastric volume of the target species of buffers within the range of possible physiological pH values (depending on species) at 37±1°.	
714	1	**See comments on line 541**	Partly accepted. See line 541 (Stakeholder No. 1).
714-718	8	**Comment**: the pH range to test may depend on the considered species. Also all representative target species should be given (dogs and cats are missing) and appropriate "*scale up*" allowed to be appropriately handled in a lab. **Proposed change**: it is suggested that the Table is completed to also indicate: - The relevant pH range per species (in which case, it may occur that 3 buffers will not be required) - The 'representative' volume that would be actually feasible from a practical lab standpoint.	Partly accepted. Solubility is now defined according to Ph. Eur criteria.
718	1	**Proposed change (if any):** Table: "Gastric volumes to be used to determine concentrations in buffer" Legend: Species / Gastric volume (suppress (to be used as volume of solvent) Please add companion animal species, particularly cats and dogs, to the table.	Partly accepted. See also lines 714-718 (Stakeholder No. 8).
718	2	**Comments:** ***Annex – BCS-bases biowaivers, Chapter 4.1, sentence 718 and Table below this sentence*** It would be very nice to also have the gastric volume of the dogs and cats included in this table. For dogs one should be aware of the differences in size. An option could be to classify the dogs into 3 categories (small, medium and large dogs). Furthermore what would be the gastric volume to use for sheep, goats and minor species?	No longer relevant following revision of the text.

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718	7	**Comments:** There is no gastric volumes for dogs and cats	Accepted. See also lines 714-718 (Stakeholder No. 8).
741-767	7	**Comments:** Repeated information that could be combined in the main part of the document	Accepted.
745-749	8	**Comment**: as commented under line 541, a justification of the change of pH from 6.8 to 7.5 would be welcomed.	See line 541 (Stakeholder No. 8).
747	1	**See comments on line 541**	
751	1	**See comment under lines:** 230-235 (whole paragraph)	
772	1	**Comments:** In this line, excipients that could have an impact are 'active' excipients only as defined line 780 **Proposed change (if any):** Suggest change "similar amount of the same excipients" to "similar active excipients"	Not accepted. Here, not necessarily 'active' excipients are meant. It is advisable to use a similar amounts of the same excipients in the composition of test like in the reference product.
773 & 774	1	**Comments:** In this line, excipients that could have an impact are 'active' excipients only as defined line 780 **Proposed change (if any):** Suggest change " active substance excipients" to "active substance, active excipients" And: Delete " the same and quantitatively"	Not accepted. Here, not necessarily 'active' excipients are meant. Accepted. Not accepted. In case of a BCS class III active substance, 'the same and quantitatively' is even more critical than in case of a BCS-class I active substance.
773-774,		**Comments:** ***Annex – BCS-bases biowaivers, Chapter 5.2, sentence 773-774*** Please refer to our previous comment on "*Annex – BCS-bases biowaivers, Chapter 3, sentence 690*"	See line 690 (Stakeholder No. 2).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
780	8	**Comment**: it may be useful to define '*active*' excipients.	An 'active' excipient is an excipient that might affect bioavailability. However, in the GL "active excipient" will be replaced by "excipient that might affect bioavailability".
782	1	**Comments:** EDTA is not always used in complexation and could just be included as a classical excipient used as a stabilising agent **Proposed change (if any):** Please delete: (e.g. complexation with EDTA)	Not accepted. Here, complexation is mentioned as an example of an unintentional interaction with the active substance.
793-814	7	**Comments:** Repeated information, already in the main part of the document	Accepted.
794-795	8	**Comment**: the concept of BCS based biowaivers is scientifically grounded and has been successfully adapted to grant a marketing authorisation for a dog product. As commented under lines 555-556, the 15 minutes threshold may be appropriate to humans with rapid gastric emptying, but is not representative of the wide range of animal species dealt with in the veterinary sector e.g. in dogs, gastric emptying differs depending on the breed, weight and can last several hours as supported by the following literature references. **Proposed change**: it is suggested that the threshold is based on the target species and the PK profile of the substance. Alternatively one can predefine 30 minutes as one threshold that would take into account the variability of physiology between target species and acknowledge the longer gastric emptying in animals.	See lines 555-556 (Stakeholder No. 8) and lines 555-558 (Stakeholder No. 1).
802	1	**Proposed change (if any):** BSC should be BCS	Accepted.
813	2	**Comments:** Additional clarification is required.	Comment not understood