11 April 2011
EMA/CVMP/676396/2010
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMEA/CVMP/016/00-Rev.2-CONSULTATION)

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

Stakeholder no.	Name of organisation or individual
1	Krka, Novo mesto, Slovenia
2	Farma Research Animal Health, The Netherlands
3	IFAH Europe, Belgium
4	Elanco
5	European Group for Generic Veterinary Products (EGGVP)
6	Association of Veterinary Consultants (AVC)

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	In the present draft, waivers from bioequivalence studies are substantially reduced. Completion with waivers fulfilling the conditions of currently valid guide EMEA/CVMP/016/00-corr-FINAL, section 4. Exemptions should be made. Besides, convenient exemptions defined by CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, i.e. "Locally acting locally applied products" should be added to the veterinary guideline.	It was decided not to add information on locally acting locally applied products as this is would go beyond the agreed scope of this guideline. This is about waivers for blood level bioequivalence, and it doesn't apply to locally administered products without systemic action.
2	We would welcome a clarification of the second phrase of the statement in lines 336 to 338 in the Draft Veterinary BE Guideline (406 to 408 in the revised draft): "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." These lines were the subject of 3 comments. 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? Important in our opinion is also the following: 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". This sentence definitely needs clarification when read in conjunction with the sentence (originally lines 148-149, 150–151 in the revised draft) on GLP and GP which was the subject of 4 comments	See previous comments.

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3	IFAH-Europe appreciates the work that has gone into the second draft of the bioequivalence (BE) guideline and for the opportunity to comment on it. It is noted that the guideline has been reviewed extensively, both on formal (organisation of section) and detailed aspects, to take into account some of the written comments from the various stakeholders on the first draft, as well as some of the discussions that took place during the Focus Group meeting in May 2009. In particular, specificities of the veterinary aspects have been taken into account better, both for in-vivo and in-vitro studies. IFAH-Europe also would like to highlight the following points: 1. We also note that the revised guideline now provides repeatedly reference to articles 13(1) to 13(3) of Directive 2001/82/EC as amended. Although it is understood that this was decided to clarify in particular concerns that may arise for generic and/or hybrid applications in particular, this approach has two unwanted consequences: - In some parts, the guideline's objective seems to have become a guideline on how to prepare a generic application rather than a guideline on a sound BE approach, as expressed in the title and scope of the document. - Due to the recurring references to the legal requirements in the text, the text of the guideline becomes in places confusing and complex for the reader. It is difficult to follow the guideline because the legal and technical guidance are mixed. This is even more of an issue as the guideline covers a wide variety of concepts. IFAH-Europe strongly recommends that the text of the guideline is kept focussed on providing guidance on how to conduct bioequivalence studies and fulfil such requirements, and avoid becoming a guideline on how to create a dossier for article 13 products. Or at least the guideline should focus on providing technical guidance and *clearly separate* the legal and technical aspects. 2. The Guideline is clearly intended for pharmaceutical formulations with a systemic action. It would be very helpful to mention this clearly in the title ("GL on the conduct of BE for VMP <u>for systemic action</u>"). Additionally, it could be stated more clearly which medicinal products are out of scope (such as intra-mammary products or non absorbed gastrointestinal formulations).	Comments have been received asking for both more information on generic applications and - as in this comment - to provide less. We believe we have found an appropriate balance and do not find that further changes are necessary on this subject.

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	3. Some issues still need further discussion and clarification. It is essential for the correct implementation of this guideline in the EU that all the stakeholders attain a good understanding of the complexity related to the veterinary sector, in particular for the physiological background of the BCS Biowaivers for the veterinary species, or issues related to topical products. We feel that some of these specific topics were brought up and discussed during the AAVPT/ECVPT workshop which took place in June 2010, and that it would be useful to share them again – for instance during another Focus Group with people from the Academy - and incorporate the outcome of the discussion as needed. 4. The additional mentioning of minor species is welcomed. 5. If modifications are made on the Directive 2001 as amended in the next revision (normally in 2014), the guidance will have to be reviewed again.	
4	Same comments as above	See previous comments
5	In the present draft, waivers from bioequivalence studies are substantially reduced. Completion with waivers fulfilling the conditions of currently valid guide EMEA/CVMP/016/00-corr-FINAL, section 4. Exemptions should be made. Besides, convenient exemptions defined by CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, i.e. "Locally acting locally applied products" should be added to the veterinary guideline.	See previous comments
5	Discussion is lacking about conduction of BE studies including such a high number of animals that due to logistic reasons they have to be split into several subgroups for administration of the formulations corresponding to each phase (period). Has this separation in different groups to be considered in the statistical analysis or can the subgroups be considered as one group?	Please see text on two stage design under evaluation. Most often it would be acceptable to have several subgroups in a cross-over designed study.
6	AVC considered that this guideline covers a large body of relevant science and brings it together in a coherent and systematic manner. This version is considered as significantly improved when compared with the previous version (Rev.1). Nevertheless, we still have a few comments.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
075 Executive Summary	3, 4	Comments: "how *in vitro* data in specific cases may be used to allow bridging of safety and efficacy data". This sentence seems confusing at this level of the guideline. Proposed change: We suggest changing the sentence to: "how *in vitro* data in specific cases may be used in lieu of *in vivo* BE to allow bridging of safety and efficacy data."	Not accepted. The text should be clear enough without changes.
077 - 80	6	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, 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 changes: Consider removing "rate" in the sentence or adding another parameter to Cmax to describe rate of absorption (e.g. Tmax). This may require additional statistical analyses to demonstrate bioequivalence on the basis of not only AUC and Cmax, but also Tmax.	Not accepted. The text should be clear enough without changes.
077 Introduction	3, 4	Comments: pharmacokinetic equivalence (i.e. bioequivalence): the two are NOT the same. Proposed changes: take out PK equivalence.	Not accepted. The text should be clear enough without changes.

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080	3, 4	Comments: estimated by Cmax (peak concentration) and AUC (total exposure over time). "Total exposure" is presented to explain AUC. However this could be AUCt, AUCtau or a fragmented AUC..., in plasma Proposed changes : delete 'total' to read "and AUC (exposure over time)" and at the end add "serum or" plasma	Not accepted. As this is a short introduction and details on AUC is given elsewhere in the document we feel the text is sufficiently clear without amendments.
081-84	3, 4	Comments: This section does not refer to the bioequivalence studies themselves but to their potential regulatory use. Proposed changes: please delete the paragraph entirely.	Not accepted. This is relevant background information.
090-93	1, 5	Comment: In the concept paper (EMEA/CVMP/EWP/295306/2006-CONSULTATION) it was stated that it had been noted that there were differences between valid guideline and both the corresponding veterinary FDA guideline (revised in 2002) and the CHMP counterpart (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) that were not scientifically justified. Several major issues for discussion were recognised, including: "Section 4 regarding exemptions requires revision. In its present version the section is difficult to interpret and several points could be merged. Further, categories of products are missing e.g. topically applied dosage forms". However, some of these concerns were not addressed in the present draft. If bioequivalence cannot be demonstrated using pharmacokinetic parameters as endpoints, pharmacodynamic or clinical endpoints may be used, in exceptional circumstances, to demonstrate similar efficacy and safety. However, this situation is outside the scope of this guideline and the reader is referred to therapeutic area guidelines where available. Target animal safety guideline should be considered as well. However, these guidelines are often concerned with	Not accepted. Data requirement for demonstration of therapeutic similarity by use of pharmacological or clinical endpoints needs to be addressed in guidelines for specific therapeutic areas. Inclusion of such information will be considered when drafting/revising such guidelines.

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		innovative active ingredients (products) and they might not cover generic products. As an example requirements for locally acting locally applied product are difficult to interpret. Additional clarification is sought in such cases (for example Question & Answers on the CVMP Guideline on "Testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/005/00-Rev 2)" – EMEA/CVMP/EWP/82829 /2009). Proposed change: The inclusion of additional guidance similar to that in Appendix II of the CHMP counterpart as well as some general guidance on pharmacologic and clinical endpoints studies (as mentioned in CHMP counterpart and FDA guideline) would be beneficial. It would reduce a need for advice and clarification of specific therapeutics area guidelines in case of generic applications.	
090-93	3, 4	Comments: 'If bioequivalence cannot be demonstrated using PK parameters…' We appreciate this statement is included again because it will explicitly allow PD or clinical endpoints to demonstrate bioequivalence, if justified. This section will make the justification of an unconventional approach easier for the applicant where most of the authorities now expect a classic PK study to happen in all circumstances.	
096-97	3, 4	Comments: Wording had been substantially changed. The sentence "the recommendations given for BE studies in this GL may also be applied to other comparative PK studies" is unclear. It is assumed that this wording refers e.g. to studies run during product development rather than generics application but this distinction seems (1) irrelevant since BE is defined above as "PK equivalence" (2) confusing since it is unclear which part of the multiple recommendations given may be applied for comparative PK studies other than BE.	Accepted. Sentence deleted.

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		Proposed changes: Please delete the sentence, in particular since further explanation is already given in section 4.	
100-103 Legal Basis	3,4	Comment: This section should be the only place where legal reference is provided (outside of the annexes). Proposed change: Therefore restrict the references to the legal text from the remainder of the guide to sections 3 and 4 (and for instance not in section 5.4). We would also suggest to change "Applicants should also refer to other relevant European and VICH guides" to "Applicants should also refer to other relevant European or international and VICH guides,"	Not accepted. We don't see any problem with including some text on legal base elsewhere in the document where appropriate.
104-131 Situation when bioequivalence may be applicable *(overall comment on section 4)*	3, 4	Comment: The explanation given and the organization in the section is very clear and seems a good place to include further discussion on most of the other legal items detailed in section 5.4 (l. 210-215, 218-226), section 5.10 (l 3.24-325), section 6.1 (l. 531-534) and section 6.2. It is therefore suggested to change the text structure to allow a simpler reading of the guideline, by differentiating the purely technical aspects from the legal aspects Proposed changes: - keep the part where the different situations are described but 'enrich' it by incorporating the other legal considerations in the corresponding subsections (described above) - re-name the whole chapter 'situations where BE may be applicable' e.g. "Special considerations depending on the type application" and move this whole 'enriched' section at the end of the document, either as a paragraph or an appendix. - add a sentence at the end of section 3. legal basis such as.: Specific considerations to be taken into account depending on the type of application as described in Directive 2001/82 as amended are detailed in the end of the document so that it is	Not accepted. We believe the text is clear as it is

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		obvious to the reader that specific legal requirements are available somewhere in the guidance document. - Make the sections 4.1 to 4.4 briefer and turn them into bullet points (an alternative location if the authors do not wish to move these shorter bullet points to the end, would be after line 96-97 ⇨ This would allow concentrating purely on the technical aspects of the studies in the body of the text, while not being side-tracked by regulatory considerations.	
110	3, 4	Comment: Due to the numerous edits in the introduction section the acronym NCE is not explained anymore in the document. Proposed change: please add 'New Chemical Entity' in the section title or in the text (line 110).	Accepted
123-124	3, 4	Comment: By definition bioequivalence is not met in such applications. The title of the guidance relates to 'Bioequivalence studies', and not 'comparative PK studies' in general, the section is thought to be out of scope. Proposed change: Suggest removing the section 4.3 or clarifying the reason for adding this section (which was not in the previous version).	Not accepted. It's not agreed that the definition of bioequivalence is not met in these applications. Although other designs for comparative PK might be more appropriate to use, bioequivalence studies are often used as part of such applications.
130-131	3, 4	Comment: Superfluous language Proposed change: Please delete at least the last sentence: "In most cases comparative pharmacokinetic data are needed as part of such applications."	Not accepted. We don't find it superfluous
139-140	3, 4	Comment: The sentence now reads "…bioequivalence or waivers cannot be used for extrapolation of withdrawal periods between products having potential to leave local residues…' Although the clarification and aligned with Title III of	Partly accepted. A new sentence has been added to the end of the paragraph to clarify that additional residue data are not needed where it is demonstrated that the formulation of generic is identical to that of the reference.

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		Annex I to Directive 2001/82 as amended (Directive 2009/9/EC) of the Agency position on local residues needs for generics is welcome, it is thought that in cases where the test and reference products are identical, the local residue depletion study should be waived, similarly to the waiver applied in section 7.1.b). Proposed changes: Clarify that the requirement for local residues testing does not apply when the reference and the generic products are identical. We also suggest adding the same clarification in the waiver section. Perhaps a better alternative could be to remove the reference to residues from the guidance as a whole.	The suggestion to remove all reference to residues from the guideline is not supported.
141	3, 4	Comment: It is noted that the Agency position on local residues needs for generics has been aligned with Title III of Annex I to Directive 2001/82 as amended (Directive 2009/9/EC), with the addition of transdermal products. Proposed changes: The last two sentences (line numbers 139-143) should be deleted as the guideline should focus on technical guidance for doing a BE study. If these two sentences are left in then they must be made completely in line with the Directive.	Partly accepted. A reference to transdermal has been added.
147 *The conduct of bioequivalence studies*	3, 4	Comment: Design should be based upon knowledge or deep knowledge. Proposed change: Remove "reasonable"	Not accepted. In many cases the knowledge is rather poor, especially for old molecules. It is not the intention to require new PK studies as background information but for the applicant to collect and present existing data.
150-151	3, 4	Comment: A study can either be GLP or GCP as appropriate, not both. Thus at least the 'and' should be deleted. Also, this sentence is somewhat contradictory to lines 406-408, since the bioanalytical part should be GLP anyway. There should be consistency with 2009/9 and line 406 and page 14 Proposed change: Please delete: "and/or GCPv, as appropriate…"	Not accepted. See previous comment.

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150-151	6	Comment: GLP/GCP Proposed changes: As stated at lines 402 - 407, bioanalyses should be conducted according to the principles of GLP (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."	Not accepted. We believe the text is clear enough as it is.
157 to 158	3, 4	Comment: 'Normally, at least 5 elimination half-lives...' check for consistency with FDA and international community and current CVMP GL. Should it be up to 10 times? Proposed change: Please replace with "sufficient number of half-lives to get BLOQ", and it would seem appropriate to align with the VICH GL on this subject.	Not accepted. It is considered that 5 times is sufficient
159-161	1, 5	Comment: Please define growing animals (change in physiology, age, weight gain)?	Not accepted. The person responsible for designing the study in question should provide such definition. There is no need for a general definition.
161	3, 4	Comment: 'Substances with a very long half-life or when growing animals are used': These are only examples. Proposed change: Add 'for instance' to the sentence.	Not accepted. The expression "such as" is already there.
166-170	3, 4	Comment: the rationale for single dose vs. multiple dose studies remains 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) alone does not qualify as a justification. Proposed change:	Not accepted. Single dose is preferred when feasible.

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		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.	
167 (also 331)	6	Comment: "a difference in rate of absorption" Proposed changes: Rate of absorption cannot be described using only AUC and Cmax parameters, see comment above (lines 150-151).	Not accepted. See above (150-151)
174-177	1, 5	Comment: Please define/add some recommendations for standardization of fasting for different animal species (dog, cat, pig, cattle, poultry, horse,…) be given, since there are some difficulties to achieve fasting conditions in some animal species.	Not accepted. There is no need for general guidance here. It's acknowledged that e.g. cattle are never fasting.
185 Special considerations modified release formulations	3, 4	Comment: 'many modified release formulations are topically applied, such as spot-on…'. This paragraph clearly suggest that topical spot-on with systemic action are in the scope of the guideline. Spot-on are not always considered as modified release. In companion animals, this type of product is often presented under different strengths (discrete dosage form), but the sections of the document providing indications on the handling of products with different strengths seems to referring mainly to oral dosing/immediate release product (5.8, 7.2) Proposed change: We suggest taking out the section on modified release formulations as AUC & Cmax are irrelevant parameters. Scientific advice should be sought. In case the CVMP do not wish to take out this section specific guidance on how to conduct a BE study on modified release products	Not accepted. In case the effect is systemic AUC and Cmax are relevant parameters. The guidance needed is given in this chapter. With regard to licking, the problem will depend on the product (active substance and formulation) and thus it is preferred

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		needs to be provided, in particular for the licking issue.	
196-199	1, 5	Comment: Please define acceptable consideration.	Not accepted. It's up to the responsible person designing the study as it will depend on product (active substance and formulation). Please seek Scientific Advice, if needed.
204-205	3	Comment: This seems to be in contrast with the statements in 5.1 on general requirements for oral formulations: "For the oral route, special attention must be paid to the different factors that are known to affect absorption of the active substance, such as feeding. Feeding may interfere with drug absorption, depending upon the characteristics of the active substance and the formulation. Feeding may also increase the inter- and intra-individual variability in the rate and extent of drug absorption". Furthermore milk is closer to liquid feed than to water and is clearly not excluded. Proposed change: IFAH Europe would request this, for reasons of consistency, would also be factored in when discussing veterinary premixes.	Line 171 amended: "for the oral route, special attention must be paid to factors that *may* ~~are known~~ to affect absorption of the a.s...." In the case of veterinary premixes the influence of feeding need not be considered in the same way as the product is, by its nature, always administered in feed.
204-205 Special considerations for products for use in medicated feeding stuffs or drinking water or milk/milk replacer	4	Comment: this seems to be in contrast with the statements in 5.1 on general requirements for oral formulations: "For the oral route, special attention must be paid to the different factors that are known to affect absorption of the active substance, such as feeding. Feeding may interfere with drug absorption, depending upon the characteristics of the active substance and the formulation. Feeding may also increase the inter- and intra-individual variability in the rate and extent of drug absorption" . Furthermore milk is closer to liquid feed than to water and is clearly not excluded. Proposed change: Elanco would request this, for reasons of consistency, would also be factored in when discussing veterinary premixes. Also at the EAVPT-AAVPT Workshop on bioequivalence, relevant papers	Not accepted. The presence/absence of feed could affect the dissolution of the product in a formulation-dependent way by means of affecting the physiology (e.g. gastric pH); but this would not be relevant for a premix as food is always present.

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		were presented by amongst others Deel Castillo, that should be reviewed. Elanco would suggest that only this would justify setting up a second focus group to align academia, competent authorities and the industry on the appropriate approach	
210-215 Reference and test products	3, 4	Comment: This guidance document is not a 'generic dossier guideline' but is to provide scientific guidance (of course in line with the law). Moreover the other fields of application should be included. The guideline should provide guidance on how to do a BE study for all types of application. Proposed change: We suggest this section is deleted here and moved to a specific section related to legal basis (see general comment on section 2).	Not accepted. We want to keep the information here
214	3, 4	Comment: 'The product used as reference product in the BE study should be part of the global marketing authorisation of the reference medicinal product'. The sentence is unclear. Proposed change: Please re-phrase.	Not accepted. It's clear from legislation.
216-217	3, 4	Comment: It is unclear why this sentence is here, as it is explained (and better detailed in section 5.6) Proposed changes: Please delete this sentence.	Accepted. Sentence deleted
218-226	3, 4	Comment: Same comment as for line 210-215. Differentiating between application types would also allow more clarity in the sentences.	Not accepted. See above (210-215)
228 243	6	Comment: Although it is the interest of the Applicant to use as similar as possible products, we cannot exclude that the difference between test and reference products may exceed 5% although both products remain in the 95-105% range. In addition, 100% accuracy of the analytical method for the reference product cannot be guaranteed (the Applicant usually does not know all	The current guideline text states 'Unless otherwise justified ……..' Therefore it would be possible to justify a greater difference between the test and the reference product but generally it would be expected that they would be within a 95-105% range of each other.

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		components of the reference product quantitatively). Proposed changes: We suggest changing 5% by 10% to take these uncertainties into account.	
231-233	3, 4	Comment: The comment makes full sense for bridging studies, in a development approach. However, for generic applications, does that mean that the applicant should test several batch of an already approved product to ensure the batch is 'representative'? If the reference product is approved and within the range of their approved shelf-life , it can be hoped that commercialized products are representative … Proposed change: Pleased amend as follows: "Batch control results of the test and reference products should be reported and the dissolution profiles and assay content of both the tested and the reference product should be presented."	Partly accepted. Accept that batches of reference product on the market can be considered representative and therefore it is not necessary to test more than one batch. Text has not been amended to limit batch control results to assay and dissolution.
237-247	3, 4	Comment: Why are items a) b) c) d) only applicable to oral solid forms for systemic actions? The same should apply to IM or topical products… Proposed change: We suggest line 236 is deleted.	Not accepted This list is an example of the criteria to be addressed for oral dosage forms in order to establish that the test product is representative. It is not a definitive list to cover all dosage forms. This is clearly indicated in the guideline.
248 – 251	5	Comment: "…Comparative dissolution profile testing should be undertaken on the first three production batches. If full scale production batches are not available at the time of submission, the applicant should not market a batch until comparative dissolution profile testing has been completed…" Why should dissolution profile testing be undertaken on 3 full-scale production batches? Please note that the guideline VICH GL3 [1], states the following for batches of final product to be placed on stability: "…The manufacturing process used for primary batches should simulate that to be applied to production	Partly accepted. According to the section 2.2.8 (Commitments) of the VICH GL3, it is envisaged that finally three production scale batches are put on stability studies (point 3). According to the guideline, three full-scale validation should be performed post-authorisation (3 consecutive batches) However, considering the approach of the stability GL and process validation guideline, it seems that for dissolution studies it would be appropriate to check the dissolution profile when scaling-up to commercial size (three standard batches), but this could be done as a post-authorisation commitment as it is for above-mentioned GLs.

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		batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified…" The latter implies that not even 1 full-scale production batch has to be used for the stability studies. Thus, why should full-scale production batches be used for dissolution comparison? Moreover, the Note for Guidance on process validation EMEA/CVMP/598/99 [2] describes the following: "…Where non-standard sterilisation methods or aseptic processing are employed, data should be provided on three consecutive batches at production scale prior to approval. For other specialised non-standard processes, data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of consistent manufacture of product by essentially equivalent process…" Again, data from only 1 or 2 production scale batches are required for process validation, except for the worst-case scenario of aseptic processing or non-standard sterilisation methods. Thus again, why would data be needed for 3 full-scale production batches. We are of the opinion that it is not necessary that the amount of data required for dissolution comparison is different from the amount of data required for stability studies and for process validation. In our opinion, dissolution comparison on 1 production scale batch, supported by data from pilot scale batches is sufficient.	Requirement not to market until the comparative dissolution data is available has been removed from the guideline.
254-255	3, 4	Comment: For other immediate release pharmaceutical forms for systemic action, justification of the representative nature of the test batch should be similarly established. Proposed change: "For other immediate release pharmaceutical forms for systemic action, justification of the representative nature of the test batch should be similarly	The current and proposed texts are the same so there is no proposed change here.

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		established."	
257-259	5	Question: In which case is it considered that the number of animals necessary to demonstrate bioequivalence cannot be precisely estimated? Wouldn't that be so in most cases, usually, there are not enough data available from the reference product.	In case the study includes too few animals, the bioequivalence limits might not be reached. The applicant needs to carefully determine the size of the study.
260-267 (identical to original 240-247)	2	Comment**:** Inter animal variation does not affect BE analysis in cross-over design studies. Your reaction was: "Agreed. However, the proposed text already allows non-homogenous stock in cross over studies." This is true but the proposed text is misleading, still incorrectly suggesting that a homogenous group is preferred in BE studies. Our suggestions (see below) first clearly state that suitable animals should be used and then the "requirements" depend on the type of BE study (parallel or cross-over) planned for. Proposed change: 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. Text is changed
264 *Animals*	3, 4	Comment: Repetition, please delete sentence. Proposed change: As each animal acts as its own control in such studies.	Agreed. Text is changed

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267	3, 4	Comment: Repetition, please delete sentence. Proposed change: This is an essential pre-requisite to give validity to the study results.	Agreed. Text is changed
269 *Species to be studied*	3, 4	Comment: We suggest the text is amended as follows for clarity. Proposed change: "The test animals should be representative of the target species intended for treatment"	Not accepted. We don't see the need for this change
273-275	3, 4	Comment: The statement 'if justified based on scientific information to demonstrate similarity in the anatomy and physiology' is self-sufficient. The items cited into brackets do not provide clear added value and may even be seen as confusing or restrictive. Proposed change: We suggest the brackets are deleted and end the sentence at 'physiology'	Not accepted. We believe some examples might by valuable
279-282 *Route of Administration*	3, 4	Comment: "For applications for generic products, the route of administration should always be the same for test and reference products. When the generic product is intended for more than one route of administration (e.g. both intramuscular and subcutaneous administration), all different routes should be tested unless justified as biowaivers." gives again only focus on generic products. The paragraph could be made much more general. Proposed change: "For applications for generic products bioequivalence, the route of administration should always be the same for test and reference products. When the generic comparative product is intended for more than one route of administration (e.g. both intramuscular and subcutaneous administration), all different routes should be tested unless justified as biowaivers."	Not accepted. We don't see the need for this change
284-287 *Strength to be*	3, 4	Comment: Only tablets and potentially injectable formulations are inferred. What about implants?	Not accepted. We don't see the need for adding more information on dose

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tested		Furthermore, even if the animals used in 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 situations is dose normalisation allowed?	normalisation. Normally dose normalisation should not be used.
292-293	3, 4	Comment: If you have an unscored tablet (which means according to the SPC not intended to be divided) but you intend to divide and provide a suitable "breakability study", this should be acceptable Proposed change: Please modify the sentence as follows: "In general, all sorts of manipulation such as grinding or filing in order to achieve equal dose should be avoided, tablets intended to be divided may be divided along their score lines but not into smaller pieces, unless adequate breakability studies are provided".	Not accepted. Providing a suitable breakability study which is representative for practical use with different users is not possible without a score line.
297 *Dose to be tested*	3, 4	Comment: 'Bioequivalence studies may be performed with any approved dose.' In the context of product development, the reference product might be not approved. Proposed change: "Bioequivalence studies may be performed with any approved dose, when demonstrating bioequivalence to an approved dose."	Partly accepted. The text is amended. "Bioequivalence studies may be performed with any approved dose, or, when conducted as part of development of a product containing a new active substance, at a dose within the proposed dose range."
308	3, 4	Comment: As lower doses will be accepted as well, a prerequisite should be no efficacy concerns. Up to date dose tables for tablets are always designed to ensure at the approved dose or overdosing, but no under-dosing. Proposed change: "If there are no tolerance and efficacy concerns,	Not accepted. Tolerance concerns refer to tolerance in the study. As efficacy is not intended in the study (the animals are healthy) there are no efficacy concerns.

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		administration of higher or lower doses than...”	
311-312	1	Questions: Does this apply also for the pharmaceutical forms that allow an indefinite number of dose levels (such as an oral suspension, injectables)? Can considerable changes in body weight be defined? Under dosing and noncompliance with the label instructions in the subsequent periods is therefore not an issue?	Yes, it also applies for pharmaceutical forms that allow an indefinite number of dose levels No, considerable changes in body weight cannot be defined. Too much change during the period will result in less likelihood of showing bioequivalence (independent of if dose adjustment is made). Under dosing is not an issue.
311-312	3, 4	Comment: “The amount administered should be the same in each individual in all periods regardless of changes in body weights between study periods, unless the change in body weight is considerable”. What is considerable, > 10%, 20%? Please specify a certain percentage in a defined period. Could we agree on 20% because this is the usual difference seen and accepted dose deviation under field conditions if no tolerance nor efficacy concerns exist. Proposed change: Please add: “unless the change is considerable (e.g. more than 20%).”	Not accepted. It’s up to the person who designs the study to define. Dose adjustment might or might not make it easier to show bioequivalence dependent on what molecule it is (if Cl show totally linear correlation with weight it’s probably a good idea to dose adjust but this is not always the case). We have decided not to require dose adjustment.
313	3, 4	Comment: This will be difficult to achieve in multi-dose studies with fast growing animals. Proposed change: “…minimise differences in weight….(as applicable).”	Accepted.
324-325 Supra-bioavailability	3, 4	Comment: Please see previous comments about references to the Directives/the type of application. The guideline should be focusing on bioequivalence studies and not on the regulatory applications. Proposed change: “It should be noted that supra-bioavailable products cannot be generics, but rather applications according to Article 13(3) of Directive 2001/82/EC, as amended, or extension applications.”	See comment above Not acceptable. We feel this is relevant information to keep here.
349-358	3, 4	Comment: To know the conditions provided then we	The guideline on chiral molecules is not totally consistent

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		suggest chiral assays need to be developing systematically if you need to know a) b) and c) to run achiral methods…. 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".	with the text here as this guideline includes linear kinetics which we have now decided not to request. Therefore we would like to keep the text as is.
353	3, 4	Comment: pronounced differences Proposed change: please specify what this means.	Not accepted. It means differences that would be clinically relevant. We cannot give more detailed general guidance on this.
360 *363*	3, 4	Comment: « the calculation of pharmacokinetic parameter should be performed using baseline correction … ». The baseline correction is not the only way to deal with the endogenous substances. In some cases it can be not suitable depending on the endogenous substance (circadian rhythm, negative feedback…). The decision of the analytical method should be scientifically justified. Proposed change: "The calculation of pharmacokinetic parameter should be performed using baseline correction or other scientifically justified methods." Line 363: "the exact method used for baseline correction should be pre-specified"	Not accepted. This is the reason why we say that "baseline correction should be pre-specified and justified in the study protocol". It's acknowledged that it might be more complicated than just a figure but some sort of baseline correction (compensating for confounding factors as appropriate) should be performed.
385 *Sampling times considerations*	3, 4	Comment/proposed change: typo (box) instead of (∞)	Accepted
388-390	3, 4	Comment/proposed change: We suggest moving the comment about baseline profile in the section 'endogenous substances' of paragraph 5.11 where the concept of baseline and baseline correction is referred to.	Not accepted. The text refers to both sections and it seems more logic to place it in the end of 5.12.
392	1, 5	Comment: Is it acceptable to use the following criteria: sampling time deviations ≥5% from the scheduled	Not accepted. We don't see the need for this figure. The important thing is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		blood sampling to be taken into account if pre-specified in the protocol or SOP?	that the exact time point is known.
394-395 Parameters	3, 4	Comment: Cmin,ss should not always be a critical variable for showing bioequivalence in steady state studies. For immediate-release formulations, it may be difficult to reliably determine Cmin. Furthermore, Cmin may be highly variable, thus a high sample size would be required for a reasonably powered study. This is not justified due to the low amount of knowledge gained by measuring Cmin. Please consider the proposed change or clarify in which situations Cmin,ss is relevant. Proposed change: We suggest to remove Cmin,ss: "In steady state studies, (…) and bioequivalence should be based on AUCtau and Cmax,ss and Cmin,ss."	As expressed earlier in the guideline, the only reason for asking for multiple dose studies would be in cases where Cmin is an important parameter. If it is important it should be similar.
397	3, 4	Comment: typo (box instead of λ)	Accepted.
411	3, 4	Comment: According to VICH GL1, the word specificity is the right term to be used and not "selectivity"" Proposed change: "analytical results are: selectivity specificity, lower limit of quantitation (…)."	Not accepted. An analytical method is specific when it can distinguish only one analyte. An analytical method is selective when it is able to distinguish more than one analyte (e.g. an enantioselective HPLC method). Thus, specificity is the limit of selectivity. Therefore, selectivity is more general than specificity.
414	3, 4	Proposed change: Insert equal "should be equal to 1/20"	Accepted
415	3, 4	Proposed change: Insert criteria : "Reanalysis criteria"	Accepted
416	3, 4	Comment: For consistency with Line 415, please replace "Subject" by study (samples). Proposed change: "study Subject samples"	Accepted
419	3, 4	Comment: The sentence is misleading. Information on the treatment as such (active ingredient as the pharmaceutical component) needs to be given to validate /run your analysis, but- the analysis should be	Accepted.

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		done without disclosure which sample is attributable to the test and the reference treatment. Proposed change: Please clarify as follows "Analysis of samples should be conducted without information on treatment groups".	
420	5	Comment: `Analysis of samples should be conducted without information on treatment.` If analysis of samples is conducted under GLP conditions, results will be reliable and reproducible, regardless treatment information. Moreover, randomization of samples, prior to analysis, will also prevent bias of the results on basis of treatment information. Proposed change: Bias of results of analysis, based on sample information should be avoided.	Not accepted. To state that bias should be avoided would be a too weak message
422 *Evaluation*	3, 4	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 listed here). Normalisation by dose should be described more accurately.	Not accepted. See comment above (line 284). We do not support extensive use of dose normalisation
437-438 439-441	5	Comment: Many times it is the bioanalytic result that confirms what really happened; therefore, it would make sense to exclude the animal from the statistical analysis after the analysis. It could be the case that the result of the analysis highlights a wrong administration of the product not observed initially and/or an unpredictable contamination. Would it be possible to exclude animals in these cases? Lines 439-441 seem extremely restrictive.	It is intended to be restrictive. Issues related to administration should be identified and known before start of the analytical part.

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442	3, 4	Question: The exception to this are… It is either/or? Or must both criteria be fulfilled? Please provide clarification.	These are two independent criteria. Either one or the other maybe fulfilled.
452-454	3, 4	Comment: Please see previous comment on lines 394-395. Proposed change: "The parameters to be analysed are AUC and Cmax and Cmin (if applicable). A statistical (…). The acceptance limits for Cmax and Cmin should also (…)."	See comment above
453	3, 4	Comments/proposed changes: 'AUCt' => For consistency please delete the "t" at the end of AUC.	Not accepted. It is intended to state AUCt in this sentence
453	3, 4	Comments/proposed changes: … if applicable…As this will only apply for multidose studies, please replace "if applicable" with " (e.g. multidose studies)"	Not accepted. We find the current text clear enough.
456-457	5	Comment: The widening of the acceptance interval has to be defined in the protocol prospectively together with a justification from efficacy and safety perspectives by the applicant. Thus the wideness of the limits should not be restricted from 70 % to 143 %. In fact the risk based und scientifically justification of the applicant defined widening should be emphasised.	Not accepted. We are not ready to accept limits outside 70 % to 143 %.
457	3, 4	Comment: … 70% to 143%... It is highly appreciated that this is taken into consideration!	
457	5	"a maximal widening of the limits to 70-143% could in rare cases be acceptable if it has been……." In veterinary studies, it is not rare (so it is very often) to have greater variability than 20% for Cmax, due to causes non inherent to formulations, like the administration way and the stress produced in the animals by some kind of administration, so the sentence "in rare cases" seems too strict in veterinary studies, especially when these studies are performed with food producing species.	Not accepted. We are aware of that 70-143 has been commonly used in history. We believe this is because companies have not performed large enough studies rather than true difference between human and veterinary medicine.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
459-461	5	Data mentioned as example of "Valid data" for widening Cmax-Cmin limits to 70-143%, are by definition not available for generic products. Those data belong to the safety and efficacy parts of the file, parts supported by the product of reference. The only data available may be from literature.	It is recommended that companies design their study using sufficient number of animals to keep within the tighter limits unless it is known from previous approvals of products with the same molecule that widened limits would be acceptable.
463	3, 4	Comment: As the Highly Variable Drug approach is now clearly recognized, including by main authorities, Cmax acceptance range widening should be possible under the following conditions: (a) provided that everything is defined in the protocol (i.e. retrospective adjustment is not acceptable after statistical analysis) and (b) considering that you can use the FDA guideline (human) as a model. Proposed wording: Please add the following sentences to the end of the paragraph (after "...when defining acceptance limits"): "In addition, the acceptance limits for Cmax can be widened if the bioequivalence study is of a replicate design where it has been demonstrated that the within-subject variability for Cmax of the reference product in the study is >30%. It is acceptable to apply either a 3-period or a 4-period cross-over scheme in the replicate design study".	Partly accepted. Although it is likely that this approach would be accepted in practice we prefer not to detail this in the guideline. This is one of several approaches to handle highly variable drugs.
466	3, 4	Proposed changes: Please replace "formulation" by "pharmaceutical forms"	Not accepted. The word formulation was intended.
467-468	1, 5	Comment: In the case that the necessity to use broader limits is due to high variation in the pharmacokinetic parameters, confirmation of the withdrawal period will only be necessary in the case that variability for the test product is significantly higher than for the reference product. If variability is comparable for both, test and reference product, there is no sound reason to assume that withdrawal periods will be different. Proposed change: If broader limits are used, then residue data to confirm	Accepted New text is provided for this paragraph: If bioequivalence data are used to substantiate an extrapolation of a withdrawal period between formulations, the 90% confidence interval for the ratio should be below the 125% acceptance limit for both AUC and $C_{max.}$ In case of breaching of the upper acceptance limit of 125%, then residue data to confirm the withdrawal period are required (see also section 4.4).

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		withdrawal period are required **in case of breaching the 90% UCI of 125%** unless their absence can be justified (see also section 4.4).	
472	3, 4	Comment: bioinequivalence We should use the same terminology across GLs. The statistical GL says to test the null hypothesis that the treatment difference is outside of the equivalence margins. We do not know if bioinequivalence is the appropriate term. Proposed changes: If possible, please consider cross-referencing to the terms used in the draft VICH GL (bio-nonequivalence?) or use a more 'usual' wording.	Not accepted. We believe the term is clear enough. The VICH guideline cannot be used as a reference at this point in time.
474-475	3, 4	Comment: using a logarithmic transformation Previously already discussed, presented at the Focus Group meeting and critically assessed. Please use log transformation for AUC and Cmax only, but not for ALL PK parameters! Proposed change: Please modify the sentence as follows: "the AUC and Cmax data should be transformed prior to analysis using a logarithmic transformation"	Accepted
477-478	3, 4	Comment: Previously already discussed, presented at Focus meeting and critically assessed. Non-parametric analysis should not be generally rejected. 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	Not accepted. We prefer to have parametric analyses and cannot see the situation when non-parametric methods would be justified and parametric non feasible

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		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".	
482	3, 4	Comment: at the end of the statistical analysis part, it would be appropriate to detail how to handle the data in case of significant effects, particularly the case of a sequence effect is not addressed. Proposed change: Please add to line a new sentence to the end of the 'Statistical analysis' section: "In the presence of a sequence effect the assumptions associated with the use of the crossover design will be invalidated, and the period 2 data cannot be used in the comparison."	Not accepted. We are not ready to invalidate the study because of a significant sequence effect. Please see further comments published after the previous consultation period.
483	3, 4	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.	Not accepted. We would prefer not to detail the text further but to leave some flexibility for the company. Prespecified in the protocol should be interpreted as before the study starts (not after the first stage and the interim analysis).
484-496	5	Question: Providing that in the BE protocol a Two stage design attempting to demonstrate bioequivalence approach is used, once the first part of the study is completed and data analysed , in case that data from the initial group already show bioequivalence, could the second part of the study be completely omitted without requiring any further action/evaluation?. Would it be possible to treat the first test independently?	Yes
495	5	Question:	No, the number of animals in the second stage is dependent

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		The sentence "the plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses", does it mean that apart from the confidence interval and the adjusted significance levels of each phase, the number of animals to include in each phase has to be exactly specified?	on the recorded variability in the first stage.
497	5	Question: What would be the consequences of an existing statistical significant difference in the stage term in the Anova?	None. Such findings should alert the investigator and the assessor to look carefully for imbalances in the dataset (e.g. it could be that dosing was not accurate in all four periods) but the significant levels in themselves are not crucial. Significance at 5 % level will occur just by chance, and the studies are not designed to allow conclusions about the magnitude of possible effects.
512-514	5	`For the normal two-period, two-sequence crossover design, the presentation should include a 2x2-table that presents for each sequence (in rows) and each period (in columns) means, standard deviations and number of observations for the observations in the respective period of a sequence.' Comment: The importance of providing this information in this format is doubtful because sequence effects are considered as not relevant (see comment on 514-516).	Please see comments published after the previous consultation period. Sequence effects should alert the investigator and the assessor to look carefully at the dataset.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
514-516	3, 4	Comment: …tests for difference and the respective confidence intervals… - 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. Proposed changes: Please keep the requirements for confidence intervals for 'treatment effect' 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."	Not accepted. "Carry-over" refers to carry-over of active substance not to any sequence effects.
514-516	5	`In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported as descriptive data.' Comment: The rationale for calculating the respective confidence intervals for period and sequence effects is unclear. Sequence and period effects are included in ANOVA and the p-values are reported. It is noted that, considering sequence effects, the Guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr states that: 'A test for carry-over is not considered relevant and no decisions regarding the analysis (e.g. analysis of the first period only) should be made on the basis of such a test.' Confidence intervals for a period and sequence effect are not relevant nor informative. For a bioequivalence study, an additional test for difference and confidence intervals for the treatment effect is not relevant because the (opposite) hypothesis is already tested by ANOVA.	Not accepted. The confidence interval is for treatment effect only.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
520	3, 4	Comment: … animals should be fully documented… Fully documented in the Final Study Report? or in the study data ? Proposed change: Please clarify	Not accepted. We don't see the need to detail that. The message is that the data should be documented and presented.
521	5	Discussion about drop-out of animals is made but nothing is discussed about withdrawal of plasmatic concentrations that could be considered as outliers.	Not accepted. It is discussed earlier in the guideline (see reasons for exclusion
527-528 *Study report*	3, 4	Comment: "Although bioequivalence studies are normally conducted to GLP standard, the animal phase of the report…"… This statement does not make sense and is confusing (if the applicant chooses to run the whole study including the animal phase according to GLP, why should he write the report on this phase as per GCP???). Proposed changes: Sentence should be deleted: "Although bioequivalence studies are normally conducted to GLP standard, the animal phase of the report should be written in accordance with the structure of VICH GL9" Alternatively, add to lines 526-527: "the report of the bioequivalence study should give … and evaluation, and should be written in accordance with the appropriate Quality standards" and remove the following sentence line 527-528.	Not accepted. We believe the text is sufficiently clear without changes.
530	3, 4	Comment: reference to 'audit certificates' generated some confusion as normally a 'QA statement' is provided. As these terms are synonymous, the guidance would be clearer if this was made evident. Proposed change: Please amend "Audit certificate(s) (also known as QA Statements) if available, should be included in the report."	Not accepted. If they are synonyms it is not found important to mention both.

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531-534	3, 4	Comment: the first part of the sentence is again a reference to a specific type of application. See other comments on this topic. Proposed change: We suggest keeping only the non-specific part of the sentence starting 'the study report should provide adequate details on the choice of the reference product is in accordance with article... This should include, including whenever appropriate: the reference product name, strength …. purchase.'	Not accepted. We don't see any problems with adding some extra information on generics as this is when bioequivalence is most commonly used.
535-537	1, 5	Comment: It would be sufficient to define the composition of the test product in the dossier since this is Sponsor's intellectual property that is not shared with CROs (involved in preparation of BEQ study report).	Not accepted We can't see why this would be a problem in practice
538-539	3, 4	Comment: Certificates of analysis of reference...It is not possible to have access to the Certificate of Analysis of a batch from a competitor from instance, so it should be clear that this refers to the analyses made by the applicant. Proposed changes: Add "determined by the applicant"	Not accepted. It is sufficiently clear as it is. It's not always the case that the reference product is owned by a competitor.
542-553	3, 4	Comments: "6.2 Other data to be included in an application". - The title of the section is misleading. There are way more data to be provided in a whole application that just those listed here. In addition it seems hardly compatible as a subsection of 'Study report'. - Should such type of information (data to be provided in an application) be given, it would be more appropriate in a general section re considerations per applications as proposed above. That does not seem really appropriate in a technical BE guideline. - The information requested in line 547-553 related to the validation of the analytical methods is usually appended to the study report so it would be more	The comment is noted. However, we are reluctant to make further changes as we prefer to keep the text as similar as possible to the corresponding text in the human guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		appropriate to have it in 6.1. Proposed changes: - do not separate section 6 'study report' into 2 subsections. - move up lines 547-553 to right after line 541 - consider deleting line 543 to 546 or put them elsewhere in the guideline (e.g. in section 4 re types of applications or 5.4 related to test products) or simply put it at the bottom of the section, as an additional indication (without suggesting that it is all that is needed as additional info in an application).	
546	5	'Comparative dissolution profiles (see section 7.2) should be provided.´ Comment: Not necessary for solutions. Proposed change): If applicable, comparative dissolution profiles (see section 7.2) should be provided.	Accepted
549-552	3, 4	Comment: A representative number of chromatograms or other raw data should be provided. This could be a large number of chromatogram to present and 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. It appears preferable and more practicable to list calibrator and QC results together with descriptive statistics in the study report and have the raw data (chromatograms, MS traces, etc) available on file. Proposed change: Please delete the last two sentences of this paragraph, from ": A representative number of chromatograms..."	Partly accepted. We ask for a representative number, not the total number.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
552-553	5	'This should include all chromatograms from at least 20% of the animals with QC samples and calibration standards of the runs including these animals.´ Comment: If study samples are randomized prior to analysis, selection of relevant chromatograms will be very labour intensive. So, in practice, this demand will influence analysis logistics; bioanalytical laboratories will be forced to analyze samples per subject, in order to prevent the necessity of submission of all analytical runs. Proposed change: This should include 20% of all chromatograms with QC samples and calibration standards. or all chromatograms from at least 20% of the animals with QC samples and calibration standards.	Not accepted. This wording has been accepted on the human side and has been complied with. It is not indented to be work intensive.
554-632 *(785-956)*	1, 5	Comment: In the present draft, some requirements for waivers of in vivo bioequivalence studies are mentioned. However they are applicable to certain (immediate release) formulations only. The requirements for waivers of in vivo bioequivalence studies for generic product (applications) should be modified. Some information on other than immediate release formulations and specific types of immediate release formulations should be mentioned in the guideline. Proposed change: It would be beneficial to include bioequivalence study requirements for different dosage forms as in the Annex II of the CHMP counterpart. Some of the forms are included in the draft (i.e. parenteral solutions or gas for inhalation). However, various forms that are often used for veterinary medicinal products are not included, such as topical (locally acting locally applied product) products in form of solutions. For the particular form (locally acting locally applied products) the following text is included in CHMP counterpart: "A waiver of the need to provide	Not accepted. Locally active products are outside the scope of guideline as it is for pharmaceutical forms with systemic action only.

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		equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved. Minor differences in the excipient composition may be acceptable if the relevant pharmaceutical properties of the test product and reference product are identical or essentially similar. Any qualitative or quantitative differences in excipients must be satisfactorily justified in relation to their influence on therapeutic equivalence. The method and means of administration should also be the same as the medicinal product currently approved, unless otherwise justified. Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured. It should be demonstrated that the systemic exposure is not higher for the test product than for the reference product, i.e. the upper limit of the 90% confidence interval should not exceed the upper bioequivalence acceptance limit 125.00." For other topically applied dosage forms intended for local therapeutic effects the waiver may be considered for non-food producing species only due to possible public health risk.	
555, chapter 7.1	6	Proposed changes: In anticipation of the VICH Bioequivalence Guideline and to clarify this chapter, we propose to change the points concerning the solution formulae (7.1.a, 7.1.b, 7.1.c) in a similar text presented in the FDA Bioequivalence Guideline: 1. Parenteral solutions intended for injection by the intravenous, subcutaneous, or intramuscular routes of administration. 2. Oral solutions or other solubilised forms. 3. Topically applied solutions intended for local	Not accepted. We are not ready to refer to the VICH guideline at this point in time

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		therapeutic effects. Other topically applied dosage forms intended for local therapeutic effects for non-food animals only.	
555-593 Waivers from bioequivalence study requirements for immediate release formulations	3, 4	Comment: 7.1 Comparisons between formulations - b) 'Topical route' should be added as part of section b) as long as active substances, excipients and their respective concentrations are the same. ; - Also the exemptions from the GL currently in application should be kept. Proposed change: Please amend b) as follows: b) "In the case of products for intramuscular or subcutaneous or topical administration 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 the same amounts as the reference product, bioequivalence studies are not required."	Accepted.
556-594	1	Comment: In the currently valid guide EMEA/CVMP/016/00-corr-FINAL a formulation is also justifiably exempted from in-vivo bioequivalence study if the following condition is fulfilled: "The **formulations are identical** (identical active and inactive substances as well as physicochemical properties (e.g. identical concentration, dissolution profile, crystalline form, dosage form and particle size distribution with identical manufacturing process) and bioavailability of the reference formulation has been adequately demonstrated in the target species;" On what grounds is the Applicant to justify the omission of in-vivo bioequivalence study for identical formulations if this condition is excluded from the guide?	Accepted.
556-594	1, 5	Comment: In the currently valid guide EMEA/CVMP/016/00-corr-FINAL a formulation is also justifiably exempted from in-vivo bioequivalence study if the following condition is fulfilled:	EWP: See comment above

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		The product is to be **parenterally or orally administered** as a solution and contains the same active substance(s) and excipients in the same concentrations as a veterinary medicinal product currently approved for use in the target species which is the subject of the new application; On what grounds is the Applicant to justify the omission of in-vivo bioequivalence study for identical orally administered oily solutions if this condition is excluded from the guide?	
578	3, 4	Comment: The concern is that some excipients of a comparable solution might still have an impact on the rate and/or extent of absorption. One of the ways such impact could happen is viscosity, but the statement should be broadened. Proposed Change: "...on the viscosity or on any other factor that might influence the rate and/or extent of absorption of the active ingredient"	Accepted
589	3, 4	Comment: 'd) The products are classified as biowaivers in accordance…' The BCS is based upon test systems validated to reflect permeability and gastrointestinal transit times in humans. This point is acknowledged in the Appendix of the draft guideline in lines 793-795. BCS as a system in veterinary medicine should therefore use test-systems validated for the appropriate species, before it could be applied. A sentence to this effect should be inserted. Proposed Change: "The products are classified as biowaivers in accordance with principles underlying the BCS (see Appendix I) when appropriate validation of the test-system in the species concerned has happened."	Accepted.

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591-593	5	It is stated that studies to compare the rate and extent of absorption between two formulations or products containing identical active substances are generally not required if "…the product is a reformulated product by the original manufacturer that is identical to the original product except for small amounts of colouring agents, flavouring agents or preservatives, which are recognised as having no influence upon bioavailability…" There are several other excipients beside colouring agents, flavouring agents and preservatives, which are recognised as having no influence on bioavailability. For this reason we propose to slightly change this sentence into the following: Proposed change: "…the product is a reformulated product by the original manufacturer that is identical to the original product except for small amounts of colouring agents, flavouring agent, preservatives or other excipients, which are recognised as having no influence upon bioavailability…"	EWP comment: Accepted
594	3, 4	Comment: f) … are recognized as having no influence… "Are recognized as": does this mean it is so or we have to provide justification anyway? Proposed Change: Please clarify.	QWP response: Normally this would be known by agencies. If not the company will be asked to provide a justification
596	3, 4	Question: 7.2 Comparison between strengths Please clarify which pharmaceutical forms are covered by this section (e.g. only solid pharmaceutical form", or does it also apply to suspensions?)	It covers suspensions.
616-617	3, 4	Comment: The criteria above apply also to the situation... 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	Not accepted. We decided not to go into detail here as it would be difficult to give general guidance without setting up too high requirement. This is to be discussed on a case by case basis.

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		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.	
619-620	5	This sentences states "…Similarity of *in-vitro* dissolution should be demonstrated at all conditions within the applied product series…" We are of the opinion that it is not necessary to demonstrate *in-vitro* dissolution at all conditions. If we can justify what the worst-case relevant conditions are and compare different strengths at this condition only, we are of the opinion that we have justified similarity for the other conditions as well.	Not accepted We would prefer to see data rather than discuss justifications for what is "worst case relevant conditions".
634	3, 4	'During the development of a veterinary medicinal product..'. Comment: It is not clear from the current text whether this applies only for oral forms (and most likely immediate-release oral forms) or if the principle is also valid for other pharmaceutical forms (while in fact the correlation between in vitro dissolution and in vivo bioavailability of an injectable product is unclear and should in general need further investigation). 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; Proposed changes: - please amend line 634 as follows: "During the development of an oral (immediate-release) veterinary medicinal product, a dissolution test..." - Please specify that dissolution tests must be performed using conditions that are validated for the physiology of the species/subspecies concerned.	Not accepted. Text is general text and further clarification is not considered necessary.
653-655	1, 5	Comment: While setting the dissolution specification it	Not accepted.

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		is important to relate to dissolution profiles of test batch but we believe that the dissolution of both reference and test batch should be considered. Proposed change: Unless otherwise justified, the specifications for the in-vitro dissolution to be used for quality control of the product should be derived from the dissolution profiles of the test product **and the reference product that were found to be bioequivalent.**	The specifications for the *in-vitro* dissolution to be used for quality control of the product should be derived from the dissolution profiles of the test product batch that was found to be bioequivalent in vivo to the reference product, even when a discrepancy results between *in vitro* dissolution profiles of test and reference product. Justification otherwise remains possible.
675	3, 4	Comment: the third pH has been changed from 6.8 (standard EP requirement) to 7.5; a justification would be welcomed. Is it because the values are only given as examples? Then it is confusing because it could be seen as guidance. Proposed change: Remove the brackets to let all flexibility to applicant to address this point or provide adequate pH values per species/subspecies (incl. production types as needed).	Not accepted. This change had been made to extend highest pH to cover intestinal pH range regarding all target species. These pH values are given as an example, whilst no reference is made to EP in particular in the section on dissolution.
676-679	1, 5	Question: Is in case of low solubility drugs achieving »sink« conditions mandatory? According to Ph.Eur. sink conditions should be achieved.	In recommendation 5.17 of EP 6.8 it is recommended to have sink conditions with dissolution testing, but not mandatory. In case of quality control testing sink conditions are considered necessary. However, in case of comparisons between strengths sink conditions may not be achievable for all strengths at all pH values.
683-687	5	In the mentioned sentences, two examples are provided to compare dissolution profiles. The first one is "…Where more than 85% of the drug is dissolved within 15 minutes…", the second one is "…In case more than 85% is not dissolved at 15 minutes but within 30 minutes…". We were wondering the following: What if we have an immediate release oral dosage form which dissolves for more than 85% in a time period exceeding 30 minutes? For example 35 minutes.	In case of an immediate release oral dosage form which dissolves for more than 85% in a time period exceeding 30 minutes normally more than three time points are required. In borderline cases where more than 85% of the drug is dissolved in e.g. 35 minutes it might be sufficient to have three time points as well, but this should be justified.
684-688	3, 4	Comment: Where more than 85% of the drug is dissolved within 15 minutes... Why 15 or 30 minutes? This doesn't account for transit out of the rumen or monogastric stomach. We feel that	15 minutes was based on the worst case scenario of gastric emptying in fasted dogs. It might be possible to justify a different time based on the gastric emptying time for the species, and administration in the fed/fasted state (if

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		it is essential to the correct implementation of this guideline that all the stakeholders can get a good understanding of the complexity of the physiology aspects behind the dissolution-based biowaivers in the veterinary medicine. Proposal: This point needs to be discussed in a focus group meeting.	relevant).
686-688	1	Comment: How should we interpret statement **»In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required».** Should similarity factor f2 be calculated only in cases where complete dissolution (>85%) is achieved between 15th and 30th minute? What about, immediate release products where it takes 45 or 60 minutes to achieve complete dissolution, how do we demonstrate similarity in those cases?	Guideline text amended to clarify Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar based on a single time point. In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required: the first time point before 15 minutes, the second one at 15 minutes and the third time point when the release is close to 85%. In these cases mathematical evaluation such as calculation of similarity factor f2 (see below) may be required to demonstrate comparable dissolution.
686-688	5	Comment: How should we interpret statement **»In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required».** Should similarity factor f2 be calculated only in cases where complete dissolution (>85%) is achieved between 15th and 30th minute?	Guideline text amended to clarify Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar based on a single time point. In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required: the first time point before 15 minutes, the second one at 15 minutes and the third time point when the release is close to 85%. In these cases mathematical evaluation such as calculation of similarity factor f2 (see below) may be required to demonstrate comparable dissolution.
707	3, 4	Typo: A full-stop "." is missing from the end of the sentence.	Accepted.
738-750 Definitions	3, 4	Comment/ Proposal: Please replace 'dosage forms' by 'pharmaceutical forms'. Please add examples of products for the sub-definitions for prolonged-release and pulsatile-release as has been	Accepted. Definitions added. For consistency with terminology used in this guideline. Prolonged-release pharmaceutical forms include e.g. insecticidal collars and slow-release i.m. or s.c. injections.

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		done for delayed-release.	Pulsatile-release pharmaceutical forms include e.g. intraruminal pulse-release devices containing anthelmintics.
756 Pharmacokinetic parameters	3, 4	Comment: the definition of AUCt should read as follows: Proposed change: "Area under the plasma concentration curve from administration to last observed concentration at a definite time t."	Not accepted. We can't see that this would be an important change.
758	3, 4	Format: AUCtau	Accepted
764	3, 4	Format: Font size for 1/2	Accepted
765	3, 4	Format: Lambda Z	Accepted
770-83 References (scientific and/or legal)	3, 4	Please add a reference to VICH GL 1 (see section 5.14 p11)	Not accepted. We don't find this necessary
785-956 (554-632)	1, 5	See above (comment on lines 554-632)	Not accepted. Currently these products are outside the scope of guideline as it is for pharmaceutical forms with systemic action only. It may be possible to add such an annex in the future but it is not practical to extend the scope of the guideline at this stage in the process.
786 Appendix	3, 4	I. Introduction Comment: It is surprising that the general classification of the BCS is not given anymore, at least as information. Proposed change: Suggest to add at the end of the 1st sentence (line 389): "As per BCS, the drugs can be classified as follows: Class I - High Permeability, High Solubility. Class II - High Permeability, Low Solubility. Class III - Low Permeability, High Solubility. Class IV - Low Permeability, Low Solubility."	QWP response: Accepted. Text added.

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796-804	5	General comment on solubility classification: The approach to fulfill any "worst case scenario" is extremely heavy. But in this case the proposed general solubility classification means a strong restriction which does not correspond to the principles of risk management of ICH Q9. Thus a risk based solubility classification specific to target animal (sub)species should be mandatory. Furthermore this risk based practice will be in terms with the upcoming revision of the DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the protection of animals used for scientific purposes. Therein will be ruled that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of animal experiments. Proposed change: Therefore, the approach presented below represents a summary of requirements to fulfill "worst case scenarios" specific to target animal (sub) species. Of note is that in order to apply the BCS system to animals, the solubility classification has been modified in comparison to that used in humans. The application of BCS-based biowaiver is restricted to active substances with high solubility in relation to dosage amount as well as with known absorption in target animals. Furthermore the active substances are considered non-critical in terms of efficacy and safety. Specific guidance is provided for biowaivers for BCS Class I substances (high solubility, high permeability) and for Class III substances (high solubility, low permeability). The classification is species specific.	Accepted.
802	3, 4	Comment: What are non critical in terms of efficacy and safety (antimicrobials?) If so, would this not exclude most premixes? Proposal: Please clarify the concept of 'non-critical in terms of safety and efficacy'	The text is deleted as the concept of "narrow therapeutic index drug" is not applied the same way as in human medicine where more narrow acceptance limits for bioequivalence is applied in some cases.

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815-816	5	The following is described in this guideline for BCS-based biowaivers: "…excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred..." The adopted human Guideline on the investigation of Bioequivalence [3] states exactly the same as described above. However, a draft version of this guideline is also written [4], which describes the following: "…excipients are not suspect of having any relevant impact on bioavailability…" The latter is much more in line with the BCS-classification description for biowaivers [5], which states that a biowaiver is applicable when: "…Excipients used in the test products should have been used previously in FDA-approved immediate release solid oral dosage forms…" For this reason we are of the opinion that we should follow the same description as described in this draft human guideline, which is more in line with the BCS – classification for a biowaiver.	Not accepted. Current wording is similar and even more general.
818-830	3, 4	Comment**:** When extending biowaivers to Class III small differences in absorption could lead to bigger changes in availability, especially in species where gastrointestinal transit time is limited. If CVMP would decide to in certain circumstances allow biowaivers for Class III compounds this should be on a case by case basis with appropriate data supporting and justifying the waiver. A sentence should be inserted in the last paragraph to stress this. Proposed Change: "BCS-based biowaivers are could potentially also be applicable for an immediate release formulation if: • the active substance has been proven to exhibit high solubility and limited absorption (BCS-Class III; for details see Annex section III), and...	Partially accepted. Text amended while retaining requirement to validate in the (sub)species concerned.

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		Generally, BCS Class III biowaivers can only be granted on a case by case basis and when justified by the appropriate supporting data. Moreover, the risks of an inappropriate biowaiver decision should be more critically ....”	
823-824	5	The following is described in this guideline for BCS-based biowaivers: “…excipients that might affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar…” Again, the adopted human Guideline on the investigation of Bioequivalence [3], states exactly the same as described above. However, a draft version of this guideline is also written [4], which describes only the following: “…excipients are qualitatively the same and quantitatively very similar…” Again, the latter is much more in line with the real BCS-classification description for biowaivers [5], which states that a biowaiver is applicable when: “…Excipients used in dosage form used previously in FDA approved immediate release solid dosage forms…” For this reason we are of the opinion that we should follow the same description as described in this draft human guideline, which is more in line with the BCS – classification for a biowaiver.	Not accepted. Current wording is similar and even more general.
829-830 *(866-867)*	1, 5	Comment: There is lack of data in the field of species specific BCS classification, may data on permeability be generated or at least supported by *in vitro* methods? What *in vitro* methods are recommended?	Although we are aware that *in vitro* methods are used for assessing permeability on the human side (Caco-2 cells etc) similar methodologies would have to be shown as having been validated for the particular veterinary species. We prefer not to specify this in the guideline text. Normally there is in vivo pharmacokinetic data available.
829-830 *(865-866)*	5	Comment: The acceptance of data only achieved from the target animal (sub)species is a strong restriction that implies the need for more animal experiments. This regulation is contradictory to the intentions of the upcoming revision of the DIRECTIVE OF THE EUROPEAN	See comment above.

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		PARLIAMENT AND OF THE COUNCIL on the protection of animals used for scientific purposes (see above). It should be permitted to prove the sufficient adsorption/ permeability by the interpretation of data achieved from replacement methods to animal experiments, e.g. from studies on (monolayer) cell cultures. Proposed change: The conformation by relevant data achieved from the target animal (sub)species is acceptable were they already exist. Where relevant data are missing in the target animal (sub)species, sufficient adsorption/ permeability may be proved by reasonable interpretation of data achieved from replacement methods to animal experiments, e.g. from studies on (monolayer) cell cultures.	
849-855	5	Moreover, the temperature at which the solubility testing is carried out should be in compliance with the body temperature of the target animal (this means about 37°C for mammals and not 15 – 25°C as mentioned in the draft guideline). In fishes for example, the temperature has to be adjusted accordingly. *In-vitro* dissolution experiments ruled by this guideline are to be carried out at 37°C , a normal bodytemperature in mammals (see line number 885). This also indicates that the solubility criteria of the Ph. Eur. are not applicable in the assessment of bioequivalence for mammals in regard to this guideline.	Accepted. New text is introduced which is more general for all species, with the onus on the applicant to justify the volume used with reference to the physiology and gastric fluid volume for the (sub)species concerned. The proposed section on solubility reads: "The pH-solubility profile of the active substance should be determined and discussed. Since gastric and intestinal fluid volumes differ markedly across animal species, the solubility classification in the context of this guideline is different to the classification applied in human medicine. In order to be eligible for a veterinary biowaiver, an amount of the active substance equivalent to twice the highest dose for the maximum anticipated bodyweight for the target species, should be soluble in a specified volume of an aqueous solution. This specified volume should be justified by reference to the physiology and gastric fluid volume for the (sub) species. Solubility should be demonstrated at the relevant body temperature, and within the range of possible physiological pH values for the (sub)species, and it requires the investigation in at least three buffers spanning this range, and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition

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			may be necessary to achieve an unequivocal solubility classification (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the active substance to a buffer." Without very specific guidance on this issue, and using only a case-by-case approach, different solubilities might be accepted by different agencies for generics with the same formulation. Applicants should therefore be strongly encouraged to get scientific advice well in advance of any such submission.
854 and 860-861	5	"…the active substance should be at least "soluble" (> 1 g /30 ml at 15- 25°C)……A lower solubility cut-off may be accepted, if fully justified…" There are multiple examples of products in which the active substance will not meet the Ph. Eur. Requirement for being "soluble", while in daily practice, solubility will never be an issue. For example: A tablet contains 10 mg of active substance. This active substance has a solubility of 100 mg/ 30 ml and is administered to a pig which has about 8 litres of gastric volume (based on the previous version (Rev 1) of this consultation paper). The amount of active substance in the tablet is 10 mg, which means that 3.0 ml of fluid is required to dissolve this active substance. The 8000 ml of gastric volume which is present in pigs, exceeds by far the 3.0 ml which is described in the guideline. Based on this example it must be concluded that solubility of the active substance is no issue when applied to swine. Besides this example there are many other examples which will have the same outcome. Consequently, we are of the opinion that it would be better to add a table of appropriate gastric volumes representing a worst-case scenario for all different species and to determine solubility in these volumes. This would be in line with the adopted human Guideline on the investigation of Bioequivalence [3], which also states a worst-case volume of 250 ml for the stomach of humans. We	Accepted. See above proposal on solubility.

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		propose the latter, because the currently proposed requirement is too stringent. Only a very few species will have a gastric volume of lower than 30 ml and most pharmaceutical formulations have an amount of active substance lower than 1 g. Thus in daily practice you will almost never have to be able to dissolve 1 gram of active substance in 30 ml.	
	1, 5	Comment: How to perform dose linearity study for low solubility drugs if surfactants are not acceptable? (Solubility differences will dictate the dissolution profile, not the properties of formulation, discriminatory power will therefore be decreased.) According to guideline the usage of surfactants is not allowed in case of BCS based biowaivers, which is understandable, since BCS based biowaivers refer to highly soluble drugs through whole physiological pH range. Does this also refer to dose proportionality, especially to drugs that are not highly soluble through whole pH range (BCS 2 and BCS 4 class)? E.g. Is it acceptable to have dissolution profile with 10% plateau? However, we believe that omission of surfactants for low soluble drugs is inappropriate. Proposed change: Use of surfactants for low solubility drugs in *in–vitro* dissolution studies is acceptable when adequately justified.	Accepted. Proposed text: "If the active substance has been demonstrated to be insoluble in classical dissolution media surfactants may be used in case of comparative dissolution testing between different strengths or variations in composition, manufacture, etc., in the lowest possible concentration where the dissolution test has sufficient discriminative power."
880-893	5	Currently, the European Pharmacopeia describes in detail the requirements for dissolution testing in chapter 2.9.3 Dissolution test for solid dosage forms. This chapter provides all information needed to conduct a dissolution test according to the established standards for dissolution testing. In our opinion, the example provided in sentences 880 – 893 is confusing as it is not identical to the European Pharmacopeia chapter 2.9.3.	Not accepted. Representative experimental conditions are given, which follow current compendial standards, not necessarily the European Pharmacopeia.
901	3, 4	Typo: "reference product" should be "reference products"	Not accepted. Singular is how it is meant.
919-924	5	Comment: If there is lack of data in the field of species	The type of supporting data provided is left open to the

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		specific impact of excipients on the above issues, may data be generated or at least supported by in vitro methods? What *in vitro* methods are recommended?	applicant".
935	3	Comment: (VI.1 Biowaiver for pharmaceutical forms for in-feed use) These products may be treated as immediate release formulations It was made clear at the AAVPT/ECVPT BE workshop in June 2010 that these are not immediate release formulations as the dose is administered over an extended period of time, making them modified release.	Not accepted. They are not modified release in the sense that release is delayed due to a certain product characteristic. In this context they will behave like immediate release formulations.
935	4	Comment: (VI.1 Biowaiver for pharmaceutical forms for in-feed use) These products may be treated as immediate release formulations It was made clear at the AAVPT/ECVPT BE workshop in June 2010 that these are not immediate release formulations as the dose is administered over an extended period of time, making them modified release. It would be interesting to invite Prof Del Castillo to the focus group to share some of his insights and publications	Not accepted. See above

References:
[1] VICH GL3: Stability: Stability testing of new veterinary drug substances and medicinal products (revision) Doc.Ref.EMEA/CVMP/VICH/899/99-Rev.1
[2] Note for Guidance on process validation. EMEA/CVMP/598/99
[3] Guideline on the investigation of Bioequivalence
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr
[4] Guideline on the investigation of Bioequivalence.
Doc. Ref. CPMP/EWP/QWP/1401/98 Rev. 1
[5] Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services; Food and Drug Administration Center for Drug Evaluation and Research (CDER) August 2000