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2 EMA/CVMP/ERA/698394/2014
3 Committee for Medicinal Products for Veterinary Use

4 Concept paper on the testing strategy and risk 5 assessment for plants in the Phase II of the 6 environmental risk assessment for veterinary medicinal 7 products

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 600 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Introduction

Plant toxicity tests are used in the terrestrial environmental risk assessment of veterinary medicinal products, as described in the VICH guideline on environmental impact assessment for veterinary medicinal products Phase II (CVMP/VICH/790/2003)[1].

In 2012 the CVMP published a reflection paper on the testing strategy and risk assessment for plants (EMA/CVMP/ERA/147844/2011)[2], in which the plant test requirements in Phase II Tier A and Tier B are explained. The reflection paper was developed to recommend a plant testing strategy for veterinary medicinal products, given that since the publication of the VICH Phase II guideline [1], the guideline recommended for plant testing, the "OECD guideline 208: seedling emergence and seedling growth test" [3] was updated, and guidance on how many plant species are needed for testing of veterinary pharmaceuticals is no longer available. Although the existing reflection paper provides recommendations on how to conduct the testing for plants in the Phase II assessment, there are a limited number of cases were the testing strategy may not be adequate to assess the toxicity of all types of substances.

This is the case for active ingredients of veterinary medicines that show a high formation of non-extractable residues or transformation products (e.g., the latter can be identified when the applicant has conducted tests on determining the fate of veterinary medicines in manure (EMA/CVMP/ERA/430327/2009)[4]). For example, experience with studies on the determination of the fate of veterinary medicinal products in manure, performed according to EMA guideline [4], has shown that some antibiotics form a high percentage of non-extractable residues. However, it is not known whether or not these are bioavailable to plants and consequently could pose a risk, as the manure matrix consists of a high percentage of organic matter and will undergo decomposition after spreading. Therefore non-extractable residues might be released and become bioavailable. In the event of assessing a substance that shows a high formation of non-extractable residues or transformation products, alternative ecotoxicity studies other than those recommended in the existing reflection paper may need to be considered for the refinement of the risk assessment following Tier B, to ensure that the toxicity of non-extractable residues is assessed.

At the time of the publication of the CVMP reflection paper [2], the reason for not including the considerations mentioned above for substances that show a high formation of non-extractable residues or transformation products, was due to fact that a standard operating procedure for this scenario was not yet developed. However, based on the recommendations on determining the fate of veterinary medicines in manure [4], applicants have already been submitting this study and developing protocols themselves as no harmonised guidelines or protocols on how to design, conduct and assess the data of such a modified test are yet available.

This concept paper has been prepared to address the need to develop a guideline on the testing strategy and risk assessment for plants in the Phase II assessment, as explained in the existing reflection paper, as well as including how to conduct a tier based assessment for plants for those substances that form high amounts of non-extractable residues or transformation products in manure.

2. Problem statement

For a plant risk assessment, the initial predicted environmental concentrations (PEC) in soil, calculated according to 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-Rev.1) [5], is compared to the predicted no effect concentration (PNEC) obtained from the seedling emergence

and seedling growth test according to OECD guideline 208 [3]. If a risk for plants is still identified in Tier B, the reflection paper [2] recommends conducting a higher tier assessment for the risk assessment by applying a statistical extrapolation technique, the so-called species sensitivity distribution (SSD). However, in some cases an alternative methodology may be preferable to the SSD approach (e.g., perform the plant test under a modified exposure scenario). There is currently no alternative approach described in any guideline.

The fact that currently there is only one option for applicants to conduct higher tier assessments when a risk is identified in Tier B, has led to discussions among scientists, regulators and applicants on the possibility of conducting a modified plant toxicity test (so called 'extended plant test') with a modified exposure for specific scenarios. The workshop: 'A new concept for a plant test with a more realistic exposure scenario via manure' [6] was held in 2013 with the aim to address the issues identified to date with the extended plant test, and to provide suggestions for improvement to applicants and assessors. The workshop was attended by industry, contract laboratories, scientists and regulators.

The 'extended plant test' is an option in case a risk for plants has been identified and the substance has been shown to form non-extractable residues in manure or transformation products ≥ 10% of the applied amount but would not be a required test from the outset.

In view of the usefulness of this 'extended plant test' for refining the risk assessment for plants when a risk is identified in Tier B, several applicants have already decided to submit this test. Although this test is considered valuable, there are no harmonised guidelines or protocols on how to design, conduct and asses the data of such modified test design.

Consequently, the CVMP considers it necessary to develop a guideline that will include the information that is already explained in the existing reflection paper, and will also include the conditions and technical specifications for those scenarios when an extended plant test should be considered by applicants and how to facilitate the assessment by assessors.

3. Discussion (on the problem statement)

The reflection paper on the testing strategy and risk assessment for plants, published by the CVMP in 2012, only presents one option for refining the risk assessment for plants in scenarios when a risk is identified in Phase II Tier B of the environmental risk assessment. However, in certain situations it has been acknowledged by applicants, assessors and the scientific community that additional tests should be considered for specific scenarios. Modified plant tests have already been submitted in dossiers for marketing authorisations, for the reasons explained above. However, a number of technical issues have been identified in the tests performed that call for the development of a guideline with the aim to harmonise the approach.

In view of the above, it is considered necessary to develop a guideline to enable a harmonised approach for applicants and assessors.

4. Recommendation

The CVMP acknowledges the need to develop a guideline that will include the information currently available in the existing reflection paper, in addition to address when and how to perform a modified plant toxicity test. This would include a detailed explanation on when the extended plant test should be conducted and the technical specifications on the test as no guideline is yet available.

The new technical aspects of the test design and data evaluation of the extended plant test should take into consideration the outcome of the research project and workshop that took place in 2013, which

addressed the issues identified to date with the extended plant test and of their results to provide suggestions for improvement. The workshop had input and participation from industry, contract laboratories, researchers and regulators.

The new guideline can be used in the preparation of the environmental risk assessment by the applicant for a marketing authorisation and in the evaluation of the studies by the competent authorities. It does not introduce new requirements to applicants.

5. Proposed timetable

June 2015 – adoption of concept paper for release for consultation by the CVMP

September 2015 – end of consultation period

Timelines for development of the guideline will be determined following review of comments received on the concept paper.

6. Resource requirements for preparation

The new guideline will involve the CVMP ERAWP, ERAWP secretariat and the CVMP. The ERAWP should appoint a rapporteur from amongst its members.

It is anticipated that development of a draft guideline may require physical drafting group meetings as well as 1-2 additional virtual meetings and discussion time during scheduled ERAWP meetings.

7. Impact assessment (anticipated)

It is anticipated that this guideline will lead to an improved and more realistic risk assessment.

No adverse impact on industry or regulators with respect to either resources or costs is foreseen. The number of products that would still indicate a risk in Tier B of the environmental risk assessment can be expected to be low. For those substances that may require additional studies when a risk for the terrestrial compartment has been identified, developing this specific guidance is viewed beneficial as applicants and laboratories will then be able to have a clear direction on the experimental design and technical aspects of the test.

8. Interested parties

Pharmaceutical industry, EU national competent authorities, consultants, contract laboratories

9. References

[1] VICH (2004). Guideline on Environmental Impact Assessment for Veterinary Medicinal Products Phase II (CVMP/VICH/790/2003).

[2] European Medicines Agency (2011). Reflection paper on testing strategy and risk assessment for plants (EMA/CVMP/ERA/147844/2011).

[3] OECD (2006). OECD guidelines for the testing of chemicals – Terrestrial Plants Test: Seedling Emergence and Seedling Growth Test (OECD 208).

[4] European Medicines Agency (2011). Guideline on determining the fate of veterinary medicinal products in manure (EMA/CVMP/ERA/430327/2009).

[5] European Medicines Agency (2008). Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

[6] German Federal Environmental Agency (UBA) (2013). Workshop on pharmaceuticals in soil, sludge and slurry. Environmental risk assessment of veterinary medicinal products – a new concept for a plant test with more realistic exposure scenario. 18-19 June 2013, Dessau, Germany.