The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

EMEA/CVMP/143/99 –**Rev 1**

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE:

CONDUCT OF PHARMACOVIGILANCE FOR VETERINARY MEDICINAL PRODUCTS AUTHORISED THROUGH THE MUTUAL RECOGNITION PROCEDURE

DISCUSSION IN PHARMACOVIGILANCE WORKING PARTY	March 1999 (written procedure)
ADOPTION BY CVMP	March 1999
REVISION BY CVMP	August 1999

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8668
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

Conduct of Pharmacovigilance for Veterinary Medicinal Products Authorised through the Mutual Recognition Procedure

I. INTRODUCTION

The objective of this paper is to develop a framework whereby all medicinal products for veterinary use authorised through the procedure of mutual recognition (MR) are closely monitored to allow timely evaluation of new information relevant to the risks and benefits of these products, so that appropriate action may be taken, when necessary, to protect animal and/or public health. Products covered by these procedures include those authorised through mutual recognition, ex-concertation products and those referred under Articles 20 and 23 of Council Directive 81/851 EEC.

The responsibility for the conduct of pharmacovigilance of any MR products rests with the Competent Authorities of all individual EU-Member States of the European Union (MS) who have granted the authorisation. For products authorised by the national procedures, a description of the conduct of pharmacovigilance is included in the general chapter " Conduct of Pharmacovigilance for Competent Authorities."

The process of MR is facilitated by the Veterinary Mutual Recognition Facilitation Group (VMRFG). It acts to support the development of consensus where differences of opinions arise so as to minimise the need for arbitration. For practical reasons, the Committee for Veterinary Medicinal Products (CVMP) and its Pharmacovigilance Working Party (PhVWP) advise Member States (VMRFG) on issues of scientific relevance. It should however be noted that this facilitation mechanism in no way changes the legal obligations for reporting of adverse reactions by all parties concerned nor for referrals to the CVMP as appropriate.

Because of the need to co-ordinate the process of pharmacovigilance and any consequential regulatory action across all relevant MS a standard operating procedure for the conduct of pharmacovigilance for MR products is necessary; this will reduce duplication of work and facilitate harmonisation between MS.

This paper presents:

- principles relevant to the conduct of pharmacovigilance for MR Products.
- a procedure for the conduct of pharmacovigilance for these products.
- the specific roles of the different parties involved in carrying out these functions

The procedures outlined in this document apply once a product has entered the MR procedure or falls within it by virtue of being part of the concertation procedure or following referral under Articles 20 and 23.

II. LEGAL FRAMEWORK

Council Directive 81/851/EEC as amended by Directive 93/40/EEC and Commission Regulation (EC) No. 541/95 as amended, set the basis for the authorisation and variation of veterinary medicinal products through the MR procedure and for pharmacovigilance thereafter. Pharmacovigilance procedures and obligations of marketing authorisation holders (MAH), Competent Authorities and the European Agency for the Evaluation of Medicinal Products (EMEA), which includes the CVMP and the Secretariat are outlined in a number of documents which will form the basis for a Community guide on Pharmacovigilance, Volume 9 of "The Rules Governing Medicinal Products in the European Union", Commission Regulation (EC) No. 541/95 as amended, provides the legislative basis for variation of MR marketing authorisations including urgent safety restrictions.

III. PRINCIPLES AND PARTIES INVOLVED

The responsibilities and functions of the various partners involved in the MR procedure are defined in the legislation for the handling of marketing authorisations and subsequent variation applications. Although there are no equivalent legislative procedures defined for the handling of pharmacovigilance issues which arise for products which have been authorised by mutual recognition Member States have agreed that similar principles should also be applied to the conduct of pharmacovigilance for MR products, with the Reference Member State (RMS) taking the lead in pharmacovigilance in close co-operation with Concerned Member States (CMS). The role of the relevant parties is presented below:

Reference Member State (RMS)
For practical reasons Member States have agreed that the RMS should be assigned responsibility for evaluating all pharmacovigilance issues relevant to a MR product, for providing assessment reports to the CMS to an agreed timetable and presenting the issues which need to be considered as appropriate by the Veterinary Pharmacovigilance Working Party (PhVWP). The RMS will be responsible for liasing with the MAH on all such matters. In cases where the original RMS expresses its inability to carry out these functions, another MS may be assigned to act as RMS. In situations where a class-related effect is identified for products with different RMS, a "lead" RMS may be appointed by agreement between the relevant RMS to take forward evaluation of the class-related effect.

Concerned Member State (CMS)
Competent Authorities of all CMS have a responsibility to continuously collect information on ADRs and play an important role in identifying and evaluating possible alerts of drug safety hazards for MR products. The CMS will work closely with RMS on such issues, and will respond to proposals from RMS within the agreed timetable.

Competent Authorities
All Competent Authorities are responsible for ensuring implementation of regulatory action in their MS. The PhVWP facilitates co-ordination of pharmacovigilance of MR products across MS (CMS and RMS) and the development of consensus to reach conclusions and agree proposed actions where differences arise between MS.

Veterinary Pharmacovigilance Working Party (PhVWP)
The PhVWP facilitates co-ordination of pharmacovigilance of MR products across MS and the development of consensus on conclusions and proposed actions. The PhVWP will be the forum for discussing all pharmacovigilance issues relevant to MR products. The present mandate of the PhVWP encompasses consideration of issues at the request of the CVMP and at the request of MS. These issues are addressed as clearly defined separate parts of the PhVWP agenda.

Veterinary Mutual Recognition Facilitation Group (VMRFG)
The VMRFG will be kept closely informed on issues relevant to it i.e. variations for safety reasons by the provision of the minutes of the PhVWP and the attendance of the PhVWP chairperson at the VMRFG on invitation as necessary.

EMEA Secretariat and CVMP
The CVMP becomes involved in issues relevant to MR products whenever there is a procedure according to Council Directive 81/851/EEC Article 20, 23a or 23b. The EMEA Secretariat accept to (1) provide administrative support to the PhVWP, (2) co-ordinate all activities in the event of referral to the CVMP and (3) be kept informed according to Council Directive 81/851/EEC Articles 21 and 23.

European Commission
The European Commission is the Competent Authority for the adoption of any decisions relating to veterinary medicinal products which have been adopted as a result of referrals according to Article 20 and 23a of Council Directive 81/851/EEC as amended.

Marketing Authorisation Holders (MAH)
The MAH is obliged to adhere to the legal requirements of pharmacovigilance (spontaneous reporting of ADRs, submission of PSURs and other information) for MR products as for any other nationally authorised products. Member States have agreed that the RMS will act as the primary liaison with the MAH, specifying issues requiring clarification, further information or specific actions by the MAH. This will be clearly presented in writing to the MAH by the RMS working closely with CMS. Meetings with the MAH should involve the RMS, and any other CMS by request. The conclusions of such meetings should be distributed to the PhVWP members and members of VMRFG.

IV Functions and Procedures

IV.A Reporting, Distribution and Evaluation of Information relevant to Pharmacovigilance of MR Products

1. During the Process of Consideration of a MR Application

In the interim time between an application for a marketing authorisation through the MR procedure and completion of this process, information relevant to the safety of the product may become available from the applicant, or MS or third countries where the product is already marketed. Since it is essential for this information to be included in the risk /benefit evaluation, the applicant is responsible for immediately informing the RMS and the other CMS. The RMS will assess whether this new information alters the overall assessment, releasing an amended assessment report as necessary.

2. After Completion of the MR Authorisation

2.1 Spontaneous single case reports

All MS Competent Authorities have spontaneous ADR reporting schemes whereby veterinarians and MAH report suspected ADRs to veterinary medicinal products. Directive 81/851/EEC lays down specific obligations on MS Competent Authorities and MAH on the expedited reporting of suspected ADRs. MS are responsible for collecting, collating and evaluating reports occurring in their respective territory. Those from outside the EU are sent by the MAH to all CMS, however Member States have assigned responsibility to the RMS to collate and to evaluate these. It is particularly important for the RMS responsible for the overall pharmacovigilance evaluation of a MR product to have access to all of the relevant information.

2.2 Periodic Safety Update Reports (PSURs) and other relevant post-authorisation information

The MAH is required to provide all Competent Authorities with PSURs and relevant safety information from post-authorisation commitments, post-authorisation studies, world literature, or other sources as outlined in the Directive 81/851/EEC and guidance for MAH. Any consequential variation should be submitted by the MAH at the same time. RMS has agreed to evaluate the information, to identify any possible hazard, and to circulate an assessment report to the CMS within 6 weeks of receipt. CMS should respond within 3 weeks of receipt of the RMS assessment report. This assessment report will, if requested by the RMS or CMS, be discussed at a PhVWP meeting, with the agreement of the CVMP.

2.3 Signal generation

It is possible that potential signals will emerge in the early stages of the marketing of a MR product especially for a new active substance. It will be important for these signals to be evaluated effectively. A signal of possible unexpected ADRs or changes in severity, characteristics of frequency of expected ADRs may be identified from many different sources of information by the MAH, the RMS, or any CMS.

It is the responsibility of each MS to identify alert issues from information arising in its territory. However, it will be important for the RMS to have the totality of information in order to have an overall view of the experience gathered in relation to the concerned MR product. As a matter of routine, the RMS should continually evaluate all newly submitted information in the context of information already available on the product, to determine the emerging ADR profile. The RMS should request additional information from the MAH as necessary. The PhVWP should regularly review emerging safety issues.

2.4 Risk evaluation

As signals of possible unexpected hazards or changes in the severity, characteristics or frequency of expected ADRs emerge, the relevant information needs to be brought together for effective evaluation over a time scale appropriate to the importance and likely impact of the signal.

Any risk evaluation prompted by a signal should normally be carried out by the RMS unless other arrangements are agreed with another MS e.g. the CMS where the original signal was identified in the case of a rapid alert when an assessment report has had to have been prepared. The RMS should in any case work closely with the originator of the signal. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the RMS or the originator MS, or jointly. Assessment reports may be discussed at the PhVWP as necessary on request of the RMS or CMS.

A MS other then the RMS should not start a full evaluation prior to having contacted the RMS, in order to prevent any unnecessary duplication of effort.

2.5 Tracking of pharmacovigilance issues

A tracking system for pharmacovigilance issues relevant to MR products will be set up - called the "MR VetDrug Monitor". It will record actions that arise from investigated signals PSURs, specific obligations and follow-up measures and will be reviewed at each PhVWP. The RMS for a particular product has agreed to be responsible for ensuring the monitor is fully up-to-date for that product and providing the relevant information to the EMEA Secretariat.

IV.B Proceedings in Case of Safety Concerns

1. Hazards During the Ongoing MR Process

If in the course of the MR process and following the assessment of all information relevant to the safety of a product the RMS considers that a significant risk has emerged to change the benefit/risk balance, the outcome of the evaluation should be discussed at the PhVWP and be taken into account in any ongoing MR procedure within the VMRFG.

2. Hazards after MR Authorisation

2.1 Non-urgent safety issues

Potential concerns that do not fulfil the criteria for a Rapid Alert should be brought to the attention of the RMS. The RMS may request further information from the CMS or the MAH. The RMS should work closely with the MS who identified the issue to evaluate the matter. Agreement needs to be reached in each case on the responsibility of evaluation of the issue by RMS or originating CMS, or jointly. Following evaluation, the need for further discussion at the PhVWP will be at the request of the RMS or CMS.

2.2 Urgent safety issues

For urgent issues the Rapid Alert System should be used by the RMS or the other MS when a signal is detected which leads to concern about the risk/benefit of a MR product and which could lead to major changes in the status of that authorisation. The Rapid Alert should be transmitted to the contact points of the RMS, the CMS, the European Commission and the EMEA Secretariat. The MAH should also be informed. The RMS should work closely with the originator of the alert to evaluate the matter. (see also Note for guidance: Revised Rapid Alert System (RAS) in Veterinary Pharmacovigilance (EMEA/CVMP/141/98))
The RMS will prepare a risk/benefit assessment report based on the assessment report of the MS, which issued the rapid alert and also decides which additional information is to be requested from the MAH and CMS. Following risk evaluation a discussion should be held at the PhVWP aimed at reaching agreement between RMS and CMS. In cases of particular urgency a special meeting of the PhVWP may need to be set up. Any MS (RMS or CMS) may initiate immediate suspension of the marketing authorisation if considered necessary (see 3.2).

3. Actions Consequential to Safety Concerns

Issues are likely to emerge from the many sources of information considered above which warrant amendment to the conditions of the marketing authorisation, usually through the process of variation. In the case of serious risk, which is considered to outweigh the benefit of a product, there may be a need to withdraw the product from the market. Such actions may be taken voluntarily by MAH or compulsorily by Competent Authorities.

3.1 Action by the marketing authorisation holder

Variations of the marketing authorisation submitted by the MAH because of safety concerns should be handled through the normal variation procedures for MR products with the RMS evaluating the variation and circulating an assessment report of the CMS within the normal time scale.

In the case of a MAH wishing to withdraw its marketing authorisation, action needs to be co-ordinated across the CMS by the RMS, including communication to practising veterinarians.

3.2 Action by the Competent Authorities

If following risk evaluation by the RMS it is considered that action is necessary to vary, suspend or withdraw the terms of the marketing authorisation of a veterinary medicinal product, the RMS should inform the CMS.
It is essential to ensure a co-ordinated approach, efforts should be made to reach a consensus on the proposed action to be taken, through discussion within the PhVWP.
Where appropriate the RMS should communicate with the MAH on the reasons for the conclusions reached by the MS and the action that should be taken by the MAH. If the MAH does not propose to voluntarily vary, suspend or withdraw the MA, a referral according to Articles 20, 23a or 23b to the CVMP is necessary. In these cases, reference should be made to the SOP on referrals in accordance with the Provision of Council Directive 81/851/EEC in the case of safety concerns related to veterinary medicinal products marketed in the European Union. The resulting CVMP Opinion will be followed by a single Decision of the European Commission binding on all MS. In urgent cases where a serious risk to public or animal health is expected, any MS may initiate immediate suspension of the marketing of a veterinary medicinal product informing all MS, the European Commission and the EMEA Secretariat within 24 hours. Such action should preferably be taken in all MS in a co-ordinated manner facilitated by a proposal from the CVMP and its PhVWP to the Competent Authorities of MS.

3.3 Communication to veterinarians and the public

Veterinarians, and if considered appropriate, the public may need to be informed about safety issues related to MR products. It is important that consistent information is provided in all MS.
In such cases, the RMS should propose the content of the information to be provided, and whenever possible, this should be agreed by the CMS and, if necessary considered by the PhVWP. There should be agreement whenever possible, on the method and timing of distribution of the information e.g. by letters from MAH or MS Competent Authorities, or through Competent Authorities' bulletins. Agreement should also be reached on the need and timing of press statements and the reaction to press enquiries.