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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for the revision on the guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-Final)

Agreed by CVMP Efficacy Working Party (EWP-V)	2 December 2015
Adopted by CVMP for release for consultation	21 January 2016
Start of public consultation	3 February 2016
End of consultation (deadline for comments)	30 April 2016

The proposed guideline will replace the current CVMP guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-FINAL).

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

Keywords	pharmacokinetics, target animal species, veterinary

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1. Introduction

The guideline for the conduct of pharmacokinetic (PK) studies in target animal species was adopted in March 2000. Since its introduction, it has been referred to extensively in full application dossiers, but also in applications to vary existing marketing authorisations, e.g. addition of a new target species or route of administration. The guideline is similar to the human regulatory guideline, *Pharmacokinetic studies in man* (3CC3A), although veterinary-specific issues are addressed. However, the latter was adopted in 1987 and, since then, a number of more specific PK guidelines have been produced or are being developed for human medicinal products. Consequently, the guidance available for the conduct of PK studies in humans is more extensive than for veterinary species. This is partly a result of greater data requirements (e.g. recommendations to conduct PK studies in subjects with impaired renal or hepatic function if certain criteria are met), but is also due to the uptake of scientific developments in this field (e.g. population PK, physiologically-based PK modelling). As these advancements could also benefit product development for veterinary species, their incorporation into the revised guideline should be considered.

2. Problem statement

The content of the current guideline originates from 2000. Since then, there have been significant advances in the field of comparative PK. In particular, population PK studies and pharmacokinetic-pharmacodynamic (PK/PD) modelling have become increasingly common in veterinary research. Furthermore, some of these approaches have already been used in studies submitted to support the EU authorisation of products. As such, a revision of the guideline is appropriate.

In addition, the principle of the 3Rs (replacement, reduction and refinement) should be considered when revising the guideline. However, any changes in this respect must not have a detrimental effect on the quality of the data generated.

3. Discussion (on the problem statement)

With respect to developments in the field of PK, issues for discussion are as follows:

- **Population PK (PPK) studies.** The use of PPK studies is addressed only briefly in the current guideline. Since this approach has already been employed in veterinary medicines to support a change in the dosage regimen, more guidance on the reporting of PPK studies should be provided.
- **Pharmacokinetic-pharmacodynamic (PK/PD) relationship.** It is considered that general guidance on PK/PD studies (e.g. selection of appropriate pharmacodynamic parameters) and reference to specific guidelines with dedicated PK/PD sections should be provided in the revised guideline.
- ***In silico* physiologically-based PK (PBPK) models.** It is recognised that the use of PBPK models in veterinary medicine is still in its infancy. However, these models could be useful tools to investigate PK profiles under various physiological conditions, thereby informing study design and, ultimately, providing end-users with more reliable information in the product literature. It should be discussed whether PBPK falls into the scope of the current revision.

With respect to the 3Rs and animal welfare, issues for discussion are as follows:

- **Section 2.1b) Absorption: active substances not intended to produce systemic effects**. Use of *in vitro* models (if validated) to study dermal or gastrointestinal drug absorption could be considered as an alternative to *in vivo* studies. If no validated model is available, an applicant should justify that the model is suitable.

- **Section 2.3 Metabolism.** Addition of guidance on the use of *in vitro* studies (e.g. hepatic microsome studies) to investigate drug metabolic pathways.

- **Section 3.6b) Sampling: other biological fluids and tissues.** It should be considered whether tissue sampling by repeated biopsy would only be acceptable in those cases where no other techniques are possible, since in Directive 2010/63/UE it is mentioned that "*special attention should be paid to ascertain absence of pain and discomfort when using a biopsy method"*.

- **Special approaches.** PK/PD studies (see above) may potentially reduce the need for comprehensive dose-finding data and, in doing so, reduce the number of animals used in product development.

Other points for discussion are as follows:

- **Section 2.2 Distribution.** In the current guideline, it is stated that the extent of distribution will often be reflected in the volume of distribution. However, this statement should be treated with caution since estimation of volume of distribution is not intended for this purpose (Toutain and Bousquet-Melou, 2004). Therefore, revision of this section is recommended.

- **Section 3.1 Subjects.** Basic PK studies are generally performed using clinically healthy animals. However, if the PK of the drug under investigation is likely to be altered by the disease for which the product is claimed to be indicated, it could be considered conducting PK studies in diseased animals (or animal models) instead. This should facilitate selection of a more appropriate dosage regimen for subsequent dose determination studies. In addition, the effect of known pharmacogenetic differences within a population and relevant co-morbidities (e.g. renal or hepatic disease) on PK profile should be considered particularly from a safety perspective but also in terms of the risk of accelerated resistance development for products containing antimicrobial or antiparasitic agents. *In silico* PBPK modelling could be a useful tool in this respect.

- When revising the guideline, it should also be considered providing more guidance on differences in PK within the same and between different species, and if such data could apply across the whole target species (e.g. all age groups, breeds).

- **Section 3.7 Analytical procedure.** More detailed guidance regarding the validation of the analytical technique (e.g. acceptance limits) is warranted or, at least, reference to relevant guidance (e.g. VICH GLs 1 and 2) should be provided.

4. Recommendation

A revision of the existing guideline is recommended, to consider the above mentioned issues.

5. Proposed timetable

21 January 2016	Concept paper adopted by CVMP for release for consultation
30 April 2016	Deadline for comments from interested parties
3Q 2017	Expected date for adoption of the draft revised guideline by EWP

4Q 2017	Expected date for adoption of the draft revised guideline by CVMP for release for consultation

6. Resource requirements for preparation

Preparation of the revision would involve one rapporteur assisted by a co-rapporteur(s). Preparation of the draft revised guideline will require discussion at EWP plenary meetings.

Rapporteurs' drafting group meetings (virtual) would be organised, as needed.

7. Impact assessment (anticipated)

The revised guideline is not intended to increase the requirements for marketing authorisation applications. Instead, it is expected to provide clearer guidance on some of the more novel methodologies in comparative pharmacokinetics, should applicants decide to use these approaches. Furthermore, through consideration of how the principle of the 3Rs can be applied to the data requirements, the revision is expected to have a positive impact on animal welfare.

8. Interested parties

Veterinary pharmaceutical industry and consultants.

Regulatory authorities.

Scientific veterinary associations, e.g. European College of Veterinary Pharmacology and Toxicology.

9. References to literature, guidelines, etc.

Cox S.R. *et al*: Population pharmacokinetics of mavacoxib in osteoarthritic dogs, Journal of Veterinary Pharmacology and Therapeutics, Vol. 34 (2011), 1-11.

European Medicines Agency. Pharmacokinetic studies in man (3CC3A) (1998).

Toutain P.-L., Bousquet-Melou A.: Volumes of distribution, Journal of Veterinary Pharmacology and Therapeutics, Vol. 27 (2004), 441-453.