Suspected Adverse Event Reports to Veterinary Medicinal Products 2010

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 events (SAEs) in animals to veterinary medicinal products (VMPs) used under normal conditions of use, but also other aspects of post-authorisation surveillance including:

- Adverse events in humans related to the use of VMPs;
- Lack of expected efficacy of VMPs;
- Off-label use of VMPs;
- 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 SAEs, which are sent to either the Irish Medicines Board (IMB) or the relevant marketing authorisation holder (MAH). Suspected adverse event 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 event report to be considered valid are detailed in **Table 1**.

2. National Pharmacovigilance Issues

The IMB received 209 national reports of SAEs to VMPs for the period 1st January 2010 to the 31st December 2010. One hundred and ninety six reports were received from MAHs, twelve reports were received directly from veterinarians or other healthcare professionals and one report was submitted by an individual animal owner. **Fig 1** shows the primary source of SAE reports received by the IMB from 2007 to 2010.

Of the 209 reports received, a total of 107 veterinary pharmaceutical products and 98 immunological products were identified as possibly associated with adverse events. Four SAE reports related to the use of pharmaceutical and immunological products concurrently. While the majority of reports related to the use of a single VMP, two or more VMPs were identified in 34 reports.

Suspected adverse events were reported in the following species: Human (nine reports), bovine (121), canine (40), ovine (25), feline (six), equine (five), porcine (two), and lizard (one).

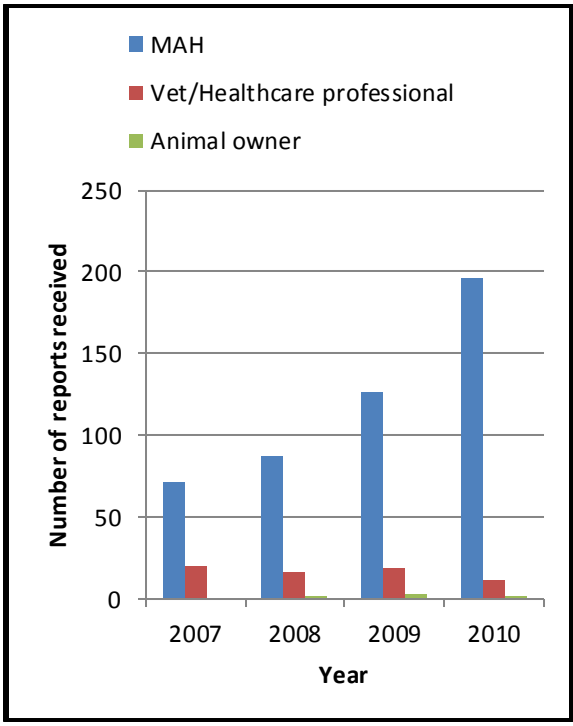

Fig 1: Source of SAE reports; 2007 to 2010

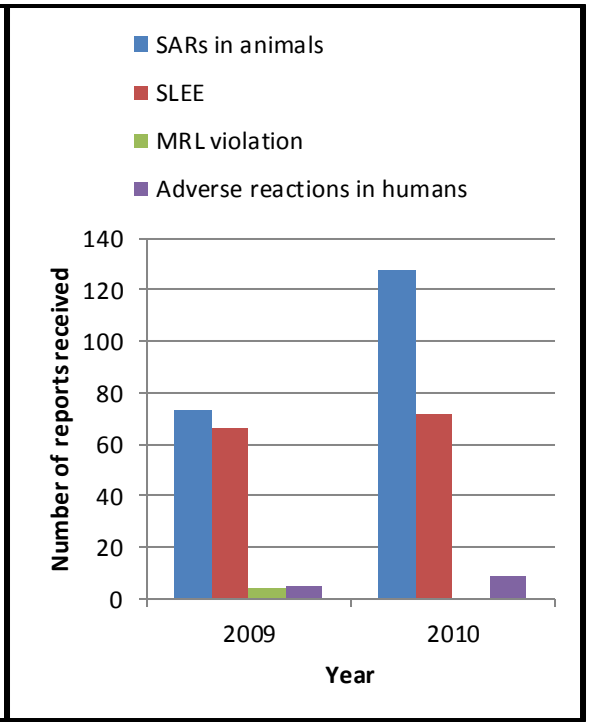

Fig 2: Types of reports received in 2009 & 2010

Of the 209 reports associated with the use of VMPs, 128 related to SAEs in the treated animals, 72 related to suspected lack of expected efficacy (SLEE) and nine reports involved SAEs in individual users following exposure to a VMP. **Fig 2** compares the types of reports received in 2010 with those received in 2009.

2.1 Reports of suspected adverse effects

Nine reports of SAEs in humans associated with exposure to VMPs were received during the reporting period.
Four reports related to injection site reactions following accidental self injection with immunological products.

Five human reports received were associated with exposure to pharmaceutical products. One report related to an injection site reaction following accidental self injection. Three reports related to localised skin reactions following topical exposure to pharmaceutical products and the remaining report concerned an individual who experienced symptoms of an unpleasant taste in the mouth and a burning sensation in the throat following use of an ectoparasiticide; however, no direct product contact was confirmed in this case and symptoms resolved within 24 hours.

Users are reminded to exercise due caution when handling VMPs and pay particular attention to any special precautions for the use of individual products as detailed in the relevant product literature.

Of the 128 reports relating to SAEs in the treated animal(s), the product was considered to have been probably or possibly associated with the observed reaction in 64 reports. In 45 reports, there

was insufficient or inconclusive information available on which to assign causality. In 17 cases it was concluded that the VMP was unlikely to be responsible for the observed reaction. Two reports relating to the use of more than one VMP had different causality assigned to each individual product associated with the observed reaction. In each report, one product was considered to have been probably or possibly associated with the observed reaction and involvement of the second product was considered unlikely. The criteria for assigning causality to a report are detailed in **Table 2**.

The individual SAE reports, originating from Ireland during 2010, 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 72 reports of SLEE submitted to the IMB in 2010.
Of these 72 reports, 23 related to SLEE of pharmaceutical products. In six reports, it was suspected that triclabendazole was ineffective for the treatment of fascioliasis in sheep and, for a further two reports, it was suspected that the same substance was ineffective for the treatment of liver fluke in cattle. It is noted that the labelling for all relevant products carry warnings relating to the potential for resistance to triclabendazole and advice on actions to be taken in the event that resistance is suspected on an individual farm.

Forty nine SLEE 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 2010 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 six products, the Committee made recommendations to amend the product literature to include information on new adverse events. Details of the products concerned were as follows:

- Cerenia (maropitant), pharmaco-therapeutic group; antiemetics and antinauseants
- Ingelvac Circoflex (*porcine circovirus type 2 ORF2 protein*), pharmaco-therapeutic group; immunologicals for suidae
- Profender (emodepside/praziquantel), pharmaco-therapeutic group; anthelmintics
- Convenia (cefovecin), pharmaco-therapeutic group; antibacterials for systemic use
- Improvac (*synthetic peptide analogue of GnRF conjugated to diptheria toxoid*), pharmaco-therapeutic group; immunologicals for suidae
- Advocate (imidacloprid/moxidectin), pharmaco-therapeutic group; endectocides

Further information concerning the changes made to the individual summaries of product characteristics for the above products can be found in the 'Public bulletin: Veterinary pharmacovigilance 2010' on the EMA website http://www.ema.europa.eu .

In May 2010, the Committee initiated an Article 78 referral procedure concerning PregSure BVD. The European Commission subsequently issued a decision concluding that the benefit/risk balance of the product had changed, with a possible association between use of the vaccine and the presence of Bovine Neonatal Pancytopenia (BNP) in calves. Consequent to this decision, the Irish marketing authorisation for PregSure BVD was suspended by the IMB in September 2010. A total of 11 reports involving 13 calves were received by the IMB in 2010 where there was a suspected link between use of the vaccine and the occurrence of BNP.

4. Conclusion

Apart from the action taken in respect of PregSure BVD, resulting from a Commission decision as detailed above, no regulatory action was required to be taken in 2010 relating to issues of target animal or user safety as a result of spontaneous adverse event reports for VMPs authorised by the IMB.

The number of SAE reports received during 2010 (209) represents a significant increase compared to the numbers received in previous years (148 in 2009; 104 in 2008; 92 in 2007 and 70 reports in 2006). The reason for the increase in numbers of reports in recent years is unclear but is likely to reflect a greater awareness of the need to report SAEs 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 SAEs 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 SAEs and all human adverse events 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 SAEs can be obtained from the Safety & Quality section of the IMB website at www.imb.ie. Suspected adverse events can now be reported using an online reporting form accessed from the homepage of the IMB website. Alternatively SAE report forms may be downloaded from the IMB website for off-line completion and submission or prepaid self-addressed forms can be requested from the veterinary medicines department of the IMB.

Table 1: Suspected adverse event reports – minimum information

A SAE 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: 2010 adverse events (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						
cypermethrin	topical	2	3	0	skin redness & peeling	<= 2 minutes
cypermethrin	topical	3	3	0	skin redness & peeling	<= 48 hours
flunixin meglumine	IV bolus	1	1	1	anaphylaxis, death	30 seconds
trimethoprim & sulphadoxine	IM & IV	1	1	1	anaphylaxis, death	30 seconds
closantel & ivermectin	SC	8	1	0	recumbency, anaphylaxis	10 minutes
oxytetracycline, dexamethasone	IV	1	1	1	recumbency, convulsions, death	immediate
meloxicam, tylosin	SC IM	1	1	1	death	5 minutes
closantel & ivermectin	topical	42	2	0	recumbency	15 minutes
tilmicosin	SC	1	1	0	injection site swelling, lameness	<= 24 hours
tilmicosin	SC	1	1	0	injection site swelling, lameness	<= 24 hours
selenium	SC	4	4	1	anaphylaxis, death	<= 30 minutes
tilmicosin, tylosin	SC IM	1	1	1	anaphylaxis, death	2 – 3 hours
levamisole & oxyclozanide	oral	20	4	4	unexplained death	48 hours
selenium	SC	60	1	1	anaphylaxis, death	1 hour
levamisole	SC	1	1	1	collapse, death	<= 30 minutes
oxyclozanide	oral	50	6	1	paresis, death	48 -72 hours
levamisole, oxyclozanide & cobalt	oral	90	20	0	scour, recumbency, bloat, staggering	<= 24 hours
levamisole, oxyclozanide & cobalt	oral	29	20	0	scour, milk production decrease	<= 7 days
levamisole & oxyclozanide	oral	16	16	2	trembling, recumbency, death	<= 48 hours
levamisole & oxyclozanide	oral	83	15	0	ataxia, anorexia, milk drop	<= 24 hours
closantel & ivermectin	topical	1	1	0	blindness, diarrhoea, lethargy	2 – 3 hours
levamisole	SC	23	1	1	neurological signs, collapse, death	minutes

closantel & ivermectin	topical	18	3	2	blindness, death	<= 24 hours
ketamine, xylazine	unknown	2	1	1	death	unknown
levamisole & oxyclozanide	oral	60	6	0	ataxia, recumbency, diarrhoea	<= 24 hours
tocopherol acetate & potassium selenate, *bovine rotavirus* & *bovine coronavirus* & *E. coli* Δ	SC IM	14	2	1 (offspring)	ataxia, hypersalivation, abortion, tachycardia, collapse	5 minutes
Canine						
trilostane	oral	1	1	0	adipsia, anorexia, shivering, lethargy	<= 30 days
diethanolamine fusidate & framycetin sulphate & nystatin & prednisolone	auricular	1	1	0	deafness	5 days
marbofloxacin & clotrimazole & dexamethasone	auricular	1	1	0	deafness	<= 48 hours
haemoglobin substitute	IV	1	1	0	increased respiratory rate, elevated temperature	2 hours
meloxicam	oral	1	1	1	inappetance, vomiting, duodenal ulcer, death by euthanasia	10 months
robenacoxib	oral	1	1	1	anorexia, emesis, polydipsia, liver failure, death by euthanasia	> 30 days
ivermectin*	oral	1	1	0	collapse, tonic-clonic seizure	<= 24 hours
robenacoxib	oral	1	1	0	elevated liver enzymes,emesis, anorexia, dullness, constipation, icterus	<= 30 days
Equine						
carprofen	IV	1	1	1	anaphylaxis, recumbency, seizure, death	2 minutes
procaine benzylpenicillin, butorphanol tartrate & detomidine	IM	2	1	1	anaphylaxis, death	immediate
Feline						
meloxicam, meloxicam	SC oral	1	1	1	emesis, loss of consciousness, anorexia, stomatitis, renal failure, convulsion, death	<= 48 hours

enrofloxacin, carprofen	SC	1	1	1	dullness, decreased body temperature, lateral recumbency, injection site erythema, death	20 minutes
Ovine						
levamisole & rafoxanide	oral	16	1	1	anaemia, diarrhoea, death	> 30 days
closantel & mebendazole	oral	240	28	0	blindness, anorexia, ataxia	<= 7 days
nitroxynil	SC	103	103	42	death	<= 24 hours
Porcine						
iron (as gleptoferron complex), amoxicillin trihydrate♦	IM SC	1100	114	114	pneumonia, sudden death	<= 24 hours
Lizard						
enrofloxacin	oral	1	1	1	circling, fitting, death	1 hour

IM: intramuscular, IV: intravenous, SC: subcutaneous

*: unauthorised species

♦: where multiple causalities were assigned to different products within a report, denotes the product possibly associated with the reaction

Δ: report listed in both tables as related to treatment with both a pharmaceutical & immunological product concurrently. Both products assigned causality 'B'.

Table 4: 2010 adverse events (reports coded 'A' or 'B') associated with the use of immunological products (excluding reports of BNP linked with BVD vaccination)

Antigenic Components	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Bovine						
Salmonella Dublin & salmonella typhimurium	SC	92	7	0	abortion, diarrhoea	> 30 days
Salmonella Dublin & salmonella typhimurium	SC	100	3	0	abortion	> 30 days
bovine rotavirus & bovine coronavirus & E. coli, tocopherol acetate & potassium selenate Δ	IM SC	14	2	1 (offspring)	ataxia, hypersalivation, abortion, tachycardia, collapse	5 minutes
Canine						
canine distemper virus & canine adenovirus & canine parainfluenza & leptospira icterohaemorrhagiae & leptospira canicola	SC	1	1	0	facial oedema, lethargy, anaphylactic type reaction	1 hour
Canine distemper, canine adeno virus, canine parvovirus, canine parainfluenza & Leptospira canicola, leptospira icterohaemorrhagiae	SC	2	1	0	vomiting, bloody diarrhoea, depression	<= 24 hours
Canine distemper, canine adeno virus, canine parvovirus, canine parainfluenza & Leptospira canicola, leptospira icterohaemorrhagiae	SC	1	1	0	vomiting, diarrhoea, lethargy	<= 24 hours
Canine distemper, canine adeno virus, canine parvovirus, canine parainfluenza	SC	3	3	1	vomiting, haemorrhagic diarrhoea, death	<= 7 days
Canine parvovirus	SC	7	4	3	drooling, seizure, opisthotonus, death	<= 24 hours
Canine distemper, canine adeno virus, canine parvovirus,	SC	9	4	3	vomiting, diarrhoea	1 week

canine parainfluenza ♦ *& Leptospira canicola, leptospira icterohaemorrhagiae*						
Equine						
Equine herpes virus	IM	1	1	1	injection site pain, recumbency, pale mucous membrane, laryngeal oedema, nasal cavity and sinus disorder, death	<= 24 hours
Feline						
Feline rhinotracheitis herpesvirus, inactivated feline Calicivirosis antigens, attenuated feline panleucopenia virus, FeLV recombinant canarypox virus	SC	1	1	0	collapse, ataxia, temporary blindness	2 – 3 hours

IM: intramuscular, SC: subcutaneous

♦: where multiple causalities were assigned to different products within a report, denotes the product possibly associated with the reaction

Δ: report listed in both tables as related to treatment with both a pharmaceutical & immunological product concurrently. Both products assigned causality 'B'.