Suspected Adverse Event Reports to Veterinary Medicinal Products received by the HPRA 2019.

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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 the organisation responsible for the regulation of health products, including veterinary medicinal products (VMPs). Our role is to protect and enhance public and animal health. Part of our remit is the ongoing monitoring of the quality, safety and efficacy of authorised VMPs (a process known as pharmacovigilance), including products that have been authorised nationally or centrally (following the opinion of the European Medicines Agency (EMA)). 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 (i.e. where a product is not used according to its authorised summary of product characteristics (SPC))
- 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 pharmaceutical companies that have been granted approval to market a VMP within the European Union (either by an EU Member State or the EMA). MAHs are required by legislation to report all serious SAEs occurring in Ireland to the HPRA within 15 days. Veterinary practitioners and other healthcare professionals as well as animal owners can also report directly. The HPRA and relevant MAHs collate and evaluate the SAE reports. In the event that a safety issue is identified through this surveillance, we can take appropriate steps to reduce the level of any associated risk e.g. by adding new warnings.

Reports of SAEs are assessed for any association between the event and the product(s) administered to the animal(s), using the methodology shown in Table 3.

SPC (Summary of Product Characteristics): A document providing officially approved information on a VMP

The minimum information required for an SAE report is 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 Practitioner/Veterinary Nurse, Pharmacist, Licensed Merchant, animal owner)
- animal/human details: species, age, sex
- the name and marketing authorisation number of the product in question
- details of the adverse event

In addition to the above, 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.

The HPRA received 25 invalid SAE reports in 2019. The reasons for this include:

- duplicates of existing reports
- reports submitted from countries of origin other than Ireland
- inadequate minimum information
- reports nullified by MAHs.

2. National Pharmacovigilance Surveillance

The HPRA received a total of 322 valid national SAE reports in 2019. These reports involved a range of animals as presented in Table 2. Eleven reports concerned SARs in humans following exposure to a VMP.

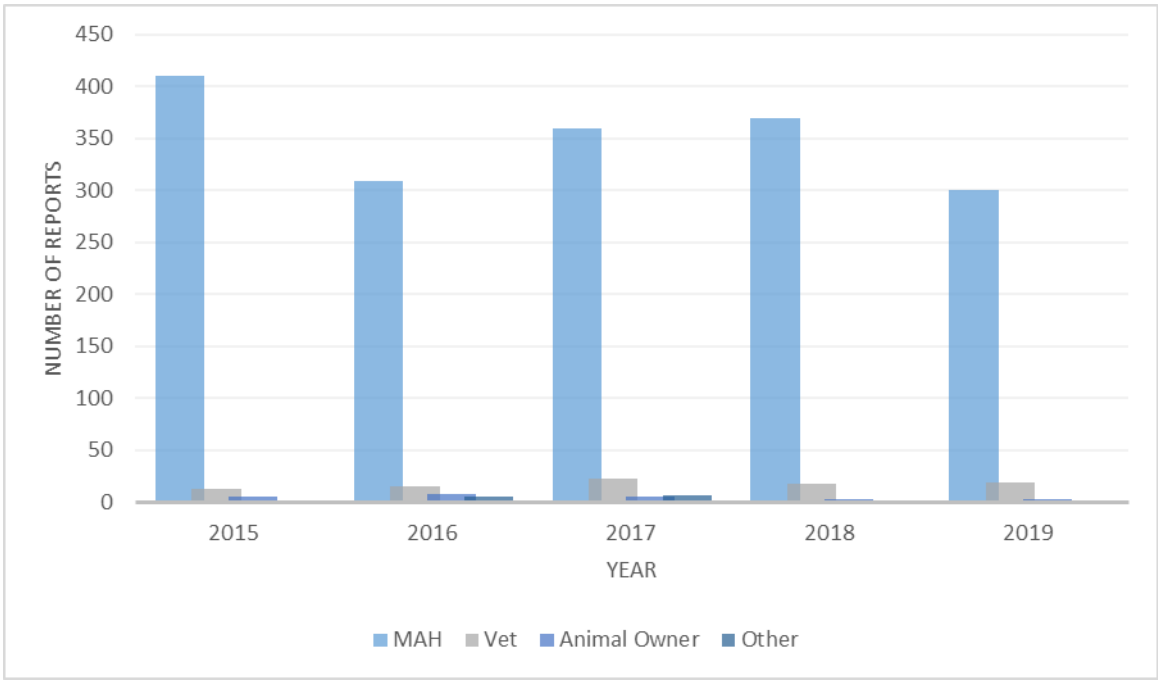
Table 2. Overview of reports received in 2019

Species	Total number of reports	Total number of reacting animals
Food producing animals		
bovine	134	2504
ovine	32	434
equine	6	14
bee	2	*4 hives
avian	2	8
porcine	5	2282
fish	1	378
Companion animals		
canine	101	120
feline	25	28
rabbit	3	3
Other		
human	11	11
Total	**322**	**5782**

*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 HPRA between 2015 and 2019.

Figure 1: Source of SAE reports from 2015 to 2019

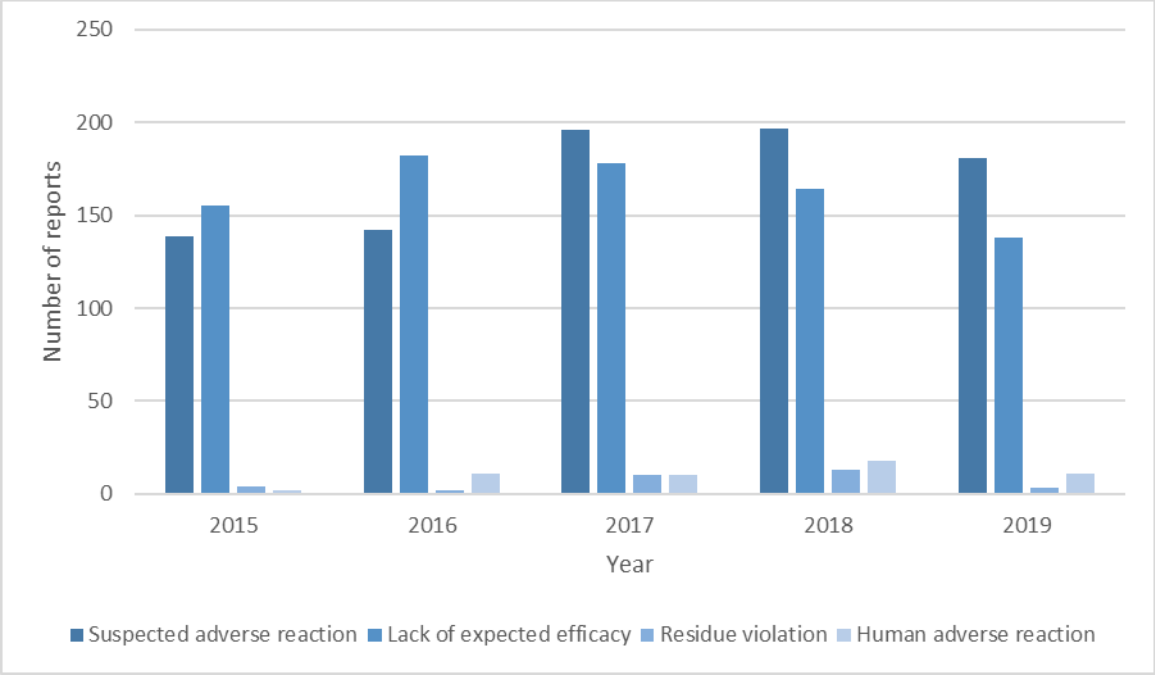


Of the 322 SAE reports received in 2019, 146 involved solely pharmaceutical products, 157 involved solely immunological products and 19 reports related to the use of both pharmaceutical and immunological products concurrently. One hundred and sixty-four reports involved SARs or serious SARs (SSAR) in animals, 138 reports involved suspected LEE, six reports involved combined SAR/LEE and three reports related to violation of an approved residue limit. Eleven reports related to SAEs in humans.

*A vaccine in an example of an **immunological** product*
*An anti-inflammatory drug is an example of a **pharmaceutical** product*

Figure 2 compares the types of reports received from 2015 to 2019.

Figure 2: Number of SAE reports by category received from 2015 to 2019



2.1 Reports of adverse reactions

An adverse event report may relate to the administration of more than one VMP. 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 therefore been counted more than once.

One hundred and sixty-four SAR/SSAR reports relating to animals were received. For a report to be considered as a serious suspected adverse reaction it must fulfil certain criteria including but not limited to:

- results in death, or
- is life-threatening, or
- results in a persistent or significant disability or incapacity or a congenital anomaly or birth defect.

These reports related to the following species: dogs (91 reports), cattle (33 reports), cats (23 reports), sheep (8 reports), horses (3 reports), rabbits (2 reports), bees (two reports), pigs (one report) and fish (1 report).

Of these reports, 101 related to pharmaceutical products. Product involvement was considered to be 'probable' (causality A) in 30 reports, 'possible' (causality B) in 33 reports, unclassifiable/unassessable (causality O1, O) in 38 reports and 'unlikely' (causality N) in two reports.

Forty-nine reports related to immunological products. Product involvement was considered to be 'probable' (causality A) in 21 reports, 'possible' (causality B) in 15 reports, unclassifiable/unassessable (causality O1, O) in 11 reports and 'unlikely' (causality N) in three reports.

Fourteen reports detailed concomitant pharmaceutical and immunological product administration. Product involvement was considered 'possible' in nine reports (causality B), in eight reports insufficient information was provided to assign a definitive association (causality O1, O), while in four reports, product involvement was considered 'unlikely' (causality N).

Eleven SAE reports of human exposure to VMPs were received during the reporting period. Those administering VMPs are reminded to pay particular attention to any special precautions for the use of individual products as detailed in the relevant product information (SPC) published on the HPRA website and the package labelling/leaflet accompanying the product. MAHs are obliged to report any symptomatic human exposure report to the relevant National Competent Authority within 15 days of receipt of the report.

2.2 Reports of lack of expected efficacy

The HPRA received 138 reports relating solely to LEE in 2019.

Of these reports, 33 related pharmaceutical products and involved cattle (26 reports), sheep (3 reports), dogs (3 reports) and cats (1 report). Product involvement was considered to be 'possible' (causality B) in seven of the 33 reports. Product involvement was not considered 'probable' (causality A) in any report. Five reports involved off-label use of one or more pharmaceuticals.

One hundred LEE reports involving immunological products were received, where the product was suspected by the reporter to have failed to induce protective immunity. The reports concerned cattle (65 reports), sheep (20 reports), dogs (5 reports), pigs (4 reports), horses (3 reports), chickens (1 reports), avian (1 report), and rabbits (1 report). In 21 reports, product involvement was classified as either 'probable' (causality A) or 'possible' (causality B), while the remainder were assessed as 'unclassifiable/unassessable' (causality O1, O) or 'unlikely' (causality N). Twenty-six 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, five LEE reports involved both pharmaceutical and immunological products. In two reports, product involvement was classified as either 'probable' (causality A) or 'possible' (causality B). No combined reports involved off-label product use.

Where it is not specified within an adverse event report whether the product use was according to its authorised SPC, it is assumed that the product has been used in accordance with its SPC i.e. as recommended.

2.3 Causality assessment

Of the 170 SAR, SSAR and combined SAR/LEE reports received in 2019, the involvement of a reported VMP with the observed reaction was considered to have been 'probable' (causality A) or 'possible' (causality B) in 111 reports. In 60 reports, there was insufficient/inconclusive information (causality O1/O) available to assign definitive causality and in 10 reports it was considered unlikely (causality N) that a reported VMP was responsible for the observed reaction. Where there is a difference in the causality assessment assigned to the report by the MAH and the Competent Authority to whom the report was sent, the causality assignment of the Competent Authority takes precedence and is the official assessment noted in the central European database.

A line listing of SAE reports originating from Ireland in 2019, organised by active substance, assigned causality 'A' (probable) or causality 'B' (possible) is included in Table 4 of the version of this report that is published on the HPRA website (www.hpra.ie).

3. European Pharmacovigilance Issues

Each year, the Committee for Medicinal Products for Veterinary Use (CVMP: an expert scientific advisory committee of the European Medicines Agency) reviews safety information for centrally authorised VMPs (CAPs). This is done by means of monitoring reports logged to the central EU database, EudraVigilance Veterinary (EVVET) as well as through the assessment of Periodic Safety Update Reports (PSURs) compiled by MAHs.

Periodic Safety Update Report (PSUR): A report compiled by an MAH detailing the post-authorisation safety and efficacy experience of a particular VMP over a specified period of time.

According to the EMA Veterinary Pharmacovigilance 2019 Annual Bulletin, the trend towards a year-on-year increase in the number of adverse events reported to EVVET continued in 2019. This reflects the growing number of centrally-authorised medicines. Another factor is an increase in reporting from countries outside the EU/EEA (Third Countries).

As in previous years, the majority of SAE reports relating to CAPs concerned companion animals, with cat and dog SAEs accounting for 87% of reports received. Reports relating to food producing animals remains comparatively low. An increased focus to improve communication with Veterinary Practitioners and the general public is a priority, in order to prepare for the implementation of Regulation 2019/6.

Further information concerning the changes made to individual product information for CAPs is published in the Veterinary Pharmacovigilance 2019 Annual bulletin on the EMA website (link here).

3.1 Regulatory action case study – recommendation on the use of live attenuated PRRSV vaccines

In December 2019, the EMA published a press release concerning a recombination event between two live attenuated Porcine Reproductive and Respiratory Syndrome virus (PRRSV) type-1 vaccine strains leading to a recombinant strain that has been associated with clinical signs of disease in PRRS-naïve herds (of pigs) in Denmark. Recombination between strains of PRRS virus is a recognised phenomenon which has been reported previously in the scientific literature.

The CVMP made a number of recommendations concerning the use of live attenuated PRRSV vaccines, including:

- in order to limit the potential risk of recombination between vaccine strains, the simultaneous or consecutive use of different live attenuated PRRSV vaccines should be avoided as much as possible (while continuing the protect animal health)
- recommending increased monitoring of any SAEs relating to clinical signs associated with PRRS, including the

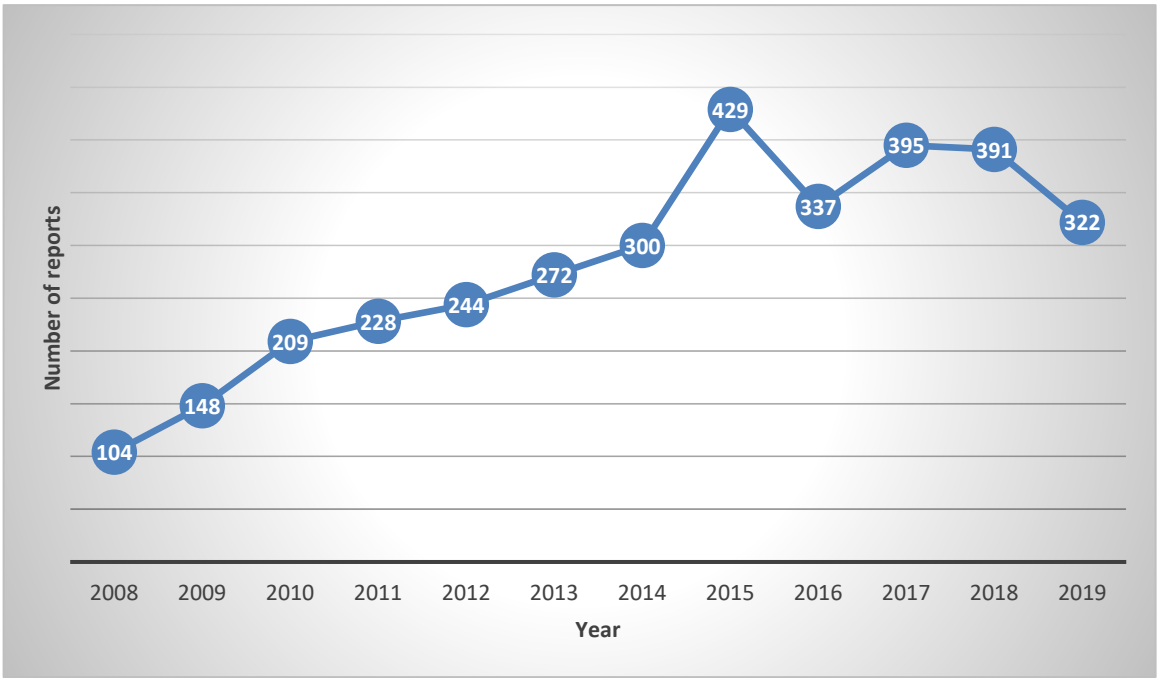
occurrence of such signs in previously vaccinated pig herds

- highlighting that sequencing data indicating recombination between vaccine strains or between vaccine strains and wild types must be regarded as pharmacovigilance data and as such, should be reported to the relevant National Competent Authority (https://www.ema.europa.eu/en/news/committee-medicinal-products-veterinary-use-cvmp-meeting-3-5-december-2019) .

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

4. Conclusion

Figure 3: Total number of SAE Reports to the HPRA from 2008-2019



There remains a general trend of increasing numbers of SAE reports since 2008 (Figure 3), which likely reflects a greater public awareness of the importance of reporting rather than an absolute increase in the number of adverse events occurring. The HPRA is encouraged by this trend 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 (19 SAE reports were submitted by veterinarians directly to the HPRA in 2019, equating to 5.9% of all reports received). 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; reports may be submitted 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 above) 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. 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.

The HPRA website now includes a webpage which contains all Annual Pharmacovigilance reports from 2014 to present, and is available here.

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

Causality 'A'	All of the following minimum criteria must be complied with: • 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)

References

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Table 4: 2019 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.
IM= Intramuscular, SC= Subcutaneous, IV= Intravenous , NOS= not otherwise specified

Table 4a: Bovine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
calcium gluconate + boric acid + magnesium hypophosphite hexahydrate	IV	1	1	1	Death	≤ 2 mins
cloprostenol	IM	5	2	0	Peritonitis	≤14 days
deltamethrin	Topical	240	17	0	Application site lesion, application site erythema, application site bleeding, application site alopecia, application site scab, application site hair coat discolouration	≤7 days
ivermectin + closantel	topical	46	1	0	Abnormal vision	≤7 days

ivermectin + closantel	topical	50	1	0	Dull, incoordination, blindness	≤24 hrs

ivermectin + closantel	topical	17	1	0	Abnormal vision	≤ 7 days
levamisole hydrochloride + oxyclozanide	oral	15	4	1	Downer animal, anorexia, dullness, depression, death by euthanasia	≤24 hrs
levamisole hydrochloride + oxyclozanide	oral	24	24	1	Death, diarrhoea, anorexia	≤24 hrs
levamisole hydrochloride + oxyclozanide	oral	20	6	2	Staggering, lateral recumbency, paddling, recumbency, depression, small liver, death	≤ 24 hrs
levamisole hydrochloride + oxyclozanide	oral	1	1	0	Recumbency, generalised weakness, bloody diarrhoea	≤ 48 hrs
moxidectin	SC	64	1	1	Downer animal, ataxia, shaking, coma	≤ 24 hrs

moxidectin	SC	15	1	0	Ataxia, blindness, depression	≤ 24 hrs
moxidectin	SC	60	30	0	Depression, ataxia, drooling, blindness	≤ 24 hrs
moxidectin	SC	34	34	8	Depression, ataxia, drooling, coma, death by euthanasia, death, hind limb paralysis	≤ 24 hrs
moxidectin	SC	45	3	1	Death by euthanasia, ataxia, coma, depression	≤ 24 hrs
moxdectin	SC	600	50	2	Death, LEE	> 30 days
oxytetracycline	IM	12	4	0	Application site reaction NOS	≤ 24 hrs
oxytetracycline	IM	1	1	0	Lateral recumbency, facial swelling	≤ 30 mins

Table 4b: Ovine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
clostantel	oral	120	40	0	Blindness, impaired vision, bumping into walls	≤ 7 days
levamisole hydrochloride + oxyclozanide	oral	150	22	1	Facial swelling, lethargy, anorexia, pinnal oedema, droopy ear, recumbency, death by euthanasia, pineal necrosis	≤ 48 hrs
diazinon (dimpylate)	topical	140	4	0	Recumbency, paresis, urinary incontinence	≤ 24 hrs
ivermectin + clostantel	SC	500	4	2	Dull, depression, staggering, lateral neck deviation, head tilt - neurological disorder, found dead	≤ 24 hrs
moxidectin	SC	49	1	1	Death	> 30 days

Table 4c: Porcine Report

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Iron (III) 200.0 (as gleptoferron 532.6 mg)	IM	12	2	2	Anaphylaxis, death	≤2 mins

Table 4d: Equine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
moxidectin + praziquantel	oral	2	2	0	Somnolence, central nervous system depression, temporary blindness	≤ 24 hrs
xylazine base	SC	1	1	0	Behavioural disorder NOS, sedation prolonged, injection site inflammation, skin harmorrhage NOS	≤ 24 hrs

Table 4e: Bee Reports

Active substance	Route(s) of administratio	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
thymol	in hive	1 colony	1 colony	0 colonies	Decreased egg laying (bees), brood removal	≤ 30 days
thymol	in-hive	3 colonies	3 colonies	1 colony	Decreased egg laying (bees), queen bee death	≤ 14 days

Table 4f: Canine Reports

Active substance(s)	Routes of Administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
alfoxolaner + milbemycin oxime	oral	1	1	0	Seizure NOS, tremor	≤ 6 hrs
carprofen	oral	1	1	0	Vomiting, blood in faeces, lethargy, polydipsia, decreased appetite, elevated liver enzymes	≤ 24 hrs
cimicoxib	oral	1	1	0	Polydipsia, polyuria, other abnormal test result NOS,	≤ 48 hrs
clostantel	oral	1	1	0	Blindness	≤ 7 days
dexamethasone sodium phosphate + dexamethasone phenylpropionate **amoxicillin**	SC SC	1	1	0	Collapse NOS, seizure NOS, dyspnoea	≤ 30 mins

dexamethasone sodium phosphate + dexamethasone phenylpropionate	SC	1	1	0	Lethargy, vomiting, limpness, pale mucous membrane, swollen face, eyelid oedema, urticaria, itchy skin	≤ 30 mins
firocoxib	oral	1	1	1	Hyperproteinaemia, elevated globulins, hyperphosphataemia, death, diarrhoea, unusual stool colour, dull, collapse NOS, not eating, acute renal failure, hyperglycaemia, elevated creatinine, elevated blood urea nitrogen (BUN)	≤ 7 days
fluralaner	oral	1	1	0	Rigidity of limbs, vomiting, foaming at the mouth, anaphylaxis, haemoconcentration, tonic-clonic seizure, loss of consciousness	≤ 12 hrs
fluralaner	oral	1	1	0	Hind limb ataxia, partial anorexia, vomiting, vomiting, twitching, elevated amylase, low serum alkaline phosphatase (SAP), increased seizure frequency, falling, seizure NOS	≤ 24 hrs

fluralaner	oral	1	1	0	Lymphocytosis, decreased packed cell volume (PCV), reluctant to move, enlarged lymph node (localised lymph node (localised), other abnormal test result NOS, depression, anorexia, abdominal discomfort, regenerative anaemia, ataxia, sternoabdominal recumbency, paddling, generalised weakness	≤ 24 hrs
fluralaner **milbemycin oxime + praziquantel**	oral oral	1	1	0	Seizure NOS, collapse of leg, shaking, foaming at the mouth, decreased cholesterol (total)	≤ 7 days
imidacloprid + moxidectin	topical	1	1	0	Agitation, excitation	≤ 30 mins
imidacloprid + moxidectin	topical	1	1	0	Excitation, Aggression	≤ 2 mins
imidacloprid + moxidectin	topical	1	1	0	Vomiting, hyperaesthesia, incoordination, blindness	≤ 24 hrs
insulin	SC	1	1	0	Lymphopenia, hypoglycaemia, lack of efficacy, diarrhoea, thrombocytosis	> 30 days

insulin	SC	1	1	0	LEE, hypoglycaemia	> 30 days
ivermectin + closantel	topical	1	1	0	Dullness, inappetence, walking difficulty, hypermetria	≤ 24 hrs
lokivetmab	SC	1	1	0	Ataxia, lethargy	≤ 24 hrs
lokivetmab	SC	1	1	0	Vomiting, pyrexia	> 30 days
marbofloxacin + clotrimazole + dexamethasone acetate	topical	1	1	0	Deafness	≤ 14 days
meloxicam	oral	4	4	0	Diarrhoea, bloody diarrhoea, vomiting	≤ 24 hrs
metronidazole	oral	1	1	0	Ataxia, sedation	≤ 30 days
miconazole nitrate + prednisolone acetate + polymixin B sulfate	topical	1	1	0	Deafness	≤ 48 hrs

nitroxynil	Unknown – possibly through laced bait	1	1	1	Death, NT - abnormal necropsy finding NOS	≤ 24 hrs
nitroxynil	oral	30	7	1	Death, increased respiratory rate, agitation, hyperthermia	≤ 6 hrs
oclacitinib maleate	oral	1	1	0	Generalised weakness, decreased activity, vomiting, dermatitis	≤ 48 hrs
orbifloxacin + mometasone furoate + posaconazole	topical	1	1	0	Deafness	≤ 14 days
prmethrin technical cis/trans ratio 25:75 + neomycin + nystatin + triamcinolone acetonide	topical	1	1	0	Deafness	≤ 7 days
pyriprole	topical	1	1	0	Leucocytosis, abnormal test result, anorexia, lethargy, enlarged liver, gall bladder inflammation, immune mediated haemolytic anaemia, elevated liver enzymes, haematuria	≤ 14 days

sarolaner	oral	1	1	0	Vomiting, diarrhoea, swollen joint, fever	≤ 7 days
sarolaner	oral	1	1	0	Petit mal epilepsy, collapse NOS	≤ 24 hrs

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	1	Elevated blood urea nitrogen (BUN), elevated creatinine, malaise, death by euthanasia	> 30 days
carprofen	oral	1	1	0	Vomiting, dehydration, elevated blood urea nitrogen (BUN)	unknown
cefovecin	SC	1	1	1	Death, dyspnoea, circulatory shock, pulmonary oedema	≤ 1 hr

fipronil + s-methoprene + eprinomectin + praziquantel	topical	1	1	1	Death by euthanasia, respiratory distress, anxiety, wide-base stance, nasal discharge, ataxia, lateral recumbency, seizure NOS	≤ 24 hrs
fipronil + s-methoprene + eprinomectin + praziquantel	topical	1	1	0	Vomiting	≤ 6 hrs
fipronil + s-Methoprene + eprinomectin + praziquantel	topical	1	1	0	Vomiting, anorexia	≤ 6hrs
fluralaner + moxidectin	topical	2	2	0	Application site alopecia, application site erythema and application site pruritus	≤ 48 hrs
imidacloprid + moxidectin	topical	2	2	0	Application site hair loss, application site reddening, application site irritation, moist dermatitis	≤ 7 days

milbemycin oxime + praziquantel	oral	1	1	0	Lethargy, collapse NOS, impaired consciousness, tremor, ataxia	≤ 6 hrs
selamectin	topical	1	1	0	Application site hair loss, application site reddening	≤ 24 hrs

Table 5: 2019 adverse reaction reports involving immunological products, in which product association was assigned causality 'A' or 'B' (listed by active substance (antigen))

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

* IM= Intramuscular, SC= Subcutaneous, IV= Intravenous, IP= Intraperitoneal, NOS= not otherwise specified

Table 5a: Bovine Reports

Active substance (Antigen)	Route(s) of administratio	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Bovine Herpes Virus type 1 (BHV-1), strain Difivac (gE-negative), min. 105.0 CCID50 modified live (attenuated) virus max. 107.0 CCID50	IM	30	2	0	Coughing up blood, dyspnoea, hyperpnoea, tachypnoea	≤ 30 mins

Table 5b: Ovine Reports

Active substance (Antigen)	Route (s) of adminis	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
C. perfringens type A (α) toxoid ≥ 0.5 U# *C. perfringens type B & C (β) toxoid ≥ 18.2 IU** *C. perfringens type D (ε) toxoid ≥ 5.3 IU** *C. chauvoeiwhole culture ≥ 90% protection*** *C. novyi toxoid ≥ 3.8 IU** *C. septicum toxoid ≥ 4.6 IU** *C. tetani toxoid ≥ 4.9 IU** *C. sordellii toxoid ≥ 4.4 U1* *C. haemolyticum toxoid ≥ 17.4 U#*	SC	500	4	4	Sudden death, LEE, injection site lump	≤ 7 days

Clostridium perfringens beta toxoid inducing 10 IU *Clostridium perfringens epsilon toxoid inducing 5 IU* *Clostridium septicum toxoid inducing 2.5 IU* *Clostridium tetani toxoid inducing 2.5IU* *Clostridium novyi toxoid inducing 3.5 IU* *Clostridium chauvoei cells and equivalent toxoid of strains 655,656,657,658, 1048.* *inducing 0.5 guinea pig PD90* *Formalin killed cells of Mannheimia haemolytica serotypes:* *A1 5 x 108 cells* *A2 5 x 108 cells* *A6 5 x 108 cells* *A7 5 x 108 cells* *A9 5 x 108 cells* *Formalin killed cells of Pasteurella trehalosi serotypes:* *T3 5 x 108 cells* *T4 5 x 108 cells* *T10 5 x 108 cells* *T15 5 x 108 cells*	SC	80	80	8	Injection site lump, injection site abscess, death	≤ 24 hrs

Clostridium perfringens beta toxoid inducing 10 IU *Clostridium perfringens epsilon toxoid inducing 5 IU* *Clostridium septicum toxoid inducing 2.5 IU* *Clostridium tetani toxoid inducing 2.5IU* *Clostridium novyi toxoid inducing 3.5 IU* *Clostridium chauvoei cells and equivalent toxoid of strains 655,656,657,658, 1048.* *inducing 0.5 guinea pig PD90* *Formalin killed cells of Mannheimia haemolytica serotypes:* *A1 5 x 108 cells* *A2 5 x 108 cells* *A6 5 x 108 cells* *A7 5 x 108 cells* *A9 5 x 108 cells* *Formalin killed cells of Pasteurella trehalosi serotypes:* *T3 5 x 108 cells* *T4 5 x 108 cells* *T10 5 x 108 cells* *T15 5 x 108 cells*	SC	85	50	1	Injection site abscess, injection site lesion, injection site reaction NOS, injection site stiffness, lameness, injection site lump, local swelling (not application site), death	≤ 7 days

Table 5c: Fish Report

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Formaldehyde inactivated culture of: Salmon Pancreas Disease Virus (SPDV) strain AL V405 RPSend a≥ 80 %	IP	6300	378	0	Fish body deformity	unknown

Table 5d: Canine reports

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
*Canine distemper virus, strain Onderstepoort not less than 104.0 TCID50** *Canine adenovirus 2, strain Manhattan LPV3 not less than 104.0 TCID50** *Canine parvovirus, strain 154 not less than 107.0 TCID50** *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U1* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1*	SC					
*Canine distemper virus, strain Onderstepoort not less than 104.0 TCID50** *Canine adenovirus 2, strain Manhattan LPV3 not less than 104.0 TCID50** *Canine parvovirus, strain 154 not less than 107.0 TCID50** *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U1* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1*	SC	1	1	0	Swollen face, tachycardia, dull, anaphylaxis	≤ 1 hr
≥108.0 and ≤109.7cfu1 of live Bordetella bronchiseptica bacteria strain B-C2 and ≥103.0 and ≤105.8 TCID50 2 of live canine parainfluenza virus strain Cornell.	Intranasal					

*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U1* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1*	SC SC	1	1	0	Vomiting, diarrhoea, breathing difficulty, anaphylaxis	≤ 6 hrs
*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000)*	SC	1	1	0	Lymphocytosis, decreased packed cell volume (PCV), reluctant to move, enlarged lymph node (localised lymph node (localised), other abnormal test result NOS, depression, anorexia,	≤ 24 hrs

3550–7100 U1 *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1*	SC				abdominal discomfort, regenerative anaemia, ataxia, sternoabdominal recumbency, paddling, generalised weakness	
*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U1* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1*	SC SC	7	2	1	Malaise, vomiting, death, lethargy, digestive tract disorder NOS	≤ 24 hrs

*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%* *Inactivated Leptospira canicola, at least 40 hamster protective doses and inactivated Leptospira icterohaemorrhagiae, at least 40 hamster protective doses*	SC SC	1	1	0	Swelling around eye, pain NOS, hypersensitivity reaction	≤6 hrs
*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U1* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1*	SC SC	1	1	1	Emesis, haemorrhagic diarrhoea, death, injection site reaction NOS, NT- intestinal intussusception	≤24 hrs

- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1						

*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%*	SC					
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U1* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1*	SC	1	1	0	Seizure NOS	≤ 30 mins
≥108.0 and ≤109.7cfu1 of live Bordetella bronchiseptica bacteria strain B-C2 and ≥103.0 and ≤105.8 TCID50 2 of live canine parainfluenza virus strain Cornell.	intranasal					

*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%* *Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test*	SC SC	1	1	0	Pyrexia, injection site abscess	≤ 14 days
*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50** **TCID50: Tissue culture infective dose 50%* *≥108.0 and ≤109.7cfu1 of live Bordetella bronchiseptica bacteria strain B-C2 and ≥103.0 and ≤105.8 TCID50 2 of live canine parainfluenza virus strain Cornell.* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U1* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U1* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U1* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U1*	SC intranasal SC	1	1	0	Lethargy, inappropriate defecation, injection site swelling, pyrexia, emesis (multiple), injection site pain, injection site abscess, abnormal cytology	≤ 12 hrs

Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Vomiting, restlessness, injection site scratching, respiratory distress, anaphylaxis	≤ 30 mins
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Vomiting, restlessness, injection site scratching, respiratory distress, anaphylaxis	≤ 30mins
Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Angiodoema, facial oedema, allergic oedma	≤ 30 mins

Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2* *CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0* *CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0* *CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Crying, injection site swelling	≤2 mins

Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Vomiting, lethargy, anaphylactic shock	≤ 1 hr
Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Anaphylaxis, dyspnoea, agitation, nasal discharge	≤ 6 hrs

Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2* *CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0* *CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0* *CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Anaphylaxis, lethargy, weakness, cyanosis, tachypnoea	≤ 2 mins

Freeze dried fraction: Vanguard DA2Pi Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50 Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50* Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50* Liquid fraction: Vanguard CPV-L Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses. *Cell culture infectious dose-50*	SC	1	1	0	Anaphylaxis, circulatory collapse, generalised weakness, lethargy, cyanosis	≤ 30 mins

Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2* *CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0* *CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0* *CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Agitation, facial swelling, anaphylaxis	≤ 1 hr

Freeze dried fraction: Vanguard DA2Pi Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50 Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50* Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50* Liquid fraction: Vanguard CPV-L Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses. *Cell culture infectious dose-50*	SC	1	1	0	Anaphylaxis, facial swelling, vomiting	≤ 6 hrs

Freeze dried fraction: Vanguard DA2Pi Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50 Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50* Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50* Liquid fraction: Vanguard CPV-L Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses. *Cell culture infectious dose-50*	SC	1	1	0	Pale mucous membrane, injection site irritation, lethargy, seizure NOS, anaphylaxis, facial oedema, vomiting, anaphylactic shock, generalised weakness, tachycardia	≤ 1 hr

Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Collapse NOS, hypothermia, hnypoglycaemia	≤ 48 hrs

Freeze dried fraction: Vanguard DA2Pi *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: 103.0 CCID50** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: 103.2 CCID50** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: 106.0 CCID50** *Liquid fraction: Vanguard CPV-L* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : 107.0 CCID50* Leptospira canicola (inactivated) at least 40 hamster protective doses Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Inappropriate urination, lethargy, increased yawning, tachycardia, pale mucous membrane, prolonged capillary refill time, tachypnoea	≤2 mins

Inactivated Leptospira canicola, at least 40 hamster protective doses and inactivated Leptospira icterohaemorrhagiae, at least 40 hamster protective doses.	SC					
Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A 103.1 TCID50* 105.1 TCID50* *Canine adenovirus Type 2, strain CAV-2 Bio 13 103.6 TCID50* 105.3 TCID50* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B 104.3 TCID50* 106.6 TCID50* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 103.1 TCID50* 105.1 TCID50* *Suspension (inactivated):* *Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089 ALR** titre ≥ 1:51* *Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090 ALR** titre ≥ 1:51* *Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 ALR** titre ≥ 1:40* *Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088 ALR** titre ≥ 1:51* ** Tissue culture infectious dose 50%.* *** Antibody micro agglutination-lytic reaction*	SC	1	1	0	Face and neck swelling, tachycardia, anaphylaxis	≤ 1 hr
≥108.0 and ≤109.7cfu1 of live Bordetella bronchiseptica bacteria strain B-C2 and ≥103.0 and ≤105.8 TCID50 2 of live canine parainfluenza virus strain Cornell.	intranasal					

*Canine distemper virus not less than 104.0 TCID50** *Canine adenovirus 2 not less than 104.0 TCID50** *Canine parvovirus not less than 107.0 TCID50** *Canine parainfluenzavirus not less than 105.5 TCID50**	SC	1	1	0	Circulatory collapse, weak pulse	≤ 30 mins
Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A 103.1 TCID50* 105.1 TCID50* *Canine adenovirus Type 2, strain CAV-2 Bio 13 103.6 TCID50* 105.3 TCID50* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B 104.3 TCID50* 106.6 TCID50* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 103.1 TCID50* 105.1 TCID50* *Suspension (inactivated): Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089 ALR** titre ≥ 1:51* *Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090 ALR** titre ≥ 1:51* *Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 ALR** titre ≥ 1:40* *Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088 ALR** titre ≥ 1:51* ** Tissue culture infectious dose 50%.* *** Antibody micro agglutination-lytic reaction*	SC	1	1	0	Vomiting	≤ 30 mins

Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A 103.1 TCID50* 105.1 TCID50* *Canine adenovirus Type 2, strain CAV-2 Bio 13 103.6 TCID50* 105.3 TCID50* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B 104.3 TCID50* 106.6 TCID50* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 103.1 TCID50* 105.1 TCID50* *Suspension (inactivated): Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089 ALR** titre ≥ 1:51* *Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090 ALR** titre ≥ 1:51* *Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 ALR** titre ≥ 1:40* *Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088 ALR** titre ≥ 1:51* ** Tissue culture infectious dose 50%.* *** Antibody micro agglutination-lytic reaction*	SC	1	1	0	Vomiting, involuntary defecation, hypersalivation, panting, drooling	≤ 30 mins

Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A 103.1 TCID50* 105.1 TCID50* *Canine adenovirus Type 2, strain CAV-2 Bio 13 103.6 TCID50* 105.3 TCID50* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B 104.3 TCID50* 106.6 TCID50* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 103.1 TCID50* 105.1 TCID50* *Suspension (inactivated): Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089 ALR** titre ≥ 1:51* *Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090 ALR** titre ≥ 1:51* *Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 ALR** titre ≥ 1:40* *Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088 ALR** titre ≥ 1:51* ** Tissue culture infectious dose 50%.* *** Antibody micro agglutination-lytic reaction*	SC	1	1	0	Anaphylaxis, circulatory collapse, inappropriate urination, involuntary defecation, tachypnoea, increased heart rate	≤ 7 days

Lyophilisate (live attenuated): *Minimum Maximum* *Canine distemper virus, strain CDV Bio 11/A 103.1 TCID50* 105.1 TCID50* *Canine adenovirus Type 2, strain CAV-2 Bio 13 103.6 TCID50* 105.3 TCID50* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B 104.3 TCID50* 106.6 TCID50* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 103.1 TCID50* 105.1 TCID50* *Suspension (inactivated):* *Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089 ALR** titre ≥ 1:51* *Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090 ALR** titre ≥ 1:51* *Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 ALR** titre ≥ 1:40* *Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088 ALR** titre ≥ 1:51* ** Tissue culture infectious dose 50%.* *** Antibody micro agglutination-lytic reaction*	SC	1	1	0	Spindle cell tumour, injection site lump	> 30 days

Lyophilisate (live attenuated): *Minimum Maximum* *Canine distemper virus, strain CDV Bio 11/A 103.1 TCID50* 105.1 TCID50* *Canine adenovirus Type 2, strain CAV-2 Bio 13 103.6 TCID50* 105.3 TCID50* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B 104.3 TCID50* 106.6 TCID50* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 103.1 TCID50* 105.1 TCID50* *Suspension (inactivated):* *Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089 ALR** titre ≥ 1:51* *Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090 ALR** titre ≥ 1:51* *Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 ALR** titre ≥ 1:40* *Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088 ALR** titre ≥ 1:51* *Rabies virus, strain SAD Vnukovo-32 ≥ 2.0 IU**** * Tissue culture infectious dose 50%.* ** Antibody micro agglutination-lytic reaction.* *** International units*	SC	1	1	0	Pale mucous membrane, generalised weakness	≤2 mins
Inactivated Leptospira canicola, at least 40 hamster protective doses and inactivated Leptospira icterohaemorrhagiae, at least 40 hamster protective doses.	SC					

Table 5e: Feline Reports

Active substance (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Inactivated feline panleucopenia virus, strain CU4 ≥ 8.50 *Inactivated feline calicivirus, strain 255 ≥ 1.26* *Inactivated feline rhinotracheitis virus, strain 605, ≥ 1.39* *Inactivated Chlamydophila felis, strain Cello, ≥ 1.69* *Inactivated feline leukaemia virus, strain 61E ≥ 1.45*	SC	1	1	0	Tachypnoea, anxiety, hyperactivity, aggression	≤ 6 hrs
Live attenuated feline calicivirus, strain F9: ≥4.6 log10 PFU1; *live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log10 PFU1;* *live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log10 CCID50 2* *1PFU: Plaque-Forming Units* *2CCID50: Cell Culture Infective Dose 50%*	SC	1	1	0	Lethargy, shaking, drooling, pyrexia, abnormal pupil light reflex, circling - neurological disorder, anaphylaxis	≤ 24 hrs

Table 5G: Rabbit Reports

Active substance	Route(s) of administration	No. treated	No. reacted	No. died	Clinical signs	Speed of onset
Inactivated rabbit haemorrhagic disease type 2 virus (RHDV2), strainV-1037……≥70% cELISA40 (*) ≥70 % of vaccinated rabbits shall give cELISA antibody titres equal to or higher than 40.*	SC	1	1	1	Injection site complication NOS, injection site pain, joint pain NOS, monoparesis (paralysis of limb)	≤ 12 hrs
Live myxoma vectored RHD virus strain 009: ≥103.0 and ≤106.1 FFU *Focus Forming Units*	SC	1	1	0	Eyelid inflammation	≤ 14 days