European Medicines Agency
Veterinary Medicines and Inspections

MEETING REPORT FROM FOCUS GROUP ON FATE OF VETERINARY MEDICINAL PRODUCTS IN MANURE LONDON, 23 JUNE 2009

Doc. Date: 7 October 2009
Doc. Ref: EMEA/CVMP/ERA/400210/2009

***Participants**: see Annex I*
***Agenda**: see Annex II*

Introduction

Kornelia Grein welcomed the participants to the meeting. She reminded participants that the objective of the meeting was to discuss the intended guidance on fate of veterinary medicinal products (VMPs) in manure (manure degradation studies) to be prepared by the ERAWP.

The future EMEA guideline would define the strategy for the assessment of manure degradation studies within the context of VICH guidelines. It was intended to provide certainty on the requirements for such studies and to indicate how these studies would be interpreted. However the guidance will not be able to replace highly technical study protocols. It was recognised that standardised protocols are missing although progress is ongoing on this area.

Presentations

Joop de Knecht gave a presentation outlining the existing information on the evaluation of degradation studies of VMPs in manure.

Leo Van Leemput gave a presentation on a practical experience with a degradation study using chicken manure. He highlighted that manure from chickens behaves differently from cattle or pig manure and concentrations should be calculated on an ash content basis.

Gregor Scheef gave a presentation on experiences with studies on degradation in bovine, pigs and poultry manure. His presentation reported on the overall conditions of the studies. All studies have been performed before the guidance in the CVMP guideline was finalised[1], consequently they are not in line with the current requirements. He indicated that those studies should be allowed to be used in the future. The approach on how to treat metabolites of parent compounds should be discussed during the preparation of the guidance. Extractable and bound residues were also discussed. Again it was stressed that there is a need for harmonised test protocols.

Robert Kreuzig gave a presentation on the reference manure concept. He detailed the experience of the 'manure project'. A meeting was held in Braunschweig (Germany) on 27 May 2009 to discuss protocols for manure degradation[2]. There are still a number of open questions on the harmonisation of those studies on manure degradation. It was indicated that regulatory requirements should be defined before the conditions of protocols can be defined.

[1] Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1), http://www.emea.europa.eu/pdfs/vet/era/41828205enfin.pdf
[2] UBA (Umweltbundesamt) project on Methodological Aspects of Laboratory Tests of VMP and Biocides in Manures and Manured Soils. Veterinary medicinal products in manure and manured soils: development of a technical protocol for laboratory tests (FKZ 20467455, http://www.umweltdaten.de/publikationen/fpdf-l/3343.pdf)

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Following these presentations Alex Tait opened discussions.

It was noted that the opinions expressed during the meeting are preliminary opinions and will be used during the preparation of guidance but should at present not be considered as the ERAWP (or CVMP) position.

The influence of several parameters (e. g. test conditions, origin of manure) on test results and the representativity of the test for storage conditions in Europe are not completely understood, yet. It was agreed that more knowledge on the transformation process and influencing parameters and conditions should be gathered and current suggestions reviewed once more knowledge is available.

Selection and handling of the manure samples

Use of control animals (animals which are under well controlled conditions) *vs* tanks of manure. The option of control animals was in principle preferred. For the control animals parameters like animal feed and the veterinary history should be recorded. If tank manure is used the same parameters have to be given.

The option of using manure collected from animals dosed with the VMP should also be permitted.

Manure could be stored at e.g. –20°C

An acclimation period for manure before it is spiked should be agreed. Twenty or twenty one days were suggested, as the appropriate time to obtain anaerobic conditions.

It was clarified that manure degradation studies will be performed under laboratory conditions and as such are a surrogate of the real situation.

Degradation studies should be performed in manure of each species to which the VMP is administered (e.g. one for pigs, one for cattle and one for poultry). For cattle for pragmatic reasons it was suggested that the selected manure should be beef cattle (not e.g. dairy cattle). More information on cattle (beef) is needed to verify the proposed standardization of cattle manure.

Classification of the reference manure should be based on dry matter content (Cattle: 10±1%, pig: 5±1%, chicken: 60%±5%).

Matrix characterisation of the manure

The parameters which needed to be taken into account for matrix characterisation were discussed. As proposed in the manure project by Robert Kreuzig it was agreed that the following parameters could be measured to characterise the manure: pH, intestinal microbial activity (assay has yet to be specified), organic matter, nitrogen and phosphorus content, redox potential, dry matter content and dissolved oxygen content.

Establishing test conditions

Cattle and pig studies should be performed under anaerobic conditions e.g. discontinuous nitrogen flow, the objective is to show that the redox potential is sufficiently low.

It would be preferred to work with spiked manure although it should be possible to deviate from this requirement (and use excrements from treated animals) with adequate justification.

For poultry manure, the conditions should be aerobic. It was agreed that it would be interesting to define poultry manure as this would include the different poultry minor species. It was recognised that it is not easy to select one condition which mimics housing conditions as these can vary, depending on the way chicken manure is treated and stored. This is most relevant for the moisture content. For pragmatic reasons, it is proposed to standardise the moisture content to a kind of time weight average

(e.g. 40%). Alternatively, the decrease in moisture content, which normally occurs under housing conditions, could be mimicked.

The suggested test duration is 100 days for Phase II tests, but could be shortened when sufficient degradation has been observed.

Sterile controls may be useful to make a distinction between biotic and abiotic degradation, however their inclusion is not mandatory. This seems to be most relevant in the event that the study is conducted with non-radio-labelled substance.

As recommended in the OECD guideline for transformation in soil (OECD 307), a test temperature is proposed of 20° C for all manure types. For the risk assessment the derived DT_{50} will be corrected to relevant environmental temperatures, which have to be defined still for each manure type.

Test substance

Radiolabelled material is, in principle, preferred because detailed mass balances can be set up considering mineralisation, extractable and non-extractable residues. When non-radiolabelled material is used, only the disappearance of the parent compound initially applied can be followed and does not provide the possibility to demonstrate mineralisation. Manure collected from animals treated with the VMP could also be used as the test substance.

Analytical methods

The validation of the analytical methods should be to the same standard for both the parent compound and the metabolites.

Extraction and determination of the test substance, metabolites and non extractable residues

The primary objective of the degradation studies is to demonstrate that the active ingredient(s) will be transformed (formation of metabolites or ultimate mineralisation). It is recommended to follow a sequential extraction method. If at time zero less than a defined amount of the analysed substance (e.g. 70%) can be extracted, it will be difficult to demonstrate degradability. An exhaustive extraction is necessary with water, organic solvents and acids. Extraction of residues should not change the chemical nature of active ingredient or its metabolites.

The interpretation of the significance of bound residues needs to be further discussed. At present bound residues are considered to be active. Bound residues can only be disregarded when it can be demonstrated (by toxicity studies) that they are not available i.e. have no effects in the toxicity studies.

Metabolites

Discussion took place on cases where the parent compound will be completely transformed into one or more metabolites. Further discussions will be required on which approach should be followed in the risk assessment. A pragmatic approach should be followed. If it is obvious that a metabolite and not the parent will enter the environment, it seems logical that the risk assessment will be focussed on this metabolite.

Requirement of manure test studies

Manure degradation test studies are not a compulsory requirement for the ERA. An applicant can carry out such tests to prove the transformation of the active substance in manure as the results may be of benefit in the risk assessment.

Participants at the meeting also made clear that companies will not invest in manure degradation studies unless is clear that regulators will accept them.

End of the meeting

Alex Tait thanked participants for their active contributions and fruitful collaboration.

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Annex I
London, 23 June 2009
EMEA/367251/2009

Focus Group: Fate of Veterinary Medicinal Products in Manure

List of Participants

Name	Surname	Affiliation
Peter	Aikens	Huntingdon Life Sciences
Yara	Antonissen	IFAH-Europe
Giovanna	Azimonti	Centro Internazionale per la Prevenzione Sanitaria (IT)
Joop	de Knecht	Rijksinstituut voor Volkgezondheid en Milieu (NL)
Jean-Christophe	Faucon	Agence Nationale du Médicament Vétérinaire (FR)
Martin	Hansen	University of Copenhagen
Silke	Hickmann	Umweltbundesamt (DE)
John	Jensen	National Environmental Research Institute (DK)
Xanthippos	Karamanlis	Aristotle University of Thessaloniki (GR)
Robert	Kreuzig	Technische Universität Braunschweig (DE)
Jennifer	Mackie	Regulatory Compliance Limited (representing Pfizer AH)
Magali	Martin-Chave	Virbac
Gregor	Scheef	Intervet Innovation
Alex	Tait	Veterinary Medicines Directorate (UK)
Markus	Tetscher	Dr Knoell Consult
Leo	van Leemput	Janssen Animal Health
Peter	Verhoeve	Eurovet Animal Health
Virpi	Virtanen	Finnish Environment Institute

Secretariat

Name	Surname	Affiliation
Kornelia	Grein	European Medicines Agency
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Annex II
London, 19 June 2009
EMEA/CVMP/ERA/ERA/233378/2009

FATE OF VETERINARY MEDICINAL PRODUCTS IN MANURE

FOCUS GROUP MEETING

23 June 2009, EMEA, Room 4C

AGENDA

TIME	AGENDA TOPIC	
10.00	**Welcome and Introduction**	Kornelia Grein
10.10 - 11.10	**Introductory presentations**	Joop de Knecht Leo van Leemput Gregor Scheef Robert Kreuzig
11.10 - 13.15	**Design of the studies**: the following topic areas were identified in the concept paper: • Selection and handling of the test manure (e.g., origin, storage, reference manure, tank manure) • Matrix characterisation of the manure (parameters to be measured) • Establishing test conditions (e.g., temperature, aerobic, anaerobic, moisture, duration, sterile, non-sterile...) • Test substance (e.g. labelled, non-labelled) and spiking procedure • Extraction and determination of the test substance, metabolites and non extractable residues (e.g. validation of analytical methods, setting criteria for recovery….) • Data analysis (e.g. kinetics)	Coordinator Alex Tait
13.15 - 14.00	***Lunch***	
14.00 - 16.00	**Evaluation and use of the test results** • Extrapolation of biotic and abiotic transformation of VMPs within and between manure types of different target species • Defining realistic and representative storage conditions for standardisation of test results (e.g. temperature, time) • Use of test results to refine PECs (e.g. dealing with non first-order dissipation interpretation, of non-extractable residues) • Identification of relevant metabolites	Coordinator Alex Tait
16:00 - 17.00	**Confirmation of recommendations and action plans**	Alex Tait
17:00	***Closure of the meeting***	

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