PHARMACOVIGILANCE OF VETERINARY MEDICINAL PRODUCTS

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1. Introduction

After the granting of a marketing authorisation, veterinary medicines must continue to meet the requirements for safety and efficacy and offer an acceptable balance between their benefits and risks. To fulfil this objective, a pharmacovigilance system is in place, the purpose of which is to monitor veterinary medicines marketed in Ireland and to ensure that pharmacovigilance data, in particular about adverse reactions in treated animals, is collected and scientifically evaluated. In addition to the monitoring of suspected adverse reactions in the treated animal(s), the scope of veterinary pharmacovigilance covers other aspects of post authorisation surveillance including: suspected adverse reactions associated with extra-label use (**Table 1**); lack of expected efficacy of a veterinary medicinal product when used in accordance with label recommendations; surveillance of resistance; surveillance of environmental impact; violations of approved residue limits; and, harmful and unintended effects in humans.

The current legal framework for the pharmacovigilance of veterinary medicinal products is set out in Council Regulation (EEC) No. 2309/93 and Council Directive 81/851/EEC as amended by Directive 93/40/EC. This legislation describes the respective obligations of the person responsible for placing the medicinal product on the market (the Marketing Authorisation Holder (MAH)) and the Competent Authorities with respect to collecting, collating and evaluating information about the safety of veterinary medicinal products under actual use conditions. Furthermore, with the adoption of the Animal Remedies Regulations 1996, there is now a legal obligation on veterinary surgeons, pharmacists and other persons licensed to sell or supply animal remedies to notify the IMB or the MAH of all suspected adverse drug reactions (SADR) that come to their attention.

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

- An identifiable reporter (e.g. veterinary surgeon, pharmacist, animal owner).
- Animal details: species, age, sex
- Suspect product: name and product authorisation number
- Reaction details (**Table 2**)

It should be stressed that these are minimum requirements and the reporter should endeavor to provide as much information as possible in order to facilitate a full scientific evaluation. Where relevant, this may include laboratory findings and post mortem examination findings. Specific SADR report forms are available from the IMB on request. When the source of a report is other than a health care professional, it is recommended that the advice of a veterinary surgeon be sought prior to reporting to ensure that the information provided is accurate and comprehensive.

The MAH is expected to fully validate and follow-up all serious SADR's reported to it directly by healthcare professionals. In addition, in the case of reports notified initially to the Competent Authority, the MAH is expected to provide all relevant follow-up information to the Competent Authority to facilitate its evaluation of cases. Where relevant, this may include product sample investigation. On the basis of the information presented, by both the reporter and the MAH, an assessment of the likely causal relationship between the administration of the suspected product(s) and the reaction(s) reported is made by the Competent Authority and the reaction is categorised using the ABON-system (**Table 3**). Should a pattern of adverse reactions involving a specific product emerge, regulatory action may be initiated. This action

may take one of a number of forms including: amendment to the conditions of product authorisation (e.g. inclusion of additional label warnings, amendment to the authorised route of administration); recall of a product (or specific batch) from the market; or, suspension/withdrawal of the product authorisation.

2. Reports of Suspected Adverse Reactions to Veterinary Medicinal Products 1999

The Irish Medicines Board (IMB) received 72 reports of SADR's to veterinary medicinal products between 01-01-99 and 31-12-99. Of these reports, 49 were notified by the MAH, 16 by veterinary surgeons in practice, three by members of the general public and two each from veterinary surgeons in Regional Veterinary Laboratories and pharmacists. Of the total number of SADR's reported, 55 involved veterinary pharmaceutical products and 15 concerned vaccines. One report was considered to be an invalid report in that it contained insufficient core data. Another SADR report involved a product that does not fall under the scope of veterinary medicinal product. In that case, a probable/possible association between the administration of the product and the reaction reported was not identified.

2.1. Veterinary Pharmaceuticals

In relation to the SADR's which involved veterinary pharmaceuticals, 21 reports were identified as probably/possibly related to the administration of anthelmintic boli. Adverse reactions were reported to have occurred in 37 animals, resulting in death in 33 cases. In all but one of the cases that died, death was attributed to either oesophageal trauma/perforation or asphyxia due to lodging of the bolus in the upper airways. Based on the information contained in the reports, only 4 of the 33 deaths were associated with the administration of the product to animals under the age/weight recommendation specified. However, in some cases, reports were only notified to the relevant MAH several weeks after the ADR had occurred and many animals had not been weighed or subjected to post mortem examination.

The high incidence of ADR's associated with the administration of anthelmintic boli was first highlighted by the IMB in 1996. As a result, in 1997, the Board met with representatives of the companies involved in the marketing of these products and agreed to a major educational campaign directed at product users to highlight awareness of the problem. In addition, in recent years, the product labelling has been revised to highlight the importance of correct administration of these products. Despite these measures, there has been little appreciable decline in the incidence of such ADR's over the past three years (**Table 4**). The Board remains concerned with the animal welfare implications of the use of anthelmintic boli and has again met with relevant companies and they have been advised to put measures in place to emphasise correct administration of these products at the point of sale.

In relation to the 34 SADR reports received in respect of other pharmaceutical products (that is, excluding anthelmintic boli), only 17 were identified as probably (n=2) or possibly (n=15) related to the administration of the product, nine were unclassified (that is, there was insufficient information on which to base a conclusion) and the results of investigations into seven reports concluded that the product was definitely not associated with administration of the product. One report, which involves a suspected human adverse reaction to organophosphate sheep dip, is currently being investigated. Neither the specific products

involved, the pattern of exposure to these products nor the symptoms experienced by the complainant are known at this time. Another report of a suspected human ADR, associated with the use of imidacloprid, was classified as 'B' (that is, possible): Two to three days after two cats were treated by topical application with the product, the owner noticed a rash on her legs. Although the owner did not handle the product directly, the possibility of an association between administration of the product and the development of the reaction cannot be excluded.

The individual SADR reports that were considered probably or possibly related to product use in other species are summarised on a species by species basis in **Table 5**. Four of these reports involved products containing levamisole and in three of these cases the observed reactions were thought to be due to overdosage. One SADR involved a product containing abamectin which was administered by an unauthorised route, while another reported death in a cat associated with the administration of a product, containing permethrin, which was indicated for use in the dog. Only two of the SADR's classified as probable/possible involved antibacterials. In one of these cases the product was used in a species other than the target species.

During the year, the IMB was made aware, by the MAH, of a suspected quality defect in an intramammary antimicrobial product. While no reports of suspected adverse reactions were notified to the IMB, a recall of the defective batch was initiated.

2.2 Veterinary Immunological Products

As with the veterinary pharmaceutical products, only those SADRs that were classified as probably/possibly related to immunological product administration are detailed in **Table 6**.

The Department of Agriculture, Food and Rural Development investigated SADR's reported in cattle following administration of multivalent clostridial vaccine[1]. Only two SADRs associated with the use of this product were reported to the IMB, but in excess of 32 animals are known to have died following its administration. The vaccine was marketed without a valid licence. A product recall was initiated.

In relation to the SADR's that were observed in piglets following the administration of the *Mycoplasma hyopneumoniae* vaccine, the clinical signs reported range from drowsiness to convulsions and death. At present, the MAH is conducting studies in an attempt to identify the mechanism of the observed adverse reactions. As an interim measure, the IMB have requested that the product labelling is amended by including a warning indicating the possibility that such reactions may occur.

3. Conclusions

- Spontaneous reporting of suspected adverse drug reactions is an inexpensive and effective method for ensuring continued safe and effective use of veterinary medicinal products following their introduction to the market place. The responsibilities of the MAH and the Competent Authority in relation to the handling of such data are well defined, but the

gathering of relevant information is dependant on the contribution and cooperation of veterinary surgeons and other healthcare professionals.

- The IMB gratefully appreciates and acknowledges the efforts of reporters in completing reporting forms and responding to requests for clarification. While an individuals experience may be limited to one or two cases it, when collated with data from other sources, may contribute considerably to the assessment of a potential safety hazard.
- It is suspected that there is a significant level of under reporting of SADR's as evidenced by the low numbers of reactions reported by veterinary surgeons and pharmacists. Persons licensed to sell or supply animal remedies are reminded of the legal obligation to notify the IMB or the MAH of all SADR's that come to their attention. Furthermore, it should be remembered that it is not necessary for the reporter to determine a causal relationship between the product administered and a subsequent event, prior to reporting a SADR.
- The Board remains concerned with the animal welfare implications of the use of anthelmintic boli and wishes to emphasise the important of communicating information on the correct administration of these products to the user at the point of sale.
- The occurrence of SADR's in animals associated with extra-label use/overdosage emphasise the importance of following the recommendations declared on product labelling. While in some cases the lack of authorised veterinary medicines may necessitate the use of an alternative indicated for another species, such usage should only be undertaken if warranted and under strict veterinary supervision.

Table 1: Definitions

Adverse Drug Reaction:	A reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modulation of physiological function.
Serious Adverse Drug Reaction:	An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated.
Extra-label use:	Refers to the use of a product outside the terms of the marketing authorisation. For example use of a product in a species other than the authorised target species, use at doses other than those recommended on the product literature.

Table 2 : Relevant Reaction Details

May include the following:

⇒ Person who administered the product
⇒ Reason for treatment
⇒ Dosage, route and site
⇒ Time between treatment and reaction
⇒ Reaction description
⇒ Number of animals with signs
⇒ Treatment of the reaction
⇒ Outcome

Table 3 : 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 fulfill 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 4 : Incidence of death associated with the use of anthelmintic boli

	1997	1998	1999
Incidence (deaths/unit administered)	1/3,644	1/4,623	1/4,187

Table 5: Adverse drug reactions to pharmaceutical products

Active Substance	Route	Number treated	Number reacted	Number died	Signs	Speed of onset
Cattle						
Moxidectin	Topical	20	4	1	respiratory distress	minutes
Moxidectin	Topical	51	1	1	respiratory distress	minutes
Levamisole	Oral	36	3	1	neurological signs collapse	minutes
Levamisole*	s/c	15	15	4	hypersalivation, neurological signs	minutes
Abamectin[#]	i/m	50	3	1	anaphylactoid reaction	minutes
Barium selenate[#]	i/m	2	1	1	anaphylactoid reaction	minutes
Sheep						
Levamisole*/ Oxyclozanide	Oral	25	25	3	diarrhoea, muscle twitching	days
Levamisole*	Oral	2	2	2	muscle tremors, collapse	minutes
Donkey						
Florfenicol[@]	i/m	3	3	3	found dead	hours
Horse						
Trimethoprim/ Sulphadoxine	i/v	1	1	0	ataxia	minutes
Dog						
Nitroscanate	Oral	2	2	0	ataxia, diarrhoea	hours
Imidacloprid	Topical	1	1	0	focal exudative dermatitis	week
Oestradiol benzoate	i/m	1	1	0	vomiting, respiratory distress, ataxia	hours
Meloxicam	Oral	1	1	0	haemorrhagic gastroenteritis	weeks
Cat						
Permethrin[@]	Topical	3	1	1	neurological signs	hours
Fipronil	Topical	1	1	0	focal exudative dermatitis	weeks

*possible overdose
[#]Extra-label use - unauthorised route of administration
[@]Extra-label use - unauthorised target species

s/c–subcutaneous
i/v-intravenous
i/m-intramusular

Table 6: Adverse drug reactions to immunological products

Active Substance	Number treated	Number reacted	Number died	Signs	Speed of onset
Cattle					
multivalent clostridial vaccine[1]	23	unknown	1	anaphylactoid reaction	minutes-hours
multivalent clostridial vaccine[1]	unknown	unknown	1	anaphylactoid reaction	minutes
multivalent clostridial vaccine[1]	21	3	3	anaphylactoid reaction	hours
multivalent clostridial vaccine[1]	45	5	5	anaphylactoid reaction	minutes
multivalent clostridial vaccine[2]	70	1	1	found dead	hours
Pigs					
Mycoplasma hyopneumoniae vaccine	284	unknown	9	neurological signs	minutes
Mycoplasma hyopneumoniae vaccine	600	unknown	6	neurological signs	minutes
[1 & 2] represent different immunological products					