Suspected Adverse Event Reports to Veterinary Medicinal Products 2011

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 228 national reports of SAEs to VMPs for the period 1st January 2011 to the 31st December 2011. Two hundred and ten reports were received from MAHs, fourteen reports were received directly from veterinarians or other healthcare professionals, three reports were submitted by an individual animal owner and one report was received from the Department of Agriculture, Food & the Marine. **Fig 1** shows the primary source of SAE reports received by the IMB from 2008 to 2011.

Of the 228 reports received, a total of 88 veterinary pharmaceutical products and 129 immunological products were identified as possibly associated with adverse events. Eleven 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 44 reports.

Suspected adverse events were reported in the following species: Human (ten reports), bovine (112), canine (56), ovine (32), feline (11), equine (four), porcine (two), and rabbit (one).

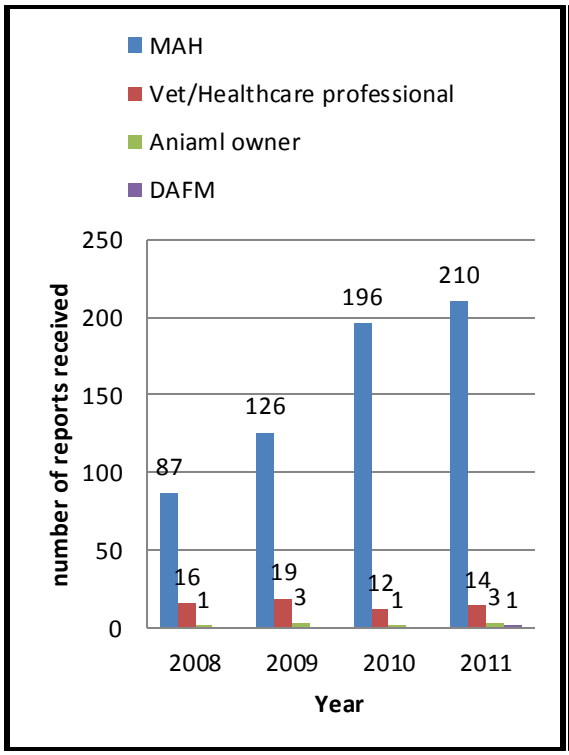

Fig 1: Source of SAE reports; 2008 to 2011

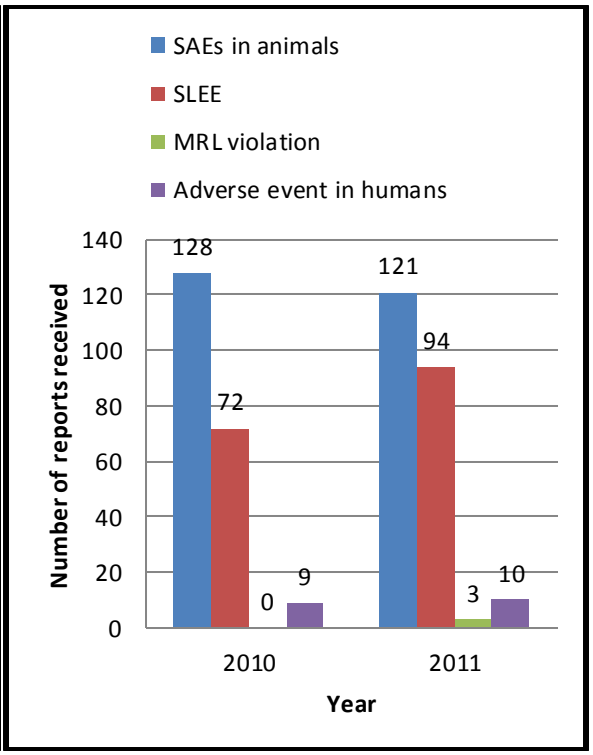

Fig 2: Types of reports received in 2010 & 2011

Of the 228 reports associated with the use of VMPs, 121 related to SAEs in the treated animals, 94 related to suspected lack of expected efficacy (SLEE) and ten reports involved SAEs in individual users following exposure to a VMP and three reports related to violations of approved residue limits. **Fig 2** compares the types of reports received in 2011 with those received in 2010.

2.1 Reports of suspected adverse effects

Ten 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.

Six human reports received were associated with exposure to pharmaceutical products. Four reports related to injection site reactions following accidental self injection. One report related to an anaphylactic reaction following topical exposure to a pharmaceutical product and the remaining report concerned an individual who experienced symptoms of breathlessness, dry mouth and throat pain following use of an endectoparasiticide; however, no direct product contact was confirmed in this case and the symptoms only persisted while the individual was exposed to the treated animals.

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 121 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 63 reports. In 37 reports, there was insufficient or inconclusive information available on which to assign causality. In 18 reports it was concluded that the VMP was unlikely to be responsible for the observed reaction. Three reports relating to the use of more than one VMP had different causality assigned to each individual product associated with the observed reaction. In two reports, one product was considered to have been probably or possibly associated with the observed reaction and involvement of the second product was considered unclassified or unlikely and in one report the one product each was considered unclassified or unlikely associated to the observed reaction. The criteria for assigning causality to a report are detailed in **Table 2**.

The individual SAE reports, originating from Ireland during 2011, 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 94 reports of SLEE submitted to the IMB in 2011.

Of these 94 reports, 17 related to SLEE of pharmaceutical products. In four reports, it was suspected that anthelmintics were ineffective for the treatment of fascioliasis in sheep. It is noted that the labelling for all relevant products carry warnings relating to the potential for resistance to anthelmintics and advice on actions to be taken in the event that resistance is suspected on an individual farm.

Seventy seven 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 2011 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 thirteen products, the Committee made recommendations to amend the product literature to include information on new adverse events, special precautions for use and/or amounts to be administered and administration route. Details of the products concerned were as follows:

- Convenia (cefovecin); pharmaco-therapeutic group: Antibacterials for systemic use (cephalosporins)
- Cortavance (Hydrocortisone aceponate); pharmaco-therapeutic group: Glucorticosteroids, dermatological preparations
- Cerenia (maropitant); pharmaco-therapeutic group: Antiemetics and Antinauseants
- Ibaflin (ibafloxacin); pharmaco-therapeutic group: antibacterial quinolone
- Metacam and Novem (meloxicam); pharmaco-therapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids (oxicams)
- Naxcel (ceftiofur); pharmaco-therapeutic group: third generation cephalosporins

- Onsior (robenacoxib); pharmaco-therapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids, (coxibs)
- Prac-tic (pyriprole); pharmaco-therapeutic group: Ectoparasiticides for topical use
- ProMeris (metaflumizone); pharmaco-therapeutic group: Ectoparasticides for topical use
- ProMeris duo (metaflumizone /amitraz); pharmaco-therapeutic group: Ectoparasiticides for topical use
- Reconcile (fluoxetine); pharmaco-therapeutic group: selective serotonin reuptake inhibitors (SSRI)
- Trocoxil (mavacoxib); pharmaco-therapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids, (coxibs)
- Zubrin (tepoxain); pharmaco-therapeutic group: Anti-inflammatory, Non Steroids

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 2011' on the EMA website http://www.ema.europa.eu .

In April 2011, the Committee initiated an Article 78 referral procedure concerning Hiprabovis Pneumos Emulsion for Injection for Cattle. 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 adverse events concerning anaphylactic-type reactions, some of which were fatal. The underlying mechanism and potential contributory factors associated with the events could not be determined and consequently no specific measures could be recommended to ensure that the product is not associated with an acceptable risk of anaphylactic-type events, under the authorised condition of use. Consequent to this decision, the marketing authorisation of Hiprabovis Pneumos Emulsion for injection for Cattle was suspended until a favourable benefit-risk balance for the product can be demonstrated. No reports were received by the IMB in 2011 where there was a suspected link between use of the vaccine and adverse events concerning anaphylactic-type reactions.

4. Conclusion

Apart from the action taken in respect of Hiprabovis Pneumos Emulsion for Injection for Cattle, resulting from a Commission decision as detailed above, no regulatory action was required to be taken in 2011 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 2011 (228) represents a modest increase compared to the numbers received in previous years (209 in 2010; 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 Veterinary Medicines →Drug Safety 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: 2011 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						
closantel & ivermectin	Unknown	59	59	0	Lameness, pyrexia, sedation, lump	<= 24 hours
levamisole,& oxyclozanide	Per oral	28	2	1	Diarrhoea, weight loss, death	<= 24 hours
levamisole,& oxyclozanide	Per oral	110	1	1	Ataxia, recumbency, death	1 hour
meloxicam	SC	1	1	1	Staggering, dyspnoea, congested mucous membrane, anaphylaxia, sudden death	<= 30 mins
nitroxynil	SC	1	1	1	Hyperventilation, distress, death	<= 24 hours
oxfendazole	Per oral	19	1	1	Respiratory distress, sudden death	< 1 minute
selenium	SC	2	2	1	Stumbling gait, muscle tremor, anaphylactic type reaction, death	<= 6 hours
tocopheryl acetate & selenium	IM	15	2	1	Hypersalivation, recumbency, hypersensitivity, death by euthanasia	<= 6 hours
Canine						
amoxicillin	SC	1	1	0	Reddening of the skin, pinnal oedema, anaphylactic-type reaction	3 hours
ciclosporin	Per oral	1	1	0	Diabetes mellitus	> 30 days
firocoxib	Per oral	1	1	0	Lethargy, limb weakness, anorexia, melaena, tachycardia, regenerative anaemia, hypoproteinaemia, gastric ulcer	<= 48 hours
medetmoidine	IM	1	1	1	Lethargy, death	<= 48 hours
metaflumizone, amitraz	Topical	1	1	1	Lethargy, emesis, panting, breathing difficulty, death	<= 12 hours
milbemycin, praziquantel	Per oral	1	1	0	Off colour, fit	<= 24 hours

milbemycin, praziquantel	Per oral	1	1	0	Vomiting, diarrhoea, muscle tremor	30 mins
phytomenadione	IV	1	1	1	Seizure, vomiting, diarrhoea, collapse, death	<= 2 mins
propofol	IV	1	1	0	Injection site lesion, injection site oedema, skin sloughing	<= 14 days
propofol	IV	1	1	0	Injection site erythema, injection site serous discharge	<= 14 days
propofol	IV	1	1	0	Injection site necrosis, injection site lesion, skin sloughing	<= 24 hours
pyriprole	Per oral*	1	1	0	Convulsions, hyperthermia	<= 24 hours
pyriprole	Per oral *	2	2	0	Seizure NOS, agitation, hyperaemic mucous membrane, pyrexia, twitching	<= 24 hours
pyriprole	Per oral *	1	1	0	Seizure, hyperthermia	<= 24 hours
pyriprole	Topical	1	1	0	Seizure NOS, panting, rigidity, twitching, anxiety, dilated pupils	<= 24 hours
thiamazole	Per oral	1	1	0	Anorexia, lethargy	> 30 days
trilostane	Per oral	1	1	0	Haemorrhagic diarrhoea	<= 24 hours
trilostane	Per oral	1	1	0	Seizure, recumbency, defecation, urination	2-3 weeks
Feline						
carprofen	IV/SC	1	1	0	Vomiting, not eating, elevated renal enzymes	48 hours
chlorhexidine, miconazole	Topical	1	1	1	Nasal discharge, tongue ulceration, drooling, anorexia, death	<= 48 hours
fipronil & methoprene	Topical	1	1	0	Application site alopecia	1-2 days
milbemycin & praziquantel	Per oral	2	2	0	Ataxia, disorientation, neurological signs NOS	3-5 hours
Ovine						
abamectin	Per oral	80	7	3	Gait abnormality, death	<= 6 hours
ivermectin & closantel	Unknown	46	6	6	Blindness, dullness, recumbency,	<= 30 mins

					depression, foaming at the mouth, death	

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

Table 4: 2011 adverse events (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
Bovine						
Salmonella Dublin & salmonella typhimurium	SC	115	2	0	abortion	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	100	1	1 (offspring)	Dyspnoea, pyrexia, mucosa peteciation, haemorrhage NOS, death	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	150	1	1 (offspring)	Haemorrhage NOS, death by euthanasia, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	100	1	1 (offspring)	Haemorrhage NOS, death, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	70	7	1 (offspring)	Haemorrhage NOS, sudden death, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	SC	1	1	1 (offspring)	Injection site bleeding, skin petechiation, pyrexia, death, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	100	1	1 (offspring)	Injection site haemorrhage, haemorrhage NOS, death, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	100	2	2 (offspring)	Injection site haemorrhage, mucosa petechiation, death, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	100	1	1 (offspring)	Injection site haemorrhage, mucosa petechiation, death, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	120	2	2 (offspring)	Lethargy, mucosa petechiation, death	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	2	2	2 (offspring)	Melaena, mucosa petechiation, anaemia NOS, haemorrhage NOS, death, BNP	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	85	1	1 (offspring)	Pyrexia, dyspnoea, mucosa petechiation, death by euthanasia, BNP	> 30 days
Bovine viral	unknown	50	1	1	Pyrexia, melaena,	> 30 days

diarrhoea virus (BVD)				(offspring)	mucosa petechiation, haemorrhage NOS, death, BNP	
Bovine viral diarrhoea virus (BVD)	unknown	110	1	1 (offspring)	Pyrexia, rale, mucosa petechiation, BNP, death	> 30 days
Bovine viral diarrhoea virus (BVD)	unknown	80	1	1 (offspring)	Rectal haemorrhage, haemorrhage NOS, epistaxis, mucosa petechiation, death	> 30 days
Bovine viral diarrhoea virus (BVD)	SC	2	2	2 (offspring)	Suspected BNP, mucosa petechiation, prolonged bleeding, pallor, death, haemorrhage	> 30 days
Bovine viral diarrhoea virus (BVD)	IM	200	6	0	Pneumonia, milk drop, nasal discharge	<= 7 days
Canine						
Canine distemper, canine adeno virus, canine parvovirus, canine parainfluenza & *Leptospira canicola, leptospira icterohaemorrhagiae*	SC	1	1	1	Injection site swelling, diarrhoea, haemorrhagic diarrhoea, lethargy, death by euthanasia	<= 7 days
Canine distemper, canine adeno virus, canine parvovirus, canine parainfluenza, Leptospira canicola, leptospira icterohaemorrhagiae	unknown	1	1	0	Fainting, weakness, staggering	<= 6 hours
Leptospira canicola, leptospira icterohaemorrhagiae	unknown	1	1	0	Injection site inflammation, injection sire oedema, injection site necrosis, injection site reaction NOS	<= 48 hours
Leptospira canicola, leptospira icterohaemorrhagiae & *Canine parvovirus*	SC	2	1	1	Vomiting, diarrhoea, death	2 hours
Canine distemper, canine adeno virus, canine parvovirus, canine parainfluenza, Leptospira canicola, leptospira icterohaemorrhagiae, canine coronavirus	SC	1	1	0	Lethargy, decreased body temperature, reluctant to move, dullness, polyarthritis	<= 30 mins
Equine						

Equine arteritis virus	IM	8	1	0	Urticaria, facial oedema, anaphylactic-type reaction	3 hours
Feline						
Feline Panleukopenia, Feline calicivirus, Feline rhinotracheitis, Feline *Chlamydophila felis*, Feline leukemia	SC	1	1	0	Lethargy, anorexia, dullness, elevated temperature, tachypnea	4 hours
Ovine						
Clostridium perfringens, Clostridium septicum, Clostridium tetani, Clostridium novyi, Clostridium chauvoei, Mannheimia haemolytica, Pasteurella trehalosi	SC	127	27	1	Injection site reaction NOS, injection site alopecia, death	>30 days
Clostridium perfringens, Clostridium septicum, Clostridium tetani, Clostridium novyi, Clostridium chauvoei, Mannheimia haemolytica, Pasteurella trehalosi	SC	30	20	1	Injection site abscess, death	<= 7 days
Clostridium perfringens, Clostridium septicum, Clostridium tetani, Clostridium novyi, Clostridium chauvoei	SC	25	21	2	Lethargy, injection site swelling, death	<= 48 hours
Clostridium perfringens, Clostridium haemolyticum, Clostridium septicum, Clostridium tetani, Clostridium novyi, Clostridium chauvoei	SC	16	8	3	Injection serosangunious discharge, cellulitis, sudden death	<= 7days
Rabbit						

Myxoma vectored RHD virus	SC	1	1	0	Facial paralysis, eye haemorrhage, corneal ulcer	<= 48 hours

IM: intramuscular, SC: subcutaneous, BNP: Bovine Neonatal Pancytopaenia