Suspected Adverse Reactions to Veterinary Medicinal Products 2009

1. Introduction

Pharmacovigilance is one of a range of post authorisation activities designed to ensure the ongoing production and use of safe, effective, high-quality veterinary medicines following their introduction to the marketplace. The scope of veterinary pharmacovigilance as defined in Article 73 of Directive 2001/82/EC covers not only suspected adverse reactions (SARs) in animals to veterinary medicinal products used under normal conditions of use, but also other aspects of post-authorisation surveillance including:

- Adverse reactions in humans related to the use of veterinary medicinal products;
- Lack of expected efficacy of veterinary medicinal product;
- Off-label use of veterinary medicinal product
- Reported violations of approved residue limits, possibly leading to investigations of the validity of the withdrawal period.
- Potential environmental problems

The primary input into the national pharmacovigilance system is reports of suspected adverse reactions (SARs), which are sent to either the Irish Medicines Board (IMB) or the relevant marketing authorisation holder (MAH). Suspected adverse reaction reports are collated and evaluated by the IMB and the MAH. In the event that a safety issue is identified post-authorisation, appropriate steps can be taken to reduce the level of any associated risk. The minimum requirements for an adverse reaction report to be considered valid are detailed in **Table 1**.

2. National Pharmacovigilance Issues

The IMB received 148 national reports of suspected adverse reactions to veterinary medicinal products (VMP) for the period 1st January 2009 to the 31st December 2009. One hundred and twenty six reports were received from marketing authorisation holders, nineteen reports were received directly from veterinarians or other healthcare professionals and three reports were received from individual animal owners. **Fig 1** shows the primary source of SAR reports received by the IMB from 2006 to 2009.

Of the 148 reports received, a total of 75 veterinary pharmaceutical products and 73 immunological products were identified as possibly associated with adverse effects. While the majority of reports related to the use of a single VMP, two or more VMPs were identified in twenty one reports.

Suspected adverse reactions were reported in the following species: Human (five reports), bovine (53), canine (52), ovine (22), feline (eight), porcine (five), equine (two), and rabbit (one).

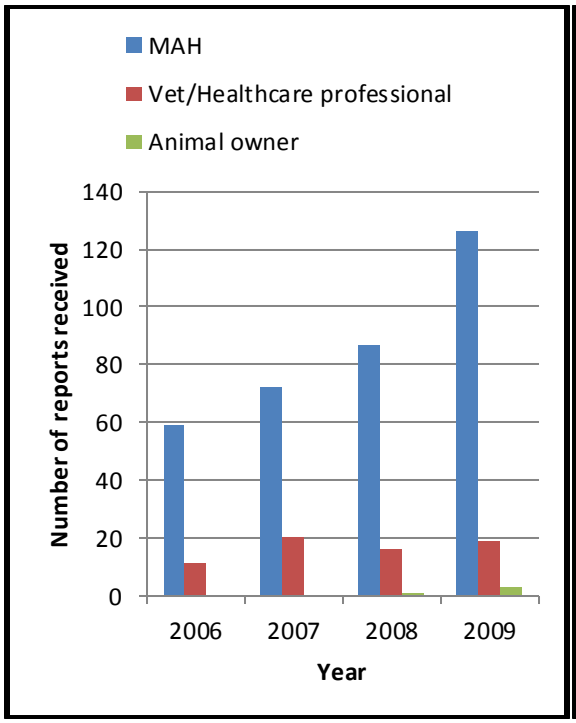

Fig 1: Source of SAR reports; 2006 to 2009

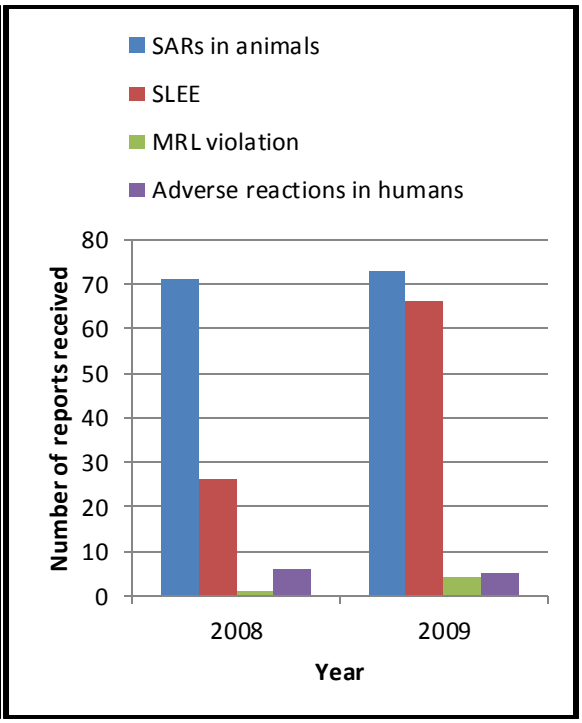

Fig 2: Types of reports received in 2008 & 2009

Of the 148 reports associated with the use of veterinary medicinal products, 73 related to suspected adverse reactions in the treated animals, 66 related to suspected lack of expected efficacy (SLEE), four related to maximum residue limit violations and five reports involved suspected adverse reactions in individual users following exposure to a veterinary medicinal product. **Fig 2** compares the types of reports received in 2009 with those received in 2008.

Of the 73 reports of suspected adverse reactions in animals, 46 related to companion animals and 27 to food producing animals. For companion animals, suspected adverse reactions were most frequently reported in dogs (38). For food producing animals, the highest number of reports was received for cattle (20).

2.1 Reports of suspected adverse effects

Three reports of suspected adverse reactions in humans associated with exposure to veterinary pharmaceutical products were received during the reporting period. One report related to symptoms of nausea and vomiting following oral exposure to an endectoparasiticide. In this case the attending physician concluded that the symptoms were related to a 24 hour virus and not as a result of exposure to the veterinary medicinal product. A second report related to accidental self-injection with an endoparasiticide. The individual developed a rash on the left side of the arm, was wheezing and coughing blood, experienced partial blindness for one night, had a fever and was hospitalised. It was noted that a reaction at the injection site did not occur. The patient had a medical history of asthma and was allergic to insect bites. It was concluded that the reaction was most likely due to the individual's allergy to insect bites and was not as a result of exposure to the

VMP by self injection. The final report concerned accidental ingestion of a nonsteroidal anti-inflammatory tablet by a child. The child was asymptomatic.

Two human reports received were associated with exposure to immunological products. Both reports related to accidental self-injection with either an inactivated avian vaccine or an inactivated bovine vaccine resulting in redness or pain at the injection site. For both reports it was considered likely that the reported symptoms were as a result of the needle stick injury.

Of the seventy three reports relating to suspected adverse reactions in the treated animal(s), the product was considered to have been probably or possibly associated with the observed reaction in 31 reports. In 32 reports, there was insufficient or inconclusive information available on which to assign causality. In ten cases it was concluded that the VMP was unlikely to be responsible for the observed reaction. The criteria for assigning causality to a report are detailed in **Table 2**.

The individual SAR reports, originating from Ireland during 2009, that were considered probably (coded 'A') or possibly (coded 'B') related to product use are summarised on a species by species basis in **Table 3** (pharmaceutical products) and **Table 4** (immunological products).

2.2 Reports of suspected lack of expected efficacy

There were 66 reports of suspected lack of expected efficacy submitted to the IMB in 2009. This was an increase of 40 on the number of SLEE reports received during 2008. The reason for the large increase in number of reports of SLEE is unclear.

Of these 66 reports, eighteen related to suspected lack of expected efficacy of pharmaceutical products. In eight reports it was suspected that triclabendazole was ineffective for the treatment of fascioliasis in sheep. Resistance to triclabendazole was suspected in four reports and, for two of these reports, this was confirmed by a positive faecal egg count reduction trial (FECRT). It is noted that the labelling for all relevant products carry warnings relating to the potential for resistance to triclabendazole and advice on what actions should be taken in the event that resistance is suspected on an individual farm.

Forty eight suspected lack of expected efficacy reports related to apparent failure to establish immunity following vaccination, resulting in the development of the disease. In a number of these cases it was established that the vaccines had not been used in accordance with label recommendations. In some other cases, it was suspected that vaccinated animals were exposed to infection before immunity had properly developed.

3. European Pharmacovigilance Issues

During 2009 the Committee for Veterinary Medicinal Products (CVMP, an expert scientific advisory committee of the European Medicines Agency) reviewed safety information, in the form of periodic safety update reports (PSUR), relating to a number of products authorised through the centralised system (pan-European authorisations). For one product (Slentrol (dirlotapide), indicated as an aid in the management of overweight and obesity in adult dogs), the Committee made recommendations to amend the product literature to include information on new adverse reactions.

Also during 2009, the Committee endorsed a public report on field safety data from the EU arising from the 2008 national vaccination campaigns against bluetongue disease (EMEA/CVMP/652019/2008) in which several vaccines were used. The report is based on a review prepared by the CVMP Pharmacovigilance Working Party and considers information provided by competent authorities in a number of Member States. The report is available on the EMA website http://www.ema.europa.eu .

4. Conclusion

For VMPs authorised by the IMB, no regulatory action was required to be taken in 2009 relating to issues of target animal or user safety as a result of spontaneous adverse reaction reports.

The number of suspected adverse reaction reports received during 2009 (148) represents a significant increase compared to the numbers received during 2008 (104), 2007 (92) and 2006 (70 reports). The reason for the increased reporting in 2009 is unclear but is likely to reflect a greater awareness of the need to report suspected adverse reactions rather than an absolute increase in the number of reactions occurring. The IMB is encouraged by this positive trend and appreciates and acknowledges the efforts of reporters in completing reporting forms and responding to requests for clarification. While an individual's experience may be limited to one or two cases, when collated with data from other sources, it will contribute considerably to the assessment of a potential safety hazard. If a safety risk relating to the use of authorised VMPs is identified, appropriate steps can be taken to reduce this risk.

Although the overall trend with regard to reporting of suspected adverse reactions is increasing, the number of reactions reported directly to the IMB by veterinary practitioners and pharmacists remains relatively low. Persons licensed to sell or supply animal remedies are reminded that, in accordance with Regulation 12 of the Animal Remedies Regulations 2007 [S.I. 786 of 2007], they are obliged to notify the IMB or the relevant MAH of all serious or unexpected SARs and all human adverse reactions associated with the use of VMPs that come to their attention within 15 days of receipt of such information. The IMB recognises that there may be a perception amongst the veterinary profession that contacting the IMB will adversely impact on their workload in that they may be asked to engage in discussion of the adverse event or case history. This is rarely the case. The reporting process itself is simple with the IMB accepting reports by a variety of different methods, and provided that the mandatory information as described in Table 1 is included in the report, the IMB will not usually actively engage with the reporter. The IMB will routinely acknowledge the report and use the information provided to contribute to the overall safety monitoring of the product.

Further information on the topic of veterinary pharmacovigilance and guidance on the reporting of suspected adverse reactions can be obtained from the Safety & Quality section of the IMB website at www.imb.ie. Specific SAR report forms may be downloaded from the IMB website for off-line completion and submission. Alternatively, prepaid self-addressed forms can be requested from the veterinary medicines department of the IMB.

Table 1: Suspected adverse reaction reports – minimum information

A SAR report will be considered as valid provided that at least the following core data are available:

- An identifiable reporter (e.g. veterinary surgeon, pharmacist, animal owner).
- Animal/human details: species, age, sex
- Suspect product: name and product authorisation number
- Reaction details

It should be stressed that these are minimum requirements and the reporter should endeavour to be as comprehensive as possible in order to facilitate a full scientific evaluation. Where relevant, this may include laboratory findings and post mortem examination findings.

Table 2: Assessing Causality

The following factors will be taken into account:

⇒ Associative connection – in time or anatomic site

⇒ Pharmacological explanation, blood levels, previous knowledge of the drug

⇒ Presence of characteristic clinical or pathological phenomena

⇒ Exclusion of other causes

⇒ Completeness and reliability of the data in case reports

Category 'A'	All of the following minimum criteria should be complied with: ⇒ There should be a reasonable association in time between the administration of the drug and the onset and duration of the reported event. ⇒ The description of the clinical signs should be consistent with the known pharmacology and toxicology of the drug. ⇒ There should be no other equally plausible explanation(s) of the reaction.
Category 'B'	When drug causality is one (of other) possible and plausible causes for the reported reaction, but where the available data do not fulfil the criteria for inclusion in Category 'A'
Category 'O'	When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality.
Category 'N'	When sufficient information exists to establish beyond reasonable doubt that drug administration was not likely to be the cause of the event.

Table 3: 2009 adverse reactions (reports coded 'A' or 'B') associated with the use of pharmaceutical products

Active Substance	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Bovine						
Abermectin	Topical	18	10	4	Shaking, ataxia, stupor, twitching/wobbling, death	1-3 days
Closantel sodium	SC	7	1	1	Anaphylaxis, death	Immediate
Closantel, Ivermectin	Topical	20	2	1	Respiratory signs, abortion, death by euthanasia	4-5 hours
Cloxacillin benzathine	Intramammary	60	9	3	Collapse, mastitis, sudden death	3 days
Flunixin meglumine	IV	1	1	1	Anaphylaxis, recumbency, anorexia, death by euthanasia	Immediate
Levamisole	Topical	30	30	5	Frothing at the mouth, tongue protruding, death	A few hours
Levamisole hydrochloride	SC	23	23	3	Hypersalivation, muscle tremor, recumbency, death	10 minutes
Levamisole hydrochloride	SC	50	5	1	Tremors, frothing, collapse, death	5 minutes up to 3 weeks (death)
Oxytetracycline	IM	4	4	0	Stiff in gait, swelling at injection site	2 days
Oxytetracycline	IM	14	2	1	Unease, heavy breathing, facial oedema, recumbency, death	Minutes
Canine						
Fipronil	Cutaneous spray	5	3	2	Ataxia, vomiting, diarrhoea, moribund, death by euthanasia	Immediate
Firocoxib	Oral	1	1	1	Collapse, death	8 days
Imidacloprid	Topical	1	1	0	Anaphylaxis	9 hours

Meloxicam	Oral	1	1	1	Vomiting, haemorrhagic diarrhoea, death	<= 48 hours
Meloxican, Trimethoprin and sulphadiazine	Oral	1	1	1	Vomiting, polydipsia, nephropathy, death	3 days
Metaflumizone and amitraz	Topical	1	1	0	Bradycardia, lethargy, ataxia	<= 24 hours
Nitroxynil*†	Oral	2	2	2	Hyperexcitability, tachycardia, death, euthanasia	Unknown
Pentosan polysulfate sodium	SC	1	1	1	Shivering, collapse, sudden death	<= 24 hours
Pentosan polysulfate sodium	SC	1	1	1	Anorexia, off colour, death	<= 24 hours
Pyriprole	Oral	1	1	1	Hyperthermia, hyperaesthesia, convulsions, tachycardia, dyspnoea, muscle spasm, death	<= 24 hours
Pyriprole	Oral	1	1	0	Collapse NOS, convulsions	<= 24 hours
Feline						
Permethrin†	Topical	1	1	0	Twitching, seizures	Hours
Ovine						
Closantel sodium	Oral	10	6	1	Blindness, death	24 hours
Doramectin	SC	84	3	2	Anorexia, collapse, trembling, death	7-24 hours
Nitroxynil	SC	11	11	11	Recumbency, hyperpnoea, hyperthermia, death	4 hours

IV: intravenous, IM: intramuscular, SC: subcutaneous
* unauthorised route of administration † unauthorised species

Table 4: 2009 adverse reactions (reports coded 'A' or 'B') associated with the use of immunological products

Antigenic Components	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Canine						
Canine distemper, canine adenovirus, canine parainfluenza	SC	1	1	0	Anaphylaxis	2-3 minutes
Canine distemper, canine adenovirus, canine parainfluenza	SC	1	1	0	Collapse, bradycardia, bradypnoea, pale mucous membranes, recumbency, anaphylaxis	5 minutes
Canine distemper, canine adeno virus, canine parvovirus, canine parainfluenza & Leptospira canicola, leptospira icterohaemorrhagiae	SC	1	1	0	Weakness, reduced responses, pale mucous membrane, low blood pressure, tachypnoea	Immediate
Rabies	SC	1	1	0	Facial swelling, breathing difficulty	2 hours
Canine distemper, canine adenovirus, canine parvovirus, canine parainfluenza, leptospira canicola, leptospira icterohaemorrhagiae	SC	1	1	0	Facial swelling, vomiting, dullness	30 minutes
Leptospira canicola, leptospira icterohaemorrhagiae	SC	1	1	0	Abortion	3 days

SC: subcutaneous