PUBLIC CONSULTATION AT STEP 4 OF THE VICH PROCEDURE
OVERVIEW OF COMMENTS RECEIVED

Draft VICH GL 52 (Bioequivalence) – Blood Level Bioequivalence Study

VICH BIOEQUIVALENCE EWG

Comment n°	Name - Country
1	Generic Animal Drug Alliance (GADA) - USA
2	European Medicines Agency/Committee for Veterinary Medicinal Products (EMA/CVMP)
3	International Federation for Animal Health (IFAH)
4	European Group for Generic Veterinary Products (EGGVP)
5	Japanese Ministry of Agriculture, Forestry, and Fisheries (JMAFF)
6	Office National de Sécurité Sanitaire des Produits Alimentaires (ONSSA)

GENERAL COMMENTS – OVERVIEW		
Comment N°	Comment received	Outcome of consideration
2	Need to mention US FDA GLP	The guideline has now been revised and phrased in a manner consistent with other VICH guidelines: *All BE studies must be conducted in a manner that assures the reliability of the data generated. To be internationally acceptable, BE studies must be performed in conformity with the principles of Good Laboratory Practices (GLP).*
15	IFAH suggests that the term" Depending on the jurisdiction you are in" be minimized	We appreciate this concern. As there were occasions where acknowledging international differences was deemed necessary, in those situations, the phrase "depending upon jurisdiction" was retained.
16, 17, 18, 19, 20, 21, 22, 23	EGGVP stated:" It would be of great help if the VICH guideline would focus even more on the performance of the in-life phase of the study/species to define the common rules throughout the VICH region and therefore enable one study fit all regulatory authorities goal. With this, also the rule of 3R's would be respected, since divergent acceptability conditions request repeat of the in-life phase. Divergent positions in relation to the analytical and data analysis phase are adding to the workload, but do not expose additional animals to experiments due to study repetition. Its limit in scope also results in this guideline being unable to function as the sole guide to follow in VICH regions." Several additional comments were made with respect to additional topics that the EGGVP requested be covered in this VICH BE guideline.	This guideline is intended solely to cover the basic BE study design and principles. This is a necessary first step before any expansion be attempted. Therefore, issues such as biowaivers, human food safety and in vitro dissolution are not addressed. Details pertaining to analytical methods/method validation are likewise not addressed. Furthermore, there are some inherent points that this guideline cannot address (e.g. what constitutes a major versus minor species). Therefore, local guidelines are suggested to be followed for issues outside the scope of the current guideline.
	A comprehensive glossary listing all terms used in different regions meaning the same thing would be greatly appreciated	A glossary of terms has been added to the guideline.
83	JMAFF general wordsmithing comments and corrections	Corrections made

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

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Line No.	Comment N°	Comment received and rationale; proposed change	Outcome of consideration
85	1	The term "serum" not used and needs to be deleted	Term was deleted.
109	3	Concurrent analysis of API content of from test and reference product is unacceptable. It is the sponsor's risk	Change not made since it was a suggestion and not a mandatory statement. Furthermore, suggestion to maintain similar content in the test and reference formulation helps to insure that in fact the comparison of treatment percent dose absorbed is not confounded by potency differences (i.e., either increasing or decreasing the likelihood of finding the two products similar with respect to AUC and Cmax).
120	4	There should not be a requirement for test product composition in the BE study report	This is required by some jurisdictions and therefore should be included in the guideline.
176	5	Remove the term "labelled dose" from the need to include the "labelled dose administered to each anima in each period of the study	Change made to remove term "labelled ".
205	6	The washout interval between doses should be increased to 10x terminal elimination half-life to be consistent with FDA Guideline	Change not accepted
353	7	The guideline should state that the example of how to estimate sample size is included in the appendix	Suggestion accepted and sentences added to alert the reader to the availability of examples in the appendix.
411	8	The term AUC_t or AUC_{tlast} may be preferable to AUC0-LOQ because the final concentration is not likely to be at the Lower Limit of Quantification	The revised sentence reads as follows*: In single dose studies, C_{max}, T_{max}, $AUC_{0\text{-}Last}$, and $AUC_{0\text{-}\infty}$ should be determined.*
411	9	Is $AUC_{0\text{-}inf}$ actually required? It is not required by CVM.	Since some jurisdictions consider $AUC_{0\text{-}inf}$ to be necessary, it is included in the guideline. Local jurisdictions can decide whether or not this metric needs to be included as a critical variable in the determination of product bioequivalence.
463	10	Prefer to omit the list of information regarding method validation in the BE study report.	The fundamental issue being communicated here is that a study is not acceptable unless there is a complete

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			method validation report. This does not constrain local jurisdications to modify the timing of submissions. Therefore, the requested change was not made.
533	11	BE acceptance criteria should specify which AUC is critical in the evaluation	Due to international differences in this decision, the term "AUC" was retained so as to allow each jurisdiction to have flexibility in this decision.
570	12	The LLOQ is determined by the sensitivity of the analytical method but the last quantifiable concentration of an incurred sample analysis is not. Therefore, the description of $AUC_{0\text{-}LOQ}$ ("the last quantifiable concentration (the limit of quantification, LOQ) is determined by the sensitivity of the analytical method") needs to be modified.	Guideline was modified, replacing $AUC_{0\text{-}LOQ}$ with $AUC_{0\text{-}Last}$. The glossary now reads as follows: **$AUC_{0\text{-}Last}$**: AUC to the last blood sampling time associated with quantifiable drug concentrations. The last quantifiable concentration (the limit of quantification, LOQ) is determined by the sensitivity of the analytical method. The last quantifiable drug concentration may occur prior to the last blood sampling time.
603	13	The term "Tlag" should be used rather than spelled out.	Change not made since Tlag had not been defined in glossary prior to the term Cmin. However, slight modification in wording was instituted. The glossary description of Cmin now contains the following statement: *In the absence of a measurable delay between drug administration and the first appearance of drug in the systemic circulation C_{min} equals C_{trough}.*
321	14	There is some concern regarding the use of fasted dogs and cats. Preference is to provide a small quantity of food prior to drug administration.	Scientific reasons why this constitutes a fed state were provided. Therefore, this change was not accepted.
30	24	It is indicated that two bioequivalent products will be interchangeable in a clinical setting. It is also true for the safety setting. **Proposed change:** therapeutically indistinguishable and therefore interchangeable in a clinical **or safety** setting.	The clinical setting comprises both effectiveness and safety. The term "clinical setting" indicates that although the product is being tested in normal healthy subjects under well controlled conditions, it is going to remain comparable when used as per reference product indications. To segregate safety into a separate issue here is inappropriate and makes it seem as though we are evaluating effectiveness and safety independently. For a

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			true bioequivalence evaluation (using the confidence interval criteria as stated in this guideline), these two are inseparable. Accordingly, the proposed modification was not accepted.
106	25	Pharmacological endpoint studies might be helpful in some instances *e.g.* if the plasma concentration of the drug does not reflect the pharmacodynamic action of the molecule. **Proposed change:** Consider bringing pharmacological endpoint studies within the scope. For instance drawing on Docket No. 94D-0401, FDA Bioequivalence Guidance. "Where the direct measurement of the rate and extent of absorption of the new animal drug in biological fluids is inappropriate or impractical, the evaluation of a pharmacologic end-point related to the labelled indications for use will be acceptable."	This issue is outside the scope of the current guideline.
106	26	Please advise in the document how to choose a reference if the original pioneer product is no longer available.	This is a challenge that needs to be considered on a case-by-case basis and therefore will not be included in this guideline.
106	27	With regard to the statement "*The reference product must be from a lot associated with a veterinary medicinal product that has been granted approval within the jurisdiction for which the generic product approval is being sought"*, this statement is in opposition to the VICH goal; namely it requests new study or adding a study arm solely due to reference product selection. We believe that all batches of reference product on the market throughout the VICH region can be considered as representative and any of them could be used in the study as appropriate reference product.	It is recognized that there can be differences in formulation or manufacturing process (machinery employed) across jurisdictions. Therefore, we cannot assume that one batch of the reference marketed in one jurisdiction will be BE to a batch manufactured across all jurisdictions. Accordingly, it is inappropriate to allow generic sponsors to pick and choose the jurisdiction from which their product most closely resembles. That can lead to very large differences in the bioavailability across generics. To avoid this problem, generic sponsors can elect to include more than one reference product in their investigation and demonstrate equivalence to both. However, this is not discussed within this guideline and we suggest that this issue be addressed on a case-by-case basis.
109	28	This statement seems to preclude to possibility of demonstrating	This issue is addressed under dose normalization. No

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		bioequivalence of a test product with a different strength than the reference product, e.g. when applying for a so-called hybrid registration. Indeed, the strength of a test product (e.g. a suspension for injection) might differ substantially from the strength of the reference product (resulting in a different injection volume), nonetheless the two products can be bioequivalent. **Proposed change**: "*For test and reference products with the same nominal strength, it is recommended that…*" or "*The API content of the test and reference products should be assayed prior to conducting the BE study. To be internationally acceptable, it is recommended that the assay content of the batches from which test and reference products were obtained should differ by no more than ±5% from each other (when dose normalized).*"	further changes made to the guideline.
113	29	Does the reference to 1/10 production scale imply GMP quality? **Proposed change:** Differentiation between generic BE and "during development bridging studies" would be helpful	The text has been modified to read as follows: *For use in the in vivo BE study, the test product should originate from a batch of at least 1/10 of production scale, unless otherwise justified.*
115	30	What does "critical attributes" mean in detail? **Proposed change:** specify which attributes are considered critical	The term critical quality attribute (CQA) have its foundation in the concepts of quality by design (e.g. refer to Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008 Apr;25(4):781-91). Because these CQAs are very product specific, it would be inappropriate for us to list these in this guideline. We therefore leave this as written with the assurance that each sponsor will have chemistry experts who understand CQA's and quality by design (QBD) and can work with the respective scientific review team to identify which of these attributes are necessary for characterization for the specific dosage form/drug product being evaluated.
119	31	The need to measure the content of the test and reference product is justifiable if no marketing authorisation is available. The measurement of the content of the test and reference product should be optional if marketing	Change not made

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		authorisation is available for the products. **Proposed change:** (including assayed content, **if applicable**)	
119	32	The meaning of "composition" is unclear in this context. **Proposed change:** please be more specific on composition in active ingredient or add a definition in the glossary.	The definition of composition has been modified.
120	33	The composition of the test product is a corporative secret and we believe inclusion in the dossier should be enough (not disseminate it through to CRO with compilation of study report.)	The sponsor has the option of electing the mechanism through which this information is conveyed to the regulatory authority. The guideline is not intended to dictate the venue through which this information is submitted but only that it needs to be submitted as part of the bioequivalence evaluation. Therefore, no changes will be made.
129	34	The linear PK of the reference product is not always known. For example for generic development the applicant is not aware of the dossier of the pioneer product and bibliographic data are not always accessible for this type of information. Normally the dose linearity is documented in the pioneer dossier. Both products need to be interchangeable at any approved doses. In the case of a bridging study during development, the dose linearity is to be checked but this forms another part of the dossier and is outside the scope of this guideline. **Proposed change:** "Bioequivalence studies may be performed with any approved dose, or, when conducted as part of development of a product containing a new chemical entity at a dose within the proposed dose range."	Firstly, note that we are not requiring that a sponsor know if the drug has linear kinetics. However, in the absence of such information, we need to be assured that differences will not be magnified if the used at higher (approved) doses than that which was used when performing the in vivo BE trial or that there is less than dose proportional absorption such that differences in product bioavailability cannot be adequately distinguished. The guideline does specify that if a sponsor wishes to argue against use of the highest approved dose, then they will need to provide scientific justification. No change made to the guideline.
129	35	It is acknowledged that for some animal species e.g. dog, it could be difficult to find animals suitable for investigation of high strength solid pharmaceutical forms. In this case overdose studies might be considered if tolerated. Please note also from the FDA guideline: *"A higher than approved dose BE study in food animals species should also be accompanied by a tissue residue withdrawal conducted at the highest approved dose for the pioneer product."*	No change made to the guideline.

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142	36	The sentence "In general, the maximum dose would be limited to 3x the highest dose approved for the reference product" may be deleted, while in the following paragraph the justification of overdosing is permitted and in some cases also higher overdosing may be justified.	No change made to the guideline.
161	37	There is still open issue between VICH regions on weight adjustment/period of administered dose for dividable dosage forms (e.g. injectables) that is acceptable by the FDA and not by the EU. (the statement in question is "*In crossover studies, the same total dose should be administered to each animal in all study periods. The use of dose adjustments in those rare situations where large weight changes are anticipated (e.g., studies conducted in rapidly growing animals) will need to be considered on a case-by-case basis*.")	Injectables are dosed on a mg/kg basis and exact amounts can be administered. Therefore, no changes to the guideline are needed.
163	38	Please define "rapidly growing animals".	For the sake of clarification, the guideline now reads as follows: *The use of dose adjustments in those rare situations where large weight changes are anticipated (e.g., studies conducted in rapidly growing animals where there is a risk of differences in drug absorption, distribution, metabolism, or elimination in period 1 vs 2 that could bias the within-subject comparison) will need to be considered on a case-by-case basis.*
179	39, 40	Bioequivalence studies may also be used to support a labeling change to include an additional new route of administration (e.g., intramuscular to subcutaneous injection) or when bioequivalence is used during product development. Does this prevent the compare different routes or sites of administration within generic BE studies? Please clarify.	When a comparative blood level study is being used by an innovator, the issues may be markedly different than what is encountered when evaluating product in vivo BE for a generic drug application. Other potential situations are covered under the guideline statement: "*Unless otherwise justified when conducting an in vivo BE study*".
205	41	*Therefore, in addition to proof of absence of pre-dose concentrations, it is recommended that the duration of the washout interval should be at least 5 times the blood terminal elimination half-life of the API-and its metabolite(s) (when there is indication that the metabolites may affect pharmacokinetics of the parent compound in the second period).*	See response to same issue raised by GADA.

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226	42	We would appreciate clarification about when this can be considered. (statement in question is *"Alternative study designs can be considered. For example:")*	The answer to this question is provided in the information immediately subsequent to the section to which you are referring.
273	43	Please define accumulation index that requires steady state study.	There are no hard and fast rules that have been applied to some critical accumulation index. However, for the sake of providing generalized guideline, the text has been revised as follows: *For extended release formulations intended for repeated dosing, demonstration of BE should be based on multiple dose studies if there is accumulation between doses (i.e., if there will be at least a 2-fold increase in drug concentrations at steady state as compared to that observed after a single dose*).
241 and 251	44	Points 2 and 3 of section D describe the replicate and the sequential study designs. It is not clear in point 4 of section D if these designs can also be used for both single and multiple dose studies. (The statement in question is: *Both single and multiple dose studies can be conducted using a crossover study or parallel design*.) **Proposed change:** …a crossover study ~~or~~**,** parallel**, replicate or sequential** design.	Replicate or sequential study designs are not appropriate when BE trials are designed as multiple dose studies. Therefore, the following text (which explains the reasons for this decision) has been added: *Both single and multiple dose studies can be conducted using a crossover study or parallel design. Due to complications associated with studies of very long duration, the use of sequential and replicate study designs are generally not recommended for multiple dose studies*.
297	45	What scientific argumentation is behind the "minimum two weeks period"? **Proposed change:** "must be free of drug residues at time of treatment"	The guideline now reads as follows: *The experimental animals should be free of any drug residues prior to the in vivo phase of the BE study. In some cases, the necessary drug-free period may need to exceed that associated with drug residues to account for potential physiological carryover effects that could influence the data generated in the BE trial.*
304	46	Please leave out as it incorrectly suggests that homogeneity and comparability in all known and prognostic variables etc. are also important and/or relevant in cross-over studies.	Change made to reflect the applicability of this concern to parallel studies: Studies should be conducted with healthy animals that are representative of the target population. *For parallel design studies, the*

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			animals/treatment groups should be homogeneous and comparable in all known and prognostic variables that can affect the PK of the API, e.g. age, body weight, gender, nutrition, physiological state, and level of production (if relevant).
290 and 304	47	EGGVP was under the impression that a study conducted on target animal species covers all categories of the species, unless there are significant and relevant maturational differences between categories. (e.g. a study performed on Beagle dogs covers also puppies)	The guideline is written to reflect this very point. However, for parallel studies, it is important to try to maintain homogeneity because unlike crossover trials where intersubject variability is removed from the treatment comparison, intersubject variability is confounded with treatment and therefore serves to widen the confidence e interval. The text will not be changed.
303	48	In a cross over design, it is also better that the groups are homogeneous. The words "Especially for parallel design" are not necessary. **Proposed change:** ~~Especially for parallel design studies,~~ ~~t~~**T**he animals/treatment groups should be homogeneous and….	See changes made as described for comment #46.
313	49	Suggestions on standardization of fasting and fed state approaches/animal species would be very much appreciated. To standardize fed state in animals the use of gavage, e.g. with regards to products administered via drinking water, to introduce the same amount of food to all animals prior test and reference product administration, would be needed. If this approach is acceptable throughout the VICH regions, please incorporate within the document. Also, even if it is considered that the use of gavage for the test and reference product administration, might affect pharmacokinetic profile, however it would not compromise discriminating between formulations. Bioequivalence studies are highly standardized experiments to distinguish between formulations and are not designed to reflect actual field conditions. Moreover, low standardization (by mimicking field conditions) might cover up formulation differences.	In putting this in the guideline, it will then require sponsors to use a gavage feeding method. Since there are many ways to minimize noise, we should not restrict the guideline to a single method. Accordingly, it is best to allow the sponsor the freedom to select a method that will minimize the variance of the observations and not put specific instructions in the guideline. Note that gavage feeding is typically not promoted by the USFDA.

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313	50	Use of fasted state for oral dosing should not be limited to dogs and cats.	This was a point debated within the BE EWG. There are some differences in opinion with regard to whether or not horse should be fasted (some jurisdictions do not want BE studies conducted in fasted horses). Also, ruminants must not be fasted. Therefore, we specify dogs and cats as agreement was achieved with respect to these two animal species. Accordingly, there will be no changes to the text.
330	51	Ideally all animals should be included in the analysis. However, animals in a cross-over study that do not provide data for both the test and reference product, cannot be included in statistical analysis using in Europe only acceptable GLM procedure.	Guideline was not changed because inclusion of a single period does not influence the confidence interval but does influence the estimation of the between treatment means. This is a correct statement, irrespective of whether one uses the Proc GLM or Proc Mixed procedure (although the two Proc's may handle imbalance of subject within sequence differently, irrespective of whether the one period is included or excluded from the dataset).
330	52	Significantly incomplete animals (i.e. only (correct) data from Period 1) should be excluded from the statistical BE evaluation. Leaving these data in the BE analysis requires software modifications not (readily) included in commercially available BE software and disrupts the "balance" of a cross-over design. The value of "half a subject" on the total subjects can never be that critical, i.e. determine yes or no bioequivalence, as in this case this single incomplete dataset would decide over yes/no bioequivalence. Note: leaving out one subject also disrupts the balance. **Proposed change** (if any): Always provide descriptive statistics with and without data from animals excluded from the BE evaluation.	To avoid statistical concerns, the guideline has been modified as follows: *To insure that all potential statistical concerns have been addressed, descriptive statistics with and without data from animals excluded from the BE evaluation should be provided.*
360	53	Please clarify if this needs to be included in the protocol and/or the report.	The guideline now reads as follows: *There are numerous situations that may occur that will necessitate removal of all or a portion of an animal's*

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			data from the study. When this occurs, adequate justification for removal should be provided in the study report, and decisions to eliminate data should be made prior to analysis of blood samples to avoid bias.
360	54	Please explain the purpose	The paragraph now reads as follows: *Sample size calculations assume that the estimates used (e.g., treatment differences and variances) will be realized in the future study. Additionally, sample sizes are generally estimated as the "minimum number" needed to demonstrate BE if those estimates are realized. A reference is provided that describes sample size calculations.*
369	55	**Proposed change**: "It should be noted that for a study to be internationally acceptable, a minimum of n=6 is necessary (with n = the number of subjects within each sequence and therefore, the total number of study animals in a two-period, two-sequence crossover study, N, should be equal to or greater than 12)."	Correction made. The paragraph now reads as follows: *It should be noted that for a study to be internationally acceptable, a minimum 12 evaluable animals per treatment is necessary. For a crossover trial, this implies that the minimum number of subjects per sequent (n) = 6 (and therefore, the total number of study animals in a two-period, two-sequence crossover study, N, should be equal to or greater than 12). For a parallel study design, there should be no less than 12 evaluable subjects per treatment group (and thus the total number of animals enrolled in the BE trial would be equal to or greater than 24).*
390	56	Please specify the AUC truncated/animal species for orally administered immediate release formulations with long elimination half-lives. (as in human guideline where AUC 0-72 is it based on total gastrointestinal transit time). This specification may be solid ground for reduction number of animals in experiments.	The guideline provides a benchmark to be considered. Because of the complexity and vast range of release characteristics of drugs approved for use in veterinary species, sponsors should consider this issue on a case-by-case basis with the regulatory authority.
397	57	Please note that C_{trough} should also be calculated in multiple dose studies	Use of term C_{min} has been replaced by the term C_{trough}.
432	58	Please clarify if the scientific rationale should be given in the study protocol instead of the study report	It is not necessary to state whether it should be motivated in the report or the protocol. The important aspect is that is is motivated. Therefore, no changes are

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			made.
447	59	Please specify that this section refers to racaemic mixtures only.	There are many situations where the mixture is not racemic (unequal amounts of the enantiomers) and yet this section will nevertheless be very relevant. Accordingly, no additional statements will be made.
447	60	Please clarify what happens if the originator has based its data on achiral methods only and no stereoselective data exists.	Based upon the guideline as currently written, this is not a problem so long as the stipulated three conditions are not an issue. However, if these three situations are a concern, then there needs to be a stereospecific method for the BE trial. Please note that in order to render the determination of answers to these three questions, there must exist a stereospecific assay. Therefore, no additional statements will be made.
447	61,63	Is the phrase "all conditions are met" correct or is one condition sufficient to ask for stereospecific methods? This is a new rule for EU region. Please explain the relevance and possible approaches to substantiate justification for achiral method selection regarding this issue.	All conditions must be met in order to require that a stereospecific method be employed. There are situations where BE can be demonstrated for one chiral form but not for the other. Therefore, if all three conditions are met, a chiral assay will be needed to insure product BE.
453	62	The AUC *ratio* of the enantiomers is modified by a difference in their respective rates of absorption.	Modification accepted
463	64	Please clarify why these be summarized in BE study report (Isn't cross reference to the validation report sufficient?) In our opinion the method validation for tissue residue analysis and plasma analysis is not really different and these residue analysis guidelines may be used also for plasma analysis. We would advise to refer to VICH GL 49.	There are aspects of GL49 that are not appropriate for a blood level BE trial. For example, there are times where blood levels are being measured at concentrations below the mcg/mL range. Based upon GL 49, we would not need a between-run precision more than 45% or a within run precision of more than 30%. Even if we go as high as 10 mcg/mL, the guideline does not require a precision of more than 32% between run or 25% within run. Such precision would be unacceptable (at least for the US FDA). Accordingly, we cannot reference GL 49. If we suggest that the validation parameters to be considered

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			are defined in GL 49, there is the potential for misleading the reader with regard to the acceptance criteria. Therefore, we will leave this as written. With respect to recommendations for summarizing within the BE report, this has been modified as follows: *The bioanalytical phase of the BE study must be based upon an appropriately validated bioanalytical method. The following aspects of bioanalytical method validation and performance should be summarized in the study report (or as otherwise deemed appropriate by the regulatory authority).*
471	65	Please clarify what is the goal of determination of the LOD for analytical methods, used in BE studies. In our opinion, the LOD is irrelevant. It is not required in human studies so we hope the use can be avoided here as well. Concerning background signal, the VICH GL49 guideline EMA/CVMP/VICH/463202/2009, which came into effect February 2012 states: *"LOD is often time difficult to determine particularly in LC/MS assays where control samples actually provide zero response at the retention time of the analyte. Without a response, it is impossible to calculate a standard deviation and therefore impossible to determine the LOD based on the mean plus 3 times the SD of the mean. Even if a mean plus 3 times the SD of the mean can be determined, it is often related to the instrument limit of detection rather than the method limit of detection."*	LOD has been removed from the GL
473	66	Please note that this is called selectivity in VICH-GL49	The term "selectivity" is now in parenthesis.
478	67	The number of incurred samples to be included should be defined **Proposed change:** *e.g.*:"10% of the samples should be reanalysed in case the number of samples is less than 1000 samples and 5% if the number of samples exceeding 1000 samples", taken from EMEA/CHMP/EWP/192217/2009	In selecting samples for reanalysis, adequate coverage of the PK profile in its entirety should be provided ad should include assessments around Cmax and in the elimination phase for all study subjects. Clearly, there are some differences in perspectives. Selecting one value (e.g., 10% reassay for all situations) would be

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			unnecessarily strict. Therefore, to address this point without imposing undue burden on sponsors, the guideline has been modified as follows*: Regulatory authorities should be contacted regarding the possible need to include incurred sample reanalysis (IRS) as a component of the method validation (where IRS is the repeat analysis of a subset of subject samples in separate analytical runs).*
492	68	Specify the preferred method to calculate AUC, e.g. linear, lin/trap **Proposed change:** add a sentence specifying the preferred calculation method	While there is a difference between the linear and ln-linear approach if one is trying to estimate the AUC for a specific drug, when dealing with BE evaluation, there is no difference in ratios of test/reference products, regardless of which method is used. Therefore, no modification is made as either method is acceptable for a BE study.
492	69,70	AUC_{0-t} is the pivotal parameter (in addition to Cmax) in EU and confidence intervals are not evaluated for the AUCinf; please consolidate or list all the required pivotal parameters throughout the VICH regions, so that one report fits all. Specify AUC please	The parameters agreed upon for acceptability throughout the VICH regions have been defined in Section J of this guideline. Accordingly, the reader is now referred to that section to address any questions regarding the parameters for which the confidence intervals should be calculated in order to be internationally acceptable: *The confidence interval approach should be applied to the individual parameters of interest, typically AUC and C_{max} (refer to section J).*
501-509	71	Please note that there is different approach toward treatment of effects in statistical model (fixed/random) between EMA and FDA.	We have addressed any differences that may need to be considered in the sentence: *The statistical model and randomization process should be defined a priori in the study protocol.* Also, please note that it is inappropriate to define one specific model since our guideline also describes the potential use of several study designs. If this is considered an important point, future guidelines can be developed to define the statistical models that should be

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			used for each of the various study designs and objectives for those models (e.g., see guideline description of alternative study designs).
521	72	The term "ratio" is used in this text but it is not clear that it is geometric mean ratio of test product / reference product. **Proposed change**: Please clarify the text.	The answer to this question is directly answered within this guideline by the fact that we are indicating that sponsors should conduct their analysis using ln-transformed data and the analysis of variance for defining residual error. By definition, the ANOVA determines the treatment differences in LnAUC and LnCmax values. Exponentiation of the differences results in ratios. Your statement is only relevant if we provided the option for using untransformed data. Therefore, no change will be made in the guideline.
525	73	To reduce variability and since manipulation with dosage forms is not acceptable, variability might be reduced by dose normalization and is considered by some EU states as sound mathematical approach . Please reconsider. If dose normalization is not allowed by this guideline, it imposes this rule all over VICH region.	Dose normalization is irrelevant when conducting a crossover study. To overcome problems in parallel studies, animal weights should be constrained. However, we can include a statement that for parallel studies, dose normalization (based upon the labeled administered dose) can be used as a mechanism for reducing intersubject variability. The guideline now states the following: *In rare instances involving BE trials designed as a parallel study and when the drugs are administered on a mg rather than on a mg/kg basis, between-animal differences in body weight could inflate the magnitude of the residual error to an extent that a prohibitively large increase in subject numbers would be necessary to maintain study power. In these situations, the acceptability of dose normalization and the corresponding method of data analysis should be discussed with the regulatory authorities during protocol development.*

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525	74	Also the drop-outs due to vomiting and/or diarrhoea,... may result in challenged homogeneity of groups in parallel design or challenged balance by stratified randomisation in cross-over design and therefore shift the point-estimate as well as its CI. Dose normalisation would reduce this effect.	When using a crossover study design, introducing dose normalization would have no influence on the within-subject comparison. Imbalance in study design is not going to influence the within-subject comparison, which is the basis for the confidence interval. If you simulated a crossover study (where doses are consistent within subjects but differ between subjects) and if you include all subjects or delete one or two subjects in one period, you will find that dose normalization has no influence on the confidence intervals that result from this study. Therefore, no changes will be added beyond what is indicated above.
533	75	Widened confidence limit might be helpful, if high inter-individual variability of plasma concentrations will be observed. The current CVMP GL on the conduct of BE studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) allows a widening of the limits to 70-143% in rare cases if it has been prospectively defined in the protocol together with a justification from efficacy and safety perspectives. It should at least be mentioned in the new Draft VICH GL 52 that there are regional/local guideline documents available that allow widening of the acceptance criteria under certain conditions. Otherwise there is a great risk that this achievement which is crucial to some veterinary medicinal products gets lost. **Proposed change:** Add the following text from EMEA/CVMP/016/00-Rev.2 "**However, as these parameters may exhibit a greater intra-individual variability, a maximal widening of the limits to 70% to 143% could in rare cases be acceptable if it has been prospectively defined in the protocol together with a justification from efficacy and safety perspectives."** Or Add after line 582 the following sentence: **"There are regional/local guideline documents available that allow widening of the acceptance criteria (e. g. 70-143%) under certain conditions."**	As this guideline is intended to represent how acceptability can be achieved across all VICH member nations, we need to go with the strictest criteria for each of the pivotal considerations. In this regard, there is no widening of confidence limits permitted for generic products within the USFDA unless a sponsor has specifically indicated a desire to use the scaled reference bioequivalence approach. Please note that this alternative approach is included in the guideline. Efforts to include country-specific differences were considered unacceptable by the VICH leadership. Accordingly, the guideline is left as currently written
533	76	There should be some sentence in the guideline to allow a widening of the	See response above

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		interval, at least for Cmax. Is it necessary to consult local regulatory authorities each time?	
NA	77, 78, 79	Please define "highly variable drug" (term used for drugs with over 30% within subject variability) Please define "extensive drug partitioning coefficient" Please define "Partial AUC": AUC estimated over a limited portion of the concentration vs. time profile.	These terms are not in the guideline and therefore not included in the glossary
716	80	20 animals in a cross-over study provide 40 data (20 on test and 20 on reference product). 20 animals in a parallel study provide 20 data (10 on test and 10 on reference product). It seems logical that a parallel design (with comparable size determining relative variation (%CV)) requires twice as much subjects (as a cross-over study). This is in line with [**Chow** (2001)]. Journal of Pharmacokinetics and Pharmacodynamics, Vol. 28, No. 2, 2001 On Sample Size Calculation in Bioequivalence Trials Shein-Chung Chow and Hansheng Wang **Proposed change** (if any): Multiply number of subject required for a parallel study (based on %CV (between subject error)) by 2.	Guideline has been modified as follows: *When considering a crossover study design, if a multiplicative model is used (where the within-subject %CV is 20 and the ratio of the test/reference products = 0.95), the equation results in an estimate of 20 subjects (10 in Sequence 1, 10 in Sequence 2). However, when this equation is applied to a parallel study design, N = the number of subjects per treatment. Therefore, 2xN =total number of subjects = N (test) + N (reference).*
718	81	"If, for example, a multiplicative model is used, where the within-subject %CV is 20 and the ratio of the test/reference formulations = 0.95, the equation results in an estimate of 20 subjects (10 in ~~Group~~ Sequence 1, 10 in ~~Group~~ Sequence 2).	Guideline has been modified (see above)
719	82	Same "miscalculation" as above. **Proposed change** (if any): However, when this equation is applied to a parallel study design, N = the number of subjects per treatment. Therefore, 2xN =total number of subjects = N (test) + N (reference).	The guideline has been modified as described above.
119	84	Regarding the text "The study report should include the reference product name, strength (including assayed content), dosage form, batch number, expiry date, and country of purchase. ", in some jurisdictions, , there are	The text is modified as follows: The study report should include the reference product name, strength (including assayed content), dosage form, batch number, expiry

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		classes of veterinary products which have no duty of expiry date description on the label. Could you change description about expiry date as optional?	date *(when available)*, and country of purchase.
134	85	With regard to the sentences "In exceptional cases where a batch of reference product with an assay content differing less than 5% from the test product cannot be found, the data could be dose normalized. In such cases, the procedure for dose normalization should be pre-specified and justified by inclusion of the results from the assay of the test and reference products in the protocol." I remember that "... the data could be normalized, if justified." in the former version of this document. Is the present version better than the former version?	Please note that the intent has not changed as the need for justification remains in the context of the dose normalization.
214	86	In the last line below, is the description "compound and/or metabolites" better than "compound/metabolites"? A parallel study design may be preferable in the following situations: • The parent compound and/or its metabolites induce physiological changes in the animal (e.g., liver microsomal enzyme induction, altered blood flow) that can alter the bioavailability of the product administered in Period 2. • The parent compound/metabolites, or drug product (e.g. flip flop kinetics).	The guideline has been modified to address these concerns: *A parallel study design may be preferable in the following situations:* • *The parent compound and/or its metabolites induce physiological changes in the animal (e.g., liver microsomal enzyme induction, altered blood flow) that can alter the bioavailability of the product administered in Period 2.* • *The parent compound and/or metabolites, or the drug product (e.g. flip flop kinetics) has a terminal elimination half-life so long that a risk is created of residual drug present in the blood at the time of Period 2 dosing (i.e., a wash-out period is not practical).*
226	87	Regarding the statements below, would it be better to add the title of "II.D.2"? *Alternative study designs can be considered. For example:* • *Replicate study designs (See subsection II. D. 2)* • *Sequential study designs (See subsection II. D 3)*	Identifying the section by numbering system is more precise and therefore the text was not modified.
626	88	In the glossary, change **"Excipient (inactive ingredient):"** to **"Excipient: (syn: inactive ingredient)"**.	Change made in guideline.
	89	Change all glossary uses of the term "pharmacokinetics" to "PK".	To be consistent with the glossary, all uses of the term

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			"PK" has been changed to "pharmacokinetics" until the term has been defined in the glossary.
Page 3, supplemental material	90	Supplemental material: please correct tabular value for difference in last table from 0.1958 to 0.01958	The change is now made in the table.
119	91	Please change from: "The study report should include the reference product name, strength (including assayed content), dosage form, batch number, expiry date, and country of purchase. The test product name, strength (including assayed content), dosage form, composition, batch size, batch number, manufacturing date, and expiry date (where available) should be provided." **To "**The report must include the name of the product, the concentration, the pharmaceutical form, the batch number, the date of manufacturing and the administered dose	This stipulation is based upon a compilation of points needed across the various VICH jurisdictions. Requested change will not be made
134	92	With respect to the comment: In exceptional cases where a batch of reference product with an assay content differing less than 5% from the test product cannot be found, the data could be dose normalized. In such cases, the procedure for dose normalization should be pre-specified and justified by inclusion of the results from the assay of the test and reference products in the protocol. 1) Please define "exceptional cases" 2) What is normalization?	What constitutes an "exceptional case" is defined in the first sentence (when assay content differing by less than 5% from the test product cannot be found). With respect to dose normalization, this is a mechanism for removing differences in plasma drug concentrations that are due to treatment differences in the mg (or mg/kg) administered doses. We do not indicate a single method by which this normalization should be generated because we wish to avoid being overly prescriptive. Therefore, no changes are to be made to the guideline.
187	93	With respect to the alternative study design section: "Alternative study designs can be considered. For example: • Replicate study designs (See subsection II. D. 2) • Sequential study designs (See subsection II. D 3) • To obtain approvals in multiple regions, a 3-treatment crossover or a multiple reference parallel study design may be considered when performing one study with two different reference products, depending on the products registered in the respective regions."	With respect to the first question, the sentence specifically states that this three period design includes a single test product and two reference products (from different jurisdiction which may differ in a way that precludes the use of a single reference product). With respect to the meaning of sequence, this is described in the statistics section, study design section, subject number section, and in the supplemental material. Accordingly, no additional changes will be made.

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		1. Does this pertain to three treatments or three periods? 2. Should it not be explained that the sequence is linked to the animals, meaning successive administration of the test and reference products to the same animals with an interval?	
364	94	With respect to the statement "Sample size for a BE study should be based upon the number of subjects needed to achieve BE for the PK parameter anticipated to have the greatest magnitude of variability and/or difference in treatment means (e.g., Cmax). Equations and examples are provided in the Appendix." The size of the sample for the bioequivalence study should be clarified.	The issue of sample size and how it can be estimated is already provided in the guideline.