

Guidance for Industry

ENVIRONMENTAL IMPACT ASSESSMENTS (EIA'S) FOR VETERINARY MEDICINAL PRODUCTS (VMP'S)- PHASE I

VICH GL6

Final Guidance

This final guidance is intended to harmonized methods used in conducting environmental assessments for veterinary medicinal products in the European Union, Japan, and the United States.

Comments and suggestions regarding the final document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Comments should be identified with the full title of the guidance document and the Docket No. 99D-2975.

For questions regarding this guidance document, contact Charles E. Eirkson, Center for Veterinary Medicine, (HFV-145), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-6958, E-mail: ceirkson@cvm.fda.gov.

**U.S. Department of Health and Human Services
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Center for Veterinary Medicine
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ENVIRONMENTAL IMPACT ASSESSMENTS (EIA'S) FOR VETERINARY MEDICINAL PRODUCTS (VMP'S) - PHASE I

Recommended for Implementation
at Step 7 of the VICH Process
on 15 June 2000
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND WAS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT IS RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN, AND USA.

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This guidance represents FDA's current thinking on this matter and does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternate method may be used as long as it satisfies the requirements of the applicable statutes and regulations.

Introduction

In 1996, the VICH Steering Committee (VICH SC) authorized formation of a working group to develop harmonized guidance for conducting environmental impact assessments (EIA's) for veterinary medicinal products (VMP's) in the European Union (EU), Japan (JP) and the United States (US). The mandate of the VICH Ecotoxicity/Environmental Impact Assessment Working Group (VICH Ecotox WG),¹ as set forth by the VICH SC, is as follows:

"To elaborate tripartite guidelines on the design of studies and the evaluation of the environmental impact assessment of veterinary medicinal products. It is suggested to follow a tiered approach based on the principle of risk analysis. Categories of products to be covered by the different tiers of the guideline should be specified. Existing or draft guidelines in the EU, Japan, and the US should be taken into account."

This document presents guidance on how to conduct Phase I EIA's for VMP's other than biological products. Consistent with the mandate, two phases of EIA are recommended. In Phase I, the potential for environmental exposure is assessed based on the intended use of the VMP. It is assumed that VMP's with limited use and limited environmental exposure will have limited environmental effects and thus stop in Phase I.² Phase I also identifies VMP's that may need a more extensive EIA under Phase II.³ Some VMP's that might otherwise stop in Phase I may need additional environmental information to address particular concerns associated with their activity and use.⁴ These situations are expected to be the exception rather than the rule and some evidence in support of the concern should be available.

¹ Current working group members include Ms. Carol Aldridge (European Medicines Evaluation Agency), Dr. Yuuko Endoh (Japanese Ministry of Agriculture, Forestry and Fisheries), Mr. Shuhei Ishihara (Japanese Veterinary Pharmaceutical Association), Dr. Charles Eirkson (US/Food and Drug Administration/Center for Veterinary Medicine), Dr. Joseph Robinson (Animal Health Institute) and Dr. Leo Van Leemput (European Federation of Animal Health).

² In the US, reference to a Phase I EIA is equivalent to either a categorical exclusion or an environmental assessment (EA) conducted under the National Environmental Policy Act (NEPA). A VMP that may stop at Phase I is equivalent to a categorical exclusion or an EA which leads to a finding of no significant impact (FONSI) under NEPA.

³ Phase II represents a second level of environmental analysis that may include testing. In the US, a Phase II EIA is equivalent to an EA with more extensive data than would be required under the US equivalent of a Phase I EIA. A Phase II EIA may lead to a FONSI or an Environmental Impact Statement under NEPA.

⁴ In the US, this is equivalent to an extraordinary circumstance under NEPA.

In an effort to harmonize the EIA to the maximum extent possible, it is expected that the EU, US, and JP will rely on this document for guidance on conducting Phase I EIA's for VMP's.

Phase I Guidance

The Phase I EIA for a VMP makes use of the decision tree in Figure 1. To use the Phase I decision tree, the applicant⁵ works through the questions until they arrive at a question which allows them to conclude that their product qualifies for a Phase I report. If there is no information on a particular question, the question is ignored and the applicant continues to the next question. If while working through the decision tree, an applicant determines that their VMP did not need an EIA, Question 1 still applies. When an applicant determines that at least one of the Phase I criteria has been met, the applicant should produce a Phase I EIA report discussing the basis for the decision. If the assessment determines that the VMP has limited exposure for more than one reason, each reason may be discussed to strengthen the Phase I EIA report. However, as suggested by the Phase I decision tree, the types of Phase II studies needed will vary based upon the concerns identified in Phase I. In situations where clarification is needed, it is important that the applicant contact the appropriate regulatory authorities.

Question 1: Is the VMP exempt from the need for an EIA by legislation and/or regulation?⁶

This Phase I question takes into account the different statutory and regulatory requirements among the EU, JP, and US. If the answer to Question 1 is yes, the applicant does not need to continue through the Phase I decision tree but should comply with the region's rules regarding submission of required documentation.

Question 2: Is the VMP a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment?⁷

It is assumed that many natural substances are already present in the environment or are rapidly degraded upon entry into the environment, such that environmental exposure is not altered. VMP's likely to stop at this question include electrolytes, peptides, proteins, vitamins, and other compounds that occur naturally in the environment. In answering this question, the applicant documents and should give a reasoned case that use of the VMP will not alter the concentration or distribution of the substance in the environment.

Question 3: Will the VMP be used only in non-food animals?⁷

⁵ In the US, the term "applicant" refers to the drug sponsor.

⁶ In the US, this includes products that are categorically excluded under NEPA. If a product is not categorically excluded due to an extraordinary circumstance, however, the answer to this question is no – the VMP is not exempt from the need for an EIA.

⁷ In the US, these VMPs are usually categorically excluded under NEPA. (21 CFR 25.33(c), 25.33(d)(1), 25.33(d)(2), 25.33(d)(3), 25.33(d)(4), 25.33(d)(5)).

Generally, non-food animals are not intensively reared. Also, products used in these animals are usually individual treatments. Approval of VMP's for use in non-food animals is likely to be associated with fewer environmental concerns than approval of VMP's in food-producing animals simply because there is less total amount of product used. The definition of non-food animals varies among the three regions.

Question 4: Is the VMP intended for use in a minor species that is reared and treated similarly to a major species for which an EIA already exists?⁷

VMP's intended for use in a minor species may stop in Phase I provided the VMP is already approved for use in a major species, the minor species is reared under similar conditions as the major species, the VMP is administered by the same route and the total dose administered to the minor species is no greater than that used in the major species. In this case, it is assumed that use in the minor species will have limited environmental impact. There are differences regarding what constitutes major versus minor species among the EU, JP, and US.

Question 5: Will the VMP be used to treat a small number of animals in a flock or herd?⁷

This question may exempt VMP's from the need for a further assessment when the product is used to treat an individual or a few animals in a flock or herd. It is assumed that the approval of VMP's captured under this question will produce environmental exposures well below concentrations that impact the environment. Products used to treat clinically mastitic cows, anesthetics used for surgical purposes, ophthalmics, and hormones used as reproductive aids for individual animals may fall within the scope of this question.

Question 6: Is the VMP extensively metabolized in the treated animal?⁸

It is assumed that VMP's that are extensively metabolized in the treated animal do not enter the environment. Demonstration of extensive metabolism may be accomplished through a radiolabeled residue depletion and excretion study. A VMP may be defined as "extensively metabolized" when analysis of excreta shows that it is converted into metabolites which have lost structural resemblance with the parent drug, are common to basic biochemical pathways or when no single metabolite or the parent drug exceeds 5% of the total radioactivity excreted.

Question 7: Is the VMP used to treat species reared in the aquatic or in the terrestrial environment?

The answer to this question defines the initial route by which the VMP enters the environment. For VMP's intended for treatment of species reared in the aquatic environment, proceed to Questions 8-13. For VMP's intended for treatment of species reared in the terrestrial environment, proceed to Questions 14-19.

⁸ In the US, information provided to respond to this question must be provided in an EA that includes documentation and mitigations, as appropriate, to support a FONSI. (21 CFR 25.40)

Aquatic Branch

Question 8: Is entry into the aquatic environment prevented by disposal of the aquatic waste matrix? ⁸

Some VMP's used in aquaculture do not enter the environment because the treatment waste is disposed of by incineration or by other means which similarly preclude entry of the VMP to the environment. These VMP's have no opportunity to impact the environment. Applicants answering yes to this question should provide documentation to demonstrate that the VMP does not enter the environment. Incineration of the waste matrix, containing the VMP, is an example of a means of disposal that may permit stopping in Phase I, if the documentation described above can be provided.

Question 9: Are aquatic species reared in a confined facility? ⁸

A confined facility is defined as one in which the effluent can be treated and the discharge controlled. This includes facilities such as tanks, lined ponds, and some raceways. VMP's introduced directly into the aquatic environment have a greater potential to contaminate aquatic habitats. This is because the aquaculture facility is contiguous with the aquatic environment, and there is no opportunity for processing or treatment of effluents. Therefore, any VMP used to treat aquatic species, where the product is placed directly into the environment, e.g., net pens, should not stop in Phase I.

Question 10: Is the VMP an ecto- and/or endoparasiticide?

The ecotoxicity database used to develop the quantitative value used in Question 11 included all classes of pharmaceuticals used in human medicine (Reference 1). Very few parasiticides are used in human therapy thus the human database is insufficient to establish a quantitative trigger value for these compounds. The ecotoxicological potential of this class of compounds should be assessed by conducting aquatic effects tests in Phase II.

Question 11: Is the environmental introduction concentration (EIC_{aquatic}) of the VMP released from aquaculture facilities less than 1 $\mu\text{g/L}$? ⁸

The rationale for selecting 1 $\mu\text{g/L}$ as the EIC_{aquatic} is provided (Reference 1). This value is below the level shown to have adverse effects in aquatic ecotoxicity studies with human drugs. The EIC_{aquatic} applies only to VMP's that will be used to treat fish and other aquatic species in confinement where the effluent can be treated and controlled prior to being discharged into the environment. In order to apply this value, it is necessary to estimate the concentration of VMP expected in the effluent from the aquaculture facility. For calculating the EIC_{aquatic} a total residue concept is adopted. This involves summing the parent drug and all related metabolites excreted by the target species and entering the aquatic environment, as well as accounting for VMP in the uneaten feed and VMP released to water. This assumes that 100% of the dose is excreted unless there are data to support a value less than 100%. The EIC_{aquatic} calculation may account for current management and engineering practices provided appropriate documentation is supplied by the applicant. The calculated value is compared against the 1 $\mu\text{g/L}$ value. If the calculated EIC_{aquatic} value for the VMP entering the environment is less than 1 $\mu\text{g/L}$, then the VMP may stop at Phase I.

Question 12: Do data or mitigations exist that alter the EIC_{aquatic} ? ⁸

The concentration of the VMP in the effluent may be decreased by filtration, settlement, dilution, or other mitigations. Other mitigations (both natural degradation and management practices) may reduce the concentration of the VMP in water and hence reduce environmental exposure. As a

specific example, the EIC_{aquatic} for an aquaculture facility may be reduced if additional volumes of water are used during treatment. In addition, UV/ozone treatments may be used to reduce the EIC_{aquatic} if the VMP is known to be labile to these treatments. When the applicant demonstrates a mitigation exists, it can be considered in the calculation of the EIC_{aquatic} .

Question 13: Is recalculated EIC_{aquatic} less than 1 $\mu\text{g/L}$?⁸

This recalculated value is then compared against the 1 $\mu\text{g/L}$ value. If the recalculated EIC_{aquatic} value for the VMP entering the environment is less than 1 $\mu\text{g/L}$, then the VMP may stop at Phase I.

Terrestrial Branch

Question 14: Is entry to the terrestrial environment prevented through disposal of the terrestrial waste matrix?⁸

Some VMPs used in intensive livestock production do not enter the environment because the treatment waste is disposed of by incineration or by other means which similarly preclude entry of the VMP to the environment. These VMP's have no opportunity to impact the environment. Applicants answering yes to this question should provide documentation to demonstrate that the VMP does not enter the environment. Incineration of the waste matrix, containing the VMP, is an example of a means of disposal that may permit stopping in Phase I, if the documentation described above can be provided.

Question 15: Are animals reared on pasture?

For intensively-reared animals that are housed or raised in feedlots, excreta is collected in the form of manure and slurries, stored, and then spread onto agricultural land, with or without ploughing. For these VMP's, advance directly to Question 17. This is in contrast to animals raised on pasture, where excretion is directly into the environment. For these VMPs advance directly to Question 16. For animals reared on pasture, there are specific concerns for certain types of products related to their direct entry into the environment. For some products both Question 16 and Question 17 will be applicable.

Question 16: Is the VMP an ecto- and/or endoparasiticide?

Ecto- and endoparasiticides have specific ecotoxicity concerns especially when used in animals reared on pasture. These VMP's are pharmacologically active against organisms that are biologically related to pasture invertebrates. Because protozoa are not biologically related to pasture invertebrates, products used to treat protozoa are not captured in this question. VMPs that are ecto- and/or endoparasiticides used in pasture should advance directly to Phase II to address specific areas of concern, e.g., dung fauna. Other VMPs used in pasture animals should advance to Question 17.

Question 17: Is the predicted environmental concentration of the VMP in soil (PEC_{soil}) less than 100 $\mu\text{g/Kg}$?⁸

The rationale for selecting the PEC_{soil} value of 100 $\mu\text{g/Kg}$ is provided (Reference 2). This value is below the level shown to have effects in ecotoxicity studies conducted on earthworms, microbes, and plants, with VMPs currently registered in the US.

In order to apply this value, it is necessary to estimate the concentration of the VMP in terrestrial ecosystems. An example on how to calculate the PEC_{soil} for VMP is provided (Reference 3). Other approaches for calculating PEC_{soil} should be used if they are more relevant for a particular region. For calculating PEC_{soil} , a total residue concept is adopted. This involves summing the parent drug with all related metabolites excreted by the treated animal. This assumes that 100% of the dose is excreted unless residue depletion data support a value less than 100%. The total residue approach is considered to be conservative in assessing effects in that it combines parent plus metabolites in calculating environmental concentrations, and metabolites generally have less biological activity than the parent compound. Results from degradation studies in manure and soils may be used to refine the estimate of the concentration of the VMP in soil (Reference 3). The calculated PEC_{soil} is compared against the value of 100 $\mu\text{g}/\text{Kg}$. If the PEC_{soil} for the VMP is less than the value, then the EIA for the VMP may stop in Phase I.

Some products used in intensively-reared livestock may also be used in pasture animals. In such cases, the PEC_{soil} calculations may differ. However, even in the pasture setting there is some migration of the VMP into soil. The PEC_{soil} estimate for a VMP excreted onto pasture assumes direct entry into soil with even distribution in the upper 5 cm of soil. This estimate for whole herd/flock treatments is based upon: (1) dose/animal based on mg/kg and body-weight of animal; (2) percentage of dose excreted by the treated animals (use 100% if no excretion data are available); (3) stocking density of treated animals (animals/hectare); (4) excreted VMP is distributed in soil to 5 cm; and (5) bulk density of soil. Effectively, this means that for a soil bulk density of 1,500 kg/m^3 , the total dose/hectare is distributed in 750,000 Kg of soil.

Question 18: Do any mitigations exist that alter the PEC_{soil} ?⁸

The concentration of the VMP in soil may be decreased by standard animal husbandry practices, manure management, or other mitigations. Other mitigations (both natural and management practices) may reduce the concentration of the VMP in soil and hence reduce the environmental exposure. As a specific example, the PEC_{soil} may be reduced if there are legal requirements for a minimum storage period for manure and there are data to show that degradation during storage occurs. When the applicant demonstrates a mitigation exists, it can be considered in the calculation of the PEC_{soil} .

Question 19: Is the recalculated PEC_{soil} less than 100 $\mu\text{g}/\text{Kg}$?⁸

The recalculated value is then compared against the 100 $\mu\text{g}/\text{Kg}$ value. If the recalculated PEC_{soil} value for the VMP entering the environment is less than 100 $\mu\text{g}/\text{Kg}$, then the VMP may stop at Phase I.

(OMB Approval No. 0910-0332)

REFERENCES

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2. AHI Environmental Risk Assessment Working Group, 1997, Analysis Of Data And Information To Support A PEC_{soil} Trigger Value For Phase I (A retrospective review of ecotoxicity data from environmental assessments submitted to FDA/CVM to support the approval of veterinary drug products in the United States from 1973-1997).
3. Spaepen, K. R. I., L. J. J. Van Leemput, P. G. Wislocki and C. Verschueren, 1997. A uniform procedure to estimate the predicted environmental concentration of the residues of veterinary medicines in soil. *Environmental Toxicology and Chemistry* 16: 1977-1982.

Figure 1. Phase I Decision Tree

