

Section 6: Pharmacovigilance

Introduction

1. An effective medicines regulatory system must be able to *estimate* the risk-benefit of medicines, *communicate* that information effectively to users and health care professionals, and *take regulatory action* when necessary to protect health. For veterinary medicines the user community will include animal owners and the protection of the environment must also be considered. All three of these tasks must continue during the life cycle of the medicinal product. As knowledge grows, the estimates of risk-benefit should become more precise. Conveying the range of uncertainty is part of the communication task, if users are to make informed judgements.
2. This paper builds on much previous work, in particular the HMA Working Group Report on Establishing a European Risk Management Strategy (ERMS), the 2001 review of European medicines legislation, the EMEA roadmap to 2010 and the HMA Benchmarking Exercise. It describes what an excellent European pharmacovigilance system would look like and what is needed to turn the concept into reality.
3. Pharmacovigilance has in the past been concerned with the detection and evaluation of adverse effects of medicines when they are being used in the population after the granting of a marketing authorisation. It has largely relied on case reporting to detect 'signals' and analytical research designs such as cohort studies and case-control studies to assess those signals. These research methods developed for human medicines have not been applied in the veterinary field because of smaller market size and economic factors. In recent years, this concept of pharmacovigilance has advanced in several important ways:
 - Estimation of risk-benefit is now seen to be of more value than the measurement of risk alone.
 - Knowledge of a medicine's properties grows continuously from its earliest development to large-scale use, with the time of licensing being a milestone rather than a boundary in that process.
 - During the early post-licensing phase, when use is often increasing very rapidly, it is particularly important to be able to detect, assess and act on emerging information on risk-benefit with minimum delay. This is the period when uncertainties around overall risk-benefit must be reduced as quickly as possible.
 - The evidence used to estimate risk-benefit should be the sum of all available data, whether from observational research or randomised trials.
 - There is increasing emphasis on proactive rather than reactive risk assessment, i.e. 'pharmacovigilance and risk management'.
4. Apart from the continuity in the growth of knowledge, there are other important links between licensing and post-licensing activities. Highly effective post-licensing monitoring systems will support earlier licensing, and therefore earlier access to innovative treatments. This in turn will help to control the costs of drug development. Public understanding of (and confidence in) risk-benefit assessment will reduce the pressure for hasty removal of a product from the

market simply because a new adverse effect has been identified. What is required is a reassessment of risk-benefit in the light of the new information. Preventing the loss of useful medicines will also help to contain the overall cost of drug development.

5. The European Medicines Regulatory Network (EMRN) must therefore develop an excellent pharmacovigilance and risk management system in order to:
 - Protect public health;
 - Enable European citizens to make informed choices on their health care;
 - Enable European doctors to prescribe medicines on the basis of best available evidence;
 - Ensure that animal medicines are used safely with regard to animals, users and consumers.
 - Maintain public confidence in the regulatory system and in pharmaceuticals;
 - Support continuing pharmaceutical innovation.
6. The EMRN has a unique opportunity to create the best pharmacovigilance system in the world. It has a linked network of agencies covering a population of over 450 million people served by advanced health care systems and correspondingly large and diverse animal population. There are many centres of scientific excellence. But this unique opportunity comes with a unique challenge – to create an effective networked system across 25 member states. If it is to work well, tasks must be shared efficiently between EMEA and member states. This paper sets out how that can be achieved. Neither a fully centralised system nor a fully distributed one would be sufficient. The vision set out here of the ERMN complements the EMEA Roadmap from the perspective of member states' responsibilities and expectations. It must co-ordinate pharmacovigilance activities for all categories of medicines used in Europe: centrally and nationally authorised, new and established, human and veterinary.

Estimating Risk-Benefit in Use and its Range of Uncertainty

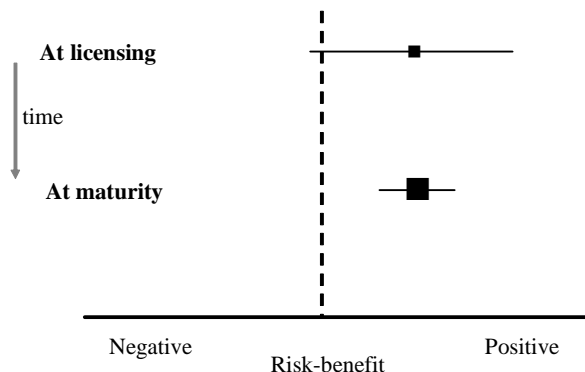


Figure1.

7. Many of the concepts outlined throughout this paper may apply to veterinary and human medicines. Methods of signal generation and confirmation are likely to be different for veterinary medicines. Harmonisation of basic pharmacovigilance

has not yet been put in place for veterinary medicines in the EU. However, it is also necessary to move from a reactive to a more proactive approach. Some other differences need to be explored further but the following issues are highly relevant:

- a) The wider scope of veterinary pharmacovigilance, which covers safety aspects in animals and humans, adverse reactions related to off-label use, lack of the expected efficacy of a veterinary medicinal product, reported violations of approved residue limits and potential environmental problems.
 - b) The relatively small market for some veterinary products also brings its own problems from an epidemiological perspective.
 - c) The organisation and structure of veterinary pharmacovigilance units in different NCAs vary widely, which has impact on the resources and structures available for proper pharmacovigilance surveillance.
8. Action Point
- To consider further the pharmacovigilance issues specific to veterinary medicines.

Reactive and Proactive Pharmacovigilance

9. European pharmacovigilance has two linked tasks: *reactive* and *proactive*. Reactive pharmacovigilance is the ability to detect, assess and act on new risk-benefit information. To protect health and retain public confidence, it must have three qualities: speed, good scientific judgement and effective communication. Proactive pharmacovigilance identifies important areas of uncertainty and puts in place the studies which will reduce these uncertainties. However, its aims must be realistic if it is not to discourage innovation in small therapeutic areas – a particular concern for veterinary products. An effective reactive function is the minimum, but on its own will not retain public confidence in medical innovation. Active steps must be taken to reduce uncertainties on risk-benefit as quickly as possible after a new medicine enters clinical use (Figure 1) and emerging information should be used to develop best clinical practice. Without this, public attention will continue to focus on ‘risk’ rather than ‘risk-benefit’ and useful innovations may be lost as a result. Proactive pharmacovigilance is only possible, however, if good mechanisms exist to respond to the new information which it generates – that is to say, reactive pharmacovigilance. The requirements of reactive pharmacovigilance are therefore considered first.

Reactive Pharmacovigilance

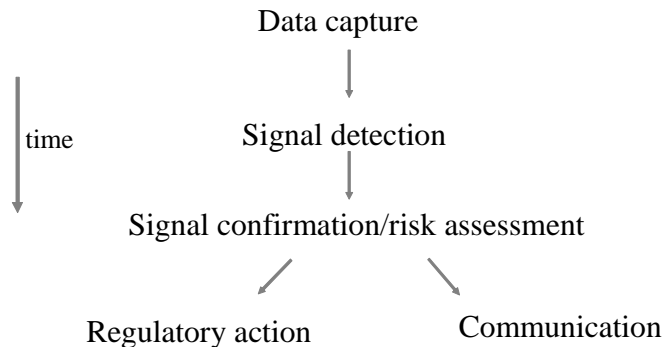


Figure 2

Reactive pharmacovigilance

10. The five requirements (Figure 2) are:

- Data capture and initial assessment
- Signal detection
- Signal confirmation/risk assessment
- Regulatory decision
- Communication

The first two steps are concerned with reports of suspected adverse drug reactions (ADRs) either in the population or in clinical trials. Other types of input (for instance arising in epidemiological studies of human medicinal products) can enter stage 3 directly.

Data capture.

11. Member states have the responsibility to maintain ADR reporting systems in their own populations (or in partnerships for veterinary medicines). This task cannot be centralised, and if it is not done well the EMRN will not gain the unique benefit of scale. Opportunities to learn from national patterns of practice and medicines use will also be lost. Different models of ADR reporting – such as the use of regional centres – have been set up in different countries to gain the active participation of health care professionals and some work is also being done on patient reporting. This experience should be shared. The ERMS Working Group has noted that the resources available to National Competent Authorities (NCAs) for pharmacovigilance are uneven and the quality of the ADR reporting systems varies. **The Benchmarking exercise now in progress will help NCAs to identify areas of weakness and to share best practice** The Network as a whole has a responsibility to help all NCAs to reach a consistent standard of reporting rates and of quality for mandatory fields.

12. By November 2005 all NCAs should be contributing their ADR data to Eudravigilance. This will allow population reporting rates to be compared, as a developmental tool to build EU population coverage to a consistent standard. Where differences are found, they should be explored in relation to national differences in ADR reporting methods and medicines use. In veterinary medicine, it has already been identified that rates of reporting depend not only on the reporting methods but mainly on the animal population that varies according to the Member States. In addition, on the human side, reporting of SUSARs from authorised clinical trials in the EU is already in place.
13. Action points:
- NCAs should complete Benchmarking as soon as possible during 2005-06 and act on identified weaknesses in pharmacovigilance. HMA (through the ERMS Working Group) should help in the sharing of best practice through workshops, exchange of pharmacovigilance staff and twinning arrangements where this might be helpful.
 - HMA should monitor population reporting rates into Eudravigilance over time and help NCAs to obtain the resources needed to achieve a consistent standard across the EMRN.
 - HMA should consider quality indicators for ADR reporting in addition to population reporting rates.
 - EMEA should make available to ERMS Working Party (representing HMA) reporting rates to Eudravigilance on a regular basis, and any supplementary data requested as quality indicators in order to promote information *exchange*.
 - EMEA should review the operation of the reporting system for SUSARs after the first year of implementation of the Clinical Trials Directive

Signal detection.

14. This function is currently carried out by individual NCAs within their own ADR databases. The methods used vary widely. A fully developed EU system for reactive pharmacovigilance needs a fully populated single database – Eudravigilance – that is systematically interrogated by the best available signal detection methods. New software for data mining is becoming available and some NCAs have experience of evaluating this. For veterinary medicines, such methods will be limited by the smaller number of ADR reports.

15. Action points:

- All NCAs (human) should complete the work needed to report ADR data into Eudravigilance by November 2005.
- During 2005-06, ERMS Working Group and EMEA should develop a strategy for signal detection within the EMRN for human ADRs, so that the pooled data in Eudravigilance are systematically interrogated using the best methodology and expertise.

Signal confirmation and risk assessment

16. A decision to review the risk-benefit of a medicine in response to a potential signal will result in a scientific effort using a range of data sources. At present, there are no explicit criteria or formal mechanisms for doing so. Considerations

might be the strength of the signal, its possible public health impact, or public concern (usually in the form of media coverage). Since there are both central and national marketing authorisations, signal assessment for a human medicine might be initiated in any part of the EMRN. Since it commits scarce scientific resources, there needs to be early communication and co-ordination of effort. In many cases there will be a decision that the assessment should be carried out once on behalf of the whole network by a rapporteur MS.

17. In some instances an epidemiological study will be necessary to confirm or refute a signal arising from a human medicine. Some NCAs possess epidemiological databases and the skills to conduct such studies in house. Independent research may be performed by academia and subsequently used for regulatory decision making. Studies may also be conducted by the marketing Authorisation Holder. Although there are a number of existing epidemiological databases, access to and use of them is limited. It is recognised that databases relevant to veterinary medicines are very few in number.
18. More sensitive signal detection techniques such as data mining will create a larger number of possible signals. 'Triage' will be needed to select out at an early stage those which are unlikely to lead to an important revision of risk-benefit. Again, good communication within EMRN will be important.
19. Action points:
 - Good lines of communication between NCAs and EMEA on pharmacovigilance need to be established for handling 'routine' business efficiently and existing guidelines need to be reviewed.
 - Criteria for starting or stopping signal assessments need to be considered, though too rigid a process would be undesirable.
 - HMA should complete an inventory of existing databases in the European Union that can be useful for performing epidemiological studies in order to confirm or refute a signal
 - HMA should consider a strategy to foster the establishment of new data sources at the European level, for example by making use of existing clinical databases developed for other purposes.
 - HMA should consider the possible need for a specific budget to fund epidemiological studies performed by NCAs themselves or through academic researchers. On the veterinary side, financial support for additional resources for dealing with harmonisation and strengthening of basic pharmacovigilance systems should be considered as the priority.

Regulatory decision

20. Actions on the Marketing Authorisation, and/or communication of new advice, need to be supported by strong and rapid scientific review. Although the Licensing Authority may be the Commission or national Government, decisions should be consistent across both central, mutual recognition and national MAs. Difficulties have arisen from this cause and also from the tension between speed and harmonisation. For human medicines, the strengthening of the work of the PhVWP to consider both centrally and nationally authorised products is a positive step. Action is needed to shorten delays in the system at several points: referral and scientific review, industry consultation and the interval between scientific

advice from the PhVWP/CHMP and the legal process to change the MA. On the veterinary side, CVMP has acted on pharmacovigilance.

21. Action points:

- The operation and support of PhVWP needs to be expanded as recommended by the ERMS Working Party.
- The relationship between PhVWP and CHMP should be clarified and strengthened.
- Timelines should be agreed by EMEA, HMA and the Commission for completing legal processes after scientific advice has been given.

Communication

22. This topic is being considered by a separate drafting group. It includes communication within the EMRN, communication with the public and healthcare professionals, and exchange of information with other regulators outside the EU. However, processes should be developed which measure the impact of safety messages on patients and healthcare professionals.

Proactive Pharmacovigilance

23. The 2001 review provides the legal framework to require a risk management plan to be developed by the applicant at the time of granting an MA where appropriate. This presents opportunities and challenges for the EMRN:

- To ensure that the plan is securely based on a scientifically strong specification of the areas of potential concern;
- To ensure that the MAH carries out the agreed studies;
- To respond appropriately to the evidence emerging from the studies.

Although detailed guidance has not yet been issued for these tasks, the objective must be to narrow the uncertainty around overall risk-benefit as quickly as possible after launch. Pharmacological insight and regulatory experience will be required to define correctly what studies are required in a particular case. These skills will need to come from the collective resources of the EMRN.

24. Reactive pharmacovigilance alone will not allay public concerns over the safety of medicines. Absence of evidence of harm might reflect absence of harm or inadequate information to detect it. What is required is positive reassessment of risk-benefit as risk management plans are delivered. The infrastructure for the specified studies is likely to require the collaboration of industry, regulators, health care providers and academia. Joint working of this kind may best be achieved in centres of excellence acting for the EMRN as a whole.

25. Action points:

- EMEA and HMA should develop guidance for the development of risk management strategies, including pharmacovigilance plans
- NCAs should consider their arrangements for pharmacovigilance input into the licensing process.
- NCAs with special interest in pharmacovigilance should discuss with industry, academia and healthcare providers the scope for collaborative post-authorisation studies.

- Strategy needs to be developed for ensuring that companies comply with agreed pharmacovigilance plans