8 March 2012
EMA/CVMP/ERAWP/409328/2010
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products

Draft Agreed by Environmental Risk Assessment Working Party	19 January 2011
Adoption by CVMP	5 May 2011
End of consultation (deadline for comments)	31 August 2011
Agreed by ERAWP	3 November 2011
Adoption by CVMP	8 March 2012

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1. Introduction

Directive 2001/82/EC as amended by Directive 2004/28/EC requires the applicant "to provide tests assessing the potential risks posed by the medicinal product for the environment. This impact shall be studied and consideration shall be given on a case-by-case basis to specific provisions seeking to limit it". The decision to authorise a veterinary medicinal product is based on there being a positive outcome to the benefit-risk assessment. Determination of the benefit:risk balance includes consideration of any risk to the environment. If the benefit-risk assessment concludes that the risk, including risks to the environment, outweighs the benefits of a product, it is possible to refuse to grant a marketing authorisation in accordance with Article 30 of the Directive.

The environmental risk assessment is carried out in accordance with VICH guidelines Phase I (VICH 2000) and Phase II (VICH 2004), supported by the Guideline on environmental impact assessment for VMPs in support of the VICH guidelines GL6 and GL38 (VICH-TGD) (EMA 2008). In accordance with VICH Phase II guidance if a risk for the environment still exists at the end of Phase II Tier B "the applicant is recommended to discuss their dossier and proposals for further data or risk mitigation with the regulatory authority". In this context applicants and/or regulators may recommend inclusion of risk mitigation measures in the Summary of Product Characteristics (SPC) with the aim of reducing exposure of the environment thereby reducing the risk to an acceptable level.

2. Objective

This reflection paper provides a critical review of the adequacy/appropriateness of risk mitigation measures included in current marketing authorisations of veterinary medicinal products. These risk mitigation measures are included on the SPCs and product literature of products for which a potential risk to the environment was identified with the intended purpose of reducing the risk, as required by the Directive. This reflection paper takes into account the current legislation and existing guidelines for veterinary medicines as well as other legislation pertaining to good agricultural practice where relevant. For example where regulations on agricultural practice, such as the EU Nitrates Directive (European Commission 1991), have been incorporated into the exposure assessment according to the supporting guideline (EMA 2008), no additional risk mitigation measures are required and the considerations are not reiterated in this reflection paper. The reflection paper is also based on the experience gained when formulating risk mitigation measures in line with the criteria specified in the VICH-TGD (EMA 2008) (see section 3).

3. Considerations

Where an unacceptable/potential risk to the environment has been identified, risk mitigation measures may be a useful tool to reduce the exposure of the environment to the active substance, thereby reducing/eliminating the identified risk. Risk mitigation measures which are agreed will be included in the SPC of the veterinary medicinal product under point 4.5: "Special precautions for use", iii) other precautions (European Commission 2006) and also included in the product literature. As required for the SPC (approved conditions of use) generally, risk mitigation measures should be clear and unambiguous.

The following guidance on the application/use of risk mitigation measures is laid out in the VICH-TGD (EMA 2008):

"Risk mitigation is an essential part of the evaluation of products; risk mitigation can be used to restrict the risk associated with a product to an acceptable level, or even to completely remove such a

risk. In principle, the applicant should propose risk mitigation measures and, if appropriate, the efficacy of such measures should be substantiated by data in the dossier.

[…]

To be effective such a risk mitigation measure should meet the following criteria:

1- Mitigate exposure of the veterinary medicinal product to the environment

2- Be in line with agricultural practice (when used in food producing species)

3- Be in agreement with the legislation of the EU and its Member States

4- Be possible to demonstrate the effect of the proposed risk mitigation measure by re-evaluating the exposure assessment with the proposed risk mitigation measure included

If a risk mitigation measure does not fulfil the criteria mentioned above then the outcome of the risk assessment is that a serious risk for the environment exists. In accordance with Directive 2001/82/EC (as amended) this risk has to be weighed against the favourable aspects of a marketing authorisation."

It has to be noted that there is no legal basis for the enforcement of any risk mitigation measures recommended on the SPC which is not different from any of the other instructions and information provided on the SPC and the product literature. It should be possible to easily incorporate risk mitigation measures in agricultural practice to ensure compliance. Measures which a substantial number of farmers are not able to comply with should not be included on the label. It is the applicant's task to submit information showing that veterinarians and farmers can easily follow the risk mitigation measure.

All the requirements for the correct use of the product need the co-operation of the users of the product. In this regard it is considered important that the potential environmental hazards and risks of the veterinary medicinal product are communicated to veterinarians, farmers and/or animal owners to maximise the responsible use of a veterinary medicinal products and to increase compliance with any risk mitigation measures.

4. Findings of the review

Examples of risk mitigation measures currently in use and an assessment of how they match with the criteria specified in VICH-TGD are presented below. They are divided into those risk mitigation measures which fulfil the guideline criteria and those which are considered not to fulfil the criteria.

4.1. Risk mitigation measures fulfilling the guideline criteria

These risk mitigation measures are considered to fulfil the criteria set out in the VICH-TGD and are all under the control of the animal owner and/or the veterinarian.

4.1.1 Treated animals (cattle, horses, and sheep) should not have access to surface water for <x> days after treatment to avoid adverse effects on aquatic organisms.

This risk mitigation measure is related to a risk identified for either direct entry of product into surface water or entry of the active substance into surface water in excreta.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Depends*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Yes

* To prevent entry of the veterinary medicinal product (active substance) into water, the risk is mitigated by denying access. Fencing off water bodies is not part of agricultural routine, but on many farms it is possible to keep the animals away from water bodies by keeping the animals in pasture without water bodies. The number of days should be related to data showing that after the proposed period the risk quotient (RQ) is below 1.

4.1.2 Animals must remain stabled for <x> days after treatment, until the concentration of <active substance> in excreta is low enough to avoid adverse effects on dung fauna and their predators.

This risk mitigation measure is related to risk identified for dung fauna.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Depends*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed RMM included	Yes

* The number of days has to be in agreement with acceptable agricultural practice and can only be applied to animals that can be stabled. Furthermore, stabling of animals for prolonged periods, for example in the middle of the grazing season, may not be feasible.

4.1.3 A discharge consent by local water authorities is required before use of <product>, because the concentration of the active substance in surface water must not exceed <x> to avoid adverse effects on the aquatic environment.

This risk mitigation measure is related to a risk identified for a veterinary medicinal product used in fish farms.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Yes
3- Be in agreement with the legislation of the EU and its Member States	Depends*
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Yes

* In countries where local authorities monitor the use of products and their discharge from aquaculture facilities, this is an effective mitigation measure. This only applies to Member States where discharge consent systems or similar are operated.

4.1.4 <Active substance> is toxic for aquatic organisms. Remove the collar before allowing the dog to swim and before bathing the dog to avoid adverse effects on aquatic organisms.

This risk mitigation measure is related to a risk identified for collars containing ectoparasiticides used on dogs, when these animals will enter water bodies.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Not applicable
3- Be in agreement with the legislation of the EU and its Member States	Not applicable
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Yes

4.1.5 <Active substance> is toxic for aquatic organisms. Treated dogs should not be allowed to enter surface water for <x> hours/days after treatment, to avoid adverse effects on aquatic organisms.

This risk mitigation measure is related to a risk identified for ectoparasiticides applied topically to dogs, when these animals will enter water bodies.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Not applicable
3- Be in agreement with the legislation of the EU and its Member States	Not applicable
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Yes*

*According to the CVMP guideline this risk mitigation measure should be used for every ectoparasiticides applied topically to dogs, otherwise an additional assessment is required. In principle the period that the treated dogs are not allowed to enter surface waters should be large enough to ensure that the release of the veterinary medicinal product from the fur after this period will not seriously impact aquatic life. Typically, the duration for which access to water should be denied is not more than 48 hours. Unless there are concerns to suggest otherwise, it is assumed that after this period release of active substance(s) from fur will be negligible.

4.2. Risk mitigation measures not fulfilling the guideline criteria

These risk mitigation measures are considered not to fulfil the criteria set out in the VICH-TGD. They have been divided into those that are under the control of the animal owner and/or the veterinarian and those which are not under the control of the veterinarian or animal owner.

4.2.1. Measures under the control of the veterinarian or animal owner:

4.2.1.1 Do not treat animals on the same pasture in successive seasons to avoid adverse effects on dung fauna and their predators.

This risk mitigation measure is related to risk identified for dung fauna. (“Successive seasons” is meant as e.g. spring, summer...)

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Depends*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Depends*

* This might be a suitable mitigation measure; however the farmer might not have the possibility to rotate pasture if mitigation of the risk to pasture fauna or flora is necessary. The possibility to rotate pasture might depend on the production system of each region with more intensive production systems making rotation more difficult, thus resulting in higher concentration of the active substance of the

veterinary medicinal product on the soil. To be a useful RMM that mitigates the risk for the environment, the SPC should contain clear information for the prescriber/farmer on the underlying reasons for this RMM and the considerations to be taken before using the product. Data will be needed from higher tier assessment for effects on dung fauna population. The assessment methods of higher tier studies are however still under development.

This measure could also be in conflict with the health/welfare requirements of the animals under treatment. That is, the prescriber/user is being requested not to use a specific treatment for the purposes of mitigating a potential risk to the environment; however, where the treatment in question is the treatment of choice, this may compromise animal welfare. Animal health and welfare considerations should be balanced with the risk for the environment during the benefit/risk assessment.

4.2.1.2 <Product> can only be used in the same production cycle for <x> treatment period(s) to avoid accumulation of <active substance*> in soil resulting in a risk for the terrestrial environment and contamination of groundwater with <active substance>.*

This measure relates to those target animals such as broiler chickens and weaner pigs where there are a number of animals occupying one stable place in a year. Each of these animals is considered as one 'production cycle'. This risk mitigation measure is particularly relevant for persistent compounds.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes*
2- Be in line with agricultural practice	Depends*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Depends*,#

* The risk mitigation measures itself is under control of the veterinarian. This might be a suitable mitigation measure; however, for intensively reared animals the veterinarian does not control the spreading of the excreta from the treated animals. Control of the excreta is most likely to be under the control of the animal owner. Furthermore, even if the product is used only for <x> production cycles in a stable, the product might still accumulate in soil if manure from more than one stable is applied to the same area of land. This is of special relevance for compounds that are persistent in the environment. The SPC should contain the information that a similar risk may exist if other veterinary medicinal products that contain the same (or related) active substance(s) is used.

For some products it may be essential that each production cycle is treated. This measure could therefore be in conflict with the health/welfare requirements of the animals under treatment. Animal health and welfare considerations should be balanced with the risk for the environment during the benefit/risk assessment.

For most products, only one treatment period per production cycle is assumed for calculation of the predicted environmental concentration.

4.2.2. Measures not under the control of the veterinarian or animal owner:

4.2.2.1 Manure from treated animals must be stored for <x> months prior to spreading and incorporating into land to allow for degradation of <active substance> prior to release into the environment.

This risk mitigation measure is related to the risk identified for soil or the aquatic environment resulting from spreading manure from stabled animals. This risk mitigation measure will require data from manure degradation studies.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	No*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Yes

*At the end of Tier A it is possible to refine the exposure calculation based on the degradation of the active ingredient in manure (EMA 2008, chapter 3.1.4.1). Those calculations take into account the storage time of manure (see table 6 of reference EMA 2008). Increasing the storage time used in this procedure is not considered in line with agricultural practice throughout the EU. If the storage times according to table 6 are used, an additional mitigation measure is not necessary.

4.2.2.2 Manure containing the active substance should not be spread on the same area of land in successive years to avoid accumulation of <active substance> which may cause adverse effects for the environment.

This risk mitigation measure is related to the risk identified for soil or the aquatic environment resulting from repeated spreading of manure from stabled animals.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Depends*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Yes

* The farmer might not have the possibility to apply manure in different areas of land. The risk mitigation measures should be communicated by the responsible veterinarian to the farmer but if the farmer is not the one who will spread the manure; the manure spreader might not be informed about this risk mitigation measure. This mitigation measure may only be suitable for national authorisations in countries without manure trading or where disposal of manure requires prior authorisation by a local agency.

4.2.2.3 When spreading manure from treated animals, a minimum distance to surface water of <x> meters has to be applied, because the manure contains <active substance> which may cause adverse effects in the aquatic environment.

This risk mitigation measure is related to a risk identified to surface water as a result of spreading manure from stabled animals.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Depends*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	No*

* The risk mitigation measures should be communicated by the responsible veterinarian to the farmer but if the farmer is not the one who will spread the manure, the manure spreader might not be informed about this risk mitigation measures. This mitigation measure may only be suitable for national authorisations in countries without manure trading. However it cannot be included in agricultural practice in countries where manure trading is common and where no prior consent is required for manure spreading. It should also be noted that buffer zones for spreading manure are normally related to the prevention of nitrogen emission to surfacewater and are fixed values. If it is determined in the ERA that the 'buffer zone' required should be greater than that required for control of nitrogen, then this would not be in line with Good Agriculture Practices and would not then be easily incorporated into agricultural practice. In addition there are no suitable models to demonstrate the effect and it does not work in areas with drainage facilities.

4.2.2.4 Do not spread more than <x> tonnes of manure per hectare per year, because manure contains <active substance> which may cause adverse effects in the environment.

This risk mitigation measure is related to a risk identified to any compartment of the environment as a result of spreading manure from stabled animals.

MEASURES	OUTCOME
1- Mitigate exposure of the veterinary medicinal product to the environment	Yes
2- Be in line with agricultural practice	Depends*
3- Be in agreement with the legislation of the EU and its Member States	Yes
4- Be possible to demonstrate the effect of the proposed risk mitigation measures by re-evaluating the exposure assessment with the proposed risk mitigation measures included	Yes

* The risk mitigation measures should be communicated by the responsible veterinarian to the farmer but if the farmer is not the one who will spread the manure, the manure spreader might not be informed about this risk mitigation measures. In addition, this mitigation measure may only be suitable for national authorisations in countries without manure trading or where disposal of manure requires prior authorisation by the local environment agency. However it cannot be included in agricultural practice in countries where manure trading is common and where no prior consent is required for manure spreading.

5. Conclusion and recommendation

The decision to grant a Marketing Authorisation is based on the outcome of the benefit-risk evaluation for the product. Part of this evaluation includes consideration of the risk to the environment. Where a potential risk to the environment associated with the use of a specific product has been identified, risk mitigation measures are important tools which can be used to reduce the risk to the environment to an acceptable level or eliminate the risk entirely. However, risk mitigation measures should not be used to replace the requirements for studies of environmental fate and effects as required by VICH Phase II guidelines where, in some cases, further fate and/or effect data may lead to the conclusion that the risk to the environment is acceptable without the need for a risk mitigation measures.

Having reviewed risk mitigation measures in current use, it is evident that a number, in most situations, are able to satisfy the criteria specified in the VICH-TGD (EMA 2008) (see section 4.1). In addition to fulfilling the criteria from the VICH-TGD, it should be noted that these risk mitigation measures are characterised by the following:

- The potential risk to the environment is clear,
- The recommended measure to mitigate the risk is specific and clear,
- The recommended measure can be readily/easily implemented,
- The measure is under the direct control of the animal owner/prescriber (that is, not relying on a third party for implementation),
- The measure does not require the animal owner/prescriber to make a direct choice between the appropriate treatment for a specific indication and protection of the environment.

It is expected that risk mitigation measures with the above characteristics are likely to result in greater animal owner/prescriber compliance. Consequently, when the product in question is used in accordance with those measures, they serve their intended purpose of reducing the exposure of the VMP to the environment with the result that the potential risk to the environment will be reduced/eliminated.

In order to ensure user/prescriber compliance with a risk mitigation measures, communication of the risk is considered essential. Therefore, the reason for the mitigation measure should be part of the information provided in section 4.5iii of the SPC. Further explanation in relation to the environmental properties of the active substance may be provided in section 5 'Environmental properties'. In addition to having this information on the SPC, it is also necessary to fully reflect the risk mitigation measures on the product literature.

Other risk mitigation measures currently in use (see section 4.2) do not fully satisfy one or a number of the guideline criteria and in addition do not meet the characteristics specified above, although fulfilment might vary depending on the production conditions. While those risk mitigation measures may provide some information to the user about a potential risk to the environment, the deficiencies identified are such that their inclusion on product literature may not have the desired effect (that is, result in reduced environmental exposure). Therefore, the risk mitigation measures specified in section 4.2 require careful consideration before applying to future marketing authorisations.

It should be noted that the mitigation measures used as examples above do not cover all potential situations and consideration will need to be given to additional mitigation measures for specific cases.

If it is not possible to construct/formulate a risk mitigation measures that satisfies the guideline criteria and the characteristics detailed above, then non-compliance must be considered a likely outcome. In the event of non-compliance, the desired objective of reducing or eliminating the potential environmental risk cannot be achieved. In this case, the potential risk must then be factored into the overall benefit risk evaluation and the regulatory authority will have to decide if the benefits of the product outweigh the risks (including the potential risk to the environment), during this benefit risk evaluation the animal health and welfare will also be taken into account.

This reflection paper provides a starting point whereby all stakeholders can work on the development of practical and effective risk mitigation measures. For future authorisation of products, further work on the wording of risk mitigation measures, including clear SPC information of the underlying risk and considerations, is required for situations where an adequate risk mitigation measure has not been identified in order to reduce risk to the environment from veterinary medicinal products.

6. References

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