European Medicines Agency
Veterinary Medicines and Inspections

London, 24 February 2009
EMEA/CVMP/PhVWP/253196/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

EMEA PUBLIC BULLETIN 2008 ON VETERINARY PHARMACOVIGILANCE

Executive summary

This is the sixth bulletin from the European Medicines Agency (EMEA) on veterinary pharmacovigilance activities, covering the year 2008. This bulletin contributes to the public communication on veterinary medicinal products to stakeholders and to veterinary health professionals, particularly on the surveillance of the safety of veterinary medicines in the European Union (EU). It is also published on the EMEA website at http://www.emea.europa.eu/htms/vet/phvwp/bulletins.htm, where the reader can also find information and documents on many other topics related to veterinary pharmacovigilance.

The numbers of serious adverse reaction and human reaction reports increased in 2008, indicating a continued increase in awareness of veterinary pharmacovigilance in EU. The higher number of reports concerning food-producing animals represents a positive signal in this direction in the network of professionals who deal with such livestock.

The implementation of electronic reporting and the use of the central database EudraVigilance Veterinary (EVVet) continued according to the action plan. A major milestone was achieved in October 2008 as marketing authorisation holders (MAHs) completed their convertion to electronic reporting of adverse event reports for centrally authorised products.

Volume 9B for pharmacovigilance of medicinal products for veterinary use of the Rules Governing Medicinal Products in the European Union was discussed with industry in an expert meeting in June 2008 and was submitted to the European Commission for review in December 2008.

Pharmacovigilance[1] for veterinary medicinal products in the EU

The main responsibility of the EMEA and its veterinary scientific committee, the Committee for Medicinal Products for Veterinary Use (CVMP)[2], in post-marketing surveillance of veterinary medicinal products in the EU is for products that reach the market by authorisation through the centralised procedure[3].

The CVMP Pharmacovigilance Working Party[4] (PhVWP-V) forms the core scientific platform in the European regulatory network on pharmacovigilance for all veterinary medicinal products authorised within the EU. Experts on veterinary pharmacovigilance from the Member States' national competent authorities contribute to this forum for the overall surveillance of adverse reactions to veterinary medicinal products. This expert group assesses pharmacovigilance issues concerning centrally authorised products on behalf of the CVMP, as well as products that have been authorised by the Member States via the national, decentralised or mutual-recognition procedures.

The current legislation, which came into force in late 2005[5], puts emphasis on the safety of products, to be achieved through pharmacovigilance. The legislative provisions encourage and support prompt reporting, especially of those suspected adverse reactions[6] that are serious and unexpected in animals, and of those occurring in human beings. The scope of pharmacovigilance includes compulsory reporting of suspected transmission of infectious agents via a veterinary medicinal product. The legislation provides for improving communication on safety of veterinary medicines by sharing information on adverse reactions. For this purpose, a central EU database (EudraVigilance Veterinary[7]) has been established to allow for full

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

electronic reporting, and use of this database has now become obligatory for marketing authorisation holders (MAHs) as well as national competent authorities within the EU.

All suspected adverse reaction reports received by a marketing authorisation holder have to be collected, collated and evaluated. A Periodic Safety Update Report (PSUR)[8] provides an update of the worldwide safety experience of a product at defined time points post-authorisation. The PSUR is prepared by the marketing authorisation holder for each product and contains all reports of adverse reactions received in relation to the amount of the drug used during a specified period, and is evaluated by the relevant competent authorities.

In addition, marketing authorisation holders have to report serious suspected adverse reactions in animals and suspected human adverse reactions after exposure to a veterinary medicinal product within a period of 15 days after receipt of the report to enable surveillance of the safety profile of the product and rapid triggering of necessary actions. Suspected adverse reactions are ordinarily evaluated by the national competent authorities (and by the Rapporteur and eventually the CVMP for veterinary medicinal products authorised through the centralised procedure) when received from marketing authorisation holders. In view of all available data, the causal relationship between suspected adverse reactions and a product is identified. This contributes to a continuous assessment of the balance between benefits and risks related to the use of the product; in case of an unfavourable change in this balance, it may become necessary to take risk management actions, such as changes to the recommendations on the use of the product.

The European Surveillance Strategy (ESS) group for veterinary medicinal products of the Heads of Veterinary Medicines Agencies (HMA-V) met in Copenhagen in May 2008. The group refined its action plan for better harmonisation of regulatory approaches in pharmacovigilance between competent regulatory authorities of the Community, for better work-sharing between these authorities, and for necessary procedures to achieve this. In 2008 much of the activity was focused on the work-sharing between Member States on assessment of pharmacovigilance data. A pilot project on work-sharing on assessment of PSURs started in January 2008, for selected active substances and one group of vaccines. The pilot project seeks to reduce the number of PSURs, harmonise submission schedules, and develop common messages to promote synchronisation and work-sharing initiatives with all stakeholders. Initial experiences gained in 2008 will be evaluated in mid 2009.

Centrally authorised products

Spontaneous reports of serious suspected adverse reactions and human adverse reactions

A total of 2,251 spontaneous serious suspected adverse reaction reports in animals (1,943) and reports of human adverse reactions (308) to centrally authorised veterinary products were received and processed in 2008. Table 1 shows the numbers of reports by target species, excluding reports in humans. A single report may relate to one or more animals and to one or more products. The trend over recent years for the number of reports to double year-on-year seems to be slowing down, but remain clearly rising, with approximately 50% more reports than in 2007. The highest increase concerned reports from the EU/EEA. This increase recorded in 2008 is still likely to reflect a greater awareness of the need to report of suspected adverse reactions rather than an absolute increase in the number of reactions occurring. Furthermore, the increased number of centrally authorised products reaching the market may also partly explain such increased reporting. However, it is important to recognise that adverse reactions are underreported in general and that information is lacking on the types of bias this may represent.

Of the 1,943 suspected adverse reactions in animals, 1,712 were for companion animals and 231 for food producing animals.

For companion animals, suspected adverse reactions in dogs (971) and cats (704) were most frequently reported.

The 231 reports received for food-producing animals (mainly in cattle, pigs, poultry and horses, with the highest number in cattle) nearly doubles the number of reports received in 2007. This increased number of reports in food-producing animals and the fact that reactions are now reported in a wider range of species is considered to represent a positive signal in the awareness for pharmacovigilance in the network of professionals concerned with food producing animals.

The reporting of adverse events must be considered in relation to the amount of product sold, to allow valid conclusions to be drawn about the benefits and risks of the products concerned. Such an evaluation of the benefit-risk balance has to be regularly provided by marketing authorisation holders as part of their PSURs.

Of all the reports received in 2008, 972 (882 concerning animal reactions and 90 concerning human reactions) were from EU/EEA countries – up nearly 65 % over the 588 EU/EEA reports received in the previous year[9]. A further 1,279 reports (1,061 concerning animal reactions and 218 concerning human reactions) were received from countries outside the EU. This is an increment of nearly 38% compared to the 929 non-EU reports received in 2007. Most of the 1,279 reports received from third countries were from the United States (88%) and from Canada (6%), but partly also from Australia, Japan and other countries.

For an assessment of the safety or 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 not always enough to establish that the suspected adverse reaction was caused by the veterinary medicinal product. Additional information is sometimes necessary.

When examining Table 1, the types of products that are authorised via the centralised procedure must be taken into consideration. Since the range of centrally authorised products is a subset of the total range of products authorised within the EU, therefore it may not be meaningful to make direct comparisons between reports for centrally authorised products and nationally authorised products.

Table 1. Centrally Authorised Products. Summary statistics on expedited reports by target species, excluding reports in humans (Reports received between 15 December 2007 and 14 December 2008)

	Treated animals that were included in the reports (n)	**Affected animals that were included in the reports (n)**	**Total expedited reports (n)**
Food-producing animals	***71,455***	***7,127***	***231***
Pigs/Porcine	62,457	4,595	84
Cattle/Bovine	7,282	2,474	119
Chickens/Avian	1,681	29	4
Horses/Equine	29	23	20
Other food producing animals	6	6	4
Companion animals	***2,027***	***1,663***	***1,712***
Dogs/Canine	1,151	931	971
Cats/Feline	828	693	704
Rodents	14	14	13
Ferrets	11	9	9
Other companion animals	23	16	15
All	**73,482**	**8,790**	**1,943**

Approximately 30% of these reports were received following the use of non-steroidal anti-inflammatory drugs (NSAID) 15% following the use of antimicrobials and another 15% following the use of antiparasitic substances (both ectoparasiticides and endectoparasiticides)). The remaining reports refer to a wide range of categories including vaccines, anaesthetics, and peripherally acting antiobesity products.

A total of 308 reactions in humans following exposure to a veterinary medicinal product were reported during 2008. This represent approximately 14% of the total received, the same percentage as was recorded in the year 2007. None of the reactions were fatal. The majority of reactions resulted from exposure to either of two topically administered products for use against parasites.

Periodic Safety Update Reports (PSURs) – centrally authorised products

A total of 95 new safety reports for centrally authorised products were received (91 PSUR and 4 PSUR addendum reports). During 2008 the assessment process was completed for a total of 82 of these reports. The assessment process of an additional 14 PSURs received in 2007 was completed in 2008. After consideration of all pharmacovigilance data detailed in these PSURs, the CVMP concluded that the benefit-risk balance was in favour of the concerned products. Regulatory action was required on the basis of 7 PSURs. In most of these cases, amendments of the product literature were recommended for the addition of new adverse reactions or modification of known ones.

Rapid alert and non-urgent information notifications

The system that has been established for national competent authorities and the EMEA for early detection and rapid notification of safety concerns, and for exchange of relevant information, was used less frequently in 2008 than in 2007 by the Member States. No rapid alert was triggered in 2008, while a total of seven new non-urgent information issues were raised, and three non-urgent information issues pending from 2007 were concluded in 2008.

In December 2007, a non urgent information had been initiated as a result of the detection of genetic material from a feline retrovirus in cell substrates of feline origin used for the production of some veterinary vaccines. In June 2008 the Committee endorsed the study methodology developed by IFAH-Europe to generate data to enable a risk assessment to be conducted to evaluate any potential impact that this finding might have on the benefit risk balance of veterinary vaccines produced on feline cell lines. First results are expected in 2009.

In February 2008, another non urgent information was initiated regarding information provided for *Mycoplasma hyopneumoniae* vaccines for swine reporting the presence of genetic material from Torque Teno virus in commercial bacterins. Detailed consideration by experts concluded that there was no evidence of any negative impact of this finding on the safety or efficacy of the bacterins. The issue is however being monitored to collect further information.

In March 2008, a non-urgent information action concerning bluetongue vaccines was initiated, before vaccination programmes started in some countries, in order to obtain information of possible adverse reactions. In the following months, a number of companies applied to the EMEA for the authorisation of inactivated vaccines against bluetongue. In July 2008, the CVMP identified that it would be useful to supplement the information on safety provided by companies with a review of adverse events emerging from the use of inactivated vaccines available for emergency use in several Member States. No major safety issues were identified in the review performed by the Pharmacovigilance Working Party of the data collected by the Member States. A public version of the review report was prepared[10] and will be published early in 2009.

CVMP opinions on pharmacovigilance matters

In general, when a Member State considers on the basis of pharmacovigilance data that a marketing authorisation needs to be suspended, withdrawn or varied to restrict the indications or availability, amend the posology, add a contraindication or add a new precautionary measure, the issue is passed to the CVMP.

Such a procedure under Article 78 of Directive 2001/82/EC had been initiated to evaluate the user-safety of 21 injectable products authorised in a member state containing alpha$_2$-adrenoreceptor agonists (romifidine, medetomidine, detomidine, xylazine) due to a published human case report reporting cardiovascular and central nervous system effects after accidental self-injection. The CVMP recommended a set of new precautionary measures relating to user safety to be reflected in the product literature. In 2008 the CVMP extended these measures to all such products with a marketing authorisation in the Community.

European guidance, focus groups, workshops and training on pharmacovigilance

There was continuous activity in the preparation of regulatory and scientific guidance on pharmacovigilance. In addition, several matters of principle were discussed by the PhVWP-V throughout the year to create and maintain harmonisation on approaches within the Community. Draft and final

guidance is published on the EMEA website (http://www.emea.europa.eu) or on the European Commission website (http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm).

The preparation for a new Volume 9B of the Rules Governing Medicinal Products in the European Union - Pharmacovigilance of Medicinal Products for Veterinary Use - continued in 2008. The contents were based upon the existing Volume 9 of 2004, Volume 9A on guidance on pharmacovigilance concerning medicinal products for human use and additional guidance on medicinal products for veterinary use. In June 2008 additional experts mainly from industry were invited to the EMEA to discuss sections of the draft Volume 9B. A total of 35 experts attended, including members of the PhVWP-V, CVMP, CMD(v), and legal and veterinary pharmacovigilance staff from the EMEA. Industry was well represented by several Qualified Persons responsible for pharmacovigilance. The meeting was considered important to enable open exchange of views and issues raised were taken into consideration in the finalisation of draft Volume 9B. The guidance was transferred to the European Commission for review and expected release for public consultation.

Further to the publication of the Simple Guide to Veterinary Pharmacovigilance in the EU[11] in English in 2006, so far the following Member States published this guide in their national language(s) to promote pharmacovigilance and safety reporting:, Austria, Belgium, Bulgaria, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Slovenia and Spain.

In November 2008 a training session was arranged at the EMEA for veterinary assessors of PSURs on the basis of the publication of the CVMP recommendation on management and assessment of PSURs of veterinary medicinal products [12] . The aim was to provide assessors with an overview of the recommendation in order to implement a harmonised approach to PSUR assessment throughout the European Union. Thirty-seven assessors contributed to this much appreciated training, including CVMP and PhVWP-V members and experts of the national competent authorities. The recommendation will also support standardisation of the format of PSUR assessment reports across the EU and was scheduled to come into effect from 1 January 2009.

The development of fibrosarcoma in cats at the site normally used for injection of veterinary medicinal products is recognised as a rare but serious occurrence. Reports of such lesions are available both in the public literature and in the European pharmacovigilance system. The Subgroup on Injection-Site Sarcoma continued its considerations on the surveillance of injection-site sarcoma in cats within the European regulatory network as a follow-up measure to an advisory notice to veterinary surgeons regarding the same topic prepared by the CVMP in 2003[13] and a focus group meeting arranged by EMEA in 2007.

EudraVigilance Veterinary

National competent authorities are using EudraVigilance Veterinary[7] (EVVet), the central EU database for electronic reporting of suspected adverse reactions to veterinary medicines, and an increase in the number of entered reports was observed in 2008. Since October 2008 submission of adverse event is only accepted via electronic means by the marketing authorisation holders as well. EVVet now contains over 23,000 adverse-event reports in animals and about 1,100 human reports. There are 30 competent authorities registered and 50 other organisations, including marketing authorisation holders MAHs and third parties. Training sessions took place in several member states to support local industry commitment and other sessions are planned. New multimedia tutorials on the use of EVWEB have been released on the EVVet website and further updates to the website are in progress. The relevant chapter on electronic reporting has been prepared for Volume 9B and the electronic reporting schema has been finalised and published on the website. The policy for access to EVVet data is in public consultation[14]. Supplementary development and improvements to EVVet were initiated from August onwards in line with the action plan that was agreed between all partners to ensure a stable and secure system with powerful analytical tools and proper access to the data. A further development stage of the Data Warehouse was concluded, providing scientific query tools to analyse the data. These tools were first tested by a subgroup of the PhVWP-V and other experts from national competent authorities in a two-day training session that took place in November.

Challenges in 2009

In 2009, veterinary pharmacovigilance will further develop in line with the work programme of the PhVWP-V[15] and within the framework of the ESS action plan, intended to be published on the HMA-V website[16]. Further challenges aim at finalisation of Volume 9B; development of guidance and the concept of risk management for veterinary medicinal products; full implementation of EVVet and development of

guidance on the use of data contained in EVVet. The pilot project on work-sharing between national competent authorities for the assessment of PSURs will be evaluated by HMA(v). In relation to the discussion on international standards between Japan, the USA and the EU, under the auspices of VICH, the EMEA will be the topic leader for the guideline on standard terms that is foreseen to be finalised in early 2009.

Consideration will also be given to more effective and targeted communication to veterinarians and other healthcare professionals and the general public, including animal owners, on issues relating to the safety of veterinary medicinal products authorised in the EU.

Glossary and References

[1] **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 animal owners or the veterinary surgeon involved (among others). Reporters may choose to contact the pharmaceutical company, which 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.

[2] **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 (relating in particular, in the context of this document, to safety and efficacy after marketing).

[3] **Authorisation procedures in the EU for veterinary medicines:**

1. **centralised procedure**, in which the EMEA, through the CVMP, evaluates veterinary medicinal products and whereby marketing authorisation is granted simultaneously in all EU Member States. 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 Member State only, or
3. **decentralised procedure**, where national authorisations are desired in several Member States simultaneously, or
4. **mutual-recognition procedure**, whereby an original national authorisation is recognised in one or more other Member States.

[4] **CVMP Pharmacovigilance Working Party**: An advisory group to the CVMP on veterinary pharmacovigilance. Its main function is to provide advice to the CVMP on pharmacovigilance issues and to develop guidance documents on veterinary pharmacovigilance on behalf of the 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] **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 and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

[6] **Adverse reaction**: A reaction that 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 that results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or that results in permanent or prolonged signs in the animal treated.

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

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

Spontaneous reaction reports: Reports submitted to the marketing-authorisation holder or the competent authority soon after the reaction's occurrence, and reported onwards in compliance with legal requirements (if serious, within 15 days).

[7] **EudraVigilance Veterinary**: The European data-processing network and database-management system for the exchange, processing and evaluation of suspected adverse reaction reports related to veterinary medicinal products authorised in the European Economic Area (EEA). For more information, see: http://eudravigilance.emea.europa.eu/veterinary/index.asp

[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 presented by the product.

[9] **EMEA public bulletin 2007 on veterinary pharmacovigilance (EMEA/CVMP/PhVWP/72829/2007)**:
http://www.emea.europa.eu/pdfs/vet/phvwp/7282907en.pdf

[10] **An overview of field safety data from the EU for Bluetongue virus vaccines serotype 8 emerging from the 2008 national vaccination campaign**
http://www.emea.europa.eu/pdfs/vet/press/pos/65201908en.pdf

[11] **A Simple Guide to Veterinary Pharmacovigilance in the EU (EMEA/CVMP/PhVWP/110607/2005)**:
http://www.emea.europa.eu/pdfs/vet/phvwp/11060705en.pdf

[12] **Recommendation on Management and Assessment of Periodic Safety Update Reports (PSURs) of Veterinary Medicinal Products(EMEA/CVMP/PhVWP/4550/2006)**:
http://www.emea.europa.eu/pdfs/vet/phvwp/455006enfin.pdf

[13] **Advisory note to veterinary surgeons regarding the development of fibrosarcomas at sites of injection of veterinary medicinal products in cats (EMEA/CVMP/205/03-FINAL)**:
http://www.emea.europa.eu/pdfs/vet/press/pp/020503en.pdf

[14] **Draft Eudravigilance Access Policy for Medicines for Veterinary Use (EMEA/113700/2008)**
http://www.emea.europa.eu/pdfs/vet/euleg/11370008en.pdf

[15] **CVMP Pharmacovigilance Working Party Work programme 2009** (EMEA/CVMP/PhVWP/208614/2007):
http://www.emea.europa.eu/pdfs/vet/phvwp/PhVWPworkprogramme.pdf

[16] Information from **Heads of Veterinary Medicines Agencies** (HMA-V) is published on the HMA-V website:
http://www.hma.eu/veterinary.html