European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE[1]

EMEA PUBLIC BULLETIN 2005 ON VETERINARY PHARMACOVIGILANCE[2]

Introduction

This is the third EMEA bulletin on veterinary pharmacovigilance activities, covering the year 2005. It is aimed at improving communication to all stakeholders but particularly to veterinary health professionals on the surveillance of the safety of veterinary medicines in the EU. A glossary of the terminology used in this report, in accordance with that referenced in EU legislation, is included.

Pharmacovigilance for veterinary medicinal products in the EU

The main responsibility of the **European Medicines Agency (EMEA)** and its **veterinary scientific committee, the Committee for Medicinal Products for Veterinary Use (CVMP)**, in post marketing surveillance of veterinary medicinal products in the EU concerns those products which reach the market by authorisation through the centralised procedure[3]. However, veterinary pharmacovigilance experts from the competent authorities of the Member States in their capacity as delegates to the **CVMP Pharmacovigilance Working Party**[4] regularly meet at the EMEA, and in addition to assessing pharmacovigilance issues for centrally authorised products, they also discuss and agree approaches to pharmacovigilance issues related to those products that have been authorised by the Member States (national or decentralised procedures, or the procedure of mutual recognition)[3] that are of specific interest in these.

Late in 2005, a **revised pharmaceutical legislation** came into force[5]. The legislation now puts more emphasis on the safety of products, through pharmacovigilance. The new provisions encourage prompt reporting of suspected adverse reactions[6], especially those being serious and unexpected in animals, or those occurring in human beings. The scope of pharmacovigilance was to include compulsory reporting of suspected transmission of infectious agents through veterinary medicinal products used. Major changes to the concept of safety of veterinary medicines were, in addition, the need for sharing information on adverse reactions. For this purpose, a central EU database has been established to allow for full electronic reporting which has now become obligatory for all marketing authorization holders as well as competent authorities within the EU.

The principles of the reporting schemes are summarised in the following: All reports on suspected adverse reactions are collected into a Periodic Safety Update Report (PSUR)[7] that is submitted at predetermined intervals. The PSURs are normally submitted at 6-monthly or 1-yearly intervals for a close follow-up of the safety of the product in practical use once the product has been introduced to the market. After the first four to five years of market experience, the PSURs are then usually submitted at 3-year intervals as long as the product is available for use, unless more frequent reporting is triggered by pharmacovigilance. Marketing authorisation holders must report all serious suspected adverse reactions in animals and in human beings after exposure to a veterinary medicinal product via an expedited route within a period of 15 days after receipt of the report to ensure surveillance of the safety profile of the product and to enable rapid triggering of actions, if necessary. Each report is evaluated to establish a causal relationship between the reaction and the veterinary medicinal product. This contributes to a continuous assessment of the **balance between risks and benefits** of the product in use.

<u>Spontaneous reports of suspected adverse reactions – centrally authorised products</u>
A total number of 354 spontaneous reports to centrally authorised veterinary products was received in 2005. This number includes reports originating from the EU and countries outside the EU, such as the

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United States. An increase was seen in the number of reports originating from the EU, from 187 in the previous year to 225 in 2005. Spontaneous reports include suspected adverse reactions in animals or humans that are reported expeditedly within a 15-day time frame. For an assessment of safety and efficacy of a veterinary medicinal product, or a comparison between such products, the data relating to suspected adverse reactions from the spontaneous reporting system are normally not sufficient. Due to insufficient data, the causality between the adverse reaction and the medicinal product can often not be assessed.

Of all reports, 305 concerned suspected adverse reactions in animals, as detailed in Table 1. In these, a total of 878 animals were treated, of which 468 showed suspected adverse reactions. A total number of 238 deaths in animals were reported. A single report may relate to one or more animals. Suspected adverse reactions in dogs (163 dogs) and cats (143 cats) were most frequently reported. The low number (32) of reports in food-producing animals – especially cattle, pigs and sheep - in relation to the high number (519) of treated animals of which less than a third (314) showed suspected adverse reactions is explained by the fact that these are seldom treated individually but rather in groups.

Table 1. Summary statistics on expedited reports by target species, excluding reports in humans (2005)

	Summary statistics on expedited reports by species Year 2005			
Species	**Treated animals that were included in the reports (n)**	**Affected animals (n)**	**Animals that died or were euthanised (n)**	**Total, expedited reports (n)**
Food producing animals	**519**	**154**	**54**	**32**
Cattle (*bovine*)	275	110	48	27
Pig (*porcine*)	230	40	6	2
Horse (*equine*)	2	2	0	2
Sheep (*ovine*)	12	2	0	1
Companion animals	**359**	**314**	**184**	**273**
Dog (*canine*)	163	163	120	161
Cat (*feline*)	188	143	57	107
Guinea pig	1	1	1	1
Rabbit	3	3	2	2
Reptiles	1	1	1	1
Rodents/ mice	3	3	3	1
All	**878**	**468**	**238**	**305**

The highest numbers of reports were received after use of non-steroidal anti-inflammatory drugs (NSAIDs), endectocides, volatile anaesthetics, anti-depressant substance and vaccines.

Following use of NSAIDs, the most frequently reported suspected adverse reactions involved the gastrointestinal tract, such as vomiting and diarrhoea. In some of these, gastrointestinal hemorrhage was reported. Gastrointestinal irritation is a known effect of NSAIDs. Neurological disorders such as ataxia and tremors were reported most often after use of endectocides. Cardiorespiratory disorders were mostly involved in reports concerning volatile anesthetics. Following vaccination, reported reactions were related to various organs.

A total of 49 reactions in humans following exposure to a veterinary medicinal product were reported during 2005. The majority of these involved exposure to an anti-depressant veterinary medicinal product due to accidental ingestion. Reactions such as drowsiness, dizziness, somnolence and nausea were reported in relation to the product. Following accidental self-injection of a vaccine, two reports were received on pain and swelling at the injection site in human beings. An itchy rash was observed in a human being following indirect exposure to a topical endectocide after handling the animal one day after treatment. No human being experienced a fatal outcome due to exposure to a centrally authorised veterinary medicinal product during 2005.

As distressing as the death of an animal is to its owner, these events must be put in relation to the amount of products sold to allow valid conclusions regarding benefits and risks afforded by the

products concerned. This information is regularly provided by MAHs as part of Periodic Safety Update Reports.

Periodic Safety Update Reports (PSURs) – centrally authorised products

A total of 42 PSURs for centrally authorised products were received, generally in a good format and in a timely manner. After consideration of all suspected adverse reactions detailed in these reports, the CVMP recommended a change to the product literature on basis of the risk/benefit.

Pharmacovigilance for other than centrally authorised products

A system has been established in previous years for Member States to enable early detection, rapid notification and exchange of relevant information of safety concerns. The matters may be related to one product, a therapeutic class or a range of products. During 2005, a total of eight new issues were raised, none of which concerned centrally authorised products. For collating available information, the Pharmacovigilance Working Party investigated the databases of the national authorities and contributions were made by the experts to thorough discussions on each of the matters. Skin reactions, including injection site reactions, generated most cases of non-urgent concern in 2005. In veterinary medicine, reports of suspected adverse reactions are for most types of products, especially those for pets, highly dependent on the observations of the owner. It is therefore possible that easily observable effects - such as changes in the skin and fur, and gastrointestinal effects - are the ones gaining most attention.

- Rapid Alert System

Two matters were raised during the year requiring rapid communication. In relation to a product for **intramammary** use for treatment of mastitis, a consumer safety concern was raised due to suspicions of an insufficient withdrawal period. Investigations were triggered while the marketing authorisation for the product was suspended in the informing Member State. Following use of a **vaccine**, cats were reported with reactions such as excessive salivation, oral changes, depression, loss of appetite and tremors. The suspected batch was withdrawn from the market and no further reports were received.

- Non Urgent Information System

Matters of a less urgent nature were raised for exchange of information between Member States.

In the early year, a long discussion on a range of **vaccines for dogs** was brought to a closure. The products were reported for observations of facial swelling and pruritus, and anaphylactic reactions. Following intensive investigations, the issue seemed restricted to one Member State, where actions were taken for the introduction of warnings in the product literature.

In relation to use of **feline vaccines**, a safety concern of injection site effects was discussed during the year on several occasions and has now triggered research projects to investigate the causal relationship of use of feline vaccines to the development of dermal fibrosarcoma in cats. The foreseen additional information may contribute to confirmation of the suspected positive causal relationship. At the end of the year, a concern was raised relating to reports of skin reactions, anxiety, and death in animals after use of an **ectoparasitic product**. Injection site reactions had been reported in animals after intravenous and intramuscular use of **NSAIDs**. Any necessary actions are for discussion and decision in 2006. A low incidence of deaths in sows in relation to the use of an **antimicrobial topdressing** was investigated and discussed. In conclusion, no actions were required. In the non-urgent cases, the regulatory measures were, if necessary, restricted to the reporting Member States.

During the year, one further matter relating to product defect was brought to the attention of the Pharmacovigilance Working Party through the established system. A **vaccine for pigs** for immunisation against porcine herpesvirus – Aujeszky's disease - was found to have been contaminated by a bacterium. The available batches of the product were withdrawn in the concerned Member State. While product defects are not included in the scope of pharmacovigilance, unless they indicate a safety concern, the Pharmacovigilance Working Party would consider these concerns until further information is received. Therefore, it is important that a link between the systems for early notification of product defects and pharmacovigilance concerns exists and is well established.

- Cox-2 inhibitors

In addition, the CVMP took note of developments concerning the increased risks of cardiovascular events in human beings following use of Cox-2 inhibitors. Following recommendations from its

Pharmacovigilance Working Party, the CVMP concluded that no action was required in relation to currently authorised veterinary products.

- Referral procedures

With regard to the referral procedure for **Micotil 300** (tilmicosin), the CVMP agreed on amended harmonised safety warnings and a revised notice to the physician with more precise information on treatment after human exposure to tilmicosin, and confirmed its previous recommendation that the administration of the product should be restricted to veterinarians only.

European guidelines on Pharmacovigilance

There was much activity in preparation of guidance not only for marketing authorisation holders but also for veterinarians in relation to pharmacovigilance. All draft and final guidance is published at the EMEA website (http://www.emea.eu.int/index/indexv1.htm).

A simple guide to encourage veterinarians to report suspected adverse reactions was prepared during the year. During consultation, positive responses from the International Federation for Animal Health Europe (IFAH Europe) and the Federation of Veterinarians of Europe (FVE) were received. This simple guide will support the promotion of pharmacovigilance that is planned for 2006.

In the light of the new pharmacovigilance provisions it became necessary to revise and update existing guidelines. Draft revisions were prepared for consultation and submitted to the European Commission. A revision of the major guidance on procedures for marketing authorisation holders in relation to pharmacovigilance for veterinary medicinal products was initiated. This guidance aids the marketing authorisation holders to implement practical procedures involved in complying with the legislation concerning pharmacovigilance. A guideline for monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections by marketing authorisation holders was drafted during the year. The document clarifies the expected level of detail of procedures within a pharmacovigilance system and how inspections of these systems will be carried out.

Among the finalised guidelines is one for the triggering of pharmacovigilance investigations. The scope of the guideline is to harmonise the approach for triggering investigations of reported adverse reactions with veterinary medicinal products. The objective of an investigation is to provide data before a decision is made on whether a regulatory action is necessary or not.

During the year considerations on the need and frame for a guideline on assessments of PSURs was prepared and published for consultation. The guideline will include procedures for assessment and aspects of risk/benefit assessment and will be developed in the new year.

The Pharmacovigilance Working Party also contributed to the revision of draft guidance on the Summary of Product Characteristics. According to this guideline, future product literature should include numerical and qualitative information on the incidence of suspected adverse reactions for the veterinary medicinal products.

A suspected adverse reaction reporting form for use by veterinarians and other veterinary health professionals has been finalised and came into effect in June 2005. This form replaces existing national forms and will facilitate reporting of suspected reactions in the EU.

EudraVigilance Veterinary

EudraVigilance Veterinary (http://eudravigilance.emea.eu.int/veterinary), the EU system for electronic reporting of suspected adverse reactions to veterinary medicines (to replace the current paper based system), has become an important tool in 2005 with the support of most national authorities. The implementation process will now get to the next stage since the Veterinary pharmaceutical industry is also required to switch to mandatory electronic reporting. In order to facilitate electronic reporting, in particular for the many smaller companies, a further veterinary specific simple reporting tool has been developed for reporting to the relevant authorities in all EU languages. Several working groups are now involved in the development of adequate guidance and procedures to optimise the functioning of electronic reporting to one single database. In collaboration with our industry partners further progress has been made for the development of specific analysing tools that will first become available by the end of 2006. The EMEA has increased its coordinating role to ensure access to quality data in the EudraVigilance Veterinary database that will become the backbone of the future surveillance of

veterinary medicinal products in the EU. Additional efforts are ongoing and will be required to obtain all EU product data for the EudraVigilance product dictionary. This is pivotal information for the analysis of the data. Currently the dictionary contains the complete product data for all centrally authorised products.

EU enlargement 2007

The integration of Observers from the two Candidate Countries (Bulgaria and Romania) into the EMEA work structure - including meetings of the CVMP Pharmacovigilance Working Party - was successfully initiated during 2005.

GLOSSARY

[1] **Committee for Medicinal Products for Veterinary Use (CVMP):** the Committee of the EMEA responsible for preparing the scientific opinions of the Agency on any question relating to the evaluation of veterinary medicinal products; in the context of this document in particular relating to safety, efficacy after marketing.

[2] **Pharmacovigilance:** the surveillance of medicinal products after authorisation to ensure their continued safety and efficacy. A major aim of pharmacovigilance is to ensure that products remain safe during use under field conditions and that they remain effective. This is achieved by reporting adverse reactions (see below) to veterinary medicines (irrespective of the procedure for authorisation as described below) to the veterinary pharmacovigilance schemes established in each member state (see below). Initial reporters may be the animal owners or the veterinary surgeon involved (among others). Reporters may choose to contact the pharmaceutical company, who is then obliged to notify the member state's pharmacovigilance scheme, or they may choose to report directly to the member state's pharmacovigilance scheme, which in turn is obliged to inform the pharmaceutical company (personal details may be withheld upon request). Member states' pharmacovigilance schemes are obliged to inform the EMEA of adverse reactions on centrally authorised (see below) veterinary products that were reported to them. It is important to note that in general not one individual report will provide sufficient scientific grounds for action (e.g. changes in warnings), most often several similar reports will indicate the emergence of a specific issue.

[3] Authorisation procedures in the EU for veterinary medicines

1. **Centralised procedure**: The EMEA by means of the CVMP evaluates veterinary medicinal products that are authorised by the centralised procedure, whereby marketing authorisation is granted simultaneously in all EU Member States (MS). This procedure is mandatory for highly innovative products or products derived from gene technology in order to ensure a uniform standard for the evaluation of such products. The centralised procedure may be chosen for other innovative products.

Alternatively veterinary medicinal products may be authorised by

2. **national procedure** in one MS only or

3. in accordance with the **decentralised procedure** where national authorisations are desired in several MS simultaneously

4. by means of the **mutual recognition procedure** of an original national authorisation in more than one MS

[4] **CVMP Pharmacovigilance Working Party**: An advisory group to the CVMP on veterinary pharmacovigilance. Its main function is to provide advice to CVMP on pharmacovigilance issues and to develop guidance documents on veterinary pharmacovigilance on behalf of CVMP, but the Working Party also serves as a discussion forum for Member States to promote harmonised approaches to pharmacovigilance for nationally authorised and mutually recognised products.

[5] **New legislation**: Directive 2004/28/EC of the European Parliament and of the Council amending Directive 2001/82/EC on the community code relating to veterinary medicinal products. Regulation (EC) No 726/2004 of the European Parliament and of The Council laying down Community procedures for the authorisation of and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

[6] **Adverse reaction**: A reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

Serious adverse reaction: An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated.

Unexpected adverse reaction: An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of the product characteristics.

Human adverse reaction: A reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine**.**

Spontaneous reaction reports: Reports submitted to the MAH or the Competent authority soon after their occurrence and reported onwards in compliance with legal requirements (if serious, within 15 days).

[7] **Periodic Safety Update Reports (PSURs):** regular update reports submitted by pharmaceutical companies to the supervisory authorities concerned (member states where the product is authorised and the EMEA for centrally authorised products) on a given veterinary medicinal product at certain defined intervals. These reports include a scientific evaluation of the reactions and an evaluation of any changes to the benefits and risks afforded by the product.

[8] **Periodic Safety Update Reports (PSURs):** regular update reports submitted by pharmaceutical companies to the supervisory authorities concerned (member states where the product is authorised and the EMEA for centrally authorised products) on a given veterinary medicinal product at certain defined intervals. These reports include a scientific evaluation of the reactions and an evaluation of any changes to the benefits and risks afforded by the product.