VETERINARY PHARMACOVIGILANCE PARTICULARITIES AND SIMILARITIES COMPARED TO PHARMACOVIGILANCE IN HUMAN MEDICINE

Cornelia Ibrahim

Head of Unit Support and surveillance after Authorisation
Deputy Head of Department Authorisation of Veterinary Medicinal Products
Federal Office for Consumer Protection and Food Safety (BVL),
Mauerstraße 39-42, D-10117 Berlin, Germany.

Pharmacovigilance is the study of safety of marketed medicinal products under practical conditions of clinical use in large populations. Safety should however always be considered in relation to the efficacy of the drug and the seriousness of the reaction as well as the indication for which the medication is used. The risk/benefit evaluation must take into account the complex situation. After the granting of a marketing authorisation, even if the requirements for authorisation relating to quality, efficacy and safety of the products are already very demanding, veterinary medicines must be continuously evaluated, to monitor the balance between their benefits and risks and assure that the benefit/risk ratio remains positive.

For this objective pharmacovigilance of veterinary drugs should improve the knowledge about prevention of adverse drug reactions (ADRs) in target animals, and also the surveillance of possible harmful effects to humans (as user or handler of the veterinary product or as a person in contact with treated animals) as well as to food safety and to the environment.

Compared to pharmacovigilance in human medicine, which is focused only on adverse reactions related to clinical symptoms in patients, on the veterinary side a much larger scope is covered.

The large scope of veterinary pharmacovigilance covers also in addition to the clinical symptoms in target animals, the lack of expected efficacy, adverse reactions after off-label use and suspected insufficient withdrawal periods after the use of products in food producing animals. In addition aspects of ecotoxicity are covered.

The legal texts in the European Union take these aspects into account and they are reflected in the definitions given in the law relating to the veterinary field.

For international harmonisation of conditions of post marketing surveillance for drugs the VICH initiative (= Veterinary International Cooperation on Harmonisation of technical requirements for the registration of Veterinary Medicinal Products) has developed guidelines in the pre-and post-approval area,

Corresponding author E.mail : cornelia.ibrahim@bvl.bund.de

which can be used by any country world-wide in view of standardized methods for a global information exchange thus also avoiding double work.

Although the main principles, legal definitions and risk management criteria are quite similar in human and veterinary pharmacovigilance there are also important particularities and differences.

A very important aspect for veterinary pharmacovigilance is the multiple species situation in the veterinary field and the categorisation of animals in food producing species and non food producing (companion) animals. Species and breed differences may lead to particular adverse drug reactions due to differences in anatomy, metabolism or enzyme patterns leading to specific sensitivities or intolerance.

A veterinary medicinal product is authorised on the basis that the balance of benefits and risks is considered positive if used under the conditions defined in the Summary of Product Characteristics (SPC) on the basis of the information available at the time of authorisation.

But it is recognised that at the time of authorisation, information on the safety of a veterinary medicinal product is relatively limited and not all actual or potential risks can be identified.This is due to many factors including the relatively small group of patients from a selected population of target animals treated in clinical trials and also restricted conditions of use of the product, restricted co-medication, relatively short duration of treatment and follow up.

During the post authorisation period the product will be used in a different setting from clinical trials and in larger populations. Much new information will be generated which may impact on the benefit or risk of the product. Thus the post-authorisation phase provides the possibilities to learn more about the safety profile of a product and if necessary adapt the product's marketing conditions to make its use safer and more efficacious under actual, realistic field conditions.

Therefore post-marketing safety data collection and risk management based on observational data are critical for evaluating and characterizing a products safety profile and for making informed decisions on risk management and risk minimization.

The pharmacovigilance system provides the tools for a continuous benefit risk assessment throughout the lifetime of a veterinary medicinal product.

The knowledge accumulated about the drug in the post-marketing phase gives the possibilities to assess benefit and risk in a more precise way, although for reasons of consistency and transparency the same methodological approach as in the pre-authorisation phase should be taken.

The main instruments for surveillance of benefit/risk in the post authorisation phase are

- The spontaneous reporting system of collecting adverse reactions, which is very important for signal generation and signal detection, especially to detect severe but rare adverse

reactions. The great strength of this system is, that it operates for all veterinary medicinal products throughout their whole lifetime. The reports received mainly from veterinarians in the field comprise the most important source of information. Further information on how to handle adverse reactions is given for Marketing Authorisation Holders (MAH) and Competent Authorities (CA) in the relevant Guidelines in Volume 9 B of the Rules governing Medicinal Products in the EU. Regular screening of the Eudravigilance database at the European Medicines Agency (EMA) in London and national databases in Member States for signals is a prerequisite for surveillance.If in the course of routine checking of reports unusual serious findings come up, one has to decide whether the evidence available is sufficient to suppose a new risk is present. In such cases more detailed research is needed to determine whether the suspicion can be confirmed. At the occurrence of serious adverse reactions, the benefit risk balance of a veterinary medicinal product may be reassessed at any time of the products life cycle.

- Periodic Safety Update Reports (PSUR) are documents allowing a periodic comprehensive assessment of the worldwide safety data of a marketed veterinary medicinal product. The PSUR creates the opportunity for a periodic overall safety evaluation to show whether a product safety profile has remained the same since it was authorised. If new risks become known by the submitted safety information, regulatory measures must be initiated to optimise the use of the product. The PSUR includes in addition to the collected adverse reaction reports also data of use of the product under field conditions including sales volume data. Thus an incidence calculation can be provided and the benefit- risk balance can be assessed with regard to a larger and more reliable base and taking into account also the additional risks not known at authorisation time.

The benefit risk balance is re-evaluated periodically through PSUR reports (Article 75, Directive 2004/28/ EC), but a PSUR can also be requested at any time if a serious signal arises from the spontaneous system.

- Post authorisation surveillance/safety studies allow a more systematic approach to clarify specific concerns and questions. Such studies can be a condition of authorisation procedure (Article 26.3, Directive 2004/28/EC). They can also be requested if safety concerns arise at any time in the products life cycle. The studies can be undertaken to generate or test hypotheses which may arise from signal detection of spontaneous reports.

- **Risk management plans**

The purpose of a risk management plan is not to replace but to compliment procedures in

place to detect safety signals. Such a plan would be needed in situations where potential or actual risks are identified that cannot be managed through routine pharmacovigilance. It would particularly apply to products authorised under exceptional circumstances and for products involving concepts completely new to veterinary medicines.

The data collected by the various instruments of the pharmacovigilance system provide a more extensive and reliable base for adequate benefit / risk assessment than the decision base at authorisation time.

If the benefit / risk assessment from authorisation time is not maintained and shifts to the unfavourable side, risk management measures and risk communication to the public and health professionals must be initiated, as laid down in the legal provisions.

If data from the spontaneous reporting system or from the PSUR show that risk management measures are needed to maintain a positive risk / benefit balance different tools are available.

Risk minimizing measures are based on EU and national legislation in Member States. Such measures are for instance:

- Hearing of experts
- Allocation of research assignments
- Recommendations or restrictions for use of veterinary medicinal products by health care professionals
- Amendments of the Summary of Product Characteristics of veterinary medicinal products i.e. change of indications for use, dosage, target species etc.
- Batch recall and warning of the public
- Amendment of the classification for the dispensing of veterinary medicinal products
- Increased surveillance of companies involved in production and distribution of veterinary medicinal products
- Increased surveillance of import of veterinary medicinal products
- Suspension and withdrawal of marketing authorization of veterinary medicinal products.

In the presentation examples of the particularities of veterinary pharmacovigilance are given, related to species and breed differences. In addition recent reports in animals from the German database are analyzed according to ATCvet code and VeDDRA terminology categorization.

Also case examples of the larger scope such as reports on ecotoxicity or food safety aspects are addressed. Although such cases are rarely reported within the spontaneous pharmacovigilance system as they are also covered by specific monitoring programmes in the EU, they show nevertheless important aspects of veterinary pharmacovigilance and post- marketing surveillance.

Another unique aspect of veterinary pharmacovigilance is to cover the reports on human safety, independent of whether people

are exposed to veterinary medicines as user (veterinarians, farmers, pet owners) or whether misuse or accidental exposure is the initial reason for the report.

Fortunately the majority of cases occurring in humans show transient mild symptoms. Sometimes it may be necessary though to include new warnings or restrict the conditions of use to mitigate possible risks to humans.

It is recommended to have a routine exchange of information with centres for human pharmacovigilance as many substances are used in both human and veterinary medicines and the data exchange or common regulatory measures may be beneficial for both sides.

In veterinary pharmacovigilance like in the human medicine field, if new risks become known through the pharmacovigilance system, it is important to share this information and use adequate communication tools.

New approaches could consist of making better use of communication tools such as internet fora dedicated to drug safety problems, circular e-mail letters, applications on smart phones, dear doctor letters send by companies, better use of websites of agencies to promote the pharmacovigilance system and give information back to users and animal owners.

The information should be short, precise and user friendly. Stakeholder communication can be considered as a measurement of efficiency of the pharmacovigilance system.

Public access to Pharmacovigilance data should be facilitated, whilst maintaining essential confidentiality and data protection requirements. Authorities will only get more information from the field, if they give useful and analysed information and advice back to the stakeholders.

Other ways to improve communication is cooperation with universities on pharmacovigilance issues or exchange of information with selected veterinary clinics.

Pharmacovigilance has the objective to ensure a positive benefit/risk profile of medicines used under field conditions and make their use even safer than at the time of authorisation, by taking into account the real life experience and adapting the conditions of use accordingly.

REFERENCES

Mann, Ronald, D., Andrews and Elizabeth, B. (2007). Pharmacovigilance. 2nd ed. John Wiley & Sons Ltd.

Ibrahim, C. and Wilke, A. (2009). Pharmacovigilance in Germany in "Adverse Reactions to Veterinary Medicinal Products" edited by K.N. Woodward Wiley, Blackwell Publishing Ltd., Pp 65-91.