Health Products Regulatory Authority: veterinary medicines report

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The Health Products Regulatory Authority (HPRA) is responsible for the ongoing monitoring of the quality, safety and efficacy of authorised veterinary medicinal products (VMPs). In relation to safety and efficacy, this role is fulfilled through a nationwide reporting system for adverse events (pharmacovigilance system), which is designed to monitor products under actual use conditions.

The scope of veterinary pharmacovigilance involves the surveillance of:

- suspected adverse reactions in animals to VMPs used under authorised conditions,
- lack of expected efficacy (LEE) of VMPs;
- off-label use of VMPs in animals;
- reported violations of approved residue limits;
- adverse reactions in humans related to the use of VMPs; and
- potential environmental problems.

These reports are collectively known as suspected adverse events (SAEs) and they are received by the HPRA primarily from marketing authorisation holders (MAHs). The MAHs are required by legislation to report all serious SAEs to the HPRA within 15 days. Less frequently, reports are also received from veterinarians and animal owners directly. The minimum requirements for an SAE report to be considered valid are detailed in Table 1. Suspected adverse event reports are collated and evaluated by the HPRA and the MAHs. In the event that a safety issue is identified through this surveillance, appropriate steps can be taken to reduce the level of any associated risk.

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

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

Table 1: Suspected adverse event reports – minimum information.

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.

NATIONAL PHARMACOVIGILANCE ISSUES

The HPRA received 429 and 337 valid national SAE reports in 2015 and 2016 respectively. The 766 valid SAE reports involved a range of food producing species and companion animals as presented in table 2 below. In addition, 18 of the reports concerned adverse reactions in humans following exposure to a VMP.

Species	Total number reports	Total number reacting
Food-producing animals:		
Bovine	335	5,527
Ovine	170	5,758
Equine	18	22
Rabbit	6	9
Bee	6	27 hives
Avian (chicken and pheasant)	5	16,579
Porcine	4	16
Caprine	1	5
Companion animals:		
Canine	162	311
Feline	41	62
Other		
Human	18	18
All	766	28,334

Table 2: Overview of reports received 2015-2016.

Seven hundred and twenty reports were received from MAHs, 28 reports were received directly from veterinarians,

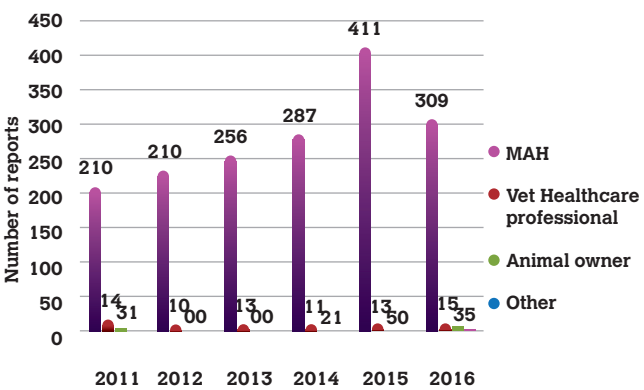

Figure 1: Source of SAE reports from 2011 to 2016.

while 13 reports were received from animal owners, and five reports were received from licensed merchants and distributors of VMPs. Figure 1 shows the primary source of SAE reports received by the HPRA from 2011 to 2016.

Of the total 766 SAE reports received, 286 involved pharmaceutical products, 442 involved immunological products and 38 reports related to the use of both

pharmaceutical and immunological products concurrently. Three hundred and one reports involved suspected adverse reactions in the treated animals, 442 involved LEE; 18 reports involved SAEs in individual users following exposure to a VMP and five reports related to violation of an approved residue limit. Figure 2 compares the types of reports received from 2014 to 2016.

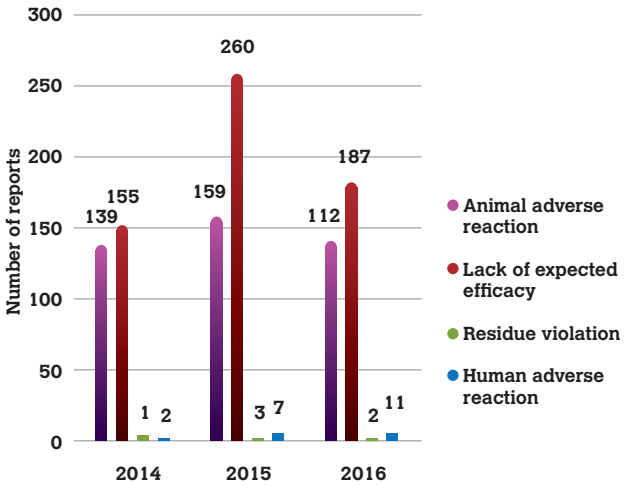

Figure 2: Number of SAE reports by category received from 2014 to 2016.

REPORTS OF ADVERSE REACTIONS

Eighteen reports of SAEs in humans associated with exposure to VMPs were received during the reporting period. 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 301 adverse reactions in the treated animal(s), the VMP was considered to have been 'probably' (causality 'A') or 'possibly' (causality 'B') associated with the observed reaction in 169 reports. In 136 reports, there was insufficient/inconclusive information (causality 'O'/'O1') available or it was considered unlikely (causality 'N') that the VMP was responsible for the observed reaction.

Note that some reports involved multiple VMPs and as causality is assigned on a product basis rather than to the overall report, reports involving multiple products with different causality have been counted twice. The criteria for assigning causality to a report are detailed in Table 3.

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.

Causality '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.**
Causality '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'.**
Causality 'O' Causality 'O1'	**When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality When a VMP association cannot be discounted but other factors prevent a conclusion being drawn**
Causality '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: Assessing causality.

A line listing of the individual SAE reports, originating from Ireland during 2015 and 2016, that were assigned causality 'A' or causality 'B' is included in a version of this report that is published on the HPRA website (www.hpra.ie).

REPORTS OF LACK OF EXPECTED EFFICACY

There were 260 LEE reports submitted to the HPRA in 2015 and 182 during 2016.

Of these reports, 79 involved pharmaceutical products and related to the following species; cattle (47 reports), sheep (17), dogs (10), cat (3), pheasant (1) and bees (1). Eighteen of the 79 reports were considered to be 'unlikely' related to the product.

Three hundred and forty-five LEE reports involved immunological products that were suspected to have failed to induce protective immunity. The reports concerned cattle (170 reports), sheep (132), dogs (27), rabbits (5), chickens (4), cats (2), horses (2), pigs (2) and goat (1). Fifty five reports were assigned causality A (probable) or B (possible) and the remainder were assessed as 'unclassifiable/inconclusive' ('O' or O1') or 'unlikely' ('N') product related. One hundred and four reports involved off-label use of one or more vaccines. In addition, 18 LEE reports involved both pharmaceutical and immunological products.

In May 2015 the HPRA published a safety advisory notice relating to lack of expected efficacy of Scabivax Contagious Pustular Dermatitis (Orf) Vaccine in sheep. No quality issue was identified, however a high number of reports of LEE or partial LEE relating to lack of vaccine take were reported during the spring of 2015 and, as a precautionary measure, the MAH of the product recalled one batch of product from the market. A total of 84 spontaneous reports of LEE or partial LEE was received by the HPRA relating to Scabivax during 2015.

EUROPEAN PHARMACOVIGILANCE ISSUES

During 2015-2016, the Committee for Medicinal Products for Veterinary Use (CVMP, an expert scientific advisory committee of the European Medicines Agency) reviewed safety information for centrally authorised VMPs by monitoring reports logged to a central EU SAE database and through the assessment of periodic safety update reports (PSURs) provided by MAHs. On the basis of these analyses, the CVMP made recommendations to update the product literature for 25 centrally authorised VMPs in line with new/emerging safety information. Further information concerning the changes made to individual product information for centrally authorised products is published in the Veterinary pharmacovigilance public bulletins 2015 and 2016 on the EMA website (www.ema.europa.eu).

In June 2016, following consultations between the EMA, the national competent authorities (NCAs) and the relevant MAH, the HPRA published a safety advisory notice relating to the centrally authorised product Velactis. Velactis, containing the prolactin inhibitor cabergoline, was authorised for use in the herd management programme of dairy cows as an aid in the abrupt drying-off by reducing milk production to reduce milk leakage at drying off, reduce the risk of new intramammary infections during the dry period, and reduce discomfort. However, following the receipt of multiple serious adverse event reports involving clinical signs including recumbency and death within four months of launching of the product on the market, the CVMP suspended the marketing authorisation for the product at its July 2016 meeting.

Although the exact cause of these adverse events was not determined, there was evidence to suggest that a number may have been linked to the use of Velactis. Given the number and severity of adverse events following use of this medicine in otherwise healthy dairy cows, the CVMP concluded that the risks outweigh the benefits of the product. The product authorisation was therefore suspended in the European Union (EU) until further information is available to show that the benefits outweigh the risks, possibly under new conditions of use. The product was also recalled from the market as a precautionary measure. It should be noted that Velactis had not been launched onto the market in Ireland prior to the decision to suspend its use throughout the EU.

CONCLUSION

On review of previous annual reports (which can be accessed on the HPRA website), it can be seen that there is a general trend towards increasing numbers of reports over the past nine years (429 in 2015, 300 in 2014, 272 in 2013, 244 in 2012, 228 in 2011, 209 in 2010; 148 in 2009; 104 in 2008 and 92 in 2007). While there was a decrease in the number of reports received in 2016 (337) compared to 2015, this is considered to be a stabilisation of normal reporting trends, following the sharp increase in reports in 2015 relating to the Scabivax issue (see section 2.2 above). This increasing trend over the past number of years 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 HPRA 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 cases reported directly to the HPRA by veterinary practitioners and pharmacists remains relatively low. Persons licensed to sell or supply animal remedies are obliged to notify the HPRA or the relevant MAH of all serious SAEs and all human adverse events associated with the use of VMPs, within 15 days of receipt of such information, (in accordance with Regulation 12 of the Animal Remedies Regulations 2007 [SI 786 of 2007]). The HPRA recognises that there may be a perception amongst the veterinary profession that contacting the HPRA will adversely impact on their workload, in that they may be asked to engage in discussion of the adverse event or case history. However, this is rarely the case. The reporting process itself is simple, with the HPRA accepting reports by a variety of different methods. Provided that the mandatory information (as described in Table 1) is included in the report, the HPRA will not usually actively engage with the reporter. The HPRA 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 section of the HPRA website at www.hpra.ie. Suspected adverse events can be reported using an online reporting form accessed from the homepage of the HPRA website.

Alternatively, SAE report forms may be downloaded from the HPRA website for offline completion and can be sent by freepost to the HPRA, or prepaid self-addressed forms can be requested from the Department of Veterinary Sciences at the HPRA.