European Medicines Agency
Veterinary Medicines and Inspections

EMEA/CVMP/638/04-FINAL

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON THE NEED TO ELABORATE SPC GUIDANCE TO MINIMISE THE DEVELOPMENT OF ANTHELMINTIC RESISTANCE

ADOPTION BY EWP	18 June 2004
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	15 July 2004
START O CONSULTATION	16 July 2004
END OF CONSULTATION	15 October 2004

Public
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.eu.int http://www.emea.eu.int

European Medicines Agency
Veterinary Medicines and Inspections

CVMP/EMEA/638/04-FINAL
London, 14 July 2004

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

DRAFT CONCEPT PAPER ON THE NEED TO ELABORATE SPC GUIDANCE TO MINIMISE THE DEVELOPMENT OF ANTHELMINTHIC RESISTANCE

- **Introduction**

Concern has been raised that the current (VICH) guidelines on efficacy of anthelminthics might not sufficiently address the possibility of development of anthelmintic resistance and leading experts are currently discussing this issue. Meanwhile it is important to maintain the efficacy of new and existing veterinary medicinal products.

- **Problem statement**

Resistance to anthelmintics has reached significant levels in countries of the Southern hemisphere. Main causes for this may be that the climate is more favourable to maintain continuous cycles of development for e.g. gastrointestinal strongyles all year round, and also the abundant use of anthelmintics in those areas. In Europe, some information is available about an increase in anthelmintic resistance in recent years. These reports relate mostly to benzimidazole resistance in ovine, caprine and equine parasites and to a lesser extent to levamisole resistance in ovine parasites and to avermectins/milbemycins.
Problems to determine anthelmintic resistance are the limited knowledge of the mechanisms of resistance and lack of standardised methods to determine resistance to anthelmintics.

- **Discussion**

Member States were requested to provide information on anthelmintic resistance available in the regulatory agencies via the VMRF Group. In addition, published reports have been used as background information about the extent of the resistance problem. In summary, there are only limited data available on anthelmintic resistance and resistance seems to concern only a limited number of animal and parasite species. The resistance problem is probably only limited to some anthelmintics (mainly benzimidazoles). However the situation may be underestimated.

Based on information available in Europe, the following information on resistance have been reported:

In sheep, benzimidazole resistance has been described in *Teladorsagia, Haemonchus contortus, Cooperia curticei,* and / or *Trichostrongylus spp*. and triclabendazole resistance in *Fasciola hepatica*. In goats, benzimidazole resistance has been found in *Haemonchus contortus, Teladorsagia circumcincta, Cooperia curticei* and *Trichostrongylus colubriformis*. Cases of resistance to levamisole and avermectins are also reported. In cattle, information on sporadic resistance has been reported for ivermectin, benzimidazole and levamisole in some European countries. In horses, the prevalence of benzimidazole resistance against cyathostome infestations is high.

Development of a population of parasites with resistance against anthelmintics is a progressive process, which could result in genetic resistance. The selection is considered to be linked to repeated misuse of anthelmintics. The higher the frequency of use is, the greater the selection pressure becomes. The highest risk for the development of resistance is caused by frequent anthelmintic use during the prepatent period of parasites. Several types of resistance have been described, from resistance of the

parasite to a group of substances with the same mode of action, to resistance to a group of substances with different modes of action. Incorrect dosing favours occurrence of anthelmintic resistance, hypothesised to be the case for benzimidazoles.

Prudent use guidance could be of help in preventing or slowing down the emergence of resistance. This guidance could include recommendations to improve management systems (hygienic measures, pasture rotation, rotation of product class, treatment age, timing of treatment, exposure of animals to permit development of immunity) and specific guidance in the product literature. The former is, however, outside the mandate of the EWP / CVMP.

SPC guidance on anthelmintic resistance could be addressed on two levels:

1. Dossier requirements and assessment criteria.
2. Prudent use issues - guidance linked to the data in the dossier or more general guidance related to risk management issues.

It is acknowledged that SPC guidance will have little impact on resistance without appropriate use by veterinarians and farmers.

- **Anticipated benefit to:**

- **Industry and Other Interested Parties**

A guidance document would give more guidance on recommendations in the SPC and product literature of veterinary medicinal products containing anthelminthics on the use of the product regarding anthelmintic resistance. By concerted use, the quantity of product consumed by the animal will be lower but a longer life for the products on the market could be expected.

Maintaining the efficacy of anthelmintic products is beneficial to animal and consumer health, and in food animals also improves the profitability of the farming.

- **Regulatory Authorities**

This guidance will help in harmonising the product literature for anthelmintic products. The document will give guidance for the assessors on requirements for SPC instructions and warnings.

- **Recommendation (points to be addressed)**

In the absence of detailed information on mechanisms of resistance, the EWP recommends that more guidance on the prudent use of anthelmintics should be given in order to prevent or slow down the emergence of resistance, if possible. The recommendations for warnings and instructions to be included in the product literature could cover the following:

- Product literature (SPC and package insert) of anthelmintics intended for use in food-producing animals should clearly state if resistance has been detected for the active substance in a particular parasite in Europe.
- Level of resistance on the farm should be determined before the use of the product if resistance has been shown in any area, in any species.
- The use of anthelmintic groups to which there is resistance should be discontinued.
- Management strategies should be addressed such as hygienic measures, quarantine measures, treatment of adult animals only if necessary and measures to ensure the correct dosage (avoiding under- or overdosage).

- **Timetable**

4Q/2005 Draft guideline to be prepared by the EWP

2Q/2006 Draft guideline to the CVMP for adoption for consultation

- **Resource requirements for preparation**

Rapporteurs to prepare the draft guideline. Member States to provide input.

- **Impact for Industry and other Interested Parties**

It is considered that the guideline would have minimal impact on industry and other interested parties in respect to the resources and costs. The guideline should improve information on product literature regarding the practical application of anthelmintics to different husbandry systems.

One anticipated criticism from industry might be the use of standard phrases instead of product and dossier specific information in the product literature.

- **Impact assessment for Regulatory Authorities**

The guideline would have no additional resource issues for regulatory authorities.