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Veterinary and Inspections Unit

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON A GUIDELINE ON THE ASSESSMENT OF PHARMACOLOGICAL/PHARMACODYNAMIC DATA TO ESTABLISH A PHARMACOLOGICAL ADI

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1. INTRODUCTION

Due to the properties of the active substances used in veterinary medicine, account must be taken not only of the toxicological properties of the substances, in the limited sense of the term (such as teratogenic, mutagenic or carcinogenic effects), but also of their pharmacological properties.

Pharmacological studies can sometimes help in the understanding of toxicological phenomena. Such studies may aid the interpretation of adverse effects arising from an exaggerated pharmacological response, whilst knowledge of absorption, distribution, biotransformation and excretion may aid the assessment of routine toxicological studies. For some substances, the NOEL/LOEL, when used as the basis for estimating the overall ADI, has to be based upon a pharmacodynamic effect if this occurred at doses lower than those required to elicit toxicity or adverse antimicrobial effects on the human gut flora.

Whilst applicants are required to provide a full set of data regarding all toxicological aspects, there are no prescribed guidelines regarding the studies necessary to establish a pharmacological ADI relating to pharmacological/pharmacodynamic effects.

2. PROBLEM STATEMENT

The draft revised Volume 8 of the Rules Governing Medicinal Products in the European Union to be published indicates: "The pharmacodynamic investigations can provide useful information on the mode of action and effects on organs and tissues. Studies should be provided that clearly identify both the primary (intended) and secondary (side effects) pharmacodynamic effects of the test substance. Such studies should clarify the dose-response relationship and identify a NOEL, where possible. For some substances (e.g. those with a history of use in human medicine) there may be human data available. These are usually the most useful data for use in identifying a pharmacological NOEL for the purpose of proposals for an ADI. In the absence of human data, laboratory studies should be performed using an appropriate animal model".

Concerning the pharmacological activity, it is not possible to propose a set of studies that will be appropriate for all the different therapeutic categories.

Different therapeutic categories have different primary and secondary pharmacological effects which, whilst desirable in a target animal are normally undesirable in consumers. For these reasons it is important to establish whether or not these potential pharmacological effects can arise at doses lower than those required to elicit toxicity.

3. DISCUSSION

It is difficult to establish where to stop when evaluating pharmacodynamic effects as there are many minor effects, such as intracellular biochemical reactions, that can be considered as pharmacological effects. Consequently, as a first step, it is important to evaluate whether or not it is necessary to establish a pharmacological ADI for the pharmacological class in question.

It will be important, for all the therapeutic classes, to establish all the potential primary and secondary adverse pharmacological effects. To assess these effects, it is probably more appropriate to carry out dose-response studies, which are normally inappropriate for evaluating variables used in toxicological studies.

Dose-response studies on pharmacological effects are normally available for the substances used in human medicine, in which case will be used to establish a pharmacological ADI.

4. RECOMMENDATION

In absence of guidelines on the studies necessary to establish a pharmacological ADI it is recommended to develop a guideline to address what data relating to pharmacological/ pharmacodynamic effects are necessary.

Because of the differences in pharmacodynamic activity of the many groups of substances used in veterinary medicine it is not possible to indicate a precise set of studies for all the different categories of active ingredients. Therefore, a two-step general approach concerning tests necessary to establish the pharmacological ADI (inspired by ICH S7A Safety pharmacology studies for human pharmaceuticals. ICH step 5. CPMP/ICH/539/00) is proposed:

Safety Pharmacology Core Battery (CB)

The purpose of the safety pharmacology core battery is to investigate the effects of the test substance on vital functions. In this regard, the cardiovascular, respiratory, and the Nervous System are usually considered the vital organ systems that should be studied in the Core Battery. The exclusion of certain organs, systems or functions should be scientifically justified.

Follow-up and Supplemental Safety Pharmacology Studies.

Adverse effects may be suspected based on the pharmacological properties or chemical class of the test substance. When such potential adverse effects raised concern for safety, these should be explored in follow-up and supplemental safety pharmacological studies, as appropriate.

5. TIMETABLE

The following timetable is foreseen for the development of the guideline further to the consideration of the comments received during the public consultation of the Concept Paper.

Preparation of the draft guideline by SWP-V	1st-2nd quarter 2006
Adoption by CVMP for release for 6 month consultation	3rd quarter 2006
Adoption of final guideline	2nd quarter 2007
Implementation	4th quarter 2007

6. RESOURCE REQUIREMENTS FOR PREPARATION

It is proposed that the SWP-V develops the guideline. A Rapporteur and Co-rapporteur will be nominated. Adequate time for discussions at the SWP-V will be required. EMEA secretariat to manage the development of the guideline and consultation process. Discussions at CVMP for final adoption.

7. IMPACT ASSESSMENT

- **Impact for Industry and other Interested Parties**

The guideline should be beneficial for industry by clarifying the studies necessary with regard to pharmacological effects on the preparation of data for MRL applications.

- **Impact assessment for Regulatory Authorities**

The guideline should be beneficial for Regulatory Authorities in finding a consistent and transparent approach on the assessment of MRL applications. It should not result in additional resource issues for Regulatory Authorities.

8. INTERESTED PARTIES

Consumers, regulators, veterinary medicines industry, learned societies (e.g. EAVPT).

9. REFERENCES TO LITERATURE, GUIDELINES ETC

ICH S7A Safety pharmacology studies for human pharmaceuticals. ICH step 5. CPMP/ICH/539/00)