



**FOCUS GROUP ON IMPLEMENTATION OF CVMP GUIDELINE ON
ENVIRONMENTAL IMPACT ASSESSMENT FOR VETERINARY MEDICINAL
PRODUCTS IN SUPPORT OF THE VICH GUIDELINES GL6 (PHASE I) AND GL38
(PHASE II)**

Summary of the meeting held on 23 January 2008

WELCOME AND INTRODUCTION TO THE GUIDELINE

Kornelia Grein (EMA) welcomed all the participants to the meeting and asked all to introduce themselves. The meeting was attended by experts on Environmental Risk Assessment from regulatory authorities (most of them from the CVMP Environmental Risk Assessment Working Party (ERAWP)), pharmaceutical industry (IFAH-Europe and EGGVP) and the Association of Veterinary Consultants (AVC).

The objective of the meeting was to provide further clarification on the CVMP Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 (Phase I) and GL38 (Phase II), (EMEA/CVMP/ERA/418282/2005-Corr; often called the "Technical Guidance Document" (TGD)). The guideline came into effect in November 2007.

Joop A. de Knecht, Chair of the ERAWP, and the members and experts of the ERAWP (see list of attendance) answered the questions posed during the discussions. Some questions were provided in writing by IFAH-Europe, allowing the ERAWP to prepare some preliminary considerations.

GENERAL POINTS

- Studies not according to the OECD guidelines and use of publicly available data
In cases of well performed studies (according to GLP guidance in some cases) but not in compliance with OECD guidance (old studies in most cases) and literature data in peer reviewed journals it was indicated that if the quality of the data is good those studies could provide relevant information, especially if the end-points are valid. These should concern only a limited number of studies in a dossier. Summaries of assessments such as EPAR, US FONSI are not sufficiently detailed to substitute studies in the Environmental Risk Assessment (ERA).
- It was confirmed that horses are minor species.
- Flow chart
Having acknowledged that the TGD guideline follows the sequence of the VICH guideline, it was proposed that in addition one or more flow charts could be provided to make it easier to follow the TGD. It was agreed that IFAH-Europe would prepare a draft flow chart for further discussion by the ERAWP/CVMP.
- Examples
It was requested to provide examples (in an Excel format), of how to apply the formulas from the TGD. Members of the ERAWP indicated that, although in principle it would be feasible to provide some examples, in many cases examples can be counter productive as they are taken as the rule. In addition it was noted that preparation of examples can be very demanding and time consuming.

SPECIFIC QUESTIONS

- Question 4 of VICH GL 6: Minor uses/minor species (MUMS)
Clarification on ERA requirements for MUMS was requested. It was clarified that VICH guidelines provide the criteria for the cases for which there is no need to perform an ERA for minor species, i.e. those in which the animals are reared and treated similarly to a major species (no increase of exposure for the environment when compared with use in major species). It was pointed out that Phase II assessments have been required for products used on rabbits. In this case no ERA was available for a similar major species product. The statement in the TGD that MUMS EIA are usually limited to Phase I does not exclude the possibility that Phase II assessments might be required for minor species.
- Question 17 of VICH GL 6: “Is the predicted environmental concentration of the VMP in soil (PEC_{soil}) less than 100 $\mu\text{g}/\text{kg}$?”
“Mixing of manure” of different species for calculations: ERAWP experts indicated that manure from different species or different production stages of the same species should not be mixed for the calculations of PEC_{soil} values.
Deviations from default values in the TGD: can be used if justified by the SPC; but members of the ERAWP indicated a strong preference for the standardised approach.
 PEC_{soil} for rabbits: it was clarified that CORPEN¹ data could be used in preparation of the default values for use in calculating the PEC_{soil} for rabbits.
- Question 19 of VICH GL 6 “Is the recalculated PEC_{soil} less than 100 $\mu\text{g}/\text{kg}$?”
The TGD indicates in Question 19. “*Is the recalculated PEC_{soil} less than 100 $\mu\text{g}/\text{kg}$? The only possible ways for excluding a product from Phase II are given in question 6 and question 18.*” The ERAWP members clarified that as indicated in the guideline, in a decision tree the questions are dealt with in a specific logical order, and that in this case the reference to question 6 and 18 refers exclusively to ways of reducing the PEC_{soil} .
- K_{oc} values
Clarification was requested on whether or not the mean, minimum or maximum K_{oc} value should be used. Members of the ERAWP clarified that the lowest K_{oc} value from 3 soils should be used especially in cases where soil conditions other than organic carbon content will influence the adsorption (e.g. effect of pH on the adsorption of ionisable substances). However, if K_{oc} values have been determined in a broader range of soils (i.e. in more than 3 soils), then the use of a mean value may be considered.
- Sum of PECs in case of combination products:
A request was made for not having to sum the different PECs of the different active principles. It was agreed that justifications like different mode of action or metabolism could be considered on a case-by-case basis.
- OECD GL222 study (subacute toxicity)
A question was raised on the need to perform an OECD GL222 study (sub-acute toxicity) in earthworms rather than OECD GL207 (acute toxicity). Members of the ERAWP confirmed that such a sub-acute study is required. However, when low toxicity is anticipated a “limit test” of the OECD 222 could be done, i.e. conducting a reproduction study with a control and one (high) exposure concentration, typically 1000 mg/kg. *Note post meeting:* to increase the validity of the “NOEC value” derived in such a limit test, the ERAWP recommends using six replicates in both exposure groups instead of the normal four replicates.
- Dilution factor for calculation of the $PEC_{surfacewater}$ from the $PEC_{pore\ water}$

¹ Management Committee for Reducing Water Pollution by Nitrates, phosphates and plant protection products derived from agricultural activities

A question was raised on why the dilution factor for calculation of the $PEC_{\text{surfacewater}}$ from the $PEC_{\text{pore water}}$ was changed from 10 to 3 in the TGD: members of the ERAWP confirmed that the dilution factor between porewater and surface water was 3 and had been changed based on calculations performed with FOCUS together with experimental data. Using a factor of 10 meant that supposed refining of the $PEC_{\text{surfacewater}}$ using FOCUS models resulted in PEC values higher than those calculated using a 10 fold dilution. This situation was not acceptable a factor of 3 was more in line with FOCUS and experimental data. In addition, this factor was also recommended in the previous EMEA/CVMP Note for guidance.

- PEC_{soil} when calculating $PEC_{\text{groundwater}}$

When calculating $PEC_{\text{groundwater}}$ the PEC_{soil} based on a 20-cm depth penetration into soil is used. This is based on the fact that when VMPs are ploughed into soil they might reach groundwater faster and is therefore considered a realistic worst case.

- FOCUS

FOCUS vs VetCalc: although the TGD recommends FOCUS in favour of VetCalc, some companies are still providing results from VetCalc, especially because its use seems easier than FOCUS. In some cases results might be different according to the software applied. The maintenance and update of VetCalc was not part of the original project remit and any updates are unlikely. Members of the ERAWP confirmed that, although VetCalc is mentioned in the TGD guideline, FOCUS is the preferred option.

Manure degradation and FOCUS: manure degradation cannot be incorporated into FOCUS, but refinements can be done manually.

Application of FOCUS in different scenarios: FOCUS might produce different results in different scenarios. It was agreed that in those cases a case by case approach would have to be taken. In the TGD a proposal is given on which scenarios can be used in a centralised and de-centralised procedure

FOCUS standard parameters: members of the industry indicated that the FOCUS surface water scenarios are highly unrealistic with the standard parameters. It was noted that the limited field data available (i.e. Boxall et al., 2006) do indicate that the FOCUS surface water scenarios are not unrealistic.

- Equations would be checked regarding consistency of the legends, corrections made to equations² 15, 16, 35, 36, 44 and 45 (PECs and PNECs for sediment) and equations would be numbered to facilitate referencing of equations.
- Additional guidance is given concerning the use of the metamodel for groundwater.

CONCLUSION

The meeting agreed that it would be desirable to update the TGD to include the changes discussed. These are mainly refinements and clarifications as well as some corrections. These amendments would not change any approach of the ERA requiring consultation, but are of more editorial nature.

Minutes of the meeting would be published along side the comments on the TGD to help implementation of the TGD GL.

It was furthermore agreed to include the outcome of the discussion in a Question and Answer document that could be updated to include further questions and clarifications that may arise in the future.

Overall it was considered that the effort to have a joint meeting was useful to experts in preparing effective ERAs. The meeting was helpful to evaluators in understanding dossier boundaries and to identify points for future attention.

² Using the numbering system of the updated guideline

It was considered it would be worth to repeat the meeting following progressing experience with the TGD.

Participants

ERA WP & experts: Joop de Knecht (NL); John Jensen (DK); Virpi Virtanen (FI); Jan Koschorreck (DE); Silke Hickmann (DE); Carina Carlsson (SE); Alex Tait (UK); Boris Kolar (SL);

IFAH Europe: Christian Corsing (Bayer); Chris Van den Eede (Alpharma); Leo Van Leemput (Janssen); Gregor Scheef (Intervet); Catherine Lunny (Pfizer); Jennifer Mackie (Pfizer); Rick Clayton (IFAH-Europe)

EGGVP: Mike Boeren; Peter Verhoeve; Maria Meinerling

AVC: Pascal Richez

EMA: Kornelia Grein; Jordi Torren Edo

AMENDMENTS TO THE CVMP TGD FOLLOWING THE RECOMMENDATIONS FROM THE FOCUS GROUP MEETING

Editorial changes have been introduced in the guideline to take into account some of the modifications proposed during the meeting.

Detailed changes:

- Equations have been numbered to facilitate reference.
- CORPEN data for rabbits have been added to the guideline.
- In some equations the legends have been clarified.
- Corrections have been made to equations² 15, 16, 35, 36, 44 and 45. The equations for PEC and PNEC sediment have been corrected.
- Under point 5.2.3 *Calculation and comparison of the PEC_{water}* , some clarification has been provided on the soil depth used for the calculation of the $PEC_{groundwater}$.
- Further clarification has been provided under Table 10 “Requirements for the K_{OM} following from Equation 39 as a function of the FOCUS”.
- References to the Dung Organism Toxicity Testing Standardisation (DOTTS) have been updated.
- Clarification has been provided on normalisation.