15 November 2010
EMA/CVMP/516817/2009
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on data to be provided in support of a request to include a substance in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009

Adoption by CVMP for release for consultation	11 November 2009
End of consultation (deadline for comments)	31 May 2010
Adoption by CVMP	11 November 2010
Date for coming into effect	1 June 2011

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Guideline on data to be provided in support a request to include a substance in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009

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Executive summary

This guideline contains guidance relating to the data to be provided in support of a request for the CVMP to consider the inclusion of an excipient in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009 (EMEA/CVMP/519714/2009).

1. Introduction (background)

The MRL legislation, the primary goal of which is to protect consumer health, requires that MRL evaluations be undertaken for the pharmacologically active substances present in veterinary medicinal products (VMPs) for use in food producing species: Article 1 of Regulation (EC) No 470/2009 states that:

> *"For the purposes of ensuring food safety, this regulation lays down the rules and procedures in order to establish:*
> *(a) the maximum concentration of a residue of a pharmacologically active substance which may be permitted in food of animal origin (maximum residue limit)…"*

A desired and actual result is that MRL evaluations are undertaken for all active substances contained in pharmaceutical VMPs for use in food producing species.

An additional result is that it may be considered that no substance (even if it is an excipient) may be used in a VMP intended for use in food producing animals unless it has either undergone an MRL evaluation or has been shown to have no pharmacological activity.

However, for many excipients it can be considered that their use in veterinary medicinal products would not be associated with relevant pharmacological activity and that there is therefore no need for a full MRL evaluation. For example, this is the case for many substances that are known constituents of the diet. With substances like this in mind the CVMP has developed the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009. Excipients are included in this list on the basis that they are not considered to have pharmacological activity when used as proposed.

Over the years, the CVMP has received many requests to clarify the kind of studies that would be appropriate to demonstrate that a substance does not have pharmacological activity and so allow its inclusion in the list. Having reflected on this issue, the CVMP has concluded that it is not possible to recommend a series of practicable pharmacology tests that could be considered to comprehensively demonstrate the lack of pharmacological activity of an excipient, and acknowledges that it may not always be appropriate to require the absence of pharmacological activity to be demonstrated by means of pharmacology tests.

This document describes what, in light of the above position, is considered to be a pragmatic approach for evaluating whether or not excipients can be included in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009.

2. Scope

This document provides guidance on the data that the CVMP would expect to see in support of a request to include an excipient[1] in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009.

[1] For the purposes of this guideline the definition of excipient as provided in the European Pharmacopoeia is used: "Excipient (auxiliary substance): Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, antimicrobial preservatives, diluents, antioxidants, for example, are excipients."

The types of substance that will be evaluated in line with this document will generally be excipients (including adjuvants and preservatives) for which a considerable body of knowledge/data is available. The existing knowledge/data may result from existing uses of the substance in fields outside of veterinary medicine (e.g. an existing use in human medicinal products or in cosmetics), or the presence of the substance in an existing commodity (typically food) to which people are regularly exposed.

This document does not relate to the requirements for active substances, for which MRL evaluations are required.

3. Legal basis

Article 6(1) of Directive 2001/82/EC, as amended by Directive 2004/28/EC and Directive 2009/9/EC requires that a veterinary medicinal product may not be subject of a marketing authorisation for food producing species unless the pharmacologically active substances which it contains appear in Annex I, II or III of Regulation (EEC) No 2377/90, which have now been replaced by Table 1 of the Annex to Regulation (EU) No. 37/2010.

4. Background

As described above, the MRL legislation requires that MRL evaluations be undertaken for the pharmacologically active substances present in VMPs for use in food producing species. However, as excipients are not designed to interact with specific physiological systems (even if they may in fact do so), it can be considered that there is no scientific justification for choosing to examine the pharmacological activity of an excipient in one set of tests rather than in another. Furthermore, given the ever expanding range of possible pharmacological systems and tests that could be investigated it would not be possible to entirely rule out the possibility that some pharmacological activity would eventually be seen if the substance were tested ad infinitum. The CVMP therefore considers that it would be unreasonable to require that all excipients be shown to have no pharmacological activity by testing them in pharmacology tests.

The Committee has therefore developed a pragmatic approach for dealing with requests to include excipients in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009: it will consider the totality of the data available on the substance, and come to a conclusion on whether or not a sufficient body of evidence has been presented to conclude that the substance cannot be expected to show pharmacological activity. If it is concluded that no pharmacological activity can be expected, then the substance will be included in the list.

In some cases a company may need to generate new data in order to allow the CVMP to draw a conclusion but in many cases it is anticipated that it will be possible to reach a conclusion based on existing data and on information relating to the proposed use of the substance. It should be noted that old data that do not comply with current guidelines and standards may be submitted and will be given due consideration. However, in reaching its conclusion the CVMP will, of course, take the quality of the data submitted into account.

5. Recommendations

The CVMP does not consider that a precisely defined set of data requirements can be specified for the purpose of demonstrating that a substance cannot be expected to have pharmacological activity. It is envisaged that most applicants will supply a combination of information on the known

pharmacodynamic, pharmacokinetic and safety profile of the substance and relate this to the proposed use of the substance.

Annex I to this guideline provides a template for the report that should be submitted to the CVMP in support of a request to include an excipient in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009. The sections and subsections included in the template do not represent mandatory data requirements. Rather, the template outlines types of data that may be considered relevant and should be completed as comprehensively as possible. Where no data are available for a particular section, the impact of this should be addressed in the overall evaluation.

The CVMP will use the report provided by the company as the basis for its evaluation.

It is envisaged that most requests to include a substance in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009 will need to be evaluated by means of a scientific advice procedure (see http://www.emea.europa.eu/htms/general/contacts/CVMP/CVMP.html for more information on Scientific Advice). However, companies are advised to submit the initial request along with the completed template (provided in Annex I) to the EMEA for presentation to the CVMP. The initial request will be handled outside of the scope of the scientific advice procedure. The CVMP's response to the initial request will then clarify whether a formal scientific advice procedure is necessary. Following the CVMP's initial response the applicant can withdraw the request if it does not intend to initiate a full scientific advice procedure. Fees will only be charged in those cases where formal scientific advice procedures follow and will be in line with standard scientific advice fees. In the case of particularly straight forward enquiries the CVMP may be able to reach a conclusion without the need for a formal scientific advice procedure.

References

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, as amended by Directive 2004/38/EC and Directive 2009/9/EC, available at http://ec.europa.eu/health/documents/eudralex/vol-5/index_en.htm

Commission Regulation (EU) No. 37/2010 of 22 November 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin, available at http://ec.europa.eu/health/documents/eudralex/vol-5/index_en.htm

Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council, available at http://ec.europa.eu/health/documents/eudralex/vol-5/index_en.htm.

Substances considered as not falling within the scope of Regulation (EC) No 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/519714/2009), available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004958.pdf

Annex I

TEMPLATE TO BE COMPLETED IN SUPPORT OF A REQUEST TO INCLUDE A SUBSTANCE IN THE LIST OF SUBSTANCES CONSIDERED AS NOT FALLING WITHIN THE SCOPE OF REGULATION 470/2009

1. Substance name and CAS number (if available)

This section should include INN and IUPAC names as well as all commonly used synonyms.

2. Origin and chemistry of the substance

This section should include information on:

- how the substance is produced
- its chemical make-up including structural formula, molecular formula and molecular weight, available information on impurities (reference to Ph Eur is acceptable)
- a description of its physicochemical properties

3. Intended function of the substance in the veterinary medicinal product

For example, antiadherent, binding agent, filler/diluent, lubricant…

4. Intended use of product (including information on species, age and weight of animals to be treated)

This section should include information on:

- the amount of the substance in the product
- the indication of the product
- the species in which the product will be used
- the age and weight of the animals to which the product will be administered
- the dosing regimen of the product, including the route of administration

5. Existing uses of the substance

This section should include an assessment of the exposure that people receive as a result of existing uses of the substance.

6. Additional background information

Any additional background information considered relevant should be provided here.

7. Pharmacodynamics

Available information on the pharmacodynamic activity of the substance should be described. This may relate to data available in the public domain or to original study data.

If it is considered relevant, the pharmacodynamic activity of chemically related substances may be described.

The conclusions that can be drawn from the information provided in this section should be presented.

Note that if the results of a comprehensive battery of pharmacology tests are provided, and the company is arguing that, based on this evidence alone, it can be concluded that the substance does not possess pharmacological activity, then there may be no need to complete the subsequent sections on toxicology and pharmacokinetics in detail, although these data could be regarded as useful supporting information.

8. Toxicology

Available information on the toxicology of the substance should be described. This may relate to data available in the public domain or to original study data. Where available, data relating to the following areas should be provided:

- Acute toxicity
- Repeat dose toxicity
- Effects on reproduction including developmental effects
- Mutagenicity
- Carcinogenicity
- Other effects (including immunotoxicity and neurotoxicity)
- Microbiological effects
- Known effects in humans

The conclusions that can be drawn from the information provided in this section should be presented.

Note that if results of toxicology studies are provided, and the company is arguing that, based on this evidence alone, it can be concluded that the substance does not represent a consumer safety concern even if high levels of residues do gain access to relevant animal tissues after the intended use of the substance, then there may be no need to complete the section on pharmacokinetics and residue depletion in detail, although these data could be regarded as useful supporting information.

9. Pharmacokinetics and residue depletion

Available information on the pharmacokinetics of the substance should be described. This may relate to data available in the public domain or to original study data.

Data relating to the ability of the substance to gain access to muscle, fat, liver, kidney, milk, eggs or honey may be of particular relevance as these are the target tissues/commodities for which MRLs are derived.

If it is considered relevant, the pharmacokinetic activity of chemically related substances may be described.

The conclusions that can be drawn from the information provided in this section should be presented.

Note that if the results of pharmacokinetic studies are provided, and the company is arguing that, based on this evidence alone, it can be concluded that the substance does not access relevant tissues or milk, eggs or honey after the intended use of the substance, then there may be no need to complete the section on toxicology in detail, although these data could be regarded as useful supporting information.

10. Worst-case estimation of dose to which a consumer may be exposed

While the CVMP has defined pharmacological activity in terms of pharmacodynamic activity at the dose at which the substance is administered to the target animal, the Committee clearly also has a duty to consider what level of residues might be ingested by the consumer. A worst-case estimation of the dose to which a consumer may be exposed should be provided, using reasonable worst-case assumptions.

11. Overall evaluation

The information provided in the preceding sections should be briefly summarised and an overall conclusion drawn and fully justified.

Examples of questions that should be addressed include:

- Do the pharmacodynamic data support the conclusion that the substance has no pharmacological activity at the dose at which it is to be administered to the target animal? What about at the dose to which a consumer may be exposed?

- Does the pharmacokinetic data demonstrate that the proposed use of the substance would not lead to residues in relevant tissues/food commodities?

- Does the available safety data support the view that the proposed use of the substance would not lead to a consumer safety concern, taking the worst-case estimation of the dose to which a consumer may be exposed into account?

- Does experience gained with the substance outside the veterinary medicines field support the view that the proposed use of the substance would not lead to a consumer safety concern, taking the worst-case estimation of the dose to which a consumer may be exposed into account?

Finally, the report should provide a justified explanation as to why it is considered that the substance cannot be expected to have pharmacological activity when used as intended.

12. References

All references cited in the report should be provided in full here. The report should be accompanied by copies of the documents/publications referred to.