European Medicines Agency
Veterinary Medicines and Inspections

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Approaches on how to consider excipients in the context of Regulation 2377/90

1. Background

Article 6 (1) of Directive 2001/82/EC, as amended by Directive 2004/28/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 2377/90.

Regulation (EEC) 2377/90 defines "residues of veterinary medicinal products" as "pharmacologically active substances, whether active principles, excipients or degradation products, and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered".

Requests from companies regarding the MRL status for excipients and questions on how to address excipients in relation to the marketing authorisation application are repeatedly being received at the EMEA. This document compiles the different options regarding excipients as to the abovementioned legal requirements.

2. Approaches

There are basically two different possibilities allowing that an excipient can be part of a veterinary medicinal product intended for food producing species:

1. the substance is included in Annex I, II or III of Regulation 2377/90, and in practice excipients will be in Annex II, or
2. the excipient is considered as not falling into the scope of Regulation 2377/90.

The reason why some substances are in Annex II, some appear in the CVMP "List of substances as not falling into scope of Council Regulation (EEC) No 2377/90", or others need to be considered separately is mainly historical.

Following the publication of Regulation 2377/90 a number of companies submitted applications for substances used in veterinary medicinal products, irrespective of the level of pharmacological action shown by such substances. The CVMP, having reviewed the lists of substances to be considered as candidates for Annex II of Council Regulation 2377/90, considered that some substances were normal components of human food, biologically inert when orally taken, or not classified as chemicals. Consequently, taking account of the scope of Regulation 2377/90, the Committee issued in 1995 a list of substances not falling within the scope of Regulation 2377/90. This list included also some substances for which no formal MRL application had been made as well as substances, which were originally the subject of an intention to submit or even an actual application, but which were subsequently classed as not within the scope of Council Regulation 2377/90.

Where MRL applications had been submitted for substances used as excipients these substances were, following their assessment, mostly included in Annex II of Council Regulation 2377/90.

Furthermore, the CVMP discussed the concept of "pharmacologically active substances" in particular considering the approach to be taken for excipients. The CVMP adopted a Position Paper on the

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definition of substances capable of pharmacological action in the context of Council Directive 2001/82/EC with a particular reference to excipients and manufacturing materials (EMEA/CVMP/072/97-Rev.1[1]), concluding that "*substances capable of pharmacological action are substances pharmacodynamically active at the dose at which they are administered to the target animal by means of the veterinary medicinal product in which they are included"*.

As no legal status was attributed to the so-called "out of scope" list established by CVMP when Council Regulation 2377/90 was amended in March 1997, the CVMP agreed in November 1997 to recommend the inclusion of all active principles in that particular list in Annex II, where appropriate. The CVMP then prepared assessments of the data submitted for the substances concerned and issued accordingly opinions and Summary Reports[2].

Many excipients are also approved food additives and fall under the Annex II entry for "substances with an E-number" which are approved as additives in foodstuffs for human consumption, with the exception of the preservatives listed in part C of Annex III to Council Directive 95/2/EC.

Having concluded the assessment of applications for the establishment of MRLs for "old substances" the EMEA published in the year 2000 a list of those substances, which remained as not being within the scope of Council Regulation 2377/90. This list of substances is, particularly with regard to excipients, in no way exhaustive and includes only substances for which requests in this respect were made to CVMP by a company or a national authority.

Since then, several amendments have been introduced following consideration of further requests and the document has been updated accordingly (see document EMEA/CVMP/046/00-Rev.7).

3. Procedure for an excipient, which is not included in Annex II or in the List of substances as not falling into scope of Council Regulation (EEC) No 2377/90

3.1. Inclusion in Annex II

A company can submit an MRL application. This approach is however in practice nowadays chosen only rarely, as a full MRL application including the payment of the full fee is required.

As the different excipients used are often quite similar amongst a group of substances, a group of substances or a specific substance may be included in Annex II following the original application, whilst similar substances are not included, as they were not mentioned in the original application due to the fact that they ere not used by the company having submitted the application.

In case the original assessment of the CVMP would cover also the similar substance(s), the CVMP would recommend the modification of the existing Annex II entry or the inclusion of the substance in Annex II.

Examples:
- Sodium propionate (sodium propionate does not constitute a new active substance and the assessments for calcium propionate and several sodium salts also apply to the above mentioned substance)
- Sorbitan trioleate (the closely-related substances sorbitan monooleate, sorbitan monostearate, sorbitan tristearate, sorbitan monolaurate and sorbitan monopalmitate being authorised food additives have already been included in Annex II of Council Regulation (EEC) No 2377/90 for all food-producing species, and sorbitan trioleate is not to be regarded as a new active substance)

[1] Initially adopted in April 1997 and further revised in July 2004. the text of 1997 only addressed excipients

[2] For some substances falling under the category "substances generally recognised as safe" no Summary Reports were prepared, but the opinion included a list of criteria for the inclusion in Annex II

In some cases, in order to clarify that a specific substance would be covered by an existent assessment, the specification of the substance concerned in the MRL Summary Report was modified, without amending the Annex II entry itself.

These approaches are based on the concept that no new MRL assessment is necessary, and therefore no detailed scientific data are required. If however a new MRL assessment by the CVMP becomes necessary, a formal application would be required.

3.2. Proof that a substance does not fall under the scope of Regulation 237/90

For excipients it has been agreed that only substances which are pharmacodynamically active at the dose administered to the target species, as a constituent of a veterinary medicinal product, in which they are included, are considered falling within the scope of Regulation 2377/90. Therefore, an excipient that is not pharmacodynamically active at the dose at which it would be administered to the target species in the finished veterinary product does not need to be included in Annex I, II or III of the Regulation. However, evidence is required that the substance is not pharmacodynamically active at the dose at which it will be administered to the target species and such evidence should be included in the Marketing Authorisation application.

Alternatively, in order to establish if the substance is pharmacodynamically active at the dose to be used in the target animal species, the opinion of the CVMP may be sought by means of a request for Scientific Advice.

A scientific advice procedure requires the submission of a scientific file and justification, and the payment of a fee, which would be the same as for a scientific advice on safety or MRL issues.

The substance which are considered as not falling within the scope of Regulation 2377/90 by the CVMP are, with the dose limit, where appropriate, added to the list of substances considered not falling within the scope of Regulation 2377/90.