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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Comments to FDA Docket No. 2004D-0156 International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products; Draft Guidance for Industry on Environmental Impact Assessments for Veterinary Medicinal Products – Phase II

The ANIMAL HEALTH INSTITUTE (AHI) provides these comments on CVM draft guidance document #166 (VICH GL38) which provides recommendations for internationally harmonized test methods used to generate environmental fate and toxicity data. AHI is a national trade association representing manufacturers of animal health products – pharmaceuticals, vaccines and feed additives used in modern food production and the medicines that keep pets healthy.

AHI acknowledges the efforts of all parties involved in developing the VICH Phase II guidance document (GL 38). The document is a significant improvement over previous versions of this guidance. It offers more transparency than earlier drafts and it appears to be a workable document from the perspective of the US animal health industry. AHI and the Canadian equivalent of AHI or CAHI recommend that the document be moved forward for ultimate implementation; however, there remain a number of important areas where a re-think and possible re-negotiation are warranted. These key areas of concern are listed below.

Metabolism Data:

1. The 5% criterion was too stringent and it is helpful to have it at 10%. AHI is most appreciative of this change and it demonstrates a willingness of the working group members to re-evaluate proposed positions on key issues where there is disagreement. In the existing Phase II (CVMP Note for Guidance), 20% is used as the criterion for defining what constitutes an ecotoxicologically relevant metabolite. Has a risk assessment ever changed because a metabolite was between 10 and 20%? In light of the experience obtained since implementation of the Note for Guidance, is it appropriate to drop this value to 10%? Unless there is specific evidence to the contrary, there is no reason to tighten cut-off and triggering criteria (same holds for values of safety factors). Surely, much has been learned about the safety of veterinary drugs since implementation

of the first Phase II in 1997. VICH guidance needs to reflect this learning to ensure limited resources are focused on areas of real concern.

2. The Phase II guidance still takes the approach that results of ADME studies are to be ignored in the calculation of worst-case PEC estimates in the first step prior to PEC refinement. It is accepted that a core effects dataset is needed once a VMP enters Phase II, but to ignore the results of ADME studies (i.e., excretion data) is unreasonable. This is equivalent to an assumption that the drug never passes through the target species and in effect is distributed directly into the soil. In principle, this is not consistent with a reasoned scientific approach.

Soil Biodegradation:

1. The guidance document does not specify how data from soil biodegradation studies are to be used in the PEC refinement stage. Presumably, this will be addressed during development of a regional Technical Guidance Document or TGD. It is important that industry play a key role in development of a scientifically valid approach to this issue. Considering the entire Tier A data package, the soil biodegradation study is the most resource intensive and at times, the most open to misinterpretation of the data obtained. One point of emphasis should again be that the DT₅₀ should not be based only on mineralization data. AHI is willing to contribute to the development and review of the TGD.
2. The following issue was expressed about the previous version of Phase II and it deserves to be re-iterated here. If sponsors have data that document rapid degradation of the VMP (including loss of bioactivity associated with incurred residues) in manures from the target species, then this information should be used in the EIA. It makes sense to use these data prior to conducting the studies in the Tier A dataset. After all, if data exists documenting that the VMP rapidly degrades in manure, why would there be a need for effects tests in the first place?

Assessment Factors:

1. The rationale for increasing the Assessment Factors (AFs) from levels of 100 to 1000 remains unjustified. Here too, the concern expressed regarding the previous version of this document still applies. The AFs in the current version of the VICH Phase II guidance are higher than the AFs in the CVMP Note for Guidance. This implies that we have less information today on the effects of VMPs on non-target species in the environment that what we did when the CVMP version of Phase II was implemented. This is clearly not the case and the previous AFs should be used or a scientifically valid rationale should be offered.

Dung Fauna:

1. AHI continues to point out that the use of the 100 micrograms/kg in soil should be the criterion for conducting testing of ecto- and endoparasiticides (ecto/endos) with all species in Phase II Tier A. The original decision to advance ecto/endos to Phase II to assess specific areas of concern, e.g., dung fauna, was made because there was not enough data to decide whether the PEC_{soil} was indicative of insecticidal effects. But, there were sufficient data in the EIAs submitted to FDA/CVM to demonstrate that ecto/endos with soil PECs of <100 micrograms/kg had no concerns for other terrestrial or aquatic species. That was why the Phase I Guideline does not indicate that these compounds need to proceed to Phase II for testing of all areas, but only areas of concerns, e.g., dung fauna. The data from ecotoxicity tests using ecto/endos were used, in part, to support the use of the soil PEC trigger limit of 100 micrograms/kg in Phase II. Full Tier A testing is now required for aquatic, terrestrial and dung fauna regardless of the PEC. How can this be defended scientifically based on the data already submitted on these compounds in previous EIAs? Ecto/endos should only be subjected to all Tier A tests in Phase II only if the PEC_{soil} is greater than 100 micrograms/kg.

PEC:

1. AHI supports that harmonization of PEC in Phase II under VICH is not possible. As noted above, AHI is keenly interested in contributing to the development of PEC calculation algorithms on a regional level (e.g., in the development of the TGD). Industry should be involved in particular in how biodegradation data are used to refine worst-case PEC estimates. As noted above, AHI continues to assert that mineralization should not be used to define the DT_{50} , but that there should be an opportunity to define the degradation half-life based on parent compound disappearance. The TGD should take this into account.

AHI appreciates the opportunity to provide these comments for consideration by the Center for Veterinary Medicine.

Sincerely,



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