Pharmacovigilance in the human medicines sector is a well-established discipline. So well established in fact that reports of adverse reactions to medicinal products are relatively common in general and specialist medical journals either as case reports or as detailed epidemiological studies. There are numerous text books on the topic or on related areas such as pharmacoepidemiology and a number of dedicated journals such as Drug Safety and Pharmacoepidemiology and Drug Safety, while publications such as the Journal of Clinical Epidemiology also regularly cover the subject. So what exactly is pharmacovigilance?

Pharmacovigilance has been described as:

‘. . . a neologism created by the European Union to cover procedures involved in the detection of unwanted adverse effects causally related to the administration of therapeutic drugs’ (Fletcher, 2000).

Regardless of whether or not the author intended a degree of cynicism or even sarcasm in this comment, it is quite a useful description, if not a definition. However, the term ‘therapeutic drugs’ is probably better replaced by medicinal products or, for the purposes of this book, veterinary medicinal products, as the discipline of pharmacovigilance covers the whole panoply of agents, including therapeutic and prophylactic drugs, vaccines and other immunological products and drugs used to alter physiological status such as those used to synchronise oestrus or promote growth in animals and drugs used as contraceptive agents in humans.

In fact pharmacovigilance is a relatively new term in the veterinary context for a well-established concept, namely the gathering of information on adverse reactions which may occur after the administration of medicinal products. Perhaps surprisingly, although the term is now widely used, there is very little by way of a formal definition. Even the Council for International Organisations of Medical Sciences’ and the World Health Organisation’s otherwise excellent document entitled Reporting Adverse Drug Reactions, which is subtitled Definitions of Terms and Criteria for Their Use, finds few places in its 146 pages to even mention the term pharmacovigilance, and none to define it (Bankowski et al., 1999).

The European Union’s Directive 2001/82/EC (as amended) requires that:

‘. . . member states shall establish a veterinary pharmacovigilance system that shall be used to collect information useful in the surveillance of veterinary medicinal products, with
particular reference to adverse reactions in animals and human beings related to the use of veterinary medicinal products, and to evaluate such information scientifically’.

However, it fails to give a concise definition. Yet all is not lost. The major aims of pharmacovigilance have been identified for human medicines (Stephens, 2000), and these can be readily adapted for veterinary medicines:

1. Identification and quantification of previously unrecognised adverse drug reactions.
2. Identification of subgroups of patients at particular risk of adverse drug reactions, e.g. relating to species, breed, age, gender, physiological status and underlying disease.
3. Continued monitoring of the safety of a product in each species for which it is authorised, to ensure that the risks and benefits remain acceptable. This should include extension of monitoring to new indications and new species.
4. Comparing the adverse reaction profile with those of products in the same therapeutic class, both within and across species.
5. Detection of inappropriate prescription and administration. With respect to the latter, administration by specific groups, e.g. farmers or the public, may need to be monitored.
6. Further investigation of a drug or product’s toxicological, pharmacological or microbiological properties in order to understand, where possible, the mechanisms underlying adverse drug reactions.
7. Detection of drug–drug interactions. This is particularly important for new drugs that are then co-administered with established products or even other new drugs.
8. Provision of appropriate information on adverse drug reaction data and drug–drug interaction information to veterinarians and others involved in the treatment of animals, e.g. veterinary nurses, farmers and other animal owners.
9. Provision of information to discount so-called ‘false positive’ reports.
10. Provision of adverse drug reaction data from permitted off-label use, e.g. under the cascade permitted in EU veterinary legislation (this permits a veterinarian or someone under his or her supervision, with a number of restrictions, to prescribe a veterinary medicine authorised in another EU member state or, if unavailable, a medicine authorised for human use or, if unavailable, a medicine prepared extemporaneously, in those circumstances where there is no authorised veterinary product available for the condition in an animal or small number of animals).
11. Identification of adverse drug reactions in humans following inadvertent exposure, e.g. occupationally or otherwise (accidental exposure or suicide or homicide attempts).

To these, others can be usefully added, although to some extent these may depend on specific national or multinational legislative requirements:

12. Adverse effects of veterinary medicinal products on the environment and on organisms in the environment.
13. The violation of permitted residue limits of veterinary medicines in food of animal origin such as meat, milk and honey.
14. Legislation and guidelines governing the requirements of pharmacovigilance.
15. Methodologies for dealing with pharmacovigilance data (e.g. databases, electronic reporting and other reporting systems).

Taking all of these into account, and perhaps put more simply, pharmacovigilance may also be defined as the process of evaluating and improving the safety of marketed medicines (Waller et al., 1996), while pharmacoepidemiology, one of the disciplines within pharmacovigilance and the application of the principles of epidemiology to drug safety, can be seen as the completion of the safety evaluation of a drug that was started before the product was authorised.
Elements of veterinary pharmacovigilance

Bégaud and Dangoumau, 2000. It includes data collection, information flow, knowledge of relevant regulations, product data and the overall management of relevant information (Allan, 1992a–c). The process of safety evaluation and continued evaluation through pharmacovigilance is illustrated in Figure 1.1.

The events following the use of the drug thalidomide in humans where birth defects (phocomelia) occurred when pregnant women were treated with the drug exemplify not only the serious nature that adverse drug reactions can take, but also the essence of pharmacovigilance in the detection of such adverse events. Indeed, the thalidomide tragedy led to the establishment of the regulation of human and veterinary medicines in the UK with the introduction of the Medicines Act 1968. Similarly, a disaster in the USA where the solvent diethylene glycol, used in a medication known as Elixir of Sulphanilamide, caused the deaths of 73 people (and associations with a further 20) in 1937 was the engine behind the passing by Congress of the Food, Drug and Cosmetic Act in 1938 (Mann, 1993; Gad and Chengelis, 2001; Collins, 2004; Barr et al., 2007).

Human medicine has since been marked by drug withdrawals and fatalities caused by medicines (Routledge, 1998; Buajordet et al., 2001; Preskhorn, 2002) and these contribute in a negative manner to both the economics and the standing of the industry (Khong and Singer, 2002; Lundquist and Jönsson, 2004).

It is evident that these early adverse drug reactions were underpinned by the toxicity of the chemicals involved. However, while this may be specific for adverse drug reactions where toxicity is the underlying cause, many adverse drug reactions are not related to toxicity. In fact this is particularly true with vaccines where the adverse reaction may be associated with a biological origin rather than a chemical origin, such as reversion to virulence leading to disease, or anaphylaxis arising from foreign proteins present in the products concerned. Overall, the term pharmacovigilance is perfectly adequate to describe the scientific study and follow-up of adverse drug reactions, whatever their underlying aetiologies, in humans and animals, including structured post-marketing surveillance activities. Indeed, there are now other, perhaps less-well recognised ‘vigilance’ disciplines associated with other areas of product safety including toxicovigilance (the study of adverse effects of chemicals in individuals and populations) (Belhadj-Tahar et al., 2003; Descotes, 2003; Keck et al., 2004; Descotes and Testud, 2005; Watson et al., 2005), cosmetovigilance (the corresponding study of cosmetics) (Tissier and Lepagnol, 2002; Di Giovanni et al., 2006), pharmacoenvironmentology (adverse effects of drugs on the environment) (Rahman et al., 2007) and, perhaps bizarrely, vaccinovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004). Most observers would regard the latter and indeed pharmacovigilance, the study of adverse effects following vaccination (Lankinen et al., 2004).
Physico-Chemical Properties:
- Water solubility
- Vapour pressure
- Dusting potential
- Log Po/w
- Stability in air, water etc
- Photodegradation

Toxicology:
- Acute
- Reproductive
- Genetic
- Carcinogenicity
- Other

Pharmacology:
- Pharmacokinetics
- Pharmacodynamics
- in laboratory species
- in target species

Microbiology:
- Effects on human gut flora
- Effects on barrier
- Induction of resistance in human gut flora
- Resistance in target pathogens
- Resistance in enzootic organisms

Target Animal Safety:
- Clinical trials
- Laboratory studies
- Tolerance studies

Food Safety

User Safety

Target Animal Safety

Environmental Safety

Residues Depletion
- Radiolabel studies
- "Cold" depletion studies
- Pharmacokinetics
- Analytical studies

Maximum Residue Limits:
- MRLs
- Toxicology
- NOEL
- ADI
- Analytical method
- Withdrawal periods

Human Studies:
- Clinical
- Volunteer
- User exposure
- Poisonings
- Epidemiology

Environmental Effects:
- Excretion
- Animal run-off
- Disposal
- Manure/soil/water levels
- Phytotoxicity
- Invertebrate toxicity
- Vertebrate toxicity

Efficacy:
- Clinical trials
- Laboratory studies
- Efficacy studies

Quality:
- Manufacture
- Stability
- Controls
- Contaminants
- Break down products

ADVERSE EVENTS/ENVIRONMENTAL EFFECTS - LACK OF EFFICACY - MRL VIOLATIONS

PHARMACOVIGILANCE

Fig. 1.1 Pharmacovigilance and the process of continuous assessment.
Regulatory Agency (MHRA, formerly the Medicines Control Agency – MCA).

Quite obviously, animals too are susceptible to the side effects of drugs. Indeed, some species may be particularly sensitive to the toxic effects of some specific drugs (and other chemicals). For example, the cat has a very low capacity to conjugate paracetamol (acetaminophen) because of its low glucuronyl transferase activity. Hence, cats are extremely sensitive to the toxic effects of paracetamol, and what is a therapeutic dose in other species may prove to be a lethal dose in the cat (Campbell and Chapman, 2000: 89–96). Similarly, dogs appear to be more sensitive to the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the gastro-intestinal tract than do other species (Campbell and Chapman, 2000: 31–38, 152–162).

However, many adverse events in animals are subtler than might be inferred from these examples. Rather than highlighting species that might be less tolerant to a particular substance or formulation, they are more likely to be seen as events in intolerant or less tolerant individuals or subpopulations of individuals, in a species that otherwise tolerates the product well. Due to these concerns, veterinary regulatory authorities around the world have introduced their own spontaneous reporting schemes. For some years, the UK scheme has served as an example and model system for regulatory authorities in other countries to adapt and adopt to fit their own requirements. Indeed, it was in existence and operating effectively long before many other countries had anything in place at all, and it has been reporting its findings since 1987. It will be used here, along with other examples, to exemplify many of the positive requirements of a pharmacovigilance scheme, as well as some of the more negative points, common to all.

The purpose of this book is to help place veterinary pharmacovigilance firmly on the scientific map. In doing so it will examine pharmacovigilance regulatory requirements and systems from across the world, as well as consider examples of adverse effects of veterinary medicinal products on animals, on exposed humans and on the environment. This latter aspect is of growing importance. There is now substantial evidence that human pharmaceuticals are entering the environment to an increasing degree and these are being found in sewage, river water and sediments (Hignite and Azarnoff, 1977; Christensen, 1998; Halling-Sørensen et al., 1998, 2000; Zuccato et al., 2000; Daughton, 2001; Castiglioni et al., 2004; Carlsson et al., 2006a, b; Hao et al., 2006; Liebig et al., 2006; Rivett et al., 2006; Williams and Cook, 2007). At high enough concentrations, some of these substances have the potential to exert harmful effects on the environment and the organisms in it (Beasley and Schaeffer, 1989; Halling-Sørensen et al., 2000; Glassmeyer and Shoemaker, 2005; Wolf and Wolfe, 2005; Yoshimura and Endoh, 2005; Robinson et al., 2005; Fent et al., 2006; Sumpter, 2007) and this may be exacerbated by mixtures of chemicals (Cleuvers, 2004; Eggen et al., 2004). Some may have the potential to harm human health, even at the low levels found in the environment (Henschel et al., 1997; Christensen, 1998; Sharpe, 2000; Pawlowski et al., 2003; Anonymous, 2004). This has led to the tighter regulation of human pharmaceutical products in a number of countries from the point of view of environmental effects (Calow, 1998; Stuer-Lauridsen et al., 2000; Länge and Dietrich, 2002; Straub, 2002; Mattson, 2007; Mattson et al., 2007; Montforts et al., 2007; Spindler et al., 2007; Webber and Spindler, 2007; Yoshioka, 2007; Adler et al., 2008) and the development of regulatory guidelines (O’Brien and Dietrich, 2004; Shaw and Barrett, 2004).

Veterinary medicines, including vaccines derived from biotechnology, also have the capacity to enter the environment and these too are subject to regulation, risk assessment and guidelines as they have the capacity to affect environmental and human health (Pastoret et al., 1995; Chung et al., 1999; Koschorreck et al., 2002; Longand Crane, 2003; Montforts et al., 2004; Woodward, 2005; Boxall et al., 2006; Sarmah et al., 2006; Robinson, 2007). The recent withdrawal of cypermethrin-based sheep dips in the UK because of environmental contamination and associated
adverse environmental effects serves as an example of what might happen – both from a scientific and regulatory viewpoint, if this area of veterinary pharmacovigilance is transgressed (Anonymous, 2006). This is an increasingly important area of veterinary pharmacovigilance and, consequently, one that is dealt with in this book. Indeed, the issue of pharmaceuticals in the environment and their potential effects on humans and other organisms has led to the coinage of the terms environmental pharmacology or ecopharmacology (Kümmerer and Velo, 2006; Rahman and Khan, 2006).

Hopefully therefore it will serve as an invaluable tool to those working in clinical veterinary medicine, toxicology, occupational health, the environmental sciences and regulatory areas. The teaching of pharmacovigilance to cover human medicines is in its infancy (Evans, 2007; May, 2007). It is hoped that this book may help to drive educational initiatives for veterinary pharmacovigilance.

References


