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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

REFLECTION PAPER ON

CONSIDERATION OF ADJUVANTS AND PRESERVATIVES UNDER COUNCIL REGULATION (EEC) No 2377/90 LAYING DOWN A COMMUNITY PROCEDURE FOR THE ESTABLISHMENT OF MAXIMUM RESIDUE LIMITS OF VETERINARY MEDICINAL PRODUCTS IN FOODSTUFFS OF ANIMAL ORIGIN

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Comments should be provided electronically to vet-guidelines@emea.europa.eu

Or by Fax +44 20 7418 8447

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. INTRODUCTION

In 1997 the Committee addressed the approach for excipients with regard to Council Regulation (EEC) 2377/90 and concluded that excipients considered not to have pharmacological activity did not fall within the scope of Regulation No 2377/90 and therefore were not required 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. The CVMP approach was reflected in the CVMP 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).

In 2001, the Position Paper mentioned above was updated to take into account new legal references and the Committee took the opportunity at that time to also clarify the approach to be taken for manufacturing materials concluding that substances used in the manufacturing process of the active ingredients, and which were not intended to be present in the final product, but which could be present in trace amounts, were considered as not falling within the scope of Regulation No 2377/90 (EMEA/CVMP/072/97-Rev.1).

The approach with regard to adjuvants was also discussed and the CVMP concluded that further considerations were still required.

No consideration was given at that time on the approach with regard to preservatives.

2. LEGAL BASIS AND SCOPE

This document intends to clarify the approach for considering adjuvants and preservatives with regard to Regulation No 2377/90.

Article 6(1) of Directive 2001/82/EC states that:

"*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.*"

Regulation No 2377/90 considers 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.

3. PROPOSED APPROACH FOR ADJUVANTS AND PRESERVATIVES

3.1 General considerations

Adjuvants are excipients used in immunological products due to their capacity to increase and/or prolong the immune response to the active ingredient. This activity is a matter separate from their potential pharmacological activity.

Preservatives are excipients used to kill or limit the growth of microorganisms in veterinary medicinal products prior to administration of the product. As is the case for adjuvants, the desired effect of preservatives is a matter separate from their potential pharmacological activity.

In order to establish whether an adjuvant or a preservative is pharmacologically active the same approach as detailed in the CVMP Position Paper EMEA/CVMP/072/97-Rev.1 applies:

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 considered capable of pharmacological action when incorporated at a different concentration in another product.

Adjuvants and preservatives considered not to have pharmacological activity do not fall within the scope of Regulation No 2377/90 and therefore are not required 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 adjuvant or a preservative can be considered excluded from the scope of Regulation No 2377/90, appropriate data to demonstrate the absence of pharmacological activity at the dose at which the substance is included in the final formulation have to be provided either with the application for marketing authorisation, or independently of the 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 the substance.

4. FUTURE STEPS

Following public consultation and consideration of comments received it is intended that the approach for considering adjuvants and preservatives with regard to Regulation No 2377/90 would be incorporated in the CVMP 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-Rev.1).