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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

EMEA PUBLIC BULLETIN 2007 ON VETERINARY PHARMACOVIGILANCE

Introduction

This is the fifth EMEA bulletin on veterinary pharmacovigilance activities, covering the year 2007. It forms part of the communication with stakeholders and particularly veterinary health professionals on the surveillance of the safety of veterinary medicines in the EU. For an extended glossary of the terminology used in this report please refer to the EMEA public bulletin 2005 on veterinary pharmacovigilance[1].

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 is for products that reach the market by authorisation through the centralised procedure[2]. This procedure is mandatory for certain veterinary medicinal products, particularly those developed by means of certain biotechnological processes. The centralised procedure may be chosen for a veterinary medicinal product that contains a novel active substance, constitutes a significant therapeutic, scientific or technical innovation or is an immunological veterinary medicinal product for the treatment of animal diseases that are subject to Community prophylactic measures, or where there is an interest of animal health at Community level. In addition, the **CVMP Pharmacovigilance Working Party**[3] **(PhVWP-V)** regularly meets at the EMEA. The PhVWP-V forms the core scientific platform in the regulatory network on pharmacovigilance for all veterinary medicinal products authorised within the European Union. Experts on veterinary pharmacovigilance from the competent authorities of each Member State contribute to this forum. This expert group assesses pharmacovigilance issues for centrally authorised products on behalf of CVMP as well as for products that have been authorised by the Member States via the national procedures[2].

In 2007, Bulgaria and Romania joined the European Union. Thereby the available expertise in veterinary pharmacovigilance was further expanded. In previous years, representatives from these two new Member States had been participating as active observers in the meetings of PhVWP-V.

This year, the activity of the PhVWP-V further intensified in terms of development of guidance and implementation of the new mandate for establishing the responsibility for surveillance of all products regardless of authorisation procedure. Tools and methods for increased involvement of the PhVWP-V in the surveillance of the safety of veterinary medicinal products were under development, as further described in this bulletin.

EU veterinary pharmacovigilance was presented and promoted on several occasions throughout the year. As part of Croatia's and Turkey's Road to EU Membership, European experts in veterinary pharmacovigilance contributed to conferences presenting the regulatory environment regulating and supervising medicinal products for human and veterinary use in these countries. These conferences were arranged following the first information meeting on participation of Croatia and Turkey in EMEA activities held at the EMEA premises on 29 September 2006. The second TOPRA Annual Veterinary Symposium held in Copenhagen on 4 October 2007 included sessions on the impact of strengthened pharmacovigilance.

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The European Surveillance Strategy (ESS) group for veterinary medicinal products of the Heads of Veterinary Medicine Agencies (HMA-V) refined its action plan aiming towards better harmonisation of regulatory approaches in pharmacovigilance between competent regulatory authorities of the Community, and work sharing between these authorities as well as plans for necessary procedures to achieve this. Primary priorities were identified and include effective communication and improved analysis of safety reports, increased emphasis on risk and incident management relevant to veterinary medicinal products, as well as worksharing between Member States on assessments of pharmacovigilance data. Preparatory actions are currently ongoing with input from industry for a pilot project in 2008 on worksharing on the assessment of safety reports Furthermore, the ESS group reconfirmed its dedication to promoting veterinary pharmacovigilance via more effective communication to health care professionals as well as initial thoughts on education in pharmacovigilance.

The current legislation that came into force in late 2005[4] puts emphasis on the safety of products, through pharmacovigilance. The provisions encourage prompt reporting especially of those suspected adverse reactions[5], which are serious and unexpected in animals, and those occurring in human beings. The scope of pharmacovigilance includes compulsory reporting of suspected transmission of infectious agents through use of veterinary medicinal products. The legislation provides for improved communication on safety of veterinary medicines by sharing information on adverse reactions. For this purpose, a central EU database (EudraVigilance Veterinary)[6] has been established to allow for full electronic reporting and use of this database has now become obligatory for all marketing authorization holders as well as competent authorities within the EU.

All suspected adverse reaction reports received by a marketing authorisation holder are collected, collated and evaluated. A Periodic Safety Update Report (PSUR)[7] is a product-specific document evaluating the safety of the product in practical use. The PSUR is prepared for each product on all reports received during a specified period and submitted to relevant competent authorities at predetermined intervals. The PSURs are initially submitted at 6-monthly or 1-yearly intervals. After the first four to five years of experience of use, the PSURs are then usually submitted at 3-year intervals as long as the product is available, unless more frequent reporting is triggered by safety concerns.

In addition, marketing authorisation holders must report serious suspected adverse reactions in animals and suspected human adverse reactions after exposure to a veterinary medicinal product via an expedited procedure. Within a period of 15 days after receipt of the report it is evaluated and forwarded to the competent authority to ensure surveillance of the safety profile of the product and to enable rapid triggering of necessary actions.

Suspected adverse reactions are evaluated by competent authorities, 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. Sometimes additional investigations are necessary before a final conclusion can be drawn on the benefit-risk balance of the product. In case of a decrease in this balance, it may become necessary to require risk management actions, such as changes to the recommendations on the use of the product.

Spontaneous reports of serious suspected adverse reactions and human adverse reactions – centrally authorised products

A total of 1517 spontaneous serious suspected adverse reaction reports in animals or reports of human adverse reactions to centrally authorised veterinary products was received in 2007. Overall, the number of suspected adverse reactions reported to EMEA in 2007 was approximately double the amount received in the previous year. This increase is the result of an increased rate of reporting to the EMEA, possibly reflecting a greater awareness for the reporting of suspected adverse reactions rather than an absolute increase in the number of reactions occurring. On the other hand, it is important to recognise the general consideration that adverse reactions are underreported, and that information is lacking on the types of bias this may cause.

Of the reports received in 2007, 588 were from EU countries. The increase almost doubles the reporting on annual basis, when compared to the 300 EU reports received in the previous year[8]. In 2007, 929 reports were received from countries outside the EU, predominantly from the United States (US) and

Canada. For an assessment of 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 normally enough to establish that the suspected adverse reaction was caused by the veterinary medicinal product. Additional information is often necessary.

Table 1 shows the numbers of expedited reports by target species, excluding reports in humans. A single report may relate to one or more animals. Of all the reports received in 2007, 1301 concerned suspected adverse reactions in animals, which was double the number received in 2006. Suspected adverse reactions in dogs (n = 706) and cats (n = 414) were most frequently reported. The reports received in 2007, identified a total of 16564 treated animals, of which 5175 showed suspected adverse reactions. A total of 1866 deaths in animals were reported. 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, and to the fact that animals receiving medicines are often very ill and may die from causes unrelated to treatment. This information is regularly provided by MAHs as part of Periodic Safety Update Reports (PSURs).

There were 145 reports relating to food-producing animals – cattle, pigs and horses – which related to the treatment of 14898 animals, of which 3989 showed suspected adverse reactions. The low number of reports in food-producing animals is consistent with previous years. The high number of treated animals of which only approximately a quarter showed suspected adverse reactions is explained by the fact that farm animals are seldom treated individually but rather in groups.

When examining the table, one needs to bear in mind the types of products that are authorised via the central procedure. Since the representation of products in this subset differs from the complete range of products authorized within the EU, therefore any comparison of the types of reports received between centrally authorized vs. nationally authorized products is irrelevant and inappropriate

Table 1. Summary statistics on expedited reports by target species, excluding reports in humans (2007)*

	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	***14898***	***3989***	***940***	***145***
Cattle (*bovine*)	8532	2192	270	103
Horse (*equine*)	153	29	12	15
Pig (*porcine*)	6213	1768	658	27
Companion animals	***1644***	***1166***	***910***	***1139***
Dog (*canine*)	791	704	553	706
Cat (*feline*)	482	416	313	414
Rabbits and hares	360	35	35	12
Rodents	11	11	9	7
Others	***22***	***20***	***16***	***17***
Others	22	20	16	17
All	**16564**	**5175**	**1866**	**1301**

* Reports received between 15 December 2006 and 14 December 2007

When considering the numbers of reports for various products, it needs to be recognised that the use of one product may cause different patterns of adverse reactions between species.

Approximately 82 % (1068/1301) of the animal reports were received following the use of non-steroidal anti-inflammatory drugs (NSAIDs), antimicrobials and antiparasitic substances.

Following the use of NSAIDs, the most frequently reported suspected adverse reactions reported related to the gastrointestinal tract e.g. vomiting and diarrhoea. Neurological and gastro-intestinal clinical signs were most frequently reported following the use of antiparasitics and antimicrobials.

A total of 216 reactions in humans following exposure to a veterinary medicinal product were reported during 2007. None of these were fatal. The majority of these resulted from exposure to three topically administered products for use against parasites, as well as one injectable antibiotic.

Periodic Safety Update Reports (PSURs) – centrally authorised products

A total of 81 new PSURs for centrally authorised products or addendum reports to these were received. The assessment process was completed for a total number of 66 PSURs during 2007. 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 six 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 Systems

The system that has been established in previous years for Member States, and the Agency, to enable early detection, rapid notification and exchange of relevant information of safety concerns was used less frequently in 2007 than in 2006 by the Member States. A total of 11 new issues were brought to the attention of the national pharmacovigilance systems, one of which initially concerned a centrally authorised product. Three of all these issues were clearly related to quality deficiencies. The PhVWP-V considered that no further action was required for these in relation to pharmacovigilance. A separate system is available for communication of rapid alerts relating to quality defects. Information may, however, be processed through both systems simultaneously in cases where the link to pharmacovigilance cannot initially be ruled out.

Of the matters raised as rapid alerts, one related to investigations of the validity of withdrawal periods of a product containing several active ingredients, including beta-lactams, intended for intramammary use. The marketing authorisation had been suspended. Therefore, the matter was considered of no immediate threat to public health on Community level. Additional information is expected in 2008 for further discussion and procedures.

Further, one quality defect for a product containing ivermectin was initially processed through this system, as was one notification concerning defective batches of a product containing an antiparasitic substance.

Seven non-urgent matters were also considered.

Changes in behaviour, gastro-intestinal and neurological signs had been reported in dogs for an antiparasitic product for topical use. The PhVWP-V advised that these should be reflected in the product information for the product.

A suspected interaction between an injectable product containing Vitamin E and selenium and vaccination was discussed in light of reports of anaphylactoid reactions received following exposure in cattle. The issue remains under consideration awaiting additional data.

The onset and duration of anaphylactoid reactions for an immunological product containing live vaccines were discussed. Reported signs included oedema of nose and around eyes and ears, itching, urticaria, vomiting, diarrhoea or erythema, or occasional anaphylactic shock with circulatory insufficiency. The monitoring of these will continue.

Fatalities in cats had been reported after off label use in this species of various topically administered products containing an antiparasitic substance. Off label use is defined as any use of a veterinary medicinal product that is not in accordance with the summary of product characteristics, including the misuse and serious abuse of the product.

The matter of considerable underreporting of reactions related to treatments of horses with procaine benzylpenicillin was raised in follow up to a recent article published in the Journal of Veterinary Pharmacology and Therapeutics[9].

Concerning a range of vaccines, investigations in relation to a potential quality defect were initiated. The relevance for safety remains to be determined.

In addition, one quality defect for a product containing a diuretic substance was processed through this system, but since the observations lacked relevance in pharmacovigilance, the matter was only noted.

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 CVMP. No procedures were initiated in 2007.

In 2006, a procedure under Article 78 of Directive 2001/82/EC had been initiated to evaluate the user safety of 21 injectable products authorised in The Netherlands, containing alpha$_2$-adrenoreceptor agonists. These substances are used for sedation and analgesia in several animal species. This procedure had been triggered further to consultation with the PhVWP-V by the competent authority in The Netherlands because of a published case report in a human after exposure to a product containing an alpha$_2$-adrenoreceptor agonist. The patient had experienced 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 of the products concerned. The CVMP further concluded that these precautionary measures also apply to other products containing alpha$_2$-adrenoreceptor agonists. Following a final decision to be taken by the European Commission, actions will be taken by national competent authorities, as necessary.

Referral procedures triggered by pharmacovigilance information

No referral procedure was triggered on basis of pharmacovigilance concerns in 2007.

Focus groups, workshops and training

During the year, the PhVWP-V continued its considerations on adverse reactions relating to various vaccines.

On 9 July 2007, the EMEA organised a focus group meeting on fibrosarcoma occurring at sites of injection (injection site sarcoma) of veterinary medicinal products in cats. This meeting involved experts from clinical practice, industry and research, as well as from the CVMP Working Parties for Pharmacovigilance, Immunologicals and Efficacy. 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 focus group meeting was held as part of the continued surveillance of injection site sarcoma in cats within the European Regulatory Network and is a follow-up measure to an advisory notice to veterinary surgeons regarding the same topic prepared by the EMEA Committee for Medicinal Products for Veterinary Use (CVMP) in 2003[10]. The focus group concluded that further research into injection site sarcoma and the suspected relationship to veterinary medicinal products is necessary. The group also supported joint efforts aimed at increasing the awareness among the veterinary profession, including veterinary pathologists, about the occurrence and nature of injection site sarcoma as well as efforts to promote reporting through the pharmacovigilance system. The group emphasised the need for a harmonised case definition as an essential first step in improving surveillance and reporting. A press release was issued from the meeting[11]. The CVMP and its Pharmacovigilance Working Party continues to consider further actions.

On 3 December 2007, a much appreciated training on pharmacovigilance systems and inspections was arranged for veterinary assessors at the EMEA. The purpose of the training was to introduce the new guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products that had been published in April 2007 by the European Commission[12].

On 4 December 2007, a workshop was organised by the EMEA for regulatory authorities and industry, including Marketing Authorisation Holders and associations representing pharmaceutical industry, on pharmacovigilance systems and inspections. The workshop convened experts on veterinary pharmacovigilance systems for an introduction to the relevant guideline, and for these stakeholders to share experiences and express their expectations on the implementation of the relevant legal provision.

The meeting was considered a success, where stakeholders took the given opportunity to clarify the guidance and identify points in need of harmonisation and better procedures. A report[13] from the meeting is available on the EMEA website.

European guidance on Pharmacovigilance

There was continuous activity in preparation of regulatory and scientific guidance not only for marketing authorisation holders but also for veterinarians in relation to pharmacovigilance. Further, 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 at the EMEA website (http://www.emea.europa.eu) or at 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 - was initiated in the second half of the year by a drafting group composed of experts in regulatory pharmacovigilance. The contents would be partly based upon the existing Volume 9 of 2004, as well as on Volume 9A, which was published in early 2007 to give guidance on pharmacovigilance concerning medicinal products for human use. It is foreseen that a draft Volume 9B will be made available by the European Commission in early 2008.

The major guidance on procedures for marketing authorisation holders in relation to pharmacovigilance for veterinary medicinal products was further reviewed and recommendations were agreed for additional improvements reflecting the current legislation. This guidance aids the marketing authorisation holders to implement practical procedures involved in complying with the legislation concerning pharmacovigilance. The guidance will be included in Volume 9B and further amended in view of additional considerations to take into account recent developments in veterinary pharmacovigilance.

A guideline[12] for marketing authorisation holders for monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections by marketing authorisation holders was finalised during the year, as mentioned above. The document clarifies the expected level of detail of procedures within a pharmacovigilance system and how inspections of these systems will be carried out. The guidance will be integrated in Volume 9B.

Further to the publication of the Simple Guide to Veterinary Pharmacovigilance in the EU[14] in English in 2006, several Member States prepared this guide in their national language(s) and made it publicly available as part of efforts to promote pharmacovigilance and safety reporting. For further information on the Simple Guide to Veterinary Pharmacovigilance in the EU, please see the EMEA Public Bulletin 2006 on Veterinary Pharmacovigilance[15].

During the year a draft guideline on assessments and management of PSURs[16] was released by the CVMP for public consultation and will be finalised in 2008 in light of comments received from stakeholders during this consultation. This document will guide assessors in their scientific and regulatory assessment of PSURs in their aims to perform assessments of high quality. The guideline will also support standardisation of the format of PSUR assessment reports across the EU. The guideline was developed in view of comments received during the public consultation on the Concept Paper on a PSUR assessment guideline for Veterinary Medicinal Products[17]. Once finalised, the guidance will be integrated in Volume 9B.

EudraVigilance Veterinary

National competent authorities increasingly have used EudraVigilance Veterinary[6] (EVVet), the EU database for electronic reporting of suspected adverse reactions to veterinary medicines, and a sharp increase in the number of entered reports was observed in 2007. 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 for a stable and secure system with powerful analysing 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 are being tested by a subgroup of the PhVWP-V.

While veterinary pharmaceutical industry's major players had indicated that they would implement electronical reporting by 2007, unfortunately only a limited number of marketing authorisation holders

have committed and only a low number of reports are currently being entered into EVVet by the companies in the EU. With the legal deadline for reporting electronically by MAHs having now passed two years ago, the EMEA has continued to encourage Member States to enforce electronic reporting via information and training sessions to the local marketing authorisation holders.

Major milestones in the discussions for international standards outside the EU have been reached in particular with an agreement between Japan, US and Europe on the required data elements for reporting and exchanging adverse events data related to veterinary medicinal products (Guideline 42 of the VICH[18] initiative).

Challenges in 2008

In 2008, veterinary pharmacovigilance will further develop in line with the work programme of the PhVWP-V[19] and within the framework of the ESS action plan, intended to be published on the HMA-V website[20]. Tools and methods for analysis of pharmacovigilance data will be further developed. Further challenges include development of guidance and the concept of risk management for veterinary medicinal products, full implementation of Eudravigilance Veterinary and promotion of pharmacovigilance. Additionally, a pilot project on worksharing between Member States for the assessment of PSURs will be performed by volunteering Member States.

During 2008, considerations will also be given for more effective and targeted communication to veterinarians and other health care professionals and the general public, including animal owners, on issues relating to the safety of veterinary medicinal products authorised in the EU.

GLOSSARY

[1] **EMEA public bulletin 2005 on veterinary pharmacovigilance.** Doc.Ref.No EMEA/CVMP/226674/2005. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/22667406en.pdf

[2] **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, or

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

[3] **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.

[4] **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.

[5] **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).

[6] **EudraVigilance Veterinary**: EudraVigilance Veterinary is the European data-processing network and database management system for the exchange, processing and evaluation of Suspected Adverse Reaction Reports (SARs) related to veterinary medicinal products authorised in the European Economic Area (EEA), this is the European Union, Norway, Iceland and Liechtenstein. For more information, see website http://eudravigilance.emea.europa.eu/veterinary/index.asp

[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] **EMEA public bulletin 2006 on veterinary pharmacovigilance.** Doc.Ref.No EMEA/CVMP/PhVWP/73213/2006. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/7321306en.pdf

[9] L. Olsén, C. Ingvast Larsson, H. Broström, P. Larsson & H. Tjälve: *Clinical signs and etiology of adverse reactions to procaine benzylpenicillin and sodium/potassium benzylpenicillin in horses* in Journal of Veterinary Pharmacology and Therapeutics, 2007, vol. 30, pp. 201-207.

[10] **Advisory note to veterinary surgeons** regarding the development of fibrosarcomas at sites of injection of veterinary medicinal products in cats, Doc.Ref.No EMEA/CVMP/205/03-FINAL. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/press/pp/020503en.pdf

[11] **EMEA press release on the focus group meeting** with stakeholders on fibrosarcoma occurring at sites of injection (injection site sarcoma) of veterinary medicinal products in cats on 9 July 2007, Doc.Ref.No EMEA/CVMP/PhVWP/296279/2007. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/press/pr/29627907en.pdf

[12] **Guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections** for veterinary medicinal products. Available on the European Commission website http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/2007_03%2027_vol9b_guidelines.pdf

[13] **Report from the workshop on Pharmacovigilance Systems and Inspections** for Veterinary Medicinal Products, held on 4 December 2007 at the EMEA for regulators and industry. Doc Ref No EMEA/575883/2007. Available on the EMEA website.

[14] **A Simple Guide to Veterinary Pharmacovigilance in the EU**, Doc Ref No EMEA/CVMP/PhVWP/110607/2005. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/11060705en.pdf

[15] **EMEA public bulletin 2006 on veterinary pharmacovigilance**. Doc.Ref.No EMEA/CVMP/PhVWP/73213/2006. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/7321306en.pdf

[16] **Guideline on Management and Assessment of Periodic Safety Update Reports** (PSURs) of Veterinary Medicinal Products. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/455006en.pdf

[17] **Concept Paper on a PSUR assessment guideline** for Veterinary Medicinal Products. Doc.Ref.No EMEA/CVMP/PhVWP/145320/2005-FINAL. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/14532005.en.pdf

[18] **VICH** is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration. Its full title is the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. VICH was officially launched in April 1996. For more information see VICH website http://www.vichsec.org/

[19] **CVMP Pharmacovigilance Working Party Work programme 2008** Doc.Ref.No EMEA/CVMP/PhVWP/208614/2007. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/PhVWPworkprogramme.pdf

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