EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Veterinary Medicinal Products (CVMP)

Concept paper for the revision of the guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4)

Agreed by Quality Working Party (QWP)	May 2024
Agreed by Efficacy Working Party (EWP-V)	June 2024
Adopted by CVMP for release for consultation	18 July 2024
Start of public consultation	26 July 2024
End of consultation (deadline for comments)	31 October 2024

The proposed guideline will replace the current "Guideline on the conduct of bioequivalence studies for veterinary medicinal products" (EMA/CVMP/016/2000-Rev.4).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu.

Keywords	pharmacokinetics, generic veterinary medicinal product, acceptance limits, biowaiver, in vitro dissolution test, bioequivalence

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1. Introduction

The CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000) was initially adopted in January 2001, with the last revision (Rev.4) carried out in July 2021 to implement administrative changes in order to align the guideline to Regulation (EU) 2019/6.

This concept paper addresses the need for a more thorough revision of the guideline also pertaining scientific content. Overall, with advancements in scientific knowledge, the need for periodic revisions of scientific guidelines is essential to ensure the guidelines remain relevant, effective, and aligned with the latest standards and best practices.

2. Problem statement

The objective of the guideline is to specify requirements for the design, conduct and evaluation of bioequivalence studies for pharmaceutical forms with systemic action. In addition, guidance is given on how, in specific cases, in vitro data may be used to allow bridging of safety and efficacy data. Overall, the recommendations included in the existing guideline are still relevant.

However, based on regulatory experience and current scientific knowledge it is considered that some sections of the guideline would benefit from the inclusion of more detail to aid applicants in preparing applications and lead to a more predictable and consistent outcome, for example: requirements for biowaivers of strengths and respective dissolution test conditions can be elaborated.

In recent years, sections and paragraphs of the guideline have been identified that leave room for interpretation which can then lead to inconsistent decisions. As a consequence, guidance has been sought repeatedly by applicants on the interpretation of those aspects. Revision of the guideline should ensure that the information needed is clearly laid down and addresses the different needs for regulators and applicants.

In addition, the need to include new sections and revise current sections of the guideline following the implementation of Regulation (EU) 2019/6 and the publication of the Guidance to applicants was identified. For example, consideration has to be given to generic drift.

Furthermore, it should be ensured that the bioequivalence guideline remains in line with other related guidance documents. It is further noted that the guideline does not make specific reference to the 3Rs principles and it is considered appropriate that this aspect is taken into account when revising the guideline.

3. Discussion (on the problem statement)

The wording of the guideline in certain sections has been open to misinterpretation which can lead to inconsistent decision making. As such, the guideline would benefit from the revision of the sections "Waivers from bioequivalence study requirements for immediate release formulations" including appendix 1, ("BCS-Based Biowaivers") "Dissolution testing" and several of the definitions. Requirements on biowaivers of strengths in particular should be clarified. Moreover, conditions on which the evaluation of the similarity factor f2 is based should be clearly presented.

Some of the wording used in the guideline is not well defined and open to interpretation. Words such as "identical", "comparable", "similar" and "very similar" are ill defined and would benefit from amendment or clarification on how they should be interpreted/what data should be provided to support compliance with the requirement. Other terms such as "immediate release", however, need to be

better defined in order to allow for consistent decisions. Moreover, some wording needs more clarification and explanation, e.g. "same pharmaceutical form" for immediate release oral formulations as the definitions have changed over time or there are different definitions used in various documents.

Regulation (EU) 2019/6 also refers to "highly similar" with regards to sourcing reference products for pre-clinical and clinical data in the context of applications under Article 19. This will be discussed.

On the other hand, there is some terminology that is not in accordance with current scientific standards, e.g. that a parent compound can be considered to be an inactive pro-drug. Thus, those sentences need a thorough revision. A revision and update of statistical methods and formulas according to current scientific standards would be beneficial. The inclusion of meaningful examples in the guideline could also aid in consistent interpretation and implementation and assist in understanding the terminology used.

Based on experience gained during past marketing authorisation procedures, reference to dissolution studies in different parts of the guideline and in different contexts can lead to misunderstandings. A clearer differentiation should be provided between:

1. dissolution testing used to demonstrate similarity of dissolution profiles e.g. for different strengths,
2. dissolution studies required to support biowaivers to show rapid in vitro dissolution characteristics of test and reference product for BCS class biowaivers,
3. solubility studies necessary to prove high solubility for BCS class biowaivers (appendix 1).

In addition, it is recommended that the section on BCS-based biowaivers is reviewed with the benefit of the experience gained in assessing claims for such biowaivers and to provide further details and examples of what is considered acceptable.

While the bioequivalence guideline was updated (Rev.4) after Regulation (EU) 2019/6 came into force, that was an administrative update and as such there are still concepts detailed that are no longer backed up by the Regulation, e.g. reference to major and minor species. These aspects should be amended accordingly.

As outlined in the Guidance to applicants, following the implementation of Regulation (EU) 2019/6, applicants can use reference products that have been authorised under Article 18 or 19. In those scenarios generic drift has to be considered, so in order to provide clear guidance to applicants on how to address the potential for generic drift, and how to proceed in such a scenario, a related section should be included in the bioequivalence guideline.

In accordance with Annex II of Regulation (EU) 2019/6, all experiments on animals should be conducted taking into account the 3Rs principles (replacement, reduction and refinement) as laid down in Directive 2010/63/EU on protection of animals used for scientific purposes, and the guideline should be updated to reflect this aspect.

Moreover, as the principles of bioequivalence studies as well as biowaivers are the same in human and veterinary medicine, some consideration should be given to differences between those guidelines, e.g. in relation to statistical parameters and if they are necessary. For example, a reference scaled approach as described in the human bioequivalence guideline may be useful for highly variable active substances or finished products in the veterinary domain as well.

4. Recommendation

The CVMP recommends the revision of the existing guideline on the conduct of bioequivalence studies for veterinary medicinal products in order to provide clearer guidance and to align the guideline with current scientific and regulatory requirements, taking into account the issues identified above.

5. Proposed timetable

July 2024	Concept paper released for public consultation
31 October 2024	Deadline for comments from interested parties
Q1/Q2 2025	Expected date for adoption of the draft revised guideline by CVMP for release for consultation
Q3/Q4 2025	Expected end of consultation on the draft revised guideline
Q2 2026	Expected date for adoption by CVMP and publication of the revised guideline

6. Resource requirements for preparation

Revision of the guideline will involve one QWP and one EWP-V rapporteur, as well as co-rapporteurs and other members from EWP-V and a subgroup from QWP tasked with revising the guideline.

Other relevant working parties may also be consulted if required.

The preparation of the draft revised guideline will require discussion at several QWP and EWP-V plenary meetings. Drafting group meetings (virtual) will be organised, as needed.

7. Impact assessment (anticipated)

The revision of the guideline is expected to improve the guidance for applicants as well as for regulatory authorities. It is not intended to increase the requirements for marketing authorisation applications for veterinary medicinal products.

8. Interested parties

- Veterinary pharmaceutical industry and consultants;
- EU regulatory authorities involved in the assessment of marketing authorisation applications for veterinary medicinal products;
- Veterinary organisations and professional bodies;
- Scientific veterinary associations.

9. References to literature, guidelines, etc.

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4)

CVMP guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)

Good Laboratory Practice (GLP) (see Directive 2004/9/EC and Directive 2004/10/EC)

133 Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement)
134 testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

135 Commission Notice – Guidance to Applicants - Veterinary Medicinal Products (C/2024/786)