6 December 2018
EMA/CVMP/755602/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.3)

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

Stakeholder no.	Name of organisation or individual
1	Association of Veterinary Consultants
2	EGGVP – European Group for Generic Veterinary Products

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1. General comments - overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
-	-	-

2. Specific comments on text

Line number(s) of the draft GL	Stakeholder number	Comment and rationale; proposed changes	Outcome
148-149	1	Comments: Highly Variable Drug products (HVD) should be explicitly defined. Proposed change: *Highly variable drug products (HVDP) are those whose within-subject variability for a parameter is larger than 30%. The 30% threshold always refer to the within-subject variability of the reference formulation. The applicant should justify that the calculated within-subject variability is a reliable estimate and that it is not the result of outliers*.	Accepted. A short definition of the Highly Variable Drug products (HVDPs) is added in section 5.1 but it slightly differs to the one proposed.
150-153	1	Comments: The use of a partial replicate design is not acceptable. - The reference formulation needs to be administered twice to check if the drug is a HDVP or not - Both the reference and test products need to be administered twice to check within-subject variability for the test formulation is not higher than that for the reference formulation. Proposed change: A full replicate study design where each subject receives the test and reference products twice is recommended.	Not accepted. We need to know the intra-individual variability for the reference product and so the reference formulation is obligatorily administered twice. The test product could be administered once (partial replicate study, 3 periods) or twice (full replicate study, 4 periods). Additionally a 3-period scheme in the replicate design study is accepted in the CHMP GL on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Such study design was also described in literature (*e.g.* Haidar et al., 2008).

Line number(s) of the draft GL	Stakeholder number	Comment and rationale; proposed changes	Outcome
			It is now clearly mentioned that the reference product must be administered twice. Also, please note that the purpose of the revision was to update the CVMP GL in line with the adopted VICH GL and proposals for amendments that go beyond this scope cannot be considered at this time.
153-154	1	Comments: Both study design and statistical analysis for HDVPs should be addressed in the guideline as it is done on the CPMP guideline since 2010. A recommendation to seek scientific advice will not ensure consistent evaluation of BE 1studies from one registration dossier to another. Appropriate statistical methods are available that have been discussed in detail in many scientific papers. The only pitfall consists in a discontinuity of the type-1 error around the threshold area (30% within-subject variability). However, straightforward improvements have been proposed recently (Munoz J, Alcaide D, Ocana J. Consumer's risk in the EMA and FDA regulatory approaches for bioequivalence in highly variable drugs. Stat Med. 2016;35(12):1933–43. doi: 10.1002/sim.6834. PubMed PMID: 26707698.) Proposed change:	Not accepted. For veterinary medicinal products a maximal widening of the acceptance range for C_{max} to 70% to 143% is accepted, if it has been prospectively defined in the protocol together with a justification from efficacy and safety perspectives, as stated in section 5.15 (Evaluation) of the guideline. This is considered sufficient for VMPs. The proposal from this stakeholder is considered stricter than the current requirement. For study design see also the proposed modification above. Also, please note that the purpose of the revision was to update the CVMP GL in line with the adopted VICH GL and proposals for amendments that go beyond this scope cannot be considered at this time.

148-158	1	Comments: A new paragraph or section should be created to address narrow therapeutic index drugs Proposed change: In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11% and should include 100%. Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations. A four-way crossover, fully replicated design is recommended to compare test and reference within-subject variances and to confirm that they do not differ significantly.	Not accepted. For VMP tightening of acceptance criteria is not applied in practice. For narrow therapeutic index drugs, the 'normal' acceptance criteria for AUC and C_{max} apply and widened limits for C_{max} to a maximum of 70%-143% are not accepted. This is in accordance with the VICH GL 52 on blood level bioequivalence study. Also, please note that the purpose of the revision was to update the CVMP GL in line with the adopted VICH GL and proposals for amendments that go beyond this scope cannot be considered at this time.
162-168		Comments: To improve legibility Proposed change: *Multiple dose designs should be justified and could be considered if, for example, poor sensitivity of analytical method preclude sufficiently precise plasma concentration measurements after single dose administration or there are saturable elimination processes*.	Accepted.
170-181	1	Comments: *"Fasting should be a minimum of 8 hours prior to dosing and 4 hours after dosing*" conflicts with "*For all species prandial*	Partly accepted. Fasting conditions are recommended under certain circumstances (e.g. immediate-release

		state and exact timing of feeding should be consistent with animal welfare (e.g., ruminants would not be fasted) and the pharmacokinetics of the active substance". Proposed change: For the oral route, special attention must be paid to the different factors that may affect absorption of the active substance, such as feeding. Fasting should be a minimum of 8 hours prior to dosing and 4 hours after dosing. However, prandial state and exact timing of feeding should be consistent with animal welfare (e.g., ruminants would not be fasted) and the pharmacokinetics of the active substance. 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. For these reasons, fasting conditions are recommended in bioequivalence studies for canine and feline immediate-release oral formulations unless the SPC of the reference veterinary medicinal product recommends administration only in the fed state, in which case the bioequivalence study should be conducted accordingly. The rationale for conducting a bioequivalence study under fasting or fed conditions should be provided in the protocol. The protocol should describe the diet and feeding regimen that will be used in the study	oral formulations in dogs and cats). The recommendations on the timing for fasting are given for dogs and cats in this situation (see also modification proposed later). There is no need to use fasted animals in most of the studies and in any case the rationale for conducting a bioequivalence study under fasting or fed conditions should be provided in the protocol. Therefore, the description of fasting is preferred at the end of the section (not the rule, and also in dogs and cats). Some wording has been amended though. See comment below.
179-180	2	Comments: Specific fasting recommendations are given but it is not completely clear that this only applies to canine and feline studies.	Partly accepted. Other species are not mentioned but reference is made to the species and formulations concerned, as follows: "**For those species and formulations**

		Proposed change: Suggest the addition of a phrase such as 'Different fasting times may be more appropriate for other species and should be justified in the protocol.	**where fasting conditions are recommended**, fasting should be a minimum of 8 hours prior to dosing and 4 hours after dosing.**"**
217 – 218	2	Comments: Given the increasing move towards globally marketed products (and the near future probability of the UK being outside the EU) it does not make sense to specify that the Reference Product used in BE studies must be specifically product with a MA within the EU. Provided that an identical product (used at the same dose rate and posology) holds a MA within the EU then product from any region (where identical product is marketed) should be acceptable in order to avoid unnecessary duplication of BE studies for each separate region. Proposed change:	Not accepted. According to the Directive 2001/82/EC as amended, the reference product used in bioequivalence studies must have a MA within the EU. In other words the quality, the safety and the efficacy of the reference product must have been assessed and approved according to EU recommendations. Also, please note that the purpose of the revision was to update the CVMP GL in line with the adopted VICH GL and proposals for amendments that go beyond this scope cannot be considered at this time.
235	2	Comments: As mentioned in previous comments the difference between Reference and Test products may be > 5% despite both being within their accepted product specifications. Some flexibility should be incorporated to allow for this rather than the vague statement 'Unless otherwise justified' which leaves the applicant open to rejection by authorities whatever justification they provide.	Not accepted. The statement 'Unless otherwise justified' is kept in the text as this leaves different justification possibilities to the applicant. The situation where a batch of reference product with an assay content differing by less than 5% from the test product cannot be found is already well described in sections 5.9 and 5.15. A reference to those sections is now added. Also, please note that the purpose of the revision was to update the CVMP GL in line with the adopted VICH GL and proposals for amendments that go beyond this scope cannot

			be considered at this time.
426-400	1	Comments: Overdosing to decrease interferences with endogenous concentrations. Proposed change: Where possible, slight to moderate overdosing might be considered for the total concentrations of the compound being less dependent on the endogenous concentrations.	Accepted with additional considerations that is the margin of safety is adequate at the higher than approved dose and the pharmacokinetics is linear.