



European Medicines Agency
Veterinary Medicines and Inspections

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)**

**CONCEPT PAPER ON THE REVISION OF THE GUIDELINE FOR THE
CONDUCT OF BIOEQUIVALENCE STUDIES FOR VETERINARY MEDICINAL
PRODUCTS (EMEA/CVMP/016/00)**

AGREED BY EFFICACY WORKING PARTY (EWP-V)	November 2006
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	14 December 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2007

The proposed guideline will replace guideline “*Conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00)*”.

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1. INTRODUCTION

The guideline for the conduct of bioequivalence studies for veterinary medicinal products was adopted in January 2000. Since then it has been referred to extensively, mainly in generic applications but also in bibliographic applications and for line extensions. The guideline is partly similar to its counterpart in human medicine (Note for guidance on the investigation of bioavailability and bioequivalence; CPMP/EWP/QWP/1401/98) and partly addresses specific veterinary issues. One main difference is that some aspects of pharmaceutical quality are covered by the CHMP guideline whereas the veterinary guideline covers preclinical and clinical aspects only. In 2006, the first centrally authorised generic product has been approved and the new legislation (Directive 2004/28/EC) has been implemented allowing generic products to be approved provided that the reference product is approved in at least one Member State. Moreover, article 13.2 of this directive widens the definition of generic medicinal products (most notably to salts and esters of an active substance), and article 13.3 opens the way for “hybrid applications” where comparative bioavailability data can also be used in some cases for products that are not strictly generic.

Therefore, the need for clear guidance on bioequivalence has increased and a revision of the guideline has been suggested.

2. PROBLEM STATEMENT

The current guideline was prepared in the 1990s when the experience of generic applications for veterinary medicinal products was still rather limited. Since then considerable experience has been gained and a number of new issues have been identified. On a number of occasions, questions have been put forward to CVMP Efficacy Working Party regarding the interpretation of the guideline. Thus it has become clear that a revision of the guideline is needed. Moreover, it has been noted that there are differences between this guideline and both the corresponding veterinary FDA guideline (revised in 2002) and the CHMP counterpart that are not scientifically justified.

3. DISCUSSION

Based on the questions put forward to EWP-V and the increased general experience regarding bioequivalence, a number of issues have been identified that should be addressed in the revised guideline. Furthermore, it has been noticed that some sections in the present guideline could be condensed whereas other sections need expansion.

The major issues for discussion are as follows:

- The definition of bioequivalence and the scope of the guideline need clarification. The focus should be on pharmacokinetic endpoints; however, in addition the use of pharmacodynamic endpoints and clinical issues such as palatability and compliance might be considered for inclusion;
- 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;
- Section 5.2 regarding *in vitro* bioequivalence studies and other relevant aspects related to the pharmaceutical quality of the product should be revised and expanded. Thus, the guideline should be a joint QWP/EWP document;
- Section 7 regarding study design should be revised. It should be clarified under which circumstances multiple dose studies and single dose studies, respectively, are required;

In addition there are several minor aspects that should be considered. Examples of those are listed below:

- The difference between “dose” and “strength” needs to be clarified. This is especially for dogs, where different breeds differ considerably in size, a number of strengths will be available, even if only one dose (per kg body weight) is approved for the reference;
- Section 6.1 regarding the choice of reference product should be revised in light of the new legislation;
- Section 9.1 regarding statistics should be revised to clarify that non-compartment analysis should be performed and thus C_{\max} and t_{\max} are observed parameters;
- Section 9.2 should be revised. When using multiple-dose design, bioequivalence should be evaluated in terms of AUC, C_{\max} and C_{\min} .

4. RECOMMENDATION

The CVMP recommends revising the current guideline to consider the above-mentioned issues. The Quality Working Party should be involved in the revision. In addition, the text would benefit from linguistic revision especially considering the use of the pharmacokinetic terminology.

5. PROPOSED TIMETABLE

December 2006	Concept paper adopted by CVMP for release for consultation
31 March 2007	Deadline for comments
3-4 Q 2007	First draft guideline to be discussed in EWP and QWP
2 Q 2008	Expected date for adoption by WPs
2-3 Q 2008	Draft guideline for discussion and adoption for public consultation to CVMP

6. RESOURCE REQUIREMENTS FOR PREPARATION

Member States to provide input via EWP and QWP. Rapporteurs to prepare the draft guideline.

7. IMPACT ASSESSMENT (Anticipate)

The anticipated benefit both to industry and regulatory authorities is due to clarification regarding study requirements.

8. INTERESTED PARTIES

Pharmaceutical industry.

Regulatory authorities.

Scientific associations, e.g. ECVPT (European College of Veterinary Pharmacology and Toxicology)