

Suspected Adverse Event Reports to Veterinary Medicinal Products received by the HPRA 2017-2018.

Orla Ní Dhúbhda BSc. RVN, MSc.,
Hannah Byrne BSc. RVN,
Alma Moffett BSc. VN, BA,
Paul McNeill MVB, MSc. DLSHTM, MRCVS
Veterinary Sciences Department,
Health Products Regulatory Authority,
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2

ABBREVIATIONS

HPRA	Health Products Regulatory Authority
VMP	Veterinary medicinal product
SAR	Suspected adverse reaction
LEE	Lack of expected efficacy
SAE	Suspected adverse event
MAH	Marketing authorisation holder
VPA	Veterinary product authorisation
SPC	Summary of Product Characteristics
CVMP	Committee for Medicinal Products for Veterinary use
PSUR	Periodic Safety Update Report
CAP	Centrally authorised product
EMA	European Medicines Agency
NCA	National Competent Authority
PI	Product information

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 (VMPs), including products that have been authorised nationally or centrally (following the opinion of the European Medicines Agency). 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 (SAR) in animals to VMPs used under authorised conditions
- off-label use of VMPs in animals
- lack of expected efficacy (LEE) of VMPs
- reported violations of approved residue limits
- adverse reactions in humans related to the use of VMPs
- potential environmental problems

These reports are collectively known as suspected adverse events (SAEs) and are received by the HPRA primarily from marketing authorisation holders (MAHs). MAHs are required by legislation to report all serious SAEs to the HPRA within 15 days. Reports may also be received from veterinary health professionals and animal owners directly. SAE reports are collated and evaluated by the HPRA and 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.

The minimum requirements for an SAE report to be considered valid are detailed in Table 1.

Table 1. Suspected adverse event reports – minimum information required

An SAE report will be considered valid when at least the following core information is provided:

- an identifiable reporter (e.g. Veterinary Surgeon/Veterinary Nurse, Pharmacist, animal owner)
- animal/human details: species, age, sex
- the name and veterinary product authorisation (VPA) number of the product in question
- details of the adverse event

While the above outlines the minimum requirements for a valid SAE report, the reporter should endeavour to provide as comprehensive an account as possible in order to facilitate a full scientific evaluation. Where relevant, this may include the provision of laboratory test results and necropsy findings.

2. National Pharmacovigilance Issues

The HPRA received 395 and 391 valid national SAE reports in 2017 and 2018 respectively. These reports involved a range of food-producing species and companion animals as presented in Table 2. Twenty-eight reports concerned SARs in humans following exposure to a VMP.

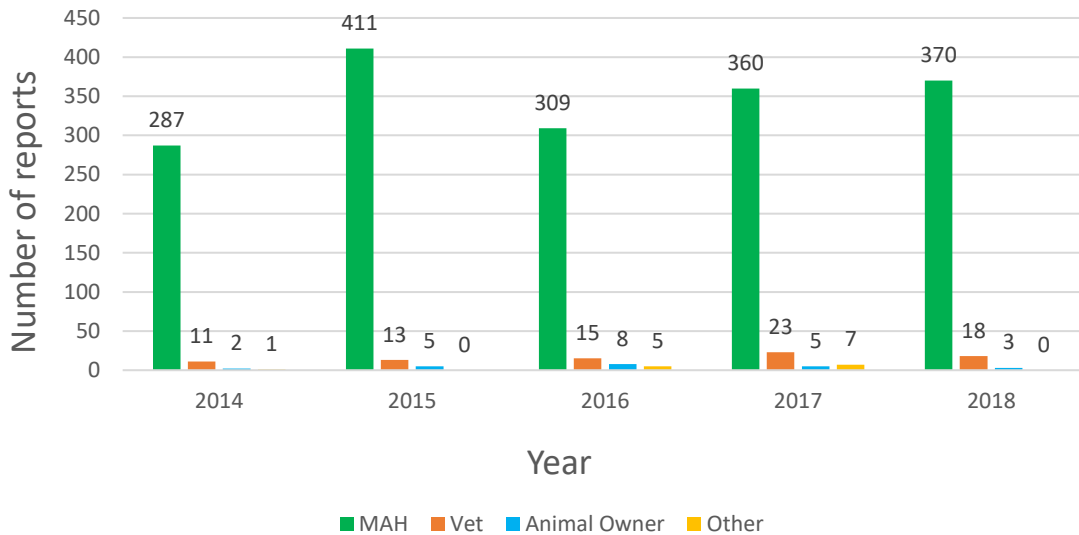
Table 2. Overview of reports received 2017-2018

Species	Total number reports	Total number reacting
Food producing animals		
bovine	302	5313
ovine	109	2187
equine	30	40
rabbit	4	6
bee	6	*11 hives
avian	5	8255
porcine	6	349
fish	2	6980
Companion animals		
canine	254	382
feline	39	44
rodent	1	80
Other		
human	28	28
Total	786	23664

*Reports relating to bees are not included in the total number of reacting animals.

Figure 1. outlines the primary sources of SAE reports received by the HPRC between 2014 and 2018.

Figure 1: Source of SAE reports from 2014 to 2018

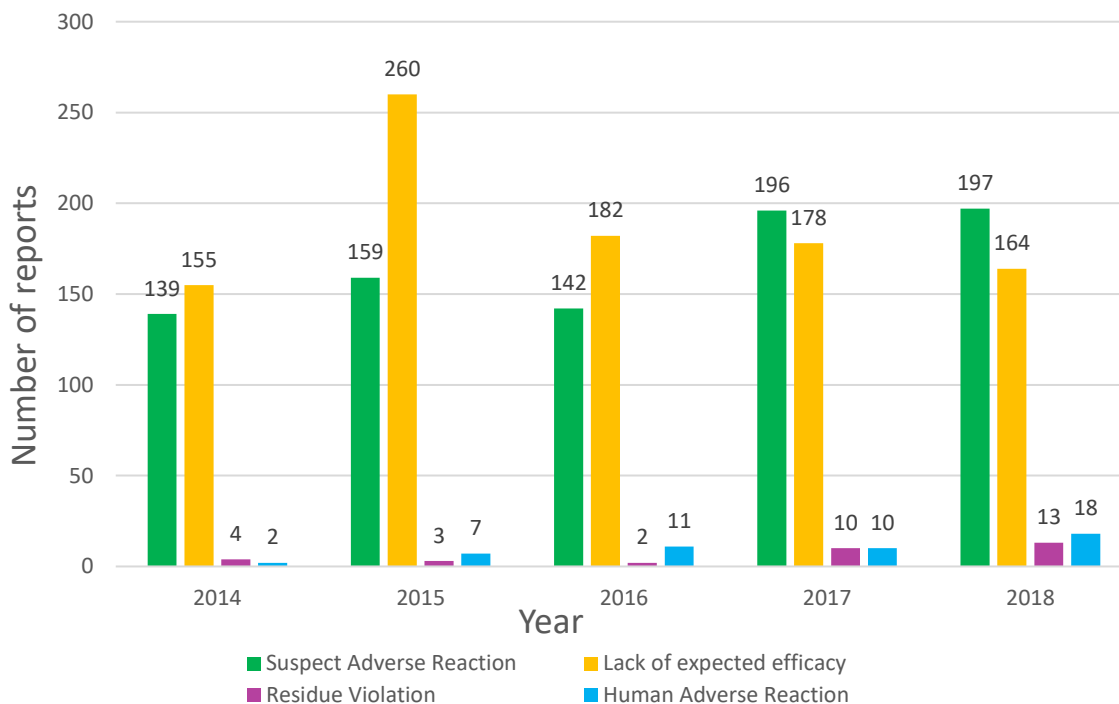


Of the 786 SAE reports received, 311 involved pharmaceutical products, 430 involved immunological products and 45 reports related to the use of both pharmaceutical and immunological products concurrently. Three hundred and ninety-three reports involved SARs in animals, 28 reports involved SAEs in humans, 342 reports involved LEE and 23

reports related to violation of an approved residue limit. Twenty-nine reports involved both SARs and LEE; for the purpose of this report they have been included in the SAR total only.

Figure 2 compares the types of reports received from 2014 to 2018.

Figure 2: Number of SAE reports by category received from 2014 to 2018



2.1 Reports of adverse reactions

Twenty-eight SAE reports of human exposure to VMPs were received during the reporting period. Those administering VMPs are reminded to exercise due caution when handling these products and to pay particular attention to any special precautions for the use of individual products as detailed in the relevant product information (the Summary of Product Characteristics (SPC) published on the HPRA website or the package labelling/leaflet accompanying the product).

Reports of SAEs are assessed by the relevant MAH and the HPRA for any association between the event and the product(s) administered to the animal(s), using an established causality assignment system as shown in Table 3. below.

2.2 Causality assessment

An adverse event report may contain details of more than one VMP administered. Where this occurs, causality is assigned on a product-specific basis rather than to the overall report. In the context of this article, reports involving multiple products with different causalities have been counted more than once. Of the 393 SAR reports (relating to 409 VMPs) received by the HPRA between 2017 and 2018, the involvement of a reported VMP with the observed reaction was considered to have been 'probable' (causality 'A') or 'possible' (causality 'B') in 233 reports.

In 127 reports, there was insufficient/inconclusive information (causality 'O'/'O1') available to assign definitive causality and in 49 reports it was considered unlikely (causality 'N') that a reported VMP was responsible for the observed reaction. The criteria for assigning causality to a report are detailed in Table 3.

A line listing of the individual SAE reports originating from Ireland during 2017 and 2018 that were assigned causality 'A' or causality 'B' is included in Table 4 of the version of this report that is published on the HPRA website (www.hpra.ie).

2.3 Reports of lack of expected efficacy

The HPRA received 178 and 164 LEE reports during 2017 and 2018 respectively.

Of these reports, 78 involved pharmaceutical products and related to cattle (37 reports), sheep (19 reports), dogs (18 reports), horses (2 reports), cat (1 report) and rodent (1 report). Fifteen of the 78 reports were considered to be 'unlikely' (causality 'N') related to the product.

Two hundred and forty-two LEE reports involved immunological products that were suspected to have failed to induce protective immunity. The reports concerned cattle (149 reports), sheep (59 reports), dogs (25 reports), chickens (3 reports), horse (1 report), pigs (3 reports), rabbit (1 report) and fish (1 report). Fifty-seven 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. Forty-five reports involved off-label use of one or more vaccines. Causality is not assigned to LEE reports following off-label use, as efficacy cannot be expected when a product is not used as recommended.

In addition, 22 LEE reports involved both pharmaceutical and immunological products.

3. European Pharmacovigilance Issues

During 2017 and 2018, 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 veterinary medicinal products. This was done by means of monitoring reports logged to a central EU database as well as through the assessment of Periodic Safety Update Reports (PSURs – a report compiled by an MAH on the safety, efficacy and sales data of a particular VMP over a specified period) provided by MAHs. In 2018 there was a significant growth in the total number of adverse events reported to the database, known as Eudravigilance Veterinary (EUVet). This was due to increased reporting from countries outside the EU as well as more targeted monitoring of products authorised within the EU (European Medicines Agency, 2019).

The majority of SAE reports concerned companion animals, with cats and dogs accounting for 90% and 81% of reports in 2017 and in 2018 respectively. Reporting in food-producing animals is comparatively low and initiatives undertaken within the EU to promote reporting in food-producing animals have been largely ineffective to date. There will be an increased focus to improve communication and the exchange of information with Veterinary Practitioners and the general public to prepare for the implementation of Regulation 2019/6.

On the basis of these analyses, during 2017 and 2018 the CVMP made recommendations to update the product literature for 26 centrally-authorised products (CAPs). Further information concerning the changes made to individual product information for CAPs is published in the Veterinary pharmacovigilance Public bulletins 2017 and 2018 on the European Medicines Agency (EMA) website ([link here](#)).

3.1 Regulatory action case study – Osumnia

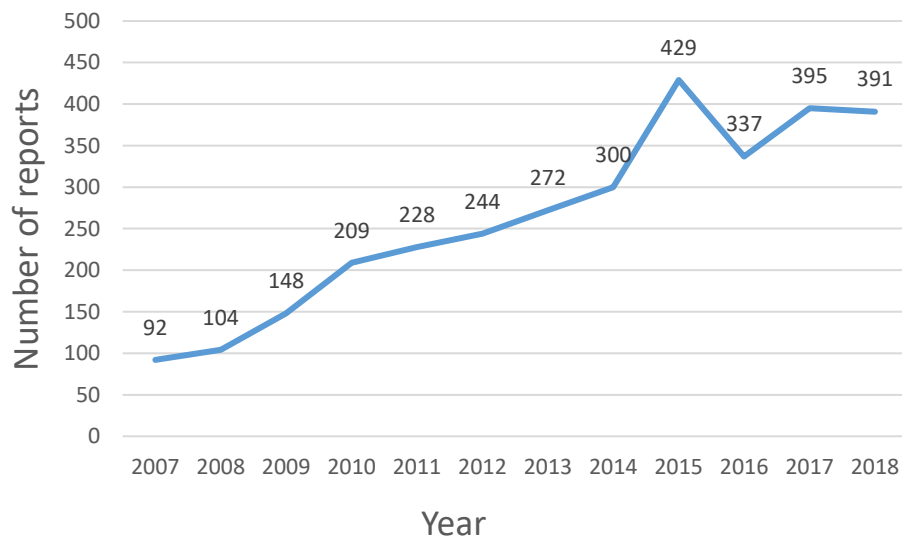
In April 2018, following consultation between the EMA, National Competent Authorities (NCAs) and the relevant MAH, the EMA published a press release in respect of the centrally-authorized product Osumnia ([European Medicines Agency, 2018](#)) and the HPRA simultaneously published a safety advisory notice ([Health Products Regulatory Authority, 2018](#)). The advisory notice concerned eye injuries to dogs and humans following accidental exposure to the product. Human exposure to Osumnia mostly occurred when the dog shook its head during or just after product application. Reported symptoms included corneal ulcer (occurring in two reported cases), eye irritation, conjunctivitis, redness, burning, stinging and itchiness. Reported clinical signs in dogs included corneal ulcers, squinting, impaired vision, conjunctivitis, redness and swelling around the eye. It was confirmed in a number of reports that ocular exposure in dogs was accidental.

Recommended action to be taken included correct restraint of dogs during treatment in order to prevent head shaking after product administration, and flushing of affected eyes with water for 10-15 minutes in the event of ocular exposure. Veterinary Practitioners were advised to request that pet owners monitor dogs treated with Osumnia and to report any potential side effects. New user safety warnings were recommended by the CVMP including an update to the product information (PI).

The EMA continue to monitor the safety of all CAPs, taking regulatory action as appropriate.

4. Conclusion

Figure 3: Total number of SAR Reports to the HPRA from 2007-2018



There is a general trend of increasing numbers of reports since 2007 (Figure 3), which likely reflects a greater awareness of the importance of reporting SAEs rather than an absolute increase in the number of reactions occurring. The HPRA is encouraged by this 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 and when a safety risk relating to the use of authorised VMPs is identified, appropriate regulatory steps can be taken by the HPRA in consultation with the MAH to reduce this risk.

Although the overall trend of reporting SAEs is increasing, the number of cases reported directly to the HPRA by Veterinary Surgeons and Pharmacists remains relatively low (only 5. % of reports received by the HPRA in 2017 and 2018 were reported by Veterinary Practitioners).. Veterinary professionals as well as persons licensed to sell or supply animal remedies are reminded of their obligation to notify the HPRA or the relevant MAH of all suspected adverse reactions. In particular, serious SAEs, all unexpected adverse reactions and all symptomatic human adverse events associated with the use of VMPs should be reported within 15 days of receipt of such information (in accordance with Regulation 12.7(a) 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; the HPRA accepts reports via a number of different methods and veterinary practitioners are encouraged to enlist their veterinary nurse colleagues' help in discharging their responsibilities to report adverse events. Provided that the mandatory information (as described in Table 1.) is included in the report, there will normally be no need for the HPRA to consult 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 in question.

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](http://www.hpra.ie). SAEs can be reported using an online reporting form accessed via 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 3: Assessing Causality

The following factors will be taken into account:

- associative connection in time or anatomic site
 - pharmacological explanation, previous experience of the drug
 - presence of characteristic clinical or pathological phenomena
 - exclusion of other causes
 - completeness and reliability of the data in case reports
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Causality 'A'	All of the following minimum criteria must be complied with: <ul style="list-style-type: none">• there must 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 must be consistent with the known pharmacology and toxicology of the drug• there must 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 'O1'	When a VMP association cannot be discounted but other factors prevent a conclusion being drawn.
Causality 'O'	When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality.
Causality 'N'	When sufficient information exists to establish beyond reasonable doubt that drug administration was not likely to be the cause of the event.

The European Commission (2011)

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The European Commission (2011) *VOLUME 9B of The Rules Governing Medicinal Products in the European Union Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use*. Luxembourg: Office for Official Publications of the European Communities. Available at: https://ec.europa.eu/health/documents/eudralex/vol-9_en (Accessed: 20th June 2019).

Table 4: 2017-2018 adverse reaction reports involving pharmaceutical products in which product association was assigned causality 'A' or 'B' (listed by active substance)

Note: some of the following reports contain multiple products and different routes of administration.

Table 4A: Bovine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
albendazole	oral	120	90	1	death, panting	unknown
albendazole	oral	24	24	3	pneumonia, respiratory distress, death, diarrhoea, ruminal bloat, unthrifty, decreased ruminal activity.	≤ 30 mins
carprofen	IV	1	1	1	recumbency, hyperaesthesia, vocalisation, sudden death	≤ 2 mins
cloprostenol	IM	40	4	0	recumbency, vocalisation, behavioural disorder NOS	≤ 6 hr
ivermectin	topical					
deltamethrin	topical	120	120	1	agitation, itching, licking, death, scour, hyperthermia	≤ 12 hr
enrofloxacin	IV	1	1	1	collapse, respiratory distress, recumbency, death, anaphylaxis	≤ 2 mins

flunixin meglumine	IM	20	1	1	injection site inflammation, lethargy, death, recumbency, respiratory sound, cutaneous oedema, haemorrhage NOS, bruising, abnormal necropsy finding.	≤ 6 hr
flunixin meglumine	IV	1	1	1	sudden death	≤ 2 mins
flunixin meglumine	IV	1	1	1	seizure NOS, sudden death	≤ 2 mins
halofuginone	oral	8	2	0	colic, temporary blindness, impaired vision	≤ 30 mins
imidocarb	SC	1	1	1	sudden death, stiffness NOS, tachycardia, collapse, muscle tremor	≤ 30 mins
ivermectin + closantel	topical	91	2	0	blindness	≤ 14 days
ivermectin + closantel	topical	18	1	0	abnormal vision, inappetence, dull, blindness	≤ 7 days
ivermectin + closantel	topical	155	3	1	recumbency, dull, weakness, anorexia, blindness, abnormal Vision, depression, death by euthanasia	≤ 7 days

ivermectin + closantel	topical	129	36	8	panic, gait abnormality, recumbency, hind limb paralysis, anorexia, diarrhoea, teeth grinding, dehydration, cough, dyspnoea, unthrifty, nasal discharge, copper deficiency signs, elevated AST, abnormal test result, elevated creatinine, elevated creatine-kinase (CK), neutrophilia, inappetence, death, death by euthanasia, found dead, dull, weakness, hind limb ataxia	> 30 days
ivermectin + closantel	SC	16	8	0	injection site oedema, injection site pain, injection site swelling	≤ 24 hr
levamisole	SC	77	1	1	hyperexcitation, hyperaesthesia, hypersalivation, recumbency, death	≤ 2 mins
levamisole	SC	21	1	1	collapse, Muscle Shaking, Seizure NOS, Death	≤ 30 mins
levamisole	SC	62	1	1	death, recumbency, hyperexcitation, hypersalivation, paddling, staggering	≤ 24 hr

levamisole	SC	30	6	0	hyperexcitation, Hyperaesthesia, Hypersalivation	≤ 30 mins
levamisole	SC	7	4	1	hypersalivation, nervous system disorder NOS, padding, recumbency, sudden death	≤ 2 mins
levamisole hydrochloride + oxyclozanide	oral	3	3	0	dullness, ataxia	unknown
monensin	oral	1	1	1	collapse, sunken eyes, not eating, death	≤ 24 hr
moxidectin	SC	300	2	1	collapse, death	≤ 1 hr
moxidectin	SC	7	1	0	nervous system disorder NOS, recumbency	≤ 6 hr
moxidectin	SC	25	2	1	collapse, shock, ataxia, death	≤ 12 hr
moxidectin	SC	8	1	1	death, ataxia, seizure NOS, shock	≤ 1 hr
moxidectin	SC	20	1	0	fit, recumbency, unresponsive to stimuli	≤ 30 mins
moxidectin	IV	7	1	1	anaphylactic shock, death	≤ 2 mins

moxidectin	SC	25	1	0	recumbency, twitching	≤ 24 hr
moxidectin	SC	20	4	1	ataxia, hypersalivation, death	unknown
moxidectin	SC	20	1	0	fit, recumbency, unresponsive to stimuli	≤ 2 mins
moxidectin	SC	25	1	0	recumbency, twitching	≤ 24 hr
oxytetracycline	IV	1	1	1	seizure NOS, recumbency, death by euthanasia, heart pounding	≤ 2 mins
oxytetracycline + flunixin	IM	17	1	1	found dead	≤ 6 hr
pegbovigrastim	SC	1	1	0	recumbency, open mouth breathing, nasal discharge, injection site swelling, vulvar oedema, anaphylaxis	≤ 6 hr
penethamate hydriodide	IM	1	1	1	collapse, death	≤ 2 mins

tocopheryl acetate + selenium	IM	100	6	0	recumbency, premature parturition, retained placenta, unsteady gait, metritis, milk production decrease, elevated ALP, elevated AST, elevated liver enzymes	≤ 24 hr
trimethoprim + sulfadiazine	IV	1	1	1	anaphylactoid reaction, sudden death	≤ 2 mins
trimethoprim + sulfadiazine	IV	1	1	1	paddling, anaphylactoid reaction, sudden death	≤ 2 mins
trimethoprim + sulfadiazine	IV	1	1	1	sudden death, anaphylactoid reaction	≤ 2 mins
vitamin A, vitamin D3, vitamin E, vitamin B1, vitamin B2, vitamin B6, nicotinamide, dexpanthenol, vitamin B12	IM	3	1	1	allergic reaction, respiratory distress, recumbency, sudden death, paddling, laboured breathing	≤ 30 mins

Table 4B: Canine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
amoxicillin + clavulanic acid	oral	1	1	0	diarrhoea, Perinatal mortality	unknown
buprenorphine	IM	1	1	0	tachypnoea, hypertension, tachycardia, pulmonary oedema, elevated liver enzymes, elevated ALT, elevated AST	≤ 30 mins
cefovecin	SC	1	1	0	distention of abdomen, congested mucous membrane, panleucopenia, decreased red blood cell count, inappetence	≤ 7 days
methylprednisolone acetate	IM					
ciclosporin	oral	1	1	0	diabetes, excessive thirst, polyuria	> 30 days
estriol	oral	1	1	1	swollen vulva, vomiting, decreased appetite, death by euthanasia, not drinking, limb weakness	≤ 48 hr
phenylpropanolamine hydrochloride	oral					

fluralaner	oral	1	1	0	hypoproteinaemia, reduced globulins, hypocalcaemic condition, hypoalbuminaemia, elevated ALT, decreased cholesterol (total), elevated creatine-kinase (CK), tense abdomen, abnormal test result, dull, elevated AST, inappetence, vomiting, diarrhoea, haemorrhagic diarrhoea, increased red blood cell count, increased packed cell volume (PCV), low platelet count, increased percentage reticulocytes	≤ 7 days
fluralaner	oral	1	1	0	sensory abnormality NOS, abnormal movement NOS, behavioural disorder NOS	≤ 2 mins
fluralaner	oral	1	1	0	vomiting, collapse	≤ 30 mins
fluralaner	oral	1	1	1	gastroenteritis, hind limb paresis, death by euthanasia	≤ 7 days
fluralaner	oral	1	1	0	vomiting	≤ 12 hr
gentamicin base + betamethasone + clotrimazole	topical	1	1	0	deafness	≤ 24 hr

imepitoin	oral	1	1	unknown	vomiting, lack of efficacy, arthritis	> 30 days
imidacloprid + moxidectin	topical	1	1	0	vomiting, facial oedema, panting, sleepiness - systemic disorder, localised rash, generalised allergic reaction NOS	≤ 1 hr
imidacloprid + moxidectin	topical	1	1	0	hypersalivation, ataxia	≤ 2 mins
insulin	SC	1	1	0	malaise, hypoglycaemia, diabetic ketoacidosis, lack of efficacy, congestion of mucous membrane, prolonged capillary refill time, lethargy, vomiting, diarrhoea, pancreatitis	≤ 14 days
insulin	SC	1	1	0	hypoglycaemia, LEE	unknown
insulin	SC	1	1	0	vomiting, LEE	unknown
insulin	SC	1	1	1	incoordination, shaking, panting, lack of efficacy, hypoglycaemia, death by euthanasia	unknown

insulin	SC	1	1	0	LEE, hypoglycaemia, leucopenia, elevated alanine aminotransferase (ALT)	> 30 days
medetomidine hydrochloride	IM					
butorphanol	IM	1	1	1	cardiac arrest, respiratory arrest, death.	≤ 1 hr
propofol	IV					
isoflurane	inhalation					
meloxicam	IV + SC	1	1	unknown	emesis, abdominal pain, increased heart rate, dehydration, azotaemia, acute renal failure, haematuria	≤ 48 hr
meloxicam	oral	1	1	0	lip disorder NOS, oral discomfort, oral haemorrhage, oral swelling	> 30 days

meloxicam	IV + oral	1	1	0	anorexia, emesis, inappropriate defecation, tachycardia, melaena, lethargy, loss of consciousness, abdominal pain, diarrhoea, other abnormal test result NOS, hyperglycaemia, electrolyte disorder, thrombocytosis, gastric ulcer, neutrophilia, anaemia NOS, acid-base disorder	≤ 14 days
milbemycin oxime + praziquantel	oral	1	1	0	dullness, ataxia, hyperreflexia, twitching, inappetence, not drinking	≤ 7 days
nitroscanate	oral	1	1	0	incoordination, recumbency, bradycardia, ataxia, tremor	≤ 24 hr
oclacitinib	oral	1	1	0	diarrhoea, haematochezia, vomiting, tachycardia, abdominal pain, pancreatitis	≤ 48 hr
oclacitinib	oral	1	1	0	cushings disease NOS, polyuria, polydipsia, elevated liver enzymes	> 30 days

oclacitinib	oral	1	1	0	skin tumour NOS	> 30 days
oclacitinib	oral	1	1	0	polyuria, polydipsia, bloated, panting, hair change, increased appetite	≤ 30 days
oclacitinib	oral	1	1	1	lymphadenopathy, lymphoma, death by euthanasia	> 30 days
oclacitinib	oral	1	1	0	seizure NOS, hyperkalemic condition, hepatic disorder NOS	≤ 7 days
oclacitinib	oral	1	1	0	skin tumour NOS	> 30 days
oclacitinib	oral	1	1	1	neoplasia NOS, death	> 30 days
oclacitinib	oral	1	1	0	lymphoma, off colour, diarrhoea	≤ 30 days
oclacitinib	oral	1	1	0	increased seizure frequency, epileptic seizure	≤ 7 days
sarolaner	oral					
orbifloxacin + mometasone furoate + posaconazole	topical	1	1	0	temporary deafness	≤ 7 days

orbifloxacin + mometasone furoate + posaconazole	topical	1	1	1	deafness	unknown
pentosan polysulphate sodium	SC	1	1	0	collapse NOS	≤ 30 mins
pimobendan	oral	1	1	0	increased heart rate, nausea, hypersalivation	≤ 12 hr
praziquantel, pyrantel + febantel	oral	1	1	0	vomiting, cold feeling of extremity	≤ 6 hr
prednisolone	oral	1	1	0	diabetes mellitus, polyuria, polydipsia	> 30 days
propofol	IV	1	1	0	tonic seizure, padding	≤ 2 mins
propofol	IV	2	2	0	central nervous system depression, respiratory depression, cardiac depression, urticaria, tremor, recovery prolonged	≤ 2 mins
pyriprole	oral	1	1	1	convulsion, death	≤ 6 hr
sarolaner	oral	1	1	0	head tilt - neurological disorder, vacant, ataxia	unknown
cimicoxib	oral					

selamectin	topical	1	1	0	lethargy, ataxia, drooling, vomiting, mydriasis, muscle tremor, anorexia, elevated liver enzymes	≤ 6 hr
trilostane	oral	1	1	Unknown	diarrhoea, vomiting, hyperkalaemia, hyponatremia, elevated BUN, inappetence, hypokalaemia, abnormal ultrasound finding	> 30 days

Table 4C: Ovine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
albendazole	oral	300	20	11	diarrhoea, death	≤ 12 hr
closantel	oral	13	2	0	blindness	≤ 7 days
levamisole hydrochloride + oxclozanide	oral	200	3	0	facial swelling, lethargy, anorexia	≤ 48 hr
levamisole hydrochloride + oxclozanide	oral	8	8	0	inappetence, scour	≤ 24 hr
tilmicosin	SC	2	1	1	collapse, death	≤ 30 mins

Table 4D: Feline Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical signs	Speed of onset
carbimazole	oral	1	1	0	vomiting, dull, anaemia NOS	≤ 30 days
cefovecin	oral	1	1	1	disorientation, circling, hemiparesis (weakness L or R side), blindness, Death by euthanasia	≤ 48 hr
fipronil	topical	1	1	0	anorexia, lethargy, eye disorder NOS, walking difficulty, hair loss NOS, falling, hypothermia, vomiting	≤ 12 hr
fipronil + (s)-methoprene + eprinomectin + praziquantel	topical	1	1	0	behavioural disorder NOS, application site pain, tachypnoea, application site lesion, application site scab, application site inflammation, application site serous discharge, restlessness, tremor, aggression, vocalisation, application site alopecia, application site erythema, application site itching, shaking, moist dermatitis	≤ 12 hr
fipronil, (s)-methoprene, eprinomectin, praziquantel	topical	1	1	0	ataxia, head tremor, confusion	≤ 6 hr

fluralaner + moxidectin	topical	1	1	unknown	elevated total bilirubin, elevated bile acids, elevated creatine-kinase (CK), decreased haemoglobin, decreased packed cell volume, red blood cell disorder, neutrophilia, uncoded sign, monocytosis, immune mediated haemolytic anaemia, abnormal test result, haemolytic jaundice, decreased red blood cell count, increased percentage reticulocytes, leucocytosis, hypochloraemia, low sodium-potassium ratio, elevated ALT	≤ 24 hr
imidacloprid + flumethrin	topical	1	1	0	contact dermatitis	≤ 7 days
imidacloprid + moxidectin	topical	1	1	0	vomiting	≤ 30 mins
imidacloprid + moxidectin	topical	1	1	unknown	moribund, inappetence	≤ 48 hr
imidacloprid + moxidectin	topical	1	1	0	application site ulcer, application site alopecia	≤ 14 days
meloxicam	SC	1	1	1	vomiting, circulatory collapse, death by euthanasia	≤ 24 hr
milbemycin oxime + praziquantel	oral	1	1	0	ataxia, increased respiratory rate, weakness	≤ 24 hr

selamectin	topical	1	1	0	hair loss, inflammation, scabbing, application site reaction	≤ 48 hr
thiamazole	oral	1	1	0	allergic pruritus, allergic skin reaction, localised skin reaction	≤ 14 days
thiamazole	oral	1	1	0	vomiting, elevated BUN, elevated creatinine	> 30 days

Table 4E: Equine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
acepromazine	oral	1	1	1	death by euthanasia, priapism, recumbency	unknown
amitraz	topical	1	1	0	dullness, sedation, bradycardia, not eating, not drinking	≤ 24 hr
chorionic gonadotrophin	IM	1	1	1	death	≤ 1 hr
deslorelin	SC	15	5	0	prolonged interestrus interval, implantation site reaction	unknown
deslorelin	SC	1	1	0	delayed interestrus interval	> 30 days
deslorelin	SC	1	1	0	abnormal cycling, implant site reaction	≤ 30 days
deslorelin	SC	1	1	0	abnormal cycling	≤ 30 days

deslorelin	SC	1	1	0	abnormal cycling	≤ 30 days
deslorelin	SC	1	1	0	abnormal cycling, implantation site swelling	≤ 30 days
deslorelin	SC	1	1	0	abnormal cycling	≤ 30 days
deslorelin	SC	1	1	0	abnormal cycling	≤ 30 days
deslorelin	SC	1	1	0	abnormal cycling, implantation site swelling	≤ 30 days
deslorelin	SC	1	1	0	abnormal cycling	≤ 30 days
detomidine hydrochloride	IV	1	1	0	abnormal breathing, shallow breathing	≤ 24 hr
butorphanol	IV					
detomidine hydrochloride	IV	1	1	0	laboured breathing, snoring, uncoded sign	≤ 24 hr
butorphanol	IV					
moxidectin + praziquantel	oral	1	1	0	colic, lethargy, anorexia, ataxia	≤ 48 hr
trimethoprim + sulfadiazine	IV	1	1	1	ataxia, collapse, death	≤ 30 mins
vitamin A, vitamin D3, vitamin E, vitamin B1, vitamin B2, vitamin B6,	IV	1	1	1	allergic reaction, laboured breathing, collapse, sudden death	≤ 30 mins

nicotinamide, dexpanthenol, vitamin B12 calcium chloride hexahydrate, magnesium sulphate heptahydrate, potassium chloride, thiamine hydrochloride, riboflavin (as sodium phosphate), pyridoxine hydrochloride, cyanocobalamin, nicotinamide + dexpanthenol						
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Table 4F: Bee Reports

Active substance	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
thymol	in hive	7 stocks	7 stocks	5 stocks	queen bee death, bee colony death	≤ 30 days
thymol	in-hive	2 colonies	2 colonies	2	death	> 30 days
thymol	in hive	7 hives	4 hives	0	off lay	≤ 7 days
thymol	in hive	7 hives	7 hives	0	agitation	≤ 2 mins

Table 5: 2017-2018 adverse reaction reports involving immunological products, in which product association was assigned causality 'A' or 'B' (listed by active substance (antigen))

Table 5A: Bovine Reports

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
<i>Formalin killed cells of Salmonella dublin strain S342/70</i> <i>Formalin killed cells of Salmonella typhimurium.</i>	SC	1	1	0	abortion	≤ 14 days
<i>Inactivated Bovine Respiratory Syncytial virus, strain EV908,</i> <i>Inactivated Parainfluenza-3-Virus, strain SF-4</i> <i>Reisinger,</i> <i>Inactivated Mannheimia haemolytica A1, strain M4/1.</i>	SC	29	1	1	death, epistaxis	≤ 1 hr
<i>Inactivated Bovine Viral Diarrhoea (BVD) type 1 virus, cytopathogenic strain 5960.</i>	SC	1	1	1	pyrexia, dyspnoea, rectal haemorrhage, tarry or black stool (see also haemorrhagic diarrhoea), gum disorder NOS, death	> 30 days
<i>Inactivated Bovine Viral Diarrhoea (BVD) type 1 virus,</i>	SC	1	1	1	multiple organ haemorrhage, rectal haemorrhage, pancytopenia,	> 30 days

<i>cytopathogenic strain 5960.</i>					abnormal necropsy finding, death	
<i>Modified live Bovine Parainfluenza type 3 virus (PI3V), thermosensitive strain RLB10³, Modified live Bovine Respiratory Syncytial virus (BRSV) strain 375.</i>	intranasal	90	25	1	LEE, cough, dyspnoea, tachypnoea, pyrexia, bronchopneumonia, death	≤ 30 days

Table 5B: Canine Reports

Active Substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
<i>Live attenuated Bordetella bronchiseptica, live, strain 92B 2.1 x 10⁶ to 5.5 x 10⁸.</i>	intranasal	2	2	0	collapse, vagal shock, pale mucous membrane	≤ 30 mins
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5. Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>	SC					

<i>Live attenuated Bordetella bronchiseptica, live, strain 92B 2.1 x 10⁶ to 5.5 x 10⁸.</i>	intranasal	1	1	0	dyspnoea	≤ 7 days
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>	SC					
<i>Lokivetmab</i>	SC	1	1	0	ataxia, tremor	≤ 6 hr
<i>Lokivetmab</i>	SC	1	1	0	hives, Facial swelling	> 30 days
<i>Lokivetmab</i>	SC	1	1	unknown	polyuria, polydipsia, diarrhoea	unknown
<i>Attenuated canine distemper virus, strain BA5, Attenuated canine adenovirus type 2, strain DK13, Attenuated canine parvovirus type 2, strain CAG2, Attenuated canine parainfluenza virus type 2, strain CGF 2004/75.</i>	SC					

Inactivated <i>Leptospira canicola</i> , Inactivated <i>Leptospira icterohaemorrhagiae</i> .	SC	1	1	0	vomiting, scratching, head shake - ear disorder, panting, excessive licking and/or grooming	≤ 6 hr
Inactivated <i>Leptospira canicola</i> , Inactivated <i>Leptospira icterohaemorrhagiae</i> .	SC					
Attenuated canine distemper virus, strain BA5, Attenuated canine adenovirus type 2, strain DK13, Attenuated canine parvovirus type 2, strain CAG2, Attenuated canine parainfluenza virus type 2, strain CGF 2004/75.	SC					
≥ 10 ^{8.0} and ≤ 10 ^{9.7} cfu ¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and ≥ 10 ^{3.0} and ≤ 10 ^{5.8} TCID ₅₀ ² of live canine parainfluenza virus strain Cornell.	intranasal	1	1	0	lethargy, periorbital oedema, facial oedema, swollen feet, anaphylaxis	≤ 6 hr
Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.	SC					
Inactivated <i>Leptospira</i> strains: - <i>L. interrogans</i>						
		1	1	0	swelling around eye, facial swelling	≤ 30 mins

<p><i>serogroup Canicola serovar Portland-verre (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i></p>	SC					
<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i></p> <p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-verre (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i></p>	SC	1	1	0	periorbital oedema, allergic oedema, emesis, diarrhoea	≤ 6 hr
<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus +</i></p>	SC					

<p>Canine parainfluenzavirus.</p> <p>Inactivated <i>Leptospira</i> strains: - <i>L. interrogans</i> serogroup Canicola serovar Portland-vere (strain Ca-12-000) - <i>L. interrogans</i> serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - <i>L. interrogans</i> serogroup Australis serovar Bratislava (strain As-05-073) - <i>L. kirschneri</i> serogroup Grippotyphosa serovar Dadas (strain Gr-01-005).</p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	<p>SC</p> <p>intranasal</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>swollen face, dull, increased respiratory rate</p>	<p>≤ 6 hr</p>
<p>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</p> <p>Inactivated <i>Leptospira</i> strains: - <i>L. interrogans</i> serogroup Canicola serovar Portland-vere (strain Ca-12-000) - <i>L.</i></p>	<p>SC</p> <p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>allergic skin reaction, wheal, vomiting</p>	<p>≤ 30 mins</p>

<p><i>interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Copenhageni</i> (strain Ic-02-001) - <i>L. interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i> (strain As-05-073) - <i>L. kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Dadas</i> (strain Gr-01-005).</p>						
<p><i>Canine distemper virus</i>, <i>Canine adenovirus 2</i>, <i>Canine parvovirus</i> + <i>Canine parainfluenzavirus</i>.</p> <p><i>Inactivated Leptospira</i> strains: - <i>L. interrogans</i> serogroup <i>Canicola</i> serovar <i>Portland-vere</i> (strain Ca-12-000) - <i>L. interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Copenhageni</i> (strain Ic-02-001) - <i>L. interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i> (strain As-05-073) - <i>L. kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Dadas</i> (strain Gr-01-005).</p>	<p>SC</p> <p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>dullness, collapse</p>	<p>≤ 24 hr</p>
<p><i>Canine distemper virus</i>, <i>Canine adenovirus 2</i>, <i>Canine parvovirus</i> + <i>Canine parainfluenzavirus</i>.</p>	<p>SC</p>					

<p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i></p>	SC	1	1	0	injection site abscess, injection site pain, elevated globulins, elevated SAP, decreased red blood cell count, decreased packed cell volume (PCV)	≤ 7 days
<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i></p> <p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i></p>	SC	1	1	1	seizure, death	≤ 6 hr

<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i></p> <p><i>Inactivated Leptospira interrogans serogroup - Canicola; serovar portland-vere, strain Ca-12-000 Icterohaemorrhagiae; serovar copenhageni, strain 820K.</i></p>	<p>SC</p> <p>SC</p>	<p>1</p>	<p>1</p>	<p>1</p>	<p>death by euthanasia, inappetence, pyrexia, injection site lump</p>	<p>≤ 7 days</p>
<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i></p> <p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005).</i></p>	<p>SC</p> <p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>injection site pain, lethargy</p>	<p>≤ 6 hr</p>

<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i></p> <p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i></p>	<p>SC</p> <p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>tonic-clonic seizure, injection site pain, injection site swelling, scratching, twitching</p>	<p>≤ 12 hr</p>
<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i></p> <p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup</i></p>	<p>SC</p> <p>SC</p>	<p>8</p>	<p>1</p>	<p>0</p>	<p>pyrexia, lethargy, injection site swelling, injection site pain</p>	<p>≤ 24 hr</p>

<p><i>Australis</i> serovar <i>Bratislava</i> (strain As-05-073) - <i>L. kirschneri</i> serogroup <i>Grippytyphosa</i> serovar <i>Dadas</i> (strain Gr-01-005).</p>						
<p><i>Canine distemper virus</i>, <i>Canine adenovirus 2</i>, <i>Canine parvovirus</i> + <i>Canine parainfluenzavirus</i>.</p> <p><i>Inactivated Leptospira</i> strains: - <i>L. interrogans</i> serogroup <i>Canicola</i> serovar <i>Portland-vere</i> (strain Ca-12-000) - <i>L. interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Copenhageni</i> (strain Ic-02-001) - <i>L. interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i> (strain As-05-073) - <i>L. kirschneri</i> serogroup <i>Grippytyphosa</i> serovar <i>Dadas</i> (strain Gr-01-005).</p>	<p>SC</p> <p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>dull, pyrexia, anaemia NOS, vomiting, neutropenia</p>	<p>≤ 24 hr</p>
<p><i>Canine distemper virus</i>, <i>Canine adenovirus 2</i>, <i>Canine parvovirus</i> + <i>Canine parainfluenzavirus</i>.</p> <p><i>Inactivated Leptospira</i> strains: - <i>L. interrogans</i> serogroup <i>Canicola</i></p>	<p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>tonic-clonic seizures, pale mucous membrane, panting, bradycardia, hypoalbuminaemia, anaphylaxis, abnormal test result</p>	<p>≤ 30 mins</p>

<p><i>serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i></p>	SC					
<p><i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i></p> <p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i></p>	SC	1	1	0	circulatory collapse, pale mucous membrane, swollen face, inappropriate urination, anaphylaxis	≤ 2 mins
<p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of</p>	intranasal	3	1	0	cough, positive tracheal pinch	≤ 7 days

<i>live canine parainfluenza virus strain Cornell.</i>						
$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu ¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID ₅₀ ² of live canine parainfluenza virus strain Cornell.	intranasal	1	1	0	collapse NOS, hypersensitivity reaction	≤ 1 hr
$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu ¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID ₅₀ ² of live canine parainfluenza virus strain Cornell.	intranasal					
Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.	SC	1	1	0	opisthotonus, pyrexia, dry coat, cardiac enlargement	≤ 6 hr
Inactivated <i>Leptospira interrogans</i> serogroup - Canicola; serovar portland-vere, strain Ca-12-000 <i>Icterohaemorrhagiae</i> ; serovar copenhageni, strain 820K.	SC					

<p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippytyphosa serovar Dadas (strain Gr-01-005).</i></p>	<p>SC</p>	<p>1</p>	<p>1</p>	<p>1</p>	<p>elevated gamma-glutamyl transferase (GGT), unresponsive to stimuli, bilirubinuria, elevated ALT, Elevated AST, hypoglycaemia, hypokalaemia, elevated cholesterol (total), elevated total bilirubin, cardiac arrest, bone marrow hyperplasia, immune mediated haemolytic anaemia, systemic disorder (NOS), death, lung oedema, abnormal radiograph finding, abnormal ultrasound finding, elevated SAP, emesis (multiple), listless, dry mucous membrane, spherocytosis, hypophosphataemia, decreased red blood cell count, eosinophilia, pancreas disorder, hepato-biliary</p>	<p>≤ 7 days</p>
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					disorder NOS, elevated globulins, pyrexia, abnormal test result, proteinuria, glucosuria, fluid in abdomen NOS, pale mucous membrane, blood in urine, decreased appetite, blood in faeces, icterus, decreased packed cell volume (PCV)	
<i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</i>	SC	1	1	0	vomiting, diarrhoea, lethargy, dull	≤ 6 hr
<i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae</i>	SC	1	1	0	dull, anaemia NOS, decreased packed cell volume (PCV)	≤ 30 days

<p><i>serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005).</i></p>						
<p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005).</i></p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	<p>SC</p> <p>intranasal</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>increased lung sounds, pale mucous membrane, polypnoea, tachycardia, elevated SAP, abnormal test result, quiet, malaise, proteinuria, cough, leucocytosis, bronchopneumonia, hiatus hernia, pneumonia, immune mediated haemolytic anaemia, decreased red blood cell count, decreased packed cell volume, decreased haemoglobin, increased percentage reticulocytes</p>	<p>≤ 7 days</p>
<p><i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola</i></p>	<p>SC</p>					

<p>serovar Portland-vere (strain Ca-12-000) - <i>L. interrogans</i> serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - <i>L. interrogans</i> serogroup Australis serovar Bratislava (strain As-05-073) - <i>L. kirschneri</i> serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	intranasal	1	1	0	collapse NOS, dull, cold feeling of extremity, weak pulse, lethargy, pale mucous membrane	≤ 6 hr
<p>Inactivated <i>Leptospira</i> strains: - <i>L. interrogans</i> serogroup Canicola serovar Portland-vere (strain Ca-12-000) - <i>L. interrogans</i> serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - <i>L. interrogans</i> serogroup Australis serovar Bratislava (strain As-05-073) - <i>L. kirschneri</i> serogroup Grippityphosa serovar Dadas (strain Gr-01-005).</p>	SC	1	1	0	vomiting, shaking, anal sac disorder, trembling, epileptic fit, unresponsive to stimuli, twitching, discomfort NOS	≤ 30 mins

<i>Canine distemper virus, Canine adenovirus 2, Canine parvovirus + Canine parainfluenzavirus.</i>	SC					
<i>Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005).</i> <i>≥ 10^{8.0} and ≤ 10^{9.7}cfu¹ of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ 10^{3.0} and ≤ 10^{5.8} TCID₅₀² of live canine parainfluenza virus strain Cornell.</i>	SC intranasal	1	1	0	hypoproteinaemia, reduced globulins, hypocalcaemic condition, hypoalbuminaemia, elevated ALT, decreased cholesterol (total), elevated creatine-kinase (CK), tense abdomen, abnormal test result, dull, elevated AST, inappetence, vomiting, diarrhoea, haemorrhagic diarrhoea, increased red blood cell count, increased packed cell volume (PCV), low platelet count, increased percentage reticulocytes	≤ 7 days
<i>Inactivated rabies virus strain Pasteur.</i>	SC	1	1	0	swollen face, swollen eye, vomiting	≤ 30 mins
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan,</i>	SC	1	1	0	collapse, inappropriate urination, pale mucous	≤ 2 mins

<i>Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>					membrane, decreased body temperature	
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>	SC	1	1	0	haemorrhagic diarrhoea, nasal bleeding, vomiting, diarrhoea, circulatory shock, dehydration, tachycardia, hypothermia, elevated creatinine, neutropenia, elevated lipase	≤ 24 hr
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>	SC	1	1	0	tachypnoea, pale mucous membrane, nystagmus, opisthotonus, unconscious	≤ 2 mins

<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	SC	1	1	0	weakness, pale mucous membrane, circulatory collapse	≤ 1 hr
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	SC	1	1	0	muscle weakness NOS, bladder incontinence, faecal incontinence, nystagmus	≤ 2 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	SC	1	1	0	immediate pain upon injection, inappropriate urination, pale mucous membrane, lethargy, vagal shock, decreased heart rate	≤ 2 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus,</i></p>	SC	22	2	0	vagal shock, pale mucous membrane, unresponsive to stimuli, inappropriate urination, faecal	≤ 30 mins

<i>strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>					incontinence, hind limb ataxia	
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>	SC	1	1	0	generalised weakness, pale mucous membrane, vagal shock	≤ 2 mins
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>	SC	1	1	1	fainting, sleepiness, generalised weakness, lethargy, death	≤ 30 mins
<i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i>	SC	1	1	0	vagal shock, collapse	≤ 2 mins

<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	SC	1	1	0	vagal shock, pale mucous membrane, lethargy, generalised weakness	≤ 30 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	SC	1	1	0	vomiting, lethargy	≤ 30 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	SC	1	1	0	collapse, anaphylactic type reaction	≤ 2 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D,</i></p>	SC	1	1	0	injection site pain, vocalisation, pale mucous membrane, ataxia, inappropriate urination	≤ 2 mins

<i>Leptospira canicola</i> , <i>Leptospira icterohaemorrhagiae</i> .						
<i>Canine distemper virus</i> , strain N-CDV, <i>Canine adenovirus Type 2</i> , strain Manhattan, <i>Canine parainfluenza virus</i> , strain NL-CPI-5, <i>Canine Parvovirus</i> , strain NL-35-D, <i>Leptospira canicola</i> , <i>Leptospira icterohaemorrhagiae</i> .	SC	2	1	0	pale mucous membrane, dyspnoea, bradycardia, collapse, anaphylaxis	≤ 30 mins
<i>Canine distemper virus</i> , strain N-CDV, <i>Canine adenovirus Type 2</i> , strain Manhattan, <i>Canine parainfluenza virus</i> , strain NL-CPI-5, <i>Canine Parvovirus</i> , strain NL-35-D, <i>Leptospira canicola</i> , <i>Leptospira icterohaemorrhagiae</i> .	SC	1	1	0	vagal shock, pale mucous membrane, respiratory distress, collapse NOS	≤ 30 mins
<i>Canine distemper virus</i> , strain N-CDV, <i>Canine adenovirus Type 2</i> , strain Manhattan, <i>Canine parainfluenza virus</i> , strain NL-CPI-5, <i>Canine Parvovirus</i> , strain NL-35-D, <i>Leptospira canicola</i> , <i>Leptospira icterohaemorrhagiae</i> .	SC	1	1	0	pale mucous membrane, bradycardia, inappropriate urination, immediate pain upon injection, anaphylactic type reaction	≤ 2 mins
<i>Canine distemper virus</i> , strain N-CDV, <i>Canine adenovirus Type 2</i> ,	SC					

<p><i>strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p><i>Live attenuated Bordetella bronchiseptica, live, strain 92B 2.1 x 10⁶ to 5.5 x 10⁸.</i></p>	<p>intranasal</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>seizure NOS, muscle weakness NOS, inappropriate urination, pale mucous membrane, weak pulse, disoriented state, vomiting</p>	<p>≤ 30 mins</p>
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p><i>≥ 10^{8.0} and ≤ 10^{9.7}cfu¹ of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ 10^{3.0} and ≤ 10^{5.8} TCID₅₀² of live canine parainfluenza virus strain Cornell.</i></p>	<p>SC</p> <p>intranasal</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>vomiting, weakness, pale mucous membrane, bradycardia, weak pulse, anaphylaxis</p>	<p>≤ 30 mins</p>
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan,</i></p>	<p>SC</p>					

<p><i>Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	intranasal	1	1	0	vomiting, pallor, collapse	≤ 1 hr
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	SC intranasal	1	1	0	vomiting	≤ 30 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2,</i></p>	SC					

<p><i>strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	intranasal	1	1	0	collapse, anaphylactic type reaction	≤ 2 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	SC intranasal	1	1	0	vagal shock, pale mucous membrane, fainting	≤ 30 mins
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2,</i></p>	SC					

<p><i>strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	intranasal	1	1	0	injection site swelling, injection site lump	≤ 7 days
<p><i>Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	SC	1	1	0	dullness, ataxia, hyperreflexia, twitching, inappetence, not drinking	≤ 7 days
<p><i>Inactivated Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine</p>	SC intranasal	1	1	0	vomiting, facial oedema, panting, sleepiness - systemic disorder, localised rash, generalised allergic reaction NOS	≤ 1 hr

<i>parainfluenza virus strain Cornell.</i>						
<i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i>	SC	1	1	unknown	injection site swelling, nystagmus, off-colour, head tilt- neurological disorder, hind limb ataxia, panting, restlessness	≤ 7 days
<i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae</i>						

<p><i>serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i></p>	SC	1	1	0	<p>injection site swelling, seizure NOS, eyes rolling back, trembling, disorientation, petit mal epilepsy</p>	≤ 7 days
<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i></p>	SC	1	1	0	<p>circulatory collapse, unresponsive to stimuli, pale mucous membrane, drooling, vomiting, bradycardia, decreased body temperature</p>	≤ 30 mins

<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i></p>	SC	1	1	1	LEE (parvovirus), death by euthanasia, vomiting, diarrhoea, dehydration, dullness, inappetence	≤ 30 days
<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089,</i></p>	SC	1	1	0	anaphylaxis, collapse	≤ 2 mins

<p><i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i>, strain MSLB 1088.</p>						
<p><i>Canine distemper virus</i>, strain CDV Bio 11/A, <i>Canine adenovirus</i> Type 2, strain CAV-2 Bio 13, <i>Canine parvovirus</i> Type 2b, strain CPV-2b Bio 12/B, <i>Canine parainfluenza</i> Type 2 virus, strain CPiV-2 Bio 15. <i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i>, strain MSLB 1088.</p>	SC	1	1	0	vagal shock, collapse NOS, immediate pain upon injection, vocalisation, dullness	≤ 2 mins

<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i></p>	SC	1	1	0	vomiting, vagal shock, pale mucous membrane, heart block NOS	≤ 30 mins
<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089,</i></p>	SC	6	5	1	dullness, pyrexia, death	unknown

<p><i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i>, strain MSLB 1088.</p>						
<p><i>Canine distemper virus</i>, strain CDV Bio 11/A, <i>Canine adenovirus</i> Type 2, strain CAV-2 Bio 13, <i>Canine parvovirus</i> Type 2b, strain CPV-2b Bio 12/B, <i>Canine parainfluenza</i> Type 2 virus, strain CPiV-2 Bio 15. <i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i>, strain MSLB 1088.</p>	SC	130	13	0	injection site pain, lethargy, collapse	≤ 2 mins

<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i></p>	SC	1	1	0	collapse, pale mucous membrane, bradycardia, faecal incontinence, vagal shock	≤ 2 mins
<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089,</i></p>	SC	1	1	0	fainting, pale mucous membrane, bradycardia, inappropriate urination, vagal shock	≤ 2 mins

<p><i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i>, strain MSLB 1088.</p>						
<p><i>Canine distemper virus</i>, strain CDV Bio 11/A, <i>Canine adenovirus</i> Type 2, strain CAV-2 Bio 13, <i>Canine parvovirus</i> Type 2b, strain CPV-2b Bio 12/B, <i>Canine parainfluenza</i> Type 2 virus, strain CPiV-2 Bio 15. <i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i>, strain MSLB 1088.</p>	SC	1	1	0	lethargy, injection site pain, vomiting, ataxia, nystagmus, hypersensitivity reaction	≤ 2 mins
<p><i>Canine distemper virus</i>, strain CDV Bio 11/A, <i>Canine adenovirus</i> Type 2, strain CAV-2</p>						

<p><i>Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15.</i> <i>Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i></p>	SC	1	1	0	allergic reaction, facial swelling, swelling NOS, preputial swelling, reddening of the skin, skin warmth	≤ 30 mins
<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15.</i> <i>Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa</i></p>	SC	1	1	0	ataxia, disorientation, unresponsive to stimuli	≤ 30 mins

<i>serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i>						
<i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i>	SC	1	1	0	generalised weakness, bradycardia, cardiac arrest	≤ 30 mins
<i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15.</i>	SC	1	1	0	collapse	unknown

<p><i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup Canicola serovar Canicola, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup Australis serovar Bratislava, strain MSLB 1088.</p>						
<p><i>Canine distemper virus</i>, strain CDV Bio 11/A, <i>Canine adenovirus</i> Type 2, strain CAV-2 Bio 13, <i>Canine parvovirus</i> Type 2b, strain CPV-2b Bio 12/B, <i>Canine parainfluenza</i> Type 2 virus, strain CPiV-2 Bio 15. <i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup Canicola serovar Canicola, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup Australis serovar Bratislava, strain MSLB 1088.</p>	SC	1	1	0	injection site reaction NOS	≤ 24 hr

<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088.</i></p> <p><i>Inactivated Leptospira canicola, Leptospira icterohaemorrhagiae.</i></p>	<p>SC</p> <p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>circulatory collapse, pallor, vomiting, inappropriate urination</p>	<p>≤ 30 mins</p>
<p><i>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain</i></p>	<p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>injection site pain, circulatory collapse, pale mucous membrane, bradycardia, vomiting</p>	<p>≤ 2 mins</p>

<p>CPIV-2 Bio 15. <i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira</i> <i>kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i>, strain MSLB 1088, <i>Rabies virus</i>, strain SAD Vnukovo-32.</p>						
<p><i>Canine distemper virus</i>, strain CDV Bio 11/A, <i>Canine adenovirus</i> Type 2, strain CAV-2 Bio 13, <i>Canine</i> <i>parvovirus</i> Type 2b, strain CPV-2b Bio 12/B, <i>Canine parainfluenza</i> Type 2 virus, strain CPIV-2 Bio 15. <i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i>, strain MSLB 1090, <i>Leptospira</i> <i>kirschneri</i> serogroup <i>Grippotyphosa</i> serovar <i>Grippotyphosa</i>, strain MSLB 1091,</p>	<p>SC</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>collapse, unconscious, urinary incontinence, loss of bowel control, dyspnoea, uncoded sign (pulse undetectable)</p>	<p>≤ 30 mins</p>

<p><i>Leptospira interrogans</i> serogroup Australis serovar Bratislava, strain MSLB 1088, Rabies virus, strain SAD Vnukovo-32.</p>						
<p>Canine distemper virus, strain CDV Bio 11/A, Canine adenovirus Type 2, strain CAV-2 Bio 13, Canine parvovirus Type 2b, strain CPV-2b Bio 12/B, Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15. <i>Leptospira interrogans</i> serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089, <i>Leptospira interrogans</i> serogroup Canicola serovar Canicola, strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091, <i>Leptospira interrogans</i> serogroup Australis serovar Bratislava, strain MSLB 1088.</p> <p>$\geq 10^{8.0}$ and $\leq 10^{9.7}$ cfu¹ of live <i>Bordetella bronchiseptica</i> bacteria strain B-C2 and $\geq 10^{3.0}$ and $\leq 10^{5.8}$ TCID₅₀² of live canine parainfluenza virus strain Cornell.</p>	<p>SC</p> <p>intranasal</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>vomiting, unsteady gait, falling, lethargy, dull, panting</p>	<p>≤ 30 mins</p>

<i>Leptospira interrogans</i> serogroup <i>Icterohaemorrhagiae</i> serovar <i>Icterohaemorrhagiae</i> strain MSLB 1089, <i>Leptospira interrogans</i> serogroup <i>Canicola</i> serovar <i>Canicola</i> , strain MSLB 1090, <i>Leptospira kirschneri</i> serogroup <i>Grippityphosa</i> serovar <i>Grippityphosa</i> , strain MSLB 1091, <i>Leptospira interrogans</i> serogroup <i>Australis</i> serovar <i>Bratislava</i> , strain MSLB 1088.	SC	1	1	0	vomiting, off colour	≤ 6 hr
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Table 5C: Ovine Reports

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
<i>C. perfringens</i> type B + C (β) toxoid, <i>C. perfringens</i> type D (e) toxoid, <i>C. chauvoei</i> whole culture, <i>C. novyi</i> type B anaculture, <i>C.</i> <i>septicum</i> toxoid, <i>C. tetani</i> toxoid, <i>C.</i> <i>haemolyticum</i> anaculture.	SC	74	21	3	death, injection site swelling, injection site skin discolouration, lameness, inappetence, injection site abscess, myositis	≤ 7 days
<i>C. perfringens</i> type B + C (β) toxoid, <i>C. perfringens</i> type D (e) toxoid, <i>C. chauvoei</i> whole culture, <i>C. novyi</i> type	SC	47	30	3	death, lameness, injection site infection, injection site oedema	≤ 7 days

B anaculture, C. septicum toxoid, C. tetani toxoid, C. haemolyticum anaculture.						
<i>Clostridium perfringens beta toxoid, Clostridium perfringens epsilon toxoid, Clostridium septicum toxoid, Clostridium tetani toxoid, Clostridium novyi toxoid, Clostridium chauvoei cells and equivalent toxoid of strains 655,656,657,658, 1048, Formalin killed cells of Mannheimia haemolytica serotypes: A1, A2, A6, A7, A9, Formalin killed cells of Pasteurella trehalosi serotypes: T3, T4, T10, T15.</i>	SC	60	3	2	facial swelling, ataxia, anaphylaxis, death	≤ 6 hr
<i>Clostridium perfringens beta toxoid, Clostridium perfringens epsilon toxoid, Clostridium septicum toxoid, Clostridium tetani toxoid, Clostridium novyi toxoid, Clostridium chauvoei cells and equivalent toxoid of strains 655,656,657,658, 1048, Formalin killed cells of Mannheimia haemolytica serotypes: A1, A2, A6, A7, A9, Formalin killed cells of</i>	SC	40	20	3	injection site swelling, death, lameness	≤ 24 hr

<i>Pasteurella trehalosi</i> serotypes: T3, T4, T10, T15.						
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Table 5D: Feline Reports

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
<i>Live attenuated feline enteritis (panleucopenia) virus (FPV), Snow Leopard strain, Live attenuated feline rhinotracheitis virus (FVR), strain FVRm, live attenuated Calicivirus, strain F9.</i>	SC	1	1	0	behavioural disorder NOS, Pain NOS, Hyperthermia	≤ 7 days
<i>Live attenuated feline calicivirus, strain F9, live attenuated feline herpes virus type 1, strain G2620A, live attenuated feline panleucopenia virus, strain MW-1.</i>	SC	1	1	0	off colour, leucocytosis, metastatic neoplasia	≤ 24 hr
<i>Live attenuated feline calicivirus, strain F9, live attenuated feline herpes virus type 1, strain G2620A, live attenuated feline panleucopenia virus, strain MW-1.</i>	SC	1	1	0	anaphylactic type reaction, tachycardia, tachypnoea, vomiting, dull, hypersalivation	≤ 30 mins

<i>Live attenuated feline calicivirus, strain F9, live attenuated feline herpes virus type 1, strain G2620A, live attenuated feline panleucopenia virus, strain MW-1.</i>	SC	1	1	0	weakness, anorexia, pyrexia, conjunctivitis, weight loss, lethargy	≤ 24 hr
<i>Attenuated feline rhinotracheitis herpesvirus (FHV F2 strain, inactivated feline calicivirus (FCV 431 and G1 strains), attenuated feline panleucopenia virus (PLI IV).</i>	SC	1	1	0	tachycardia, decreased cholesterol (total), stiffness limb, abnormal posture, depression, off colour, lethargy, inappetence, aggression, pyrexia, poor coat condition, anxiety, not drinking, enlarged lymph nodes	≤ 7 days
<i>Attenuated feline rhinotracheitis herpesvirus (FHV F2 strain, inactivated feline calicivirus (FCV 431 and G1 strains), attenuated feline panleucopenia virus (PLI IV).</i>	unknown	1	1	1	distress, vocalisation, cyanosis, death by euthanasia	≤ 30 mins
<i>Attenuated feline rhinotracheitis herpesvirus (FHV F2 strain, inactivated feline calicivirus (FCV 431 and G1 strains), attenuated feline panleucopenia virus (PLI IV).</i>	SC	1	1	0	vomiting	≤ 30 mins

<i>Attenuated feline rhinotracheitis herpesvirus (FHV F2 strain, inactivated feline calicivirus (FCV 431 and G1 strains), attenuated feline panleucopenia virus (PLI IV).</i>	SC	1	1	0	hypersensitivity NOS, anaphylaxis, malaise, lethargy, balance problem, distension of abdomen, laboured breathing, increased respiratory rate, injection site pain, injection site reaction NOS	≤ 6 hr
<i>Attenuated feline rhinotracheitis herpesvirus (FHV F2 strain, inactivated feline calicivirus (FCV 431 and G1 strains), attenuated feline panleucopenia virus (PLI IV).</i>	SC	1	1	unknown	inappetence, pyrexia	≤ 14 days

Table 5E: Equine Reports

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
<i>Inactivated equine influenza virus, strains: A/equi-1/Prague/56, A/equi-2/Suffolk/89 (European type), A/equi-2/Newmarket/1/93 (American type), Tetanus toxoid.</i>	SC	1	1	0	injection site abscess	≤ 7 days
<i>Inactivated EHV type 1, strain 438/77,</i>	IM	14	4	0	pyrexia, Injection site abscess, neurological signs NOS	≤ 24 hr

<i>Inactivated EHV type 4, strain 405/76.</i>						
<i>Influenza A/eq/Ohio/03 [H₃N₂] recombinant Canarypox virus (vCP2242), Influenza A/eq/Richmond/1/07 [H₃N₂] recombinant Canarypox virus (vCP3011, Clostridium tetani toxoid.</i>	IM	10	1	0	pyrexia, anorexia, muscle pain, injection site stiffness	≤ 24 hr

Table 5F: Avian Report

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
<i>Inactivated Newcastle Disease Virus, strain La Sota.</i>	SC	200	15	2	lethargy, incoordination, unexplained death	≤ 24 hr

Table 5G: Rabbit Report

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical signs	Speed of onset
<i>Live myxoma vectored RHD virus strain 009.</i>	SC	1	1	1	constipation, anorexia, digestive tract stasis, pain NOS, hypothermia, death	≤ 24 hr