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Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

REFLECTION PAPER ON THE IMPLEMENTATION OF DIRECTIVE 2001/82/EC, AS AMENDED, IN RESPECT TO THE ASSESSMENT OF ENVIRONMENTAL RISKS OF VETERINARY MEDICINAL PRODUCTS

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1. Introduction

Directive 2001/82/EC, as amended by Directive 2004/28/EC [1], includes new provisions regarding the consideration of effects on the environment in the benefit/risk assessment of veterinary medicinal products and on the data requirements regarding such effects.

Directive 2001/82/EC, as amended by Directive 2004/28/EC, includes a new definition of the risks relating to the use of veterinary medicinal products and introduces the definition of a risk/benefit analysis.

- The definition for the "*Risks relating to use of the product*" (Article 1, point 19) is as follows:
  "- any risk relating to the quality, safety and efficacy of the veterinary medicinal products as regards animal or human health;
  - any risk of undesirable effects on the environment."

- According to the definition of the "Risk/benefit balance" (Article 1, point 20):
  "*An evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks as defined above"*, the consideration of any risk of undesirable effects on the environment shall be part of the risk/benefit balance for a given veterinary medicinal product.

- Article 12 (j), third indent of Directive 2001/82/EC requires that the file for a marketing authorisation application shall contain results of:
  "- 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."[1]

This document describes the CVMP considerations based on the legal interpretation of the provisions by the European Commission and the advice by its Environmental Risk Assessment Working Party, and consultations with the CMD(v).

2. General principles

a) An environmental risk assessment (ERA) is mandatory for all new applications for a central or national marketing authorisation irrespective of the underlying legal basis.

b) Generic products require an ERA since Article 13 (1) of Directive 2001/82/EC does not contain a derogation from Article 12 (3) (j) 4th indent. For generic applications no automatic cross-reference to ERA data[2] is possible irrespective of whether the data protection for the originator has expired. Reference to ERA data contained in the original dossier is only possible if the originator company agrees to make the ERA data available to the other company. It is also not possible for competent regulatory authorities to simply refer to ERA data of the original dossier, or to any other dossier for a similar product without consent of the company holding the marketing authorisation.

c) Type II variations as well as extensions need to contain an ERA whereas Type IA and IB variations do not require an ERA.

d) Data possibly available in the public domain can be used to generate an ERA for any type of application.

[1] The risk mitigation measures referred to in this indent are to be understood as measures limiting the risk, rather than limiting the assessment requirements.
[2] In the context of this document the term "data" is understood as experimental studies (effect studies and environmental fate studies), i.e. data required in an ERA Phase II.

The guidance provided in the Notice to Applicants (NTA) [2] regarding published data applies.[3] Expert judgement will be required to decide on the reliability of the data. Further details on how to classify the reliability of submitted studies are provided in the CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38, EMEA/CVMP/ERA/418282/2005-corr [3][4]. Published data provided must be of a standard to enable an assessment of the risks to the environment which is equivalent to that enabled by specifically generated studies in accordance with agreed guidelines, i.e. they can only be used to substitute studies, if the publication contains a sufficient amount of data and sufficient details on the design and conduct of the study to allow a full and independent assessment. Therefore, the provision of only end point values or a published summary of an assessment is not sufficient to substitute ERA data.

It is expected that for products that have been on the market for some time more data will be available in the public domain.

e) All ERA should follow the phased, step-wise approach detailed in the guidelines as issued by VICH and adopted by CVMP. These guidelines are structured in such a way that unnecessary requests for data are prevented (via decision tree in Phase I, a targeted approach when possible in Phase II) [4,5].

f) From a scientific point of view an ERA for one veterinary medicinal product is in principle also valid for another similar product containing the same active ingredient and leading to the same environmental exposure due to the similarity of other parameters of the product, such as dose, species and route of administration. This principle provides for co-operation between companies to develop jointly ERA data or share data for products containing the same active ingredient.

g) Applicants are encouraged to co-operate with other companies in developing ERA data or sharing existing data.

3. Specific considerations

3.1 New Marketing Authorisation Applications

For all new marketing authorisation applications an ERA is required. This requirement applies not only to applications for marketing authorisations containing a new active substance but also to generic and so-called "hybrid" applications (Article 13(1), (3)), bibliographical applications (Article 13a(1)), and informed consent applications (Article 13c).

For the cases where the ERA can be stopped at Phase I, which is in the majority of cases, the preparation of the ERA only requires limited data insofar as it can rely on information already available in the dossier and requiring a simple calculation, when applicable. The CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38, EMEA/CVMP/ERA/418282/2005-corr [3] provides details on how to conduct an ERA and gives indications of the types of products, which will require a Phase II assessment[5].

[3] According to the NTA Vol. 6A, Chapter 1, section 5.4, Documentation "published literature implies that the text must be freely available in the public domain and published by a reputable source preferably peer-reviewed. The published information should be presented in sufficient detail so that the quality of the results can be established.

[4] Chapter 8 of the Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38, EMEA/CVMP/ERA/418282/2005-corr

[5] The conduct of an ERA does not require animal-testing on mammals.

3.2 Variations

As Type II variations should follow the data requirements of marketing authorisation applications, they require an ERA to be provided with the application. However, the applicant will need to consider whether or not the change to the authorisation will/could result in an increase in exposure of the environment. This can be due to an increase in the quantity of the active ingredient entering the environment and/or due to the fact that the active ingredient will/may enter a previously unexposed environmental compartment. If an increase or change in exposure is not expected as a result of the change to the marketing authorisation applied for in the variation a justification for not providing further details on the assessment is required.

The CVMP considered that in most cases for Type II variations no increase of the environmental exposure is expected, but the following Type II variations were identified as having the potential to increase environmental exposure to the product. As a result applications for a variation for one of the reasons below will require the provision of an ERA:

- increase in dose rate for an existing food producing species;
- addition of an indication for an existing food producing species.

In the application dossier for any of the above variations the applicant should provide an ERA specific to the variation and addressing only the new change in the way the product is used. It is generally agreed that assessment of aspects of the dossier not directly related to the variation being applied for should not be conducted.

For the above variations, no new ERA would be necessary, if it can be justified that there is no increase of environmental exposure.

3.3 Extensions

Extensions require an ERA. As with variations, the need for new data will depend on whether or not the change to the authorisation will/could result in an increase in exposure of the environment. This can be due to an increase in the quantity of the active ingredient entering the environment and/or due to the fact that the active ingredient will/may enter a previously unexposed environmental compartment. If an increase or change in exposure is not expected as a result of the change to the marketing authorisation applied for in the extension then a justification for not providing further details on the assessment is required.

The following extensions are expected to/may result in an increased exposure:

- change or addition of a new route of administration
- change or addition of food producing species;

In the application dossier for any of the above extensions the applicant should provide an ERA specific to the extension and addressing only the new change in the way the product is used. It is generally agreed that assessment of aspects of the dossier not directly related to the extension being applied for should not be conducted.

For the above extensions, no ERA would be necessary, if it can be justified that there is no increase of environmental exposure.

3.4 Renewals

For renewals the requirement to include an ERA does not apply, as Article 28(2) of Directive 2001/82/EC and Article 39(2) of Regulation (EC) No 726/2004, respectively, do not foresee the submission of new data. However, these legal provisions on renewals require “a re-evaluation of the risk-benefit balance”. The risk-benefit balance as defined in Article 1(20) of Directive 2001/82/EC includes an evaluation of the risks referred to in Article 1(19), which in turn includes “any risk of undesirable effects on the environment”. This means that in order to re-evaluate the risk-benefit balance of the product an ERA is necessary, in principle.

The Commission clarified that the precise level, quality and range of data necessary for the evaluation of those "risks of undesirable effects on the environment" in the context of a renewal should be determined on a case-by-case basis particularly relying on data already available or on scientific justification, carefully balancing the environmental risk-benefit evaluation with the availability of veterinary medicinal products.

It is recognised that due to the absence of a legal requirement for an ERA in the past (authorisation before 1992 for new products, authorisation before November 2005 for all other products and renewals) or lack of guidance on how to prepare an ERA before 1998, together with differences in implementation of legislation by Member States (some Member States requested an ERA at renewal under the old legislation for all products, others did not) consistent ERA data for all products are not available to Member States throughout the Community.

Considering that renewals have already been granted under the new legislation for the majority of old products without requesting ERA data, it is considered proportionate that ERA data at renewal are normally requested only if:

- A potential risk to the environment is identified and/or if the presence of an active in the environment has been recorded (for instance by monitoring data or pharmacovigilance data).
- Data have become available indicating a potential problem. As for initial authorisations, cross reference between proprietary data provided by companies as part of their applications is not possible unless such information is also available in the public domain.

It is also worth pointing out that if a potential risk for the environment is identified further data or risk mitigation measures can be requested at any stage in the life cycle of a product.

4. Additional considerations

4.1 ERA Monographs

The CVMP proposed earlier to consider developing ERA monographs, i.e. documents, in which information on fate and effects of active substances in the environment is summarised that could be used for Phase II assessments of products containing that substance. This approach would prevent unnecessary repetition of experiments would save resources and would lead to a more harmonised assessment of environmental risks. Monographs could be a valuable instrument for supporting availability of veterinary medicines.

It is up to the industry now to make use of the concept and to provide the necessary data to develop such monographs. The CVMP continues to be open to contribute in developing the monographs.

5. References

[1] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Official Journal L 311, 28/11/2001 p. 1 - 66). Amended by Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products (Official Journal L 136, 30/4/2004 p. 58 - 84).

[2] Volume 6 of The Rules Governing Medicinal Products in the European Union - Notice to Applicants: Veterinary Medicinal Products

[3] CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38, EMEA/CVMP/ERA/418282/2005-corr, London, September 2007.

[4] CVMP/VICH Topic GL6 (Ecotoxicity Phase I). Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I, CVMP/VICH/592/98-FINAL, London, June 30 2000

[5] CVMP/VICH Topic GL38. Guideline on Environmental Impact Assessment for Veterinary Medicinal Products - Phase II, CVMP/VICH/790/03-FINAL, London, October 2005

[6] Guideline on the definition of a potential serious risk to human or animal health or for the environment in the context of Article 33(1) and (2) of Directive 2001/82/EC (Official Journal C 132, 7/6/2006 p. 32 - 35).