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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON HIGHER TIER TESTING OF ANTIPARASITICS TO DUNG ORGANISMS

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1. INTRODUCTION

The EMEA has released the revised guideline *Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38* (EMEA/CVMP/418282/2005-Rev.1) which gives further technical support to the implementation of the VICH guidelines GL6 and GL38 on the environmental risk assessment (ERA) of veterinary medicinal products (VMPs). The guideline provides algorithms, models and default values for the determination of the predicted environmental concentration (PEC) of VMPs in the environment, and a list of recommended ecotoxicity tests to be used in order to establish predicted no effect concentration (PNEC) values for various groups of organisms, including dung organisms. However, the guideline does not include any reference on how to proceed if the initial Tier A risk assessment indicates a risk to dung flies or beetles.

2. PROBLEM STATEMENT

Recently a standardised test method to test the ecotoxicity of antiparasitic substances to dung flies has been developed within OECD (OECD guideline for the testing of chemicals. Test No. 228). A guidance document on how to test the ecotoxicity to dung beetles should be available in 2009/2010. However, in cases where risk is identified on the basis of these two tests, no guidance on Tier B testing is available. The CVMP guideline states that "…further testing should be conducted to determine the risk…" and "Regulatory guidance should be sought on appropriate studies." The fact that no guidance is given on Tier B and higher tier test strategy and that it is likely that many antiparasitic substances will need to go to Tier B, calls for further guidance on this issue.

The CVMP has identified that there is a need to develop further guidance on the design and the evaluation of studies intended to elucidate the effect of VMPs to dung organisms at Tier B level.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

In 2007 a group experts met in Aveiro (Portugal) to discuss higher-tier testing with dung organisms. Four subgroups were set up: 1) dung ecology and field testing; 2) extended laboratory tests; 3) exposure and assessment factors and 4) modelling. The issue of modelling has not been developed further since 2007, whereas the three other issues have been evaluated and described in three separate working documents not yet published. Using the information provided at the three workshops, the working documents and following a discussion of the issue by the CVMP Environmental Risk Assessment Working Party (ERAWP), the following were identified as key points, which need to be addressed to develop further guidance on how to assess the effect of VMPs on dung organisms at Tier B level.

The guidance would address the following points:

TESTING STRATEGY

- Pros and cons of field testing and extended laboratory testing;
- Evaluation of the use of assessment factors in order to establish PNEC on the basis of Tier B as well as higher tier ecotoxicity data;
- Evaluation of suitable modelling strategies and input data for predicting effects on population level;

TIER B TOOLS – DESIGN OF EXTENDED LABORATORY STUDIES

- Selection of test species (e.g. Tier A species or new species);
- Selection of endpoints (e.g. more sensitive chronic and/or life-cycle endpoints) and sensitive life stages;
- Selection and handling of the test dung (e.g. spiked dung or dung from medicated animals) ;
- Matrix characterisation of the dung (parameters to be measured);
- Establishing test conditions (e.g. temperature, moisture, duration, sterile, non-sterile);
- Test substance (e.g. labelled, non-labelled) and spiking procedure if this approach is chosen;
- Requirements for extraction and determination of the test substance, metabolites and non-extractable residues (e.g. validation of analytical methods, setting criteria for recovery);

- Data analysis (e.g. ECx or NOEC approach);
- Recommendation of suitable assessment factors in order to establish PNEC;

HIGHER TIER TOOLS – DESIGN OF FIELD STUDIES

- Selection of field test strategy (e.g. controlled study with introduced species and spiked dung or monitoring study of naturally occurring species in dung pats from field animals);
- Time of year, location, duration and sampling replication of the study;
- Selection of minimum taxonomic resolution in field monitoring study (e.g. species or family level; Only fast inhabiting species like dung flies and beetles or also slow inhabiting species like earthworms and springtails);
- Selection and handling of the test dung (e.g. spiked dung or dung from medicated animals);
- Matrix characterisation of the dung (source and quality of dung pats);
- Requirements for extraction and determination of the test substance, metabolites and non-extractable residues (e.g. validation of analytical methods, setting criteria for recovery);
- Data analysis (e.g. statistical evaluations, multi-variate approaches);
- Recommendation of suitable assessment factors in order to establish PNEC;
- Extrapolation between dung types (e.g. horse pats and cow pats);
- Extrapolation of results in one EU region to another (e.g. minimum requirements to geographic and climatic coverage);

HIGHER TIER TOOLS – ECOLOGICAL MODELLING

- Selection of model ("test") species and numeration of critical lifecycle data and annual life history of these;
- "Representative role" of species used for ecological modelling regarding ecosystem structure and function;
- Recommendation of standard scenarios for modelling (e.g. number of target animals per ha, presence of untreated animals, number of pats per animal per day, seasonal variation of dung turnover etc.);
- Establishing time window of toxicity based on laboratory data;
- Model prediction of long term population dynamics and effects.

4. RECOMMENDATION

There is a need to develop further guidance on the design and the evaluation of studies intended to elucidate the Tier B and higher tier effects of VMPs on dung dwelling organisms. It is intended to obtain views of all interested parties by the circulation of this concept paper.

Following this consultation it is the intention for the CVMP ERAWP to hold a workshop in early 2010 in order to exchange the views and experiences of researchers, industry and authorities in this area.

The objective is to prepare a CVMP guideline on the design, execution and interpretation of Higher Tier studies and models on the toxicity of VMPs in dung, which can be used in the preparation of the ERA by the applicant for a Marketing Authorisation and in the evaluation of the studies by the competent authorities.

5. PROPOSED TIMETABLE

Adoption by CVMP for release for Consultation: September 2009

End of consultation: End November 2009

Workshop (if required): February 2010

Preparation of draft guidance by ERAWP: First half 2010

Adoption by CVMP for release for consultation: End of 2010/beginning 2011

End of consultation: First quarter 2011

Discussion of comments received at ERAWP: Second quarter 2011

Adoption of revised guideline by CVMP: End of 2011

6. RESOURCE REQUIREMENTS FOR PREPARATION

The development of the guidance might require one workshop with specialists from third parties. The guidance will be prepared using the standard ERAWP meetings and virtual meetings as required. However, it is anticipated to require substantial drafting effort of working party members and/or external experts between the regularly ERAWP meetings. Experts may be invited to the ERAWP meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is foreseen that the guidance document will enable applicants to design, carry out and report on the higher tier effect studies with dung organisms based on agreed criteria. This will provide applicants with a better predictability of requirements and acceptability of their applications and will enhance harmonisation of the design and interpretation of such studies by applicants and regulators and by consequence enhance agreement between Member States with the possible benefit of fewer referrals.

8. INTERESTED PARTIES

Industry, commercial consultancies, research organisations and regulators.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- CVMP/VICH Topic GL6 (Ecotoxicity Phase I) Guideline on environmental impact assessment (EIAS) for veterinary medicinal products – Phase I, CVMP/VICH/592/98-FINAL, http://www.emea.europa.eu/pdfs/vet/vich/059298en.pdf;
- CVMP/VICH GL 38 Environmental impact assessment for veterinary medicinal products - Phase II, CVMP/VICH/790/03-FINAL, http://www.emea.europa.eu/pdfs/vet/vich/079003en.pdf;
- CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38, EMEA/CVMP/ERA/418282/2005-Rev.1, http://www.emea.europa.eu/pdfs/vet/era/41828205enfin.pdf;
- OECD Guidelines for the Testing of Chemicals. Test No. 228. Determination of Developmental Toxicity of a Test Chemical to Dipteran Dung Flies *(Scathophaga stercoraria* L. (Scathophagidae), *Musca autumnalis* De Geer (Muscidae)). OECD guidelines for the testing of chemicals no. 228. Adopted 3rd. of October 2008. http://titania.sourceoecd.org/vl=3062954/cl=52/nw=1/rpsv/cgi-bin/fulltextew.pl?prpsv=/ij/oecdjournals/1607310x/v1n2/s28/p1.idx.