Suspected Adverse Event Reports to Veterinary Medicinal Products 2014

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1. Introduction

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

The scope of veterinary pharmacovigilance (as defined in Article 73 of Directive 2001/82/EC) 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 (SAE) and they are primarily received by the HPRA from marketing authorisation holders (MAH). 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. The minimum requirements for an SAE report to be considered valid are detailed in Table 1. Suspected adverse event reports are evaluated and collated 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.

2. National Pharmacovigilance Issues

In 2014 the HPRA received 310 national SAE reports involving VMPs. Ten of these reports were considered to be invalid for reasons including being sent to the HPRA in error, treatment happening outside of Ireland, duplicate report, or use of an unauthorised product. The 300 valid SAE reports involved a range of food producing species and companion animals as presented in table 2 below. In addition, two reports concerning human adverse reactions were also received.

Species	**Total number reports**	**Total number reacting**
Food producing animals		
ovine	34	455
bovine	139	2373
porcine	10	5977
equine	9	51
rabbit	1	1
bee	1	1 beehive
fish	1	80,000
Companion animals		
canine	88	184
feline	15	37
Other		
human	2	2
All	300	89,080 (and 1 beehive)

Table 2. Overview of reports received in 2014

Two hundred and eighty seven reports were received from MAHs, ten reports were received directly from veterinarians, two reports were received from animal owners, one report was received from an animal care worker and one report was received from a licensed merchant. Figure 1 shows the primary source of SAE reports received by the HPRA from 2009 to 2014.

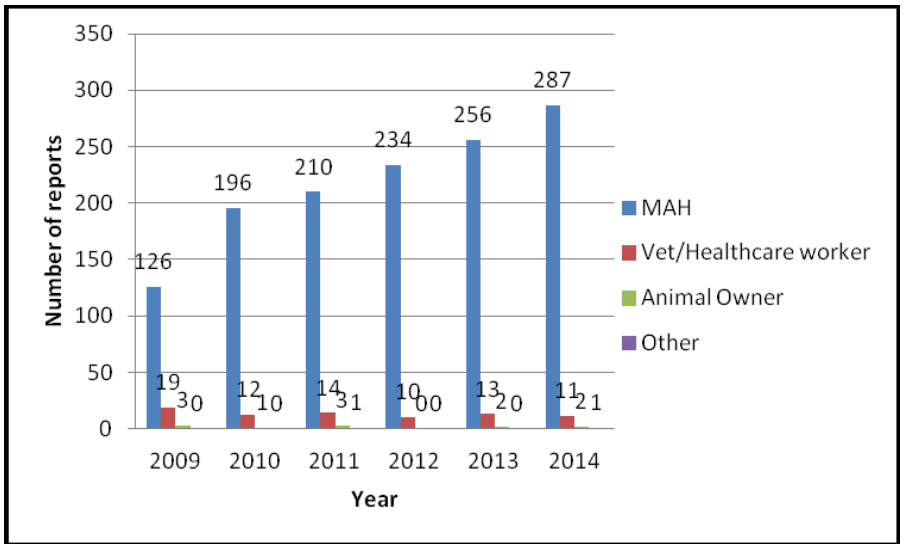

Figure 1: Source of SAE reports from 2009 to 2014

Of the total 300 SAE reports received, 123 involved pharmaceutical products, 166 involved immunological products and 11 reports related to the use of both pharmaceutical and immunological products concurrently.

One hundred and thirty nine reports involved suspected adverse reactions in the treated animals, 155 involved LEE; 2 reports involved SAEs in individual users following exposure to a VMP and 4 reports related to violation of an approved residue limit. Figure 2 compares the types of reports received in 2014 with those received in 2013 and 2012.

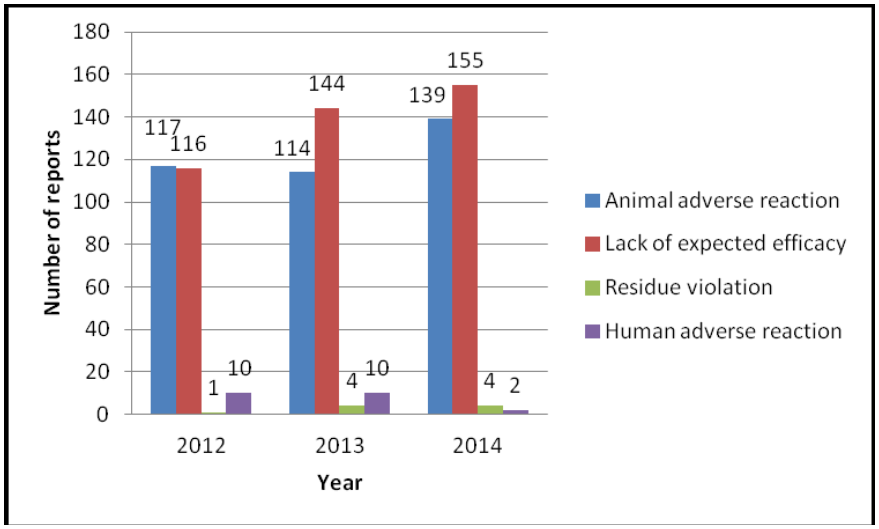

Figure 2: Number of SAE reports by category received in 2012 to 2014

2.1 Reports of adverse reactions

Two reports of SAEs in humans associated with exposure to VMPs were received during the reporting period. One related to an injection site reaction following accidental self injection with a pharmaceutical product. The second report concerned a farmer that experienced malaise after spilling a pharmaceutical product on himself.

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 139 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 84 reports. In 55 reports, there was insufficient/inconclusive information available or it was considered unlikely that the VMP was responsible for the observed reaction. The criteria for assigning causality to a report are detailed in Table 3.

The individual SAE reports, originating from Ireland during 2014, that were assigned causality 'A' or causality 'B' are listed according to species in Table 4 (pharmaceutical products) and Table 5 (immunological products).

2.2 Reports of lack of expected efficacy

There were 155 LEE reports submitted to the HPRA in 2014.

Of these reports, 34 involved pharmaceutical products and related to the following species; cattle (14 reports), sheep (6) dogs (12), cat (1) and fish (1). Nineteen of these reports involved products classified as anti-parasitic products and 9 reports involved antiepileptic products. Eight of the 34 reports were considered to be 'unlikely' related to the product.

One hundred and twelve LEE reports involved immunological products that were suspected to have failed to induce protective immunity. The reports concerned cattle (73 reports), sheep (16), dogs (18), horses (1) and pig (4). Twenty eight reports were assigned causality 'B' and the remainder were assessed as 'unclassifiable/inconclusive' ('O' or O1') or 'unlikely' ('N') product related as there were no test results to conclusively determine the causative agent of the infection. In a number of cases it was established that the vaccines had not been used in accordance with label recommendations.

In addition, 9 LEE reports involved both pharmaceutical and immunological products.

3. European Pharmacovigilance Issues

During 2014, the Committee for Veterinary Medicinal Products (CVMP, an expert scientific advisory committee of the European Medicines Agency) reviewed safety information for centrally authorised VMPs through the surveillance of a central EU SAE database and the assessment of periodic safety update reports (PSUR) provided by MAHs. On the basis of these analyses, the

CVMP made recommendations to update the product literature for 6 centrally authorised VMPs in line with new/emerging safety information.

One centrally authorised product for which an update to the product literature was recommended is an anti-epileptic for dogs, Pexion (imepitoin), a product first authorised by the European Commission in February 2013. In 2014, based on reports submitted to the HPRA and other national competent authorities in the EU, a potential risk was identified relating to the use of this product. These reports included both suspected adverse reactions, often involving clinical signs similar to those already listed in the Summary of Product Characteristics (SPC), and reports of suspected lack of expected efficacy. It was noted that many of the reports describing suspected lack of efficacy involved use other than in strict accordance with the SPC.

Pexion is authorised "for the reduction of the frequency of generalised seizures due to idiopathic epilepsy in dogs for use after careful evaluation of alternative treatment options". Therefore it is not authorised for the treatment of seizures due to other causes and Pexion should only be used after consideration is given to other treatments available for the control of seizures due to idiopathic epilepsy. This means that, in line with the recommendations of the MAH, veterinary practitioners should not transition dogs onto Pexion from other treatments in those situations where the dog is stable on its current treatment regime and the dog is not suffering from any adverse effects.

Section 4.4 of the SPC should also be noted; "the efficacy of the product in dogs with status epilepticus and cluster seizures, has not been investigated". Therefore, Pexion should not be used as the primary treatment in these dogs. Transition to other types of antiepileptic therapy should be done gradually and with appropriate clinical supervision.

A notice advising of the concerns identified was published in the Veterinary Ireland Journal in December 2014.

Further information concerning the changes made to individual product information for centrally authorised products is published in the Veterinary pharmacovigilance public bulletin on the EMA website.

4. Conclusion

On review of previous annual reports (which can be accessed on the HPRA website), it can be seen that the number of SAE reports received by the HPRA continues to increase year on year (272 in 2013, 244 in 2012, 228 in 2011, 209 in 2010; 148 in 2009; 104 in 2008 and 92 in 2007). The reason for the increase in numbers of reports in recent years is unclear. It 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 [S.I. 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. The HPRA created a new 'Reporting Adverse Events' leaflet for veterinary medicines in 2014. This was posted to all registered veterinary practioners and all Licensed Merchants at the beginning of 2015 to raise awareness regarding reporting of adverse events.

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 off-line completion and can be sent by freepost to the HPRA, or prepaid self-addressed forms can be requested from the Veterinary Sciences Department of the HPRA.

Table 1: Suspected adverse event reports – minimum information

An 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 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

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'	When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality.
Causality 'O1'	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 4: 2014 adverse reactions assigned causality 'A' or 'B' associated with the use of pharmaceutical products

Table 4A: Bovine Reports

Active Substance	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
butylscopolamine bromide & metamizole	IV	1	1	1	vocalisation, seizure NOS, increased respiratory rate, respiratory distress, transient blindness, death, head tilt, collapse NOS	<= 2 minutes
ceftiofur	IV	1	1	1	sudden death	<= 2 minutes
cloprostenol sodium	IM	1	1	1	sudden death	<= 2 minutes
closantel & ivermectin	topical	28	3	0	anorexia, dullness, depression, disorientation, impaired vision	<= 7 days
closantel & ivermectin	SC	40	6	0	anorexia, dullness, depression, recumbency, impaired vision	<= 24 hours
closantel & ivermectin	topical	7	7	0	allergic reaction, hyperexcitation, trembling, ataxia	5 minutes
levamisole	SC	10	10	2	neurological signs NOS, hyperactivity, collapse, foaming at the mouth, death	<= 2 minutes
levamisole hydrochloride	topical	48	24	1	tremor, hypersalivation, hyperexcitation, death	<= 12 hours

marbofloxacin	IV	1	1	1	collapse, sudden death	< 6 hours
moxidectin	SC	38	1	1	ataxia, death by euthanasia	<= 48 hours
moxidectin		10	1	1	ataxia, opisthotonus, blindness, death by euthanasia	<= 2 minutes
moxidectin	SC	29	1	1	collapse, death	<= 12 hours
moxidectin	SC	50	1	1	death	<= 24 hours
moxidectin	SC	150	1	1	injection site abscess, death	> 30 days
oxyclozanide	oral	1	1	0	recumbency	<= 24 hours
oxytetracycline hydrochloride & flunixin meglumine	unknown	1	1	1	circulatory collapse, respiratory distress, death	<= 30 minutes

procaine benzylpenicillin & dihydrostreptomycin	IM	1	1	1	involuntary movement, collapse, death	<= 2 minutes
selenium	SC	21	5	0	facial oedema	unknown
vitamins	IV	2	2	2	shock, sudden death	< 6 hours

Table 4B: Canine Reports

Active Substance	**Route**	**No Treated**	**No Reacted**	**No Died**	**Clinical signs**	**Speed of onset**
carprofen	oral	1	1	0	lethargy, inappropriate defecation/urination	4 days
carprofen	oral	1	1	1	blood in vomit, blood in faeces, increased heart rate, death	<= 14 days
cefovecin	SC	1	1	0	lethargy, inappetance, regenerative anaemia, non-regenerative anaemia, immune mediated haemolytic anaemia	> 30 days
cyclosporin A	oral	1	1	0	metastatic neoplasia, digestive tract neoplasm NOS	> 30 days
cyclosporin A	oral	1	1	0	polyuria, polydipsia, weight loss, diabetes mellitus	> 30 days
diethanolamine fusidate, framycetin sulphate, nystatin, prednisolone	topical	1	1	0	deafness	<= 48 hours

dimpylate	topical	1	1	1	neurological signs NOS, ataxia, nystagmus, death by euthanasia	<= 24 hours
doramectin	oral	3	3	1	neurological signs NOS, seizure NOS, death	<= 48 hours
fipronil	topical	1	1	0	application site reaction NOS, application site pain	<= 2 minutes
gentamicin, betamethasone & clotrimazole	auricular	1	1	0	deafness	<= 48 hours
imepitoin	oral	1	1	0	somnolence, ataxia	<= 24 hours
imepitoin	oral	1	1	1	seizure NOS, death	<= 48 hours
imepitoin	oral	1	1	0	somnolence	>30 days
imidacloprid and moxidectin	topical	1	1	0	application site alopecia/erythema/pruritus/reddening/ulcer/scab, dermal thickening	<= 24 hours
insulin	SC	1	1	0	dyspnoea, anorexia, facial swelling (see also 'skin')	<= 24 hours
isoflurane	Inhalation	1	1	0	tachypnoea, bradycardia, muscle tremor, dyspnoea	<= 30 minutes
meloxicam	oral	1	1	0	facial swelling	<= 30 mins
oxyclozanide	oral	1	1	0	respiratory distress, pyrexia	<= 48 hours
proligestone	SC	1	1	0	pyometra	> 30 days
propofol	IV	2	2	0	apnoea, decreased heart rate, respiratory depression	<= 30 minutes

propofol	IV	3	3	0	cardiac arrest	<= 30 minutes
pyriprole milbemycin oxime & praziquantel	oral	1	1	0	recumbency, tachypnoea, hyperaesthesia, muscular hypertonicity	<= 24 hours

Table 4C: Ovine Reports

Active Substance	**Route**	**No Treated**	**No Reacted**	**No Dead**	**Clinical signs**	**Speed of onset**
albendazole	oral	37	37	0	infertility NOS	> 30 days
closantel	oral	10	5	1	downer animal, incoordination, death by euthanasia	<= 24 hours
levamisole & oxyclozanide	oral	65	40	6	lethargy, malaise, death	<= 24 hours
oxfenbendazole & closantel	oral	40	4	1	impaired vision, dullness, death	<= 7 days
procaine benzlypenicillin & dihydrostrepto mycin sulphate	IM	1	1	1	sudden death	<= 2 minutes

Table 4D: Feline Reports

Active Substance	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
ciclosporin	oral	1	1	0	weight loss, anorexia, gingival hyperplasia, oral pain, thrombocytopenia	> 30 days
insulin porcine	SC	1	1	0	hypoglycaemia, collapse	<= 48 hours
milbemycin oxime and praziquantel	oral	1	1	0	ataxia, lethargy, central nervous system depression	<= 24 hours
pimobendan	oral	1	1	0	hind limb ataxia	<= 24 hours
xylazine	unknown	1	1	0	respiratory failure	< 30 minutes

Table 4D: Equine Reports

Active Substance	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
procaine benzylpenicillin	IM	1	1	0	agitation, head-shaking. Followed by urticaria	unknown
xylazine	IV	1	1	1	death by euthanasia, collapse, nystagmus, dilated pupils, paddling, abnormal breathing, anaphylactic type reaction	<= 2 minutes

IM: intramuscular, IV: intravenous, SC: subcutaneous

Table 5: 2014 adverse reactions assigned causality 'A' or 'B' associated with the use of immunological products

Table 5A: Bovine Reports

Active Substance (antigen)	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
bovine rotavirus, bovine coronavirus & *E. coli*	IM	25	17	0	injection site abscess, injection site swelling	<= 30 days

Table 5B: Canine Reports

Active Substance (antigen)	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
Bordetella bronchiseptica & canine parainfluenza virus	IN	1	1	0	cough	<= 7 days
Bordetella bronchiseptica & canine parainfluenza virus	IN	1	1	1	collapse, sudden death	< 6 hours
Bordetella bronchiseptica & canine parainfluenza virus & *Leptospira interrogans*	SC IN	1	1	0	collapse, diarrhoea, tachypnoea, distension of abdomen	<= 1 hour
Bordetella bronchiseptica & canine parainfluenza virus	IN	1	1	0	conjunctivitis, dry eye	<= 7 days

Bordetella bronchiseptica & canine parainfluenza virus	IN	1	1	0	cough, nasal discharge, anorexia, dyspnoea, tracheal and laryngeal disorder NOS	<= 7 days
Bordetella bronchiseptica & canine parainfluenza virus	IN	1	1	0	nasal discharge, bronchitis	<= 48 hours
Bordetella bronchiseptica & canine parainfluenza virus	SC	1	1	0	listless, lameness, shivering, muscle stiffness	<= 6 hours
canine parvovirus	SC	1	1	1	dyspnoea, nasal discharge, anaphylaxis, death	<= 30 minutes
canine distemper virus, canine adenovirus & canine parainfluenza virus,	SC	1	1	1	collapse NOS, dehydration, vomiting, diarrhoea, cervical ventroflexion, pale mucous membrane, decreased body temperature, hypoglycaemia, anaphylactic reaction, death	<= 48 hours
canine distemper virus, canine adenovirus canine parainfluenza virus, canine parvovirus & *Leptospira interrogans*	SC	1	1	1	lethargy, ataxia, tongue protrusion, circling, head pressing, anorexia, death by euthanasia	<= 24 hours
canine distemper virus, canine adenovirus canine	SC	1	1	0	swelling NOS	<= 6 hours

parainfluenza virus, canine parvovirus *Leptospira interrogans*						
canine distemper virus, canine adenovirus canine parainfluenza virus	SC	1	1	0	abortion, intrauterine death	<= 14 days
canine distemper virus, canine adenovirus canine parainfluenza virus, canine parvovirus *Leptospira interrogans*	SC	1	1	0	vomiting, diarrhoea, off colour	<= 24 hours
canine distemper virus, canine adenovirus canine parainfluenza virus, canine parvovirus *Bordetella bronchiseptica* canine parainfluenza virus *Leptospira interrogans*	SC SC IN	1	1	0	facial swelling, lateral recumbency	<= 30 minutes

canine distemper virus, canine adenovirus canine parainfluenza virus, canine parvovirus, canine parainfluenza *Leptospira interrogans*	SC SC	1	1	0	circulatory collapse, cyanosis, tachycardia	<= 2 minutes
canine distemper virus, canine adenovirus canine parainfluenza virus, canine parvovirus *Leptospira interrogans*	SC SC	1	1	1	sudden death, dyspnoea, cough	<= 24 hours
canine distemper virus, canine adenovirus canine parainfluenza virus, canine parvovirus *Leptospira interrogans*	SC	1	1	0	tongue oedema, periorbital oedema, facial oedema, dyspnoea	hours
Leptospira interrogans	SC	1	1	0	hives, behavioural disorder NOS, epileptic seizure	<= 24 hours
rabies virus glycoproteins	SC	1	1	0	injection site ulcer, injection site necrosis, injection site inflammation, injection site reddening, vascular inflammation, ischaemic necrosis	<= 48 hours

Table 5D: Feline Reports

Active Substance (antigen)	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
feline calicivirus, feline herpes virus feline panleucopenia virus	SC	1	1	0	unconscious, reduced responses	<= 24 hours
feline calicivirus, feline herpes virus feline panleucopenia virus	SC	4	1	0	lethargy, anorexia, tonic-clonic seizure, blindness	<= 24 hours

Table 5E: Porcine Reports

Active Substance (antigen)	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
Mycoplasma hyopneumoniae	IM	400	12	12	death, injection site haemorrhage	<= 24 hours
Mycoplasma hyopneumoniae PRRS virus *Mycoplasma hyopneumoniae*	IM IM Intradermal	800	300	8	lethargy, death	<= 24 hours
porcine circovirus	IM	40	15	4	vomiting, ataxia, unexplained death	<= 1 hours

Table 5F: Ovine Reports

Active Substance (antigen)	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Clostridium perfringens, clostridium haemolyticum, clostridium chauvoei,	SC	122	122	3	injection site abscess, death	<= 7 days

clostridium novyi, clostridium septicum, clostridium tetani toxoid						
Clostridium perfringens, clostridium chauvoei, clostridium novyi, clostridium septicum, clostridium tetani Mannheimia haemolytica	SC	80	12	0	injection site swelling, cellulitis	<= 7 days
Clostridium perfringens, clostridium chauvoei, clostridium novyi, clostridium septicum, clostridium tetani Mannheimia haemolytica	SC	225	1	1	sudden death	1.5 hours

Table 5G. Equine report

Active Substance (antigen)	**Route**	**No Treated**	**No Reacted**	**No Dead**	**Clinical signs**	**Speed of onset**
equine influenza virus	IM	1	1	0	injection site inflammation, injection site swelling, injection site pain, injection site stiffness	<= 48 hours

Table 5H. Rabbit report

Active Substance (antigen)	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
myxoma vectored RHD virus	SC	1	1	1	anorexia, lethargy, death	<= 24 hours

IM: intramuscular, SC: subcutaneous, IN: Intranasal;

Abbreviations

HPRA: Health Products Regulatory Authority
IM: intramuscular
IN: intranasal
IV: intravenous
LEE: lack of expected efficacy
PSUR: periodic safety update report
SAE: suspected adverse event
SC: subcutaneous
VMP: veterinary medicinal product