The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMEA/CVMP/457/03

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

POSITION PAPER REGARDING AVAILABILITY OF VETERINARY MEDICINAL PRODUCTS – EXTRAPOLATION OF MRLs

ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	14 May 2003
START OF CONSULTATION	15 May 2003
END OF CONSULTATION	15 September 2003
ADOPTION BY CVMP FOLLOWING CONSULTATION	10 December 2003

Public

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POSITION PAPER REGARDING AVAILABILITY OF VETERINARY MEDICINAL PRODUCTS – EXTRAPOLATION OF MRLs

Background

The Committee for Veterinary Medicinal Products (CVMP) has in recent years considered in detail the problem of the lack of medicines to treat certain diseases in major species, and in minor species in general, and communicated its concerns and proposals at several occasions in various CVMP documents, which are listed below:

- Position Paper on Availability of Veterinary Medicines adopted 18 March 1999 (EMEA/CVMP/151/99-FINAL)
- Updates on the Position Paper in respect to the progress to salvage essential substances and establish MRLs for these of 12-14 October (EMEA/CVMP/731/99-FINAL), 9 February 2000 (EMEA/CVMP/130/00-FINAL) and of 21 June 2000 (EMEA/CVMP/411/00-FINAL)
- Position Paper regarding Availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03-CONSULTATION)

The present document addresses uniquely the aspect of the establishment of MRLs in relation to veterinary medicinal products for food-producing animals.

Having completed the task of setting MRLs for existing substances in accordance with Article 7 of Council Regulation (EEC) No. 2377/90, the CVMP conducted a review of the risk assessment approach for the establishment of MRLs, with a view to establishing a more pragmatic approach in securing the provision of medicines for treating animals, especially those classed as minor species, whilst at the same time guaranteeing consumer safety. The outcome of this review resulted in the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL) which provides for the extrapolation of MRLs to additional species or even all food-producing animals, if certain requirements regarding the availability of analytical methods for these additional species are fulfilled. This guideline was expected to present an incentive to industry to develop urgently needed veterinary medicinal products for certain animal species.

The approach on how to implement this Note for Guidance was explained in the CVMP Document on the Implementation of the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/069/02). The CVMP reported that for 12 substances meeting the criteria stated in the Note for Guidance and qualifying for the extrapolation to the existing MRLs to all food producing species, the appropriate extensions had been recommended by the CVMP without formal applications. In the meantime these recommendations have been converted into legislation by the European Commission and the MRLs have been published in the Official Journal of the European Communities.

The document stated also that the CVMP had concluded that further “automatic” extrapolations of MRLs to additional species would not be undertaken at that stage, but that specific applications from the veterinary pharmaceutical industry for extensions of MRLs to additional animal species would be required. The “automatic” review of all species specific MRLs with the view of extrapolating them if the requirements of the Note for Guidance mentioned above were met would have placed considerable demands on the resources of the CVMP and its Safety Working Party. It was noted that in all likelihood many of the theoretically possible extrapolations were in practice not relevant, as they would in many cases relate to species for which the substances concerned would not be used and for which marketing authorisations were not be intended. However, it was also concluded that the EMEA would continue exploring this matter further.

"Automatic" extrapolation of existing MRLs

The EMEA, having reflected further on the practical experience gained with the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin with particular attention as to whether an increased number of applications for extensions of existing MRLs to additional species have been submitted, noted with some disappointment that not much interest had been shown in submitting such applications.

The EMEA recognised that MRLs are only the first step in the pathway for obtaining a marketing authorisation for a veterinary medicinal product for food-producing animals and the subsequent introduction into the market, and had highlighted already previously the need for the consideration of other elements beyond the consumer safety requirements in the debate to overcome the availability problem. However, considering that the existence of an MRL could nevertheless provide an incentive for industry to develop the required products, the CVMP agreed to examine the possibilities to establish MRLs for substances, which are considered essential for certain therapeutic indications in certain species for which no alternatives would be available. The CVMP therefore agreed to identify a list of essential substances, for which MRLs had been established for one or more species, but where they were lacking for other species, with the objective to extend the existing MRLs to these additional species. Having set MRLs for these it is hoped that companies would be in a better position to identify possible market opportunities and develop the remaining studies necessary to obtain a marketing authorisation.

In identifying those substances which are regarded as essential and therefore qualifying as candidates for such extrapolations the CVMP reconfirmed that the activity should not be exhaustive to consider all substances that qualify for MRL extrapolation, but instead concentrate on specific areas where a shortage of veterinary medicines for certain minor species is recognised. It was defined as a stepwise process identifying a list of essential substances for a certain minor species and therapeutic indication, and establish MRLs for these, possibly to be followed by similar actions for other minor species. As additional criteria, it was agreed that the identified essential substances should have generic status thus not providing an exclusive marketing advantage for a specific company, and that products containing the particular substances/species concerned would have been on the market before 2000 but MRLs would not have been set in these species. Finally, the substances and their MRLs would need to qualify for MRL extrapolation in accordance with the CVMP Note for Guidance, especially in relation to the available analytical methods.

As a first step substances essential for the treatment of sheep and goats were identified. Veterinary medicinal products urgently needed were products containing agents against ecto- and/or endo-parasites, and also the corticosteroid dexamethasone for the treatment of inflammatory diseases was identified as being essential to be available for the treatment of sheep and goats.

> Having reviewed the available analytical methods and the existing MRLs in order to establish if, an extrapolation in accordance with the Note for Guidance would be possible, the CVMP identified the substances qualifying for an "automatic" extrapolation, i.e. under the availability activity without having received an application for MRL extension.

Consultation and conclusions

This proposal was published for consultation and Interested Parties were invited to comment on the approach as such as well as on the individual substances concerned. The CVMP indicated in the consultation document its willingness to examine the possibility of extrapolating existing MRLs to sheep and goats for urgently needed substances from the same therapeutic groups as the abovementioned substances upon request from companies intending to develop products. . The CVMP clarified that however for any other extension of MRLs applications for the requested extension would continue to have to be submitted in accordance with Article 6 of Regulation 2377/90. Further to the consultation the CVMP would review whether similar actions in respect to other minor species should be repeated in the future.

During the consultation proposals for extrapolation of further ecto- and/or endo-parasitisites were received, which were considered by the CVMP as to whether they fulfilled the criteria established before.

Regarding proposals received during the consultation period for the extrapolation of existing MRLs for substances other than anti-parasitic agents (a β-adrenergic substance and several antibiotics) to sheep and/or goats within the availability exercise, the CVMP concluded that these other therapeutic classes could not be considered as essential.

The CVMP agreed to recommend the following extrapolations of existing MRLs in accordance with the Note for Guidance (List of substances and outcome of analysis and consideration of proposals: see Annex 1, considerations regarding ivermectin and levamisole are still ongoing):

1. Albendazole: Extrapolation of existing MRLs to all ruminants including milk
2. Febantel: Extrapolation of existing MRLs to all ruminants including milk
3. Fenbendazole: Extrapolation of existing MRLs to all ruminants including milk
4. Oxfendazole: Extrapolation of existing MRLs to all ruminants including milk
5. Oxyclozanide: Extrapolation of existing MRLs to all ruminants including milk
6. Thiabendazole: Extrapolation of existing MRLs to goats including milk
7. Amitraz: Extrapolation of existing MRLs to goats including milk
8. Cypermethrin: Extrapolation of existing MRLs to all ruminants including milk
9. Deltamethrin: Extrapolation to all ruminants including milk
10. Dexamethasone: Extrapolation of MRLs to goats including milk

For other substances not belonging to the therapeutic groups above, or for substances where data are lacking a MRL extension by extrapolating the existing values will only be considered upon receipt of an application for the extension of MRLs, supported by the appropriate data in accordance with the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL).

The CVMP however agreed to continue with the activity of extrapolating MRLs for essential substances to other minor species or other areas of lack of veterinary medicines without specific applications. As a priority the CVMP would address the extrapolation of MRLs from chicken to poultry. The CVMP remains also open to consider proposals for extrapolations for other urgently needed substances or species.

Progress report on other MRLs issues

– Essential substances with no MRL at all –

The CVMP also reviewed the situation regarding urgently needed substances for veterinary therapy for which however no MRL at all exists. The CVMP had considered this matter already before in 1999 and 2000. On these occasions the CVMP identified the essential substances among those compounds that had been used in authorised veterinary medicines prior to the deadlines for the implementation of Regulation 2377/90 of 31 December 1997 and 1999, respectively, but for which no MRL could be established. After 31 December 1997 the pre-condition for a marketing authorisation was that the substance had been defended, i.e. a MRL application had been submitted, and after 31 December 1999 all substances had to be included in Annex I, II or III of Regulation 2377/90. The reasons that no MRL could be established were that either insufficient data were provided by the sponsors, the applications for establishing MRLs had been withdrawn by the applicant companies or the substances had not been defended at all (for reference, see CVMP Position Papers listed under "Background"). It was recognised that the problems identified at that time in respect to certain indications and species unfortunately remain unchanged, and no undertaking by industry or other institutions to carry out the necessary studies to establish MRLs are reported. Whether it would be possible that safety data on these substances can be generated through any public funding will be further explored as it is further elaborated in the Position Paper regarding Availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03-CONSULTATION).

A lack of authorised veterinary medicines is specially noted for the sectors of aquaculture and apiculture, where it has been reported that chemical substances not having undergone a safety assessment in accordance with the legislation on veterinary medicines are sometimes used for the treatment of diseases.

Consultation and conclusions
The CVMP's next activities in this field will concern the review of data requirements for the establishment of MRLs for veterinary medicines for use in apiculture and the availability of MRLs for substances suitable for treatment of histomoniasis in poultry, particularly in turkeys.

– **Annex II substances** –
The CVMP also reviewed all species-specific Annex II entries with the view of possible extensions to all food producing species provided that the criteria for Annex II classification according to the aforementioned CVMP Note for Guidance on Risk Analysis Approach were fulfilled. The analysis of all the species specific Annex II entries showed that the vast majority of these were scientifically justified and had to be maintained, and only 10 substances would quality for an extension to all food producing species or additional species, as appropriate, taking account of consumer health concerns and the data available (list of substances: see Annex 2).

As the substances eligible for extension appear in general to have little relevance, the CVMP considered no need for any action unless specific requests from the veterinary pharmaceutical industry would be made. Examples of substances for which such requests have been made include acetylsalicylic acid and sulphur and extensions of the Annex II entries have now been recommended.

In addition, the CVMP noted the need for authorised veterinary medicinal products containing the substance lidocaine for further species, in particular cattle and other ruminants and pigs. Lidocaine is included in Annex II, however only for horses and with the restriction for local-regional anaesthesia. The reasons for the limitation to *Equidae* species of the Annex II entry were that genotoxicity studies carried out with the lidocaine metabolite 2,6-xylidine had equivocal results, which indicated that 2,6-xylidine is a mutagenic agent *in vitro* and has genotoxic characteristics *in vivo*. As pharmacokinetic data were available in horses showing a rapid metabolism and extensive excretion of lidocaine in this species, it was possible to recommend the inclusion of lidocaine in Annex II for horses, for the abovementioned use. However, in absence of adequate studies providing information regarding potential residues for other species an extrapolation of these conclusions to other species was not possible. (see CVMP Summary Report for Lidocaine, EMEA/MRL/584/99-FINAL, July 1999). It is hoped that industry would develop the missing data in order to allow the extension of the Annex II entry, the existing marketing authorisations and the veterinary medicinal products, so that lidocaine can also be used in the other species for which it is much needed.

Consultation and conclusions

Proposals for extension of Annex II entries to aditional species were received during consultation for 5 specific substances not listed in Annex 2. Having reviewed the proposals the CVMP concluded that, as a general rule, any such extensions could only be considered on the basis of specific applications and providing additional data.

The CVMP agreed to provide free scientific advice regarding the data requirements for extension applications for minor species/minor uses products as a pilot project for a period of 12 months.

Annex 1

Substances, which are essential for sheep and goats

Substance	Indication		Species for which MRLs exist	Consideration of requirements of NfG and criteria	Proposal
Agents acting against endoparasites:					
Albendazole	Gastrointestinal infestations with roundworms, lungworms, tapeworms and adults flukes of *F.hepatica*		Bovine and ovine (including milk)		Extrapolation to all ruminants (including milk)
Febantel	Gastrointestinal infestations with roundworms, lungworms and tapeworms		Bovine, ovine, porcine, *Equidae*		Extrapolation to all ruminants (including milk)
Fenbendazole	Gastrointestinal infestations with roundworms, lungworms and tapeworms		Bovine and ovine (including milk), porcine, *Equidae*		Extrapolation to all ruminants (including milk)
Oxfendazole	Gastrointestinal infestations with roundworms, lungworms and tapeworms		Bovine and ovine (including milk), porcine, *Equidae*		Extrapolation to all ruminants (including milk)
Oxyclozanide	Fascioliasis		Bovine (including milk) and ovine tissues		Extrapolation to all ruminants (including milk)
Thiabendazole	Gastrointestinal roundworms		Bovine including milk	Due to lack of appropriate residue data for sheep no extrapolation possible without application and additional data	Extrapolation to goats (including milk)
Triclabendazole	Fascioliasis		Bovine and ovine tissues	Due to lack of data no extrapolation possible without application and additional data	

Agents acting against endoparasites:					
Rafoxanide	Fascioliasis		Bovine and ovine (milk not included)	MRLs between species not similar, therefore no extrapolation possible. For MRL extension, applicaton and further data would be necessary	
Closantel	*F. hepatica*		Bovine and ovine (milk not included)	Due to lack of data no extrapolation without application and additional data	
Levamisole	Gastrointestinal infestations and lungworms		Bovine, ovine, porcine, poultry.	No "automatic" extrapolation at present. Available data to be further reviewed before final decision can be taken	
Morantel	Gastrointestinal infestations with roundworms and tapeworms		Bovine, ovine, porcine,	No valid MRL at present to consider extrapolation	
Agents acting against endo- and ecto parasites: Avermectins					
Abamectin	Endo-ecto parasites		Bovine and ovine	No products for goats were authorised before 2000. Therefore, extension/extrapolation of MRLs only upon application.	
Doramectin	Endo-ecto parasites		Bovine, ovine, deer, porcine	No products for goats were authorised before 2000, generic status not confirmed. Therefore, extension/extrapolation of MRLs only upon application.	
Ivermectin	Endo-ecto parasites		Bovine, ovine, deer, porcine, *Equidae*	No "automatic" extrapolation at present. Available residue data to be further reviewed before final decision can be taken	
Moxidectin	Endo-ecto parasites		Bovine, ovine, *Equidae*	Proprietary molecule. Therefore, extension/extrapolation of MRLs only upon application	
Agents acting against ectoparasites:					

Amitraz	Ectoparasites		Bovine and ovine (including milk), porcine, honey bees		Extrapolation to goats (including milk)
Cypermethrin	Ectoparasites		Bovine (including milk), ovinetissues, *Salmonidae*		Extrapolation to all ruminants (including milk)
Deltamethrin	Ectoparasites		Bovine (including milk), ovine tissues, chicken, *Salmonidae*		Extrapolation to all ruminants (including milk)
Corticoids					
Dexamethasone	Inflammatory diseases, ketosis		Bovine (including milk), porcine and *Equidae*	Due to lack of residue data for sheep no extrapolation without application and additional data	Extrapolation to goats (including milk)

Annex 2

Species specific Annex II entries eligible for extension

	Pharmacologically active substance(s)	Animal species	Other provisions	Therapeutic use	Possible extension
1	Acetylsalicylic acid and salts	Bovine, porcine and chickens	Not for use in animals from which milk or eggs are produced for human consumption	Anti-inflammatory, antipyretic and analgesic agent	Extension to all food producing species.
2	Sodium chlorite	Bovine	For topical use only	Teat dip (mastitis)	Extension to ovine and caprine only
3	Diethylene glycol monoethyl ether	Bovine, porcine		Excipient	Extension to all food producing species.
4	Hesperidin	*Equidae*		Vascular protectant in horses	Unlikely to be useful in other species
5	Hesperidin methyl chalcone	*Equidae*		Vascular protectant in horses	
6	Hexetidine	*Equidae*	For topical use only	Antiseptic, antifungal and antiparasitic agent, used in shampoo and dermal dressings in horses (also in cats/dogs). Also known to be used as teat dip/spray.	Extension to bovine, ovine and caprine only
7	Methyl nicotinate	Bovine, *Equidae*	For topical use only	Rubefacient, treatment of respiratory diseases, vascular disorders, rheumatoid disorders in cattle & horses, topical use.	No information on possible use in other species. Extension to all mammalian food producing species only
8	Terpin hydrate	Bovine, porcine, ovine, caprine		Antiseptic agent and expectorant (oral, iv/sc/im injection)	Extension to all mammalian food-producing species only
9	Oxidation products of *terebinthinae oleum*	Bovine, porcine, ovine, caprine	For topical use only	Topical use, mastitis, rubefacient, treatment of tendonitis and rheumatic disorders.	Extension to all mammalian food-producing species only
10	Sulphur	Bovine, porcine, ovine, caprine, *Equidae*		Antiseptic, antiparasitic, anti-acne, antiseborrheic agent (topical route) in bovine, ovine, caprine, equine. Nutritional supplement in herbivores (oral route).	Extension to all food producing species