European Medicines Agency
Veterinary Medicines and Inspections

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CVMP EFFICACY WORKING PARTY

DRAFT MINUTES OF THE FOCUS GROUP MEETING ON PHARMACOKINETIC/ PHARMACODYNAMIC (PK/PD) MODELLING IN VETERINARY MEDICINES

24 September 2008, EMEA, London

WELCOME AND INTRODUCTION

David Mackay (EMEA) welcomed all the participants to the meeting and Michael Holzhauser-Alberti (EWP, chairman) asked all participants to briefly introduce themselves. The meeting was mainly attended by representatives from regulatory authorities and the pharmaceutical industry and also university/academia.

PK/PD MODELLING WITHIN REGULATORY SUBMISSIONS OF VETERINARY MEDICINES – IS IT USED? CAN IT BE USED AND IF YES, WHERE?

Karolina Törneke, CVMP member and senior expert from the Swedish Medical Products Agency, started the session with a presentation on the regulatory aspects of PK/PD (modelling). In the dossier for a veterinary marketing authorisation, PK/PD relationships could provide a valuable tool for the safety and efficacy data (i.e. part 3 and 4). However, the studies should be carefully designed and appropriate endpoints should be used.

Pierre-Louis Toutain, professor at the Ecole Nationale Vétérinaire de Toulouse, France, provided an overview on the concept of PK/PD modelling and its use in veterinary medicine development. The advantages of PK/PD modelling as compared to the "traditional" dose-titration studies in the determination of the effective dose and duration of treatment were introduced and examples for the use of PK/PD for certain drug classes were given. The main limitation of the approach was considered in the use of "surrogate" pharmacodynamic endpoints as compared to clinical endpoints. Participants were also reminded that models need to be specifically designed for the purpose and this would require specialist expertise. From the academic view, pharmaceutical companies should be encouraged to make more use of PK/PD modelling.

Erik De Ridder from Elanco Animal Health, Belgium (representing IFAH Europe) provided the views from the veterinary pharmaceutical industry on the use of PK/PD modelling. A major limitation is the restricted availability of (established) models, while the main advantages of PK/PD is its use to support applications for clinical trials, dose determination and data extrapolations e.g. for extensions. It was stressed that PK/PD modelling would provide a valuable tool in product development and should be accepted (when available), but should not be an additional requirement or systematically requested. PK/PD should not be a tool to assess the efficacy of well established products that have demonstrated efficacy under normal conditions of use and for which there are no pharmacovigilance alerts or changing resistance rates.
Also clearer guidance would be useful on the conditions under which PK/PD modelling could substitute other methods. PK/PD modelling also requires expertise in a number of scientific areas such as comparative physiology statistics, pharmacokinetics, pharmacology, toxicology, clinical models etc.

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Discussions

In the discussions following the presentations a number of questions were raised by the participants with regard to regulatory issues or the use of the model. It was stressed that the meeting was not organised in order to develop new CVMP guidelines or data requirements, but to explore the use (and potential training needs) for PK/PD modelling.

It was highlighted that PK/PD modelling is limited to certain classes / product groups and might only be used on a case-by-case basis, not as a general requirement.

A question was raised on the possibility to use PK/PD for residue assessment. It was considered that it might be a valuable tool when establishing MRLs based on a pharmacological ADI, whereas residue studies would only relate to PK.

Regulators confirmed that for some product applications, PK/PD have been used (and accepted) to replace dose titration studies or to bridge between different formulations or routes of administration. In particular, the MUMS guidelines indicate the use of bridging studies for which PK/PD data could be useful. However, it was stressed that any deviation from the usual dossier requirements should be justified on a case-by-case basis and could not be accepted as a general proposal

A number of questions were raised in relation to the model(s). The design of the studies would need to be specially adapted to the particular product, and no general recommendation could be made. The choice of the design should be justified on a case-by-case basis for the particular product application and the rational for the choice of the PK/PD model should be presented.

No clear guidance could be given on the standards under which a study should be done (GCP or GLP). Usually, preclinical studies would require GLP, but some mathematical models might be difficult to validate.

Regarding the number of doses to be used, it was felt that two dose levels would usually provide more conclusive results than a single one; however, this would also depend on the variability in studies and the particular case.

Within one species, pharmacokinetic data are usually comparably reliable; however, pharmacodynamic endpoints might show substantial differences, e.g. geographical differences in MIC values. However, in case of species bridging, it should be considered that both parameter (PK and PD) might differ between species. Also, differences in PD could depend on the type of underlying disease.

When using PK/PD for dose determination, the importance of a clear definition of suitable endpoints/parameters was stressed in order to avoid unsatisfactory results. For some classes, surrogate endpoints might not be as clear as clinical endpoints and PK/PD modelling might not be suitable. Data to validate a surrogate endpoint as replacement for a clinical endpoint would also depend on the substance. Also, some endpoints are species dependent and as an example some surrogate endpoints used in human medicines would not be suitable for veterinary medicines.

TRAINING - WHAT SORT OF TRAINING IS NEEDED? HOW IS TRAINING BEST SUPPLIED?

David Mackay, Head of the Veterinary Unit at the EMEA, explained that one of the tasks of the EMEA is to provide training within the regulatory network. This includes a wide range of disciplines and would also address different levels of expertise. However, due to limited resources within the agencies, "outside" experts (e.g. from academia) are often consulted for specialised areas.

Participants agreed that more training would be needed for both the pharmaceutical industry and regulatory agencies, however, different levels of training for different groups were highlighted:

- A very basic, "**essential awareness**" session to understand the basic principles of PK/PD modelling could be provided in 1-2 hours and could be part of a larger, general training course e.g. for new assessors.

- **Basic knowledge** of assessors at regulatory agencies or regulators at veterinary pharmaceutical companies would be required, to allow a common understanding and sufficient information to make a judgement to see if a model used in a product application is suitable.

- Scientists involved in the development of suitably designed models for PK/PD would need to have **specialist knowledge** for which intensive training would be required. Such training would be outside the facilities and scope of the EMEA's or HMA's regulatory training programme but specialists' courses might be provided by universities or academia such as ECVPT/EAVPT. Pharmaceutical companies might for example consult or employ such specialists when developing a model or method for a particular product application.

Participants agreed that joint training for assessors and pharmaceutical industry would facilitate better understanding and would be useful to allow industry and regulators to "speak the same language". It was suggested to have such training maybe in several sessions or modules including examples of benefits and limitations of PK/PD modelling in certain product groups, e.g. NSAIDs or antimicrobials.

Although existing training courses offered for example by ECVPT/EAVPT were considered useful, it was felt that more "tailor-made" training sessions for assessors and pharmaceutical industry would be required.

CONCLUSIONS / RECOMMENDATIONS

Regulators confirmed that PK/PD modelling has already been used (and accepted) for some applications for veterinary medicines; however, this method is limited to certain classes / product groups and is not a general requirement. Standard recommendation for a suitable model cannot be given and endpoints should be carefully chosen.
Currently, PK/PD modelling is not widely used by industry in veterinary medicine and more basic knowledge/training of assessors and the pharmaceutical industry is needed on this topic. However, specialist knowledge might only be necessary for experts involved in the development of a model for a particular product application. Joint training sessions for assessors and pharmaceutical industry on this topic were considered useful.

LIST OF PARTICIPANTS

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EWP: CVMP's Efficacy Working Party; SWP: CVMP's Safety Working Party