European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

(CVMP)

REVISED POSITION PAPER ON

THE DEFINITION OF SUBSTANCES CAPABLE OF PHARMACOLOGICAL ACTION IN THE CONTEXT OF COUNCIL DIRECTIVE 2001/82/EC, AS AMENDED, WITH PARTICULAR REFERENCE TO EXCIPIENTS AND MANUFACTURING MATERIALS

ADOPTION OF POSITION PAPER BY CVMP	February 1997
REVISED BY CVMP	October 2002
FINAL ADOPTION BY CVMP	15 July 2004
PRESENTATION TO VMRFG	16 July 2004
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Note:

This Position Paper has been revised in line with changes to the European legislation and to clarify the approach taken for manufacturing materials. No consultation is necessary.

Public

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1. Background

Council Regulation (EEC) No 2377/90 establishes the procedure for the establishment of maximum residue limits for 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. Active principles of biological origin intended to produce active or passive immunity or to diagnose a state of immunity used in immunological veterinary medicinal products are excluded from the scope of the Regulation.

In 1997 the Committee considered the definition of pharmacological action with regard to excipients taking into account the legal requirement that it is a prerequisite for a marketing authorisation of a veterinary medicinal product intended for administration to food-producing animals that the active substance or substances capable of pharmacological action contained in the product are mentioned in Annex I, II or III of Council Regulation (EEC) No 2377/90.

It was noted that many Member State competent authorities would interpret the text as applying to any substance, that has potential to show pharmacological action (i.e. regardless of what concentration the substance is included in the final product), and in particular to excipients. The problem appeared to be a basic one of interpretation of the Directive as to the definition of a substance capable of pharmacological action.

Further to these considerations the CVMP adopted in 1997 a Position Paper on the definition of substances capable of pharmacological action in the context of Council Directive 81/851/EEC with particular reference to excipients (EMEA/CVMP/072/97-FINAL) establishing the principle that pharmacologically active substances should be interpreted as substances which are 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.

In 2001 Council Directive 81/851/EEC was replaced by Council Directive 2001/82/EC, which was subsequently amended by Council Directive 2004/28/EC. Therefore, an update of the position paper with regard to the legal references (Article 6 of Council Directive 2001/82, as amended) was required. Article 6 states:

"A veterinary medicinal product may not be the subject of a marketing authorisation for the purpose of administering it to one or more food-producing species unless the pharmacologically active substances which it contains appear in Annexes I, II or III of Regulation (EEC) No 2377/90."

The Committee took this opportunity to also clarify the approach to be taken for manufacturing materials with regard to the establishment of MRLs. Further considerations are still ongoing with regard to adjuvants and the present text will be revised once the approach regarding adjuvants has been finalised.

2. Current Position

General

As a general principle the potential for toxicity of any substance included in a veterinary medicinal product should be addressed in the safety file for applications for the granting of marketing authorisations.

Excipients included in veterinary medicinal products intended for administration to food producing animals

The CVMP considers that substances capable of pharmacological action are substances which are 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. Therefore, one substance can potentially be considered as non-pharmacologically active when incorporated at a specific

concentration in one veterinary medicinal product but be capable of pharmacological action when incorporated at a different concentration in another product.

Excipients considered not to have pharmacological activity do not fall within the scope of Council Regulation (EEC) No 2377/90 and therefore do not require to be included in Annex I, II or III of the Regulation prior to granting a marketing authorisation for a veterinary product containing such excipients.

In order to establish if an excipient can be considered excluded from the scope of the Regulation (EEC) No 2377/90, appropriate data to demonstrate the absence of such activity at the dose at which it is included in the final formulation have to be provided with the application for the marketing authorisation or independent of an application for a marketing authorisation as a request for scientific advice.

Should the substance be pharmacologically active at the doses at which it is administered to the target animals an MRL application would be required. In this case the inclusion of the substance in Annex I, II or III of the Regulation would be a prerequisite to the granting of a marketing authorisation for the veterinary medicinal product containing such substance.

Manufacturing materials

Substances used in the manufacturing process of the active ingredients, which are not intended to be present in the final product, but of which traces only might be present, are considered as not falling within the scope of Council Regulation (EEC) No 2377/90.