Veterinary Medical Writing

SECTION EDITOR

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Editorial

Cemile Jakupoglu of Cyton AH Biosciences GmbH and Maggie Fisher of Veterinary Research Management give the Veterinary Medical Writing section of the journal an overview of some major changes involved in the revision of the "Guideline on the conduct of bioequivalence studies for veterinary medicinal products", EMA/CVMP/016/ 2000-Rev.3, which came into effect on July 1, 2019.[1] This article is based on a more detailed article previously published.[2]

References

1. European Medicines Agency. Guideline on the conduct of bioequivalence studies for veterinary medicinal products. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-conduct-bioequivalence-studies-veterinary-medicinal-products-revision-3_en.pdf.
2. Jakupoglu C, Fisher M. Experts outline ramifications of revised European bioequivalence studies guideline. Animal Pharm (15 Aug 2019). Available at: https://animalpharm.agribusinessintelligence.informa.com/AP016126/Experts-outline-ramifications-of-revised-European-bioequivalence-studies-guideline.

Bioequivalence studies in veterinary medical writing

Bioequivalence (BE) studies are used in a variety of situations. Most often, a sponsor wishes to produce a generic version of an already approved product for which the data protection period has expired. BE studies provide pivotal data within marketing authorization applications for generic veterinary medicinal products, as they allow bridging of the safety and efficacy data associated with the reference veterinary medicinal product.

A need to update the CVMP Guideline was identified with the purpose to bring it in line with the VICH GL52 Bioequivalence: blood level bioequivalence study. Additionally, the analytical methods used in BE studies must now, according to the revised guideline, comply with standard criteria of validation as given in the Committee for Medicinal Products for Human Use guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009-Rev.1).

The definition of BE has been updated. In Revision 2, BE was defined as: "The similarity between two products that contain the same active substance(s) and shows similar rate and extent of absorption of the active substance(s). In most cases, the rate and extent of absorption are expressed as concentration (C) and area under the curve (AUC). The aim is to show that two medicinal products are similar to such degree that their systemic effects, with respect to both efficacy and safety, will be essentially the same." In Revision 3, the new definition of BE reflects the attention to metabolites and the site of action as following: "Absence of a difference (within predefined acceptance criteria) in the bioavailability of the active pharmaceutical ingredient (API) or its metabolite(s) at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study."

In the updated guideline, the randomised, two-period, two-sequence, single-dose crossover study design is still recommended as a preferred first choice, where appropriate. However, alternative study designs are mentioned and in certain situations – a parallel study design might be more appropriate.

Highly Variable Drug Products (HVDPs), now defined as those for which the intra-individual variability for a parameter for the reference product is larger than 30%, might need a replicate partial crossover study or crossover with four periods design. It is recommended scientific advice is sought before embarking on designs more complex than a simple crossover due to the nature of the animals or substances being evaluated.

The dose to be tested should normally be at the highest labelled dose approved for the reference product. This shall allow the detection of significant formulation differences more easily. Lower or higher doses must be scientifically

justified. Exceptions include where there are substances with non-linear pharmacokinetics and where the highest level is undetectable in blood (so it may be necessary to go above the highest recommended dose rate). 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 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.

The sample size (number of subjects needed) should now be based on the pharmacokinetic parameter anticipated to have the greatest magnitude of variability and/or difference in treatment means (e.g., C). To maintain statistical power, replacement of study animals during an ongoing study might be allowed. However, the removal criteria should be provided in the protocol.

Conclusion

The new guideline provides considerably more guidance on the details of crossover designs, when to choose parallel studies over crossover designs, and study animals – particularly considerations on numbers to be included and doses to be tested.

Broadly, this is likely to assist those designing studies and there remains the option to seek scientific advice if the guidance fails to address a particular circumstance. As ever, care should be taken to ensure that sufficient planning is undertaken to address the specific requirements of a particular BE evaluation so that it has maximum opportunity to demonstrate BE sufficiently, and it addresses the key recommendations made in the guideline.

Reference

3. European Medicines Agency. Guideline on the conduct of bioequivalence studies for veterinary medicinal products. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-conduct-bioequivalence-studies-veterinary-medicinal-products-revision-3_en.pdf.

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