Suspected Adverse Event Reports to Veterinary Medicinal Products received by the HPRA during 2020

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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 an independent public sector organisation responsible for the regulation of health products, including veterinary medicinal products (VMPs). Our mission is to protect and enhance public and animal health through the regulation of medicines, medical devices and other health products. 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). 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 European Medicines Agency). MAHs are required by legislation to report all serious SAEs occurring in Ireland 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 relevant 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.

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.

SPC: A document providing officially approved information on a VMP

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

Table 1: Suspected Adverse Events - 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.

In 2020 the HPRA received eight invalid reports. The reasons for this include:

- duplicates of reports submitted (n=2)
- reports submitted from countries of origin other than Ireland (n=4)
- reports sent in error by MAHs (n=2)

2. National Pharmacovigilance Surveillance

The HPRA received 383 valid national SAE reports in 2020. These reports involved a range of animals as presented in Table 2. Twelve reports concerned SARs in humans following exposure to a VMP.

Table 2. Overview of reports received in 2020

Species	Total number reports	Total number reacting
Food producing animals		
bovine	149	3930
ovine	51	984
equine	9	119
avian	5	3789
porcine	2	202
Companion animals		
canine	115	207
feline	29	33
rabbit	9	12
ferret	2	2
Other		
human	12	12
Total	**383**	**9290**

Figure 1 outlines the primary sources of SAE reports received by the HPRA between 2016 and 2020 and Figure 2 shows a detailed look at the source of SAE reports received by the HPRA in 2020.

Figure 1: Source of SAE reports from 2016 to 2020

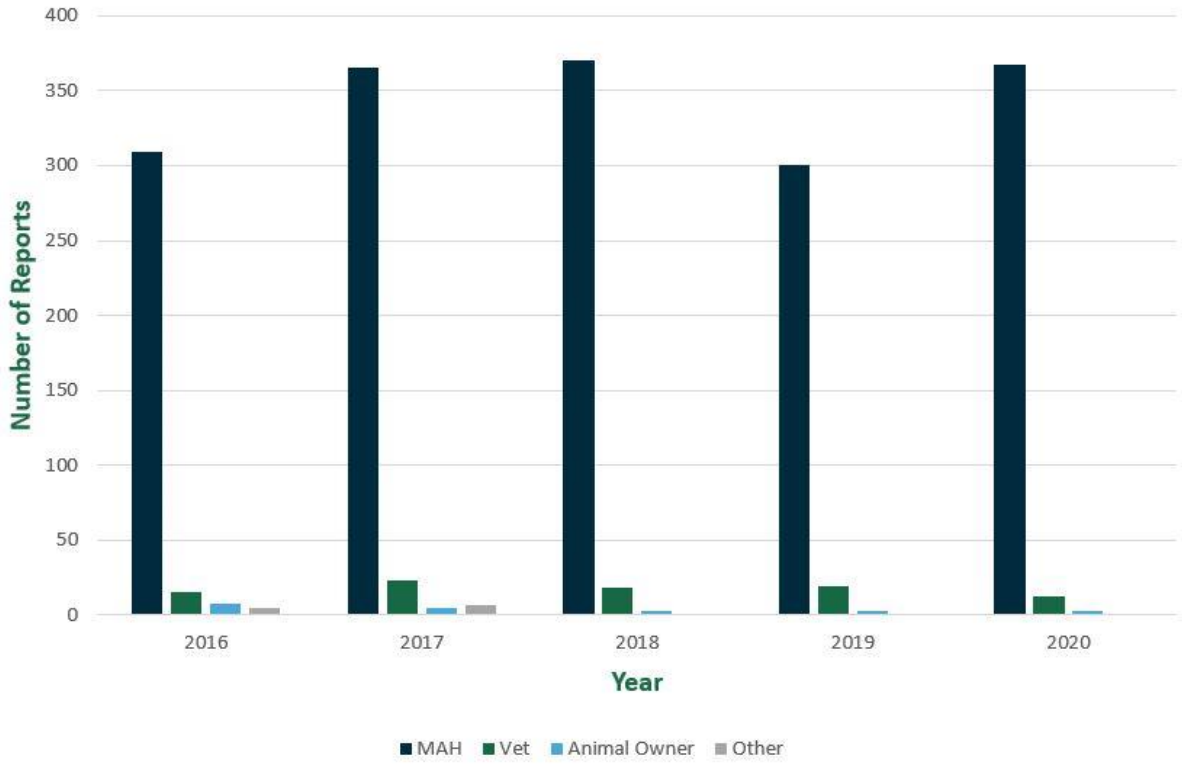
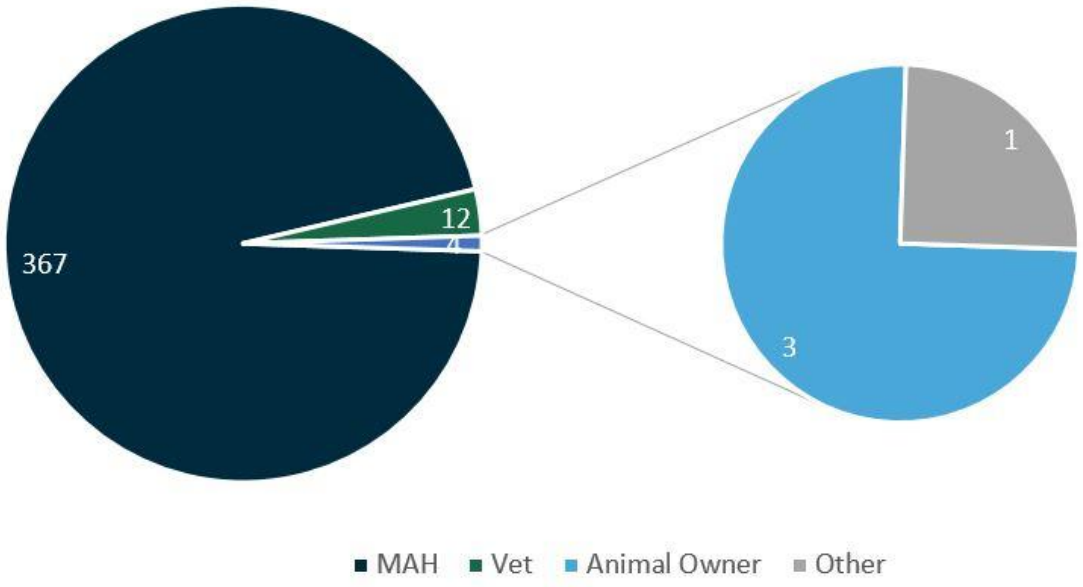


Figure 2: A detailed look at the number of SAE reports from sources in 2020

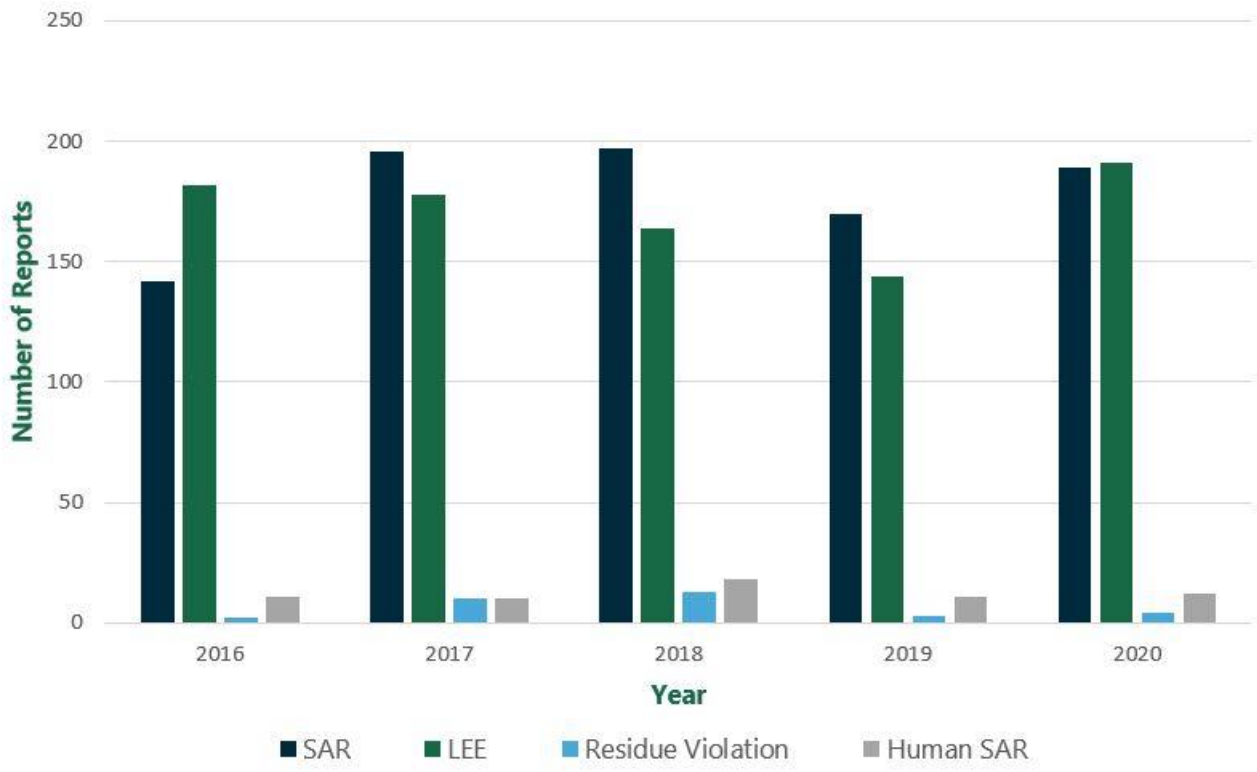


Of the 383 SAE reports received in 2020, 160 reports involved solely pharmaceutical products, 205 reports involved solely immunological products and 18 reports related to the use of both pharmaceutical and immunological products concurrently. There were 176 reports that involved SARs or serious SARs (SSAR) in animals, 173 reports involved suspected LEE, 13 reports involved combined SAR/LEE and four reports related to violation of an approved residue limit. Twelve reports related to SAEs in humans. A comparison of the types of reports received from 2016 to 2020 is shown in Figure 3 below.

A vaccine is an example of an ***immunological*** product

An anti-inflammatory is an example of a ***pharmaceutical product***

Figure 3: Number of SAE reports by category received from 2016 to 2020



2.1 Reports of adverse reactions

**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.*

There were 176 SAR/serious SAR reports relating to animals received. For a report to be considered as a serious suspected adverse reaction (SSAR), it must fulfil certain criteria including:

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

These reports related to a number of species including dogs (100 reports), cattle (28 reports), cats (28 reports), sheep (6 reports), rabbits (6 reports), horses (5 reports), ferrets (2 reports) and pigs (one report).

Of these reports, 84 related only to pharmaceutical products. Twelve reports were considered to be 'probably' (causality 'A') product related, 39 reports were considered to be 'possibly' (causality 'B') product related, in 34 reports there was insufficient information (causality 'O1'/'O') to assign definitive causality and three reports were considered 'unlikely' to be product related (causality 'N'). Four reports contained multiple products which were assigned different causalities.

Seventy-eight reports related only to immunological products. Product involvement was considered 'probable' (causality 'A') in 21 reports, possibly related (causality 'B') in 30 reports, in 20 reports there was insufficient information to assign a definitive product association (causality 'O1'/'O'), and in seven reports product involvement was considered 'unlikely' (causality N).

Twelve reports detailed concurrent pharmaceutical and immunological administration. Product involvement was considered 'possible' in seven reports (causality 'B'), in six reports insufficient information was provided to assigned a definitive association (causality 'O1'/'O'), while in one report, product involvement was considered 'unlikely' (causality 'N'). Two reports contained multiple products which were assigned different causalities.

Twelve SAE reports of human exposure to VMPs were received during the reporting period. As per established pharmacovigilance practice for veterinary medicinal products, causality assessments of human adverse reactions have not been conducted by the HPRA for these reports.

Those administering VMPs are reminded to exercise due caution when handling veterinary medicinal products and 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 or the package labelling/leaflet accompanying the product.

MAHs are reminded of their obligation to report any adverse events occurring following human exposure to a veterinary medicinal product 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 178 reports relating solely to LEE in 2020.

Of these reports, 57 related only to pharmaceutical products and involved cattle (35 reports), sheep (14 reports), dogs (4 reports), horses (3 reports) and cats (1 report). Eleven of the 57 reports were considered to be 'possibly' (causality 'B') related to product use. No reports were considered 'probably' (causality 'A') related to product use. In 30 reports insufficient information was provided to assigned a definitive association (causality 'O1'/'O') while in six reports, product involvement was considered 'unlikely' (causality 'N'). In 10 reports no assessment was performed. Eleven reports involved off-label use of one or more pharmaceuticals.

There were 117 LEE reports received that only involved immunological products, where the product was suspected to have failed to induce protective immunity. The reports concerned cattle (72 reports), sheep (29 reports), dogs (7 reports), avian (5 reports), rabbits (3 reports) and pigs (1 report). In 28 reports, product involvement was classified as 'B' (possible). No reports were classified as 'A' (probable). Forty-two reports were assessed as 'unclassifiable/inconclusive' ('O' or O1') and 42 reports were classed as 'N' (unlikely). No assessment was performed in 18 reports. Fourteen reports contained multiple products which were assigned different causalities Twenty-four reports involved off-label use of one or more products. Efficacy of a product cannot be expected when it has not been used according to the information given in the SPC.

In addition, four LEE reports involved both pharmaceutical and immunological products. Immunological product involvement was classified as 'O1' (inconclusive) in one report and as 'N' (unlikely) in two reports. No assessment was performed in one report as it involve doff-label use.

Where it is not specified within an adverse event report whether product use was according to its authorised SPC or not, a worst case scenario is assumed – i.e. the report will be classified as though the product was used as recommended.

2.3 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 SAR, SSAR and combined SAR/LEE reports received by the HPRA in 2020 containing multiple products, the involvement of a reported VMP with the observed reaction was considered to have been 'probable' (causality 'A') in 35 reports and 'possible' (causality 'B') in 40 reports. In 46 reports, there was insufficient/inconclusive information available to assign definitive causality (causality 'O'/'O1') and in 27 reports it was considered unlikely (causality 'N') that a reported VMP was responsible for the observed reaction. In six reports no assessment was performed. 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 NCA takes precedence and is the one uploaded to the central European database.

A line listing of SAE reports originating from Ireland in 2019, organised by active substance, 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

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 veterinary medicinal products (CAPs). This is done by means of monitoring reports logged to a central EU database by a process known as signal detection as well as through the assessment of Periodic Safety Update Reports (PSURs – regular reports compiled by an MAH on the safety, efficacy and sales data of a particular VMP over a specified period) provided by MAHs.

While the EMA 2020 Annual Pharmacovigilance Bulletin is currently awaiting publication, the 2019 bulletin detailed that the majority of SAE reports received concerned companion animals, with cats and dogs accounting for 87% of reports. Reporting in food-producing animals is still comparatively low.

On the basis of these analyses, during 2019 the CVMP made recommendations to update the product literature for 23 CAPs and the MAH was requested to monitor suspected adverse events in 56 CAPs . Further information concerning the changes made to individual product information for CAPs is published in the Veterinary pharmacovigilance Public bulletin 2019 (the 2020 bulletin is yet to be published) and on the European Medicines Agency (EMA) website (link here).

3.1 Changes to Pharmacovigilance arising from the New Veterinary Regulation (EU) 2019/6

Preparations are underway for the implementation of the New Veterinary Regulation (NVR) which will come into effect on 28/01/2022.

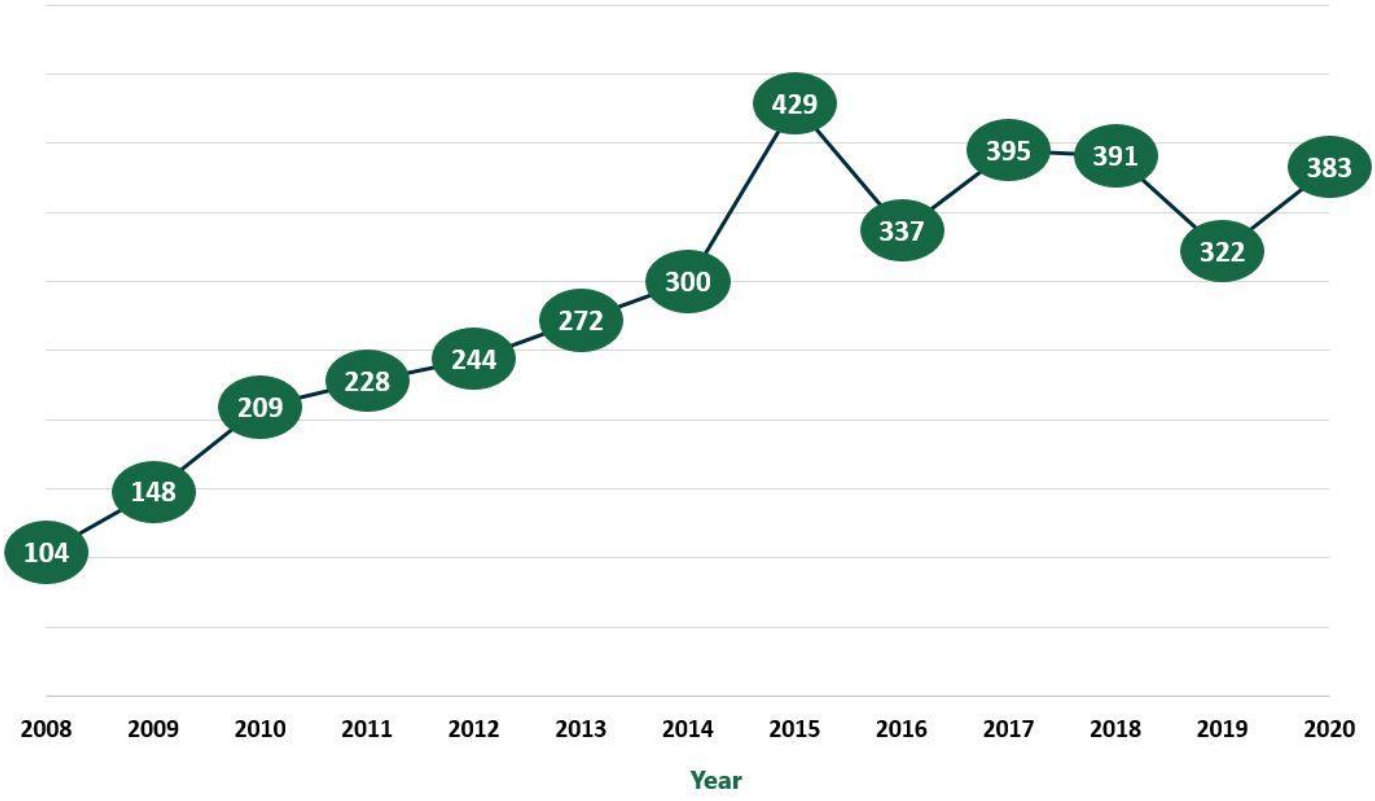
The main pharmacovigilance changes relating to the NVR are as follows:

- From 28/01/2022, in accordance with Article 76.2 of the regulation, MAHs will need to upload **all** suspected adverse event reports reported to them to the Union Pharmacovigilance Database within 30 days of receipt of the reports. At present, MAHs are only required to report serious adverse event reports to the HPRA within 15 days of receipt of the report.
- Periodic Safety Update Reports (PSURs) will no longer be required under the NVR. Instead, MAHs will need to carry out a signal management process for their veterinary medicinal products, the outcome of which must be recorded on the European Medicines Agency's Union Pharmacovigilance Database. This database is currently being developed.
- In accordance with Article 77.2 of the Regulation, from 28 January 2022, MAHs must have in place a PSMF that describes in detail the pharmacovigilance system for their product(s). This replaces the current Detailed Description of the Pharmacovigilance System (DDPS). The PSMF is to be located at the site location where the main pharmacovigilance activities of the MAH are performed, or where the QQPV operates (within the EU).

  The HPRA publishes monthly updates on the implementation of Regulation 2019/6 and these are available on the HPRA website (link here). A recording of a webinar held by the HPRA providing information on the NVR, along with a Q&A document, is also available (link here).

4. Conclusion

Figure 4: Total number of SAE Reports to the HPRA from 2008-2020



There remains a general trend of increasing numbers of reports since 2008 (Figure 4), which likely reflects a greater public awareness of the importance of reporting SAEs rather than an absolute increase in the number of adverse reactions occurring. The HPRA remains 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 (12 SAE reports were submitted by veterinarians directly to the HPRA in 2019, equalling 3.1% of 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.) 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 contains a webpage which contains each of the Annual Pharmacovigilance reports from 2014 to present, 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)

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Table 4: 2020 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
bismuth subnitrate	Intramammary	32	7	4	Death, gangrenous mastitis	≤24 hr
bismuth subnitrate	Intramammary	60	27	4	Acute mastitis, death	≤48 hr
deltamethrin	Topical	200	30	0	Agitation, pacing, restlessness, anaphylactic-type reaction, abortion	≤24 hr
fenbadazole	Oral	155	3	3	LEE (endoparasite) NOS, death, pericardial haemorrhage, oedema NOS	>30 days
halofuginone base	Oral	150	75	2	Death, inappetence, diarrhoea	≤7 days
halofuginone base	Oral	2	2	1	Lethargy, dehydration, anorexia, death	≤48 hr
ivermectin	SC	36	1	1	Found dead	≤6 hr
ivermectin + closantel	Topical	7	1	1	Dull, depression, anorexia, recumbency, death by euthanasia	≤7 days

levamisole	IM	13	13	0	Twitching, hypersalivation, ataxia	≤6 hr
levamisole	Oral	5	2	1	Ataxia, spasm, shivering, trembling, found dead	≤6 hr
moxidectin	SC	24	1	0	Ataxia, blindness, increased salivation, recumbency	≤24 hr
moxidectin	SC	60	35	1	Death	>30 days
oxytetracycline	IM	1	1	1	Sudden death	≤2 mins
oxytetracycline	IM	1	1	0	Shock, respiratory depression	≤2 mins
tolfenamic acid	IV	1	1	0	Anaphylaxis, collapse NOS	≤30 mins

Table 4b: Ovine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
procaine hydrochloride + epinephrine tartrate	IM + SC	1	1	1	Panting, lying down, death	≤6 hr
levamisole hydrochloride + oxyclozanide	Oral	300	25	2	Diarrhoea, general illness, dullness, inappetence, not drinking, death, lack of efficacy (roundworm)	≤24 hr
moxidectin **closantel**	SC Oral	160	9	6	Death, downer animal, liver disorder NOS, anorexia, foetal death	≤24 hr

Table 4c: Equine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
flunixin	IV	1	1	1	Lateral recumbency, collapse NOS, dyspnoea, paddling, anaphylaxis, death, LEE, intestinal disorder NOS	≤2 mins
flunixin **butylscopolamine bromide + metamizole**	IV IV	1	1	0	Uritcaria, pruritus	≤30 mins
hydrochlorothiazide + dexamethazone	IM	1	1	0	Injection site infection, injection site inflammation, injection site necrosis	≤24 hr
ivermectin + praziquantel	Oral	20	6	0	Swollen gum, gum pain, gum disorder	≤30 mins
procaine benzylpenicillin + dihydrostreptomycin	IM	1	1	1	Sudden death	≤2 mins
xylazine base **meloxicam** **butorphanol**	IV IV IV	2	2	1	Nystagmus, tremors, incoordination, collapse, tachycardia, convulsion, cardiac arrest, death, star-gazing, balance impaired	≤30 mins

Table 4d: Canine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
amoxicillin	IM	1	1	0	Central nervous system disorder NOS	≤1 hr
amoxicillin + clavulanic acid **dexamethasone** **milbemycin oxime + praziquantel** **oclacitinib** **fluralaner**	Oral IM Oral Oral Oral	1	1	0	Excessive thirst, polyuria, polyphagia, dehydration, elevated liver enzymes, elevated cholesterol (total)	≤24 hr
carprofen	Oral	1	1	0	Haemorrhagic diarrhoea, inappetence, lymphocytosis, leukaemia	≤24 hr
carprofen	Oral	1	1	1	Decreased appetite, haematemesis, distress, death	>30 days
dexmedetomidine	IM	1	1	0	Surgical site haemorrhage, bradycardia, hypercapnia	≤6 hr
dexmedetomidine	IM	1	1	0	Surgical site haemorrhage, bradycardia, hypercapnia	≤6 hr
febantel, pyrantel + praziquantel	Oral	1	1	0	Hyperactivity	≤30 mins

fluralaner	Oral	1	1	0	Emesis (multiple), diarrhoea, lethargy, anorexia, disorientation, pruritic rash, erythematous rash, abnormal stool discolouration	≤12 hr
gentamicin + betamethasone + clotrimazole	Topical	1	1	0	Decreased hearing	≤48 hr
isoflurane	Inhalation	1	1	1	Partial LEE, abnormal breathing, cardiac arrest, death	≤ 1 hr
lokivetmab **oclacitinib**	SC Oral	1	1	1	Diarrhoea, regenerative anaemia, fever, partial anorexia, death by euthanasia	≤24 hr
meloxicam	Oral	1	1	0	Blood in urine	≤48 hr
miconazole nitrate + prednisolone acetate + polymyxin B sulfate	Topical	1	1	0	Impaired hearing, deafness	≤14 days
milbemycin oxime + praziquantel	Oral	1	1	0	Ataxia, incoordination, stupor, temporary blindness	≤24 hr
milbemycin oxime + paziquantel	Oral	1	1	0	Lethargy, anorexia, haemorrhagic diarrhoea, collapse NOS	≤6 hr
milbemycin oxime + praziquantel	Oral	1	1	0	Facial swelling, emesis, lip oedema	≤30 mins

milbemycin + praziquantel **sarolaner**	Oral Oral	1	1	0	Elevated serum alkaline phosphatase (SAP), hypophosphataemia, lethargy, not eating, musculoskeletal pain, injection site pain, diarrhoea, jaw pain, pyrexia, increased red blood cell count, hyperproteinaemia	≤1 hr
febantel + pyrantel	Oral	1	1	0	Emesis, prolonged capillary refill time, pale mucous membrane, anaphylaxis	≤30 mins
nitroxynil	Oral	2	2	1	Vomiting, hyperthermia, panting, shaking, rigidity, collapse NOS, medication error, death	unknown
orbifloxacin + mometasone furoate + posconazole	Topical	1	1	0	Deafness	≤30 days
praziquantel + pyrantel + febantel	Oral	1	1	0	Vomiting, lethargy	≤6 hr
propofol	IV	1	1	0	Bradycardia, hypothermia, apnoea, muscle spasm NOS, muscle rigidity	≤2 mins
propofol	IV	1	1	1	Cardiac arrest, sudden death	≤6 hr
pyrantel pamoate + sarolaner	Oral	1	1	0	Knuckling, ataxia, musculoskeletal	≤6 hr

					pain, impaired proprioception	
sarolaner + moxidectin+ pyrantel	Oral	1	1	0	Vomiting, diarrhoea	≤24 hr
tigilanol tiglate	Intratumoural	1	1	1	Injection site infection, malaise, weakness, inappetence, lethargy, petechiae NOS, elevated renal parameters, elevated liver enzymes, death by euthanasia	≤7 days
trilostane	Oral	1	1	0	Vomiting, diarrhoea, lethargy, seizure NOS, polyphagia, anisocoria	≤24 hr

Table 4e: Feline Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
amoxicillin	IM	1	1	0	Central nervous system disorder NOS	≤1 hr
fipronil + s-methoprene + eprinomectin + praziquantel	Topical	7	1	0	Application site hair discolouration	≤12 hr
fipronil + s-methoprene + eprinomectin + praziquantel	Topical	1	1	1	Increased salivation, vocalisation, ataxia, seizure NOS, death	≤24 hr
fluralaner + moxidectin	Topical	1	1	0	Open mouth breathing, increased respiratory rate, respiratory distress, hyperaesthesia, hyperactivity	≤2 mins
fluralaner + moxidectin	Topical	1	1	0	Vomiting, bloody diarrhoea, twitching, not eating	≤6 hr
miconazole nitrate, prednisolone acetate + polymixin B sulfate	Topical	1	1	0	Deafness	≤24 hr
milbemycin oxime + praziquantel	Oral	2	2	1	Lethargy, vomiting, weakness, recumbency,	≤24 hr

					death, hypoglycaemia	
milbemycin oxime + praziquantel	Oral	1	1	0	Lethargy, anorexia, pyrexia, general pain	≤12 hr
milbemycin + praziquantel	Oral	1	1	1	Collapse NOS, anaphylaxis, death, fluid from nose, pleural effusion	≤6 hr
selamectin	Topical	3	3	2	Staggering, death	≤24 hr
thiamazole	Oral	1	1	0	Neutropenia, anorexia	unknown

Table 5: 2020 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(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Formalin killed cells of Salmonella dublin strain S342/70 1 x 10^9 cells, *Formalin killed cells of Salmonella typhimurium strain S341/70 1 x 10^9 cells*	SC	16	1	1	Sudden death	≤6 hr
Inactivated Bovine Respiratory Syncytial virus, strain EV908 $10^{5.5}$ - $10^{6.4}$ $TCID_{50}$,* *Inactivated Parainfluenza-3-Virus, strain SF-4 Reisinger $10^{7.3}$ - $10^{8.3}$ $TCID_{50}$*,* *Inactivated Mannheimia haemolytica A1, strain M4/1 9 x 10^9 cells cells*	SC	60	35	1	Death	>30 days
Inactivated Leptospira interrogans serovar Hardjo 204 2 -3 x 10^9 organisms *C. perfringens type A (α) toxoid ≥ 0.5 U#* *C. perfringens type B & C (β) toxoid ≥ 18.2*	SC SC	50	6	2	Injection site swelling, respiratory signs, death	≤7 days

*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#*						

Table 5b: Ovine reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
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* PD_{90} *Formalin killed cells of Mannheimia haemolytica serotypes:* *A1* 5×10^8 *cells* *A2* 5×10^8 *cells* *A6* 5×10^8 *cells* *A7* 5×10^8 *cells* *A9* 5×10^8 *cells* *Formalin killed cells of Pasteurella trehalosi serotypes:* *T3* 5×10^8 *cells* *T4* 5×10^8 *cells* *T10* 5×10^8 *cells* *T15* 5×10^8 *cells*	SC	70	1	0	Ataxia, temporary blindness, head down	≤30 mins

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 PD_{90}* *Formalin killed cells of Mannheimia haemolytica serotypes:* *A1 5 x 10^8 cells* *A2 5 x 10^8 cells* *A6 5 x 10^8 cells* *A7 5 x 10^8 cells* *A9 5 x 10^8 cells* *Formalin killed cells of Pasteurella trehalosi serotypes:* *T3 5 x 10^8 cells* *T4 5 x 10^8 cells* *T10 5 x 10^8 cells* *T15 5 x 10^8 cells*	SC	50	30	10	LEE, sudden death, injection site abscess, injection site lump	≤7 days
Inactivated Leptospira interrogans serovar Hardjo 204 2 -3 x 10^9 organisms	SC	20	1	1	Lump, death	≤24 hr

Table 5c: Canine reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica 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	Vomiting, diarrhoea, lethargy	≤24 hr
≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2] of live canine parainfluenza virus strain Cornell *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar*	Intranasal SC	1	1	0	Laboured breathing, respiratory distress, hyperexcitation, anaphylaxis	≤1 hr

Dadas (strain Gr-01-005) 650–1300 U[1]						
≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] *of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$*[2] *of live canine parainfluenza virus strain Cornell* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U*[1] *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U*[1] *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U*[1] *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U*[1]	Intranasal SC	1	1	0	Circulatory response, tachycardia, anaphylaxis	≤1 hr
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$**	SC	1	1	0	Lethargy, anorexia, haemorrhagic diarrhoea, collapse NOS	≤6 hr

**$TCID_{50}$: Tissue culture infective dose 50%*						
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$** **$TCID_{50}$: Tissue culture infective dose 50%*	SC	1	1	0	Vomiting, hyperventilation	≤1 hr
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	SC					

*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$** **$TCID_{50}$: Tissue culture infective dose 50%*	SC	1	1	0	Facial swelling, emesis, lip oedema	≤30 mins
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	SC					

*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$** **$TCID_{50}$: Tissue culture infective dose 50%*	SC	2	2	0	Swollen eye, facial swelling (see also 'skin')	≤6 hr
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	SC					

*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$** **$TCID_{50}$: Tissue culture infective dose 50%*	SC	1	1	0	Facial oedema	≤6 hr
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	SC					
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not*	SC					

less than $10^{5.5}$ $TCID_{50}$ *$TCID_{50}$: Tissue culture infective dose 50%* *≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2] of live canine parainfluenza virus strain Cornell* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	Intranasal SC	1	1	0	Fly biting behaviour, ear twitching, epileptic seizure, localised pain NOS, lateral neck deviation, rubbing, ear infection NOS	≤6 hr
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not*	SC					

less than $10^{5.5}$ $TCID_{50}$ *$TCID_{50}$: Tissue culture infective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	SC	1	1	0	Swollen lip, anal oedema, vulvar oedema	≤6 hr
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$* *$TCID_{50}$: Tissue culture infective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola*	SC	1	1	0	Facial oedema	≤6 hr

serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1] *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	SC					
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$** **$TCID_{50}$: Tissue culture infective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]*	SC SC	1	1	0	Elevated serum alkaline phosphatase (SAP), hyperphosphatemia, lethargy, not eating, musculoskeletal pain, injection site pain, diarrhoea, jaw pain, pyrexia, increased red blood cell count, hyperproteinaemia	≤1 hr

- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1] *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*						
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$** **$TCID_{50}$: Tissue culture infective dose 50%* *Inactivated Leptospira interrogans serogroups: Canicola; serovar Portland-vere, strain Ca-12-000 >957-1,676 Units/ml*, Icterohaemorrhagiae; serovar Copenhageni, strain 820K > 625-1,335 Units/ml*	SC SC	1	1	0	Recumbency, pyrexia, vocalisation, general pain, dull	≤6 hr
*Canine distemper virus not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus not less than $10^{7.0}$ $TCID_{50}$** *Canine parainfluenzavirus not less than $10^{5.5}$ $TCID_{50}$**	SC					

*$TCID_{50}$: Tissue culture infective dose 50% *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*	SC	1	1	0	Pallor, ataxia, unable to stand, vocalisation, anaphylaxis	≤1 hr
*Canine distemper virus, strain Onderstepoort not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2, strain Manhattan LPV3 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus, strain 154 not less than $10^{7.0}$ $TCID_{50}$** *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000)*	SC SC	1	1	0	Injection site pain, shivering, pale mucous membrane, anaphylaxis	≤6 hr

3550–7100 U[1] *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]*						
*Canine distemper virus, strain Onderstepoort not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2, strain Manhattan LPV3 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus, strain 154 not less than $10^{7.0}$ $TCID_{50}$**	SC					
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri*	SC	1	1	0	Emesis, prolonged capillary refill time, pale mucous membrane, anaphylaxis	≤30 mins

serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1] *≥ 10*[8.0] *and ≤ 10*[9.7] *cfu*[1] *of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ 10*[3.0] *and ≤ 10*[5.8] *TCID*$_{50}$[2] *of live canine parainfluenza virus strain Cornell*	Intranasal					
Canine distemper virus, strain Onderstepoort not less than 10[4.0] *TCID*$_{50}$* Canine adenovirus 2, strain Manhattan LPV3 not less than 10*[4.0] *TCID*$_{50}$* Canine parvovirus, strain 154 not less than 10*[7.0] *TCID*$_{50}$* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U*[1] *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U*[1] *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U*[1] *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U*[1]	SC SC	1	1	0	Vomiting, diarrhoea, anorexia	≤2 mins

≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2] of live canine parainfluenza virus strain Cornell	Intranasal					
Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$ Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$* Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$* Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$* 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	Injection site swelling, injection site pain	≤6 hr

*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *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	Vagal shock, pale mucous membrane, shaking	≤24 hr
*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$**	SC	1	1	0	Periorbital oedema, swollen face, general pain	≤6 hr

Liquid fraction: *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*						
Freeze dried fraction: *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction:* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *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, pale mucous membrane, reduced responses, eyes rolling back	≤30 mins

*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *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	Allergic reaction, swollen face, loss of voice, lethargy	≤30 mins
*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$**	SC	2	2	0	Vomiting, facial oedema	≤6 hr

Liquid fraction: *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*						
Freeze dried fraction: *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction:* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *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	Lethargy, swollen face, periorbital oedema	≤6 hr

*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *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	Facial swelling	≤6 hr
*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$**	SC					

Liquid fraction: *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50* *Live attenuated Bordetella bronchiseptica, live, strain 92B 2.1 x 10^6 to 5.5 x 10^8 CFU(*)* *(*) CFU : colony forming unit*	Intranasal	1	1	0	Vomiting, hypersalivation, collapse NOS, reduced responses, pharyngeal oedema, pale mucous membrane, tachycardia, asphyxia, anaphylaxis	≤30 mins
Freeze dried fraction: *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction:* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum*	SC					

titre : $10^{7.0}$ $CCID_{50}$ Leptospira canicola (inactivated) at least 40 hamster protective doses Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses. *Cell culture infectious dose-50*		1	1	0	Quiet, fever, elevated amylase	≤24 hr
≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2] of live canine parainfluenza virus strain Cornell	Intranasal					
Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$ Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$* Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$* Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$* Leptospira canicola (inactivated) at least 40 hamster protective*	SC					

doses *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50* *Live attenuated Bordetella bronchiseptica, live, strain 92B 2.1 x 106 to 5.5 x 108 CFU(*)* *(*) CFU : colony forming unit*	Intranasal	1	1	0	Facial oedema, anaphylaxis	≤30 mins
Freeze dried fraction: *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction:* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.*	SC					

**Cell culture infectious dose-50* *≥ $10^{8.0}$ and ≤ $10^{9.7}$ cfu[1] of live Bordetella bronchiseptica 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	Vomiting, swelling around eye, eye redness, pruritus, hypersensitivity reaction, anaphylaxis	≤6 hr
Freeze dried fraction: *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction:* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC					

≥$10^{8.0}$ and ≤$10^{9.7}$cfu[1] of live Bordetella bronchiseptica 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	Collapse (NOS), urination, pale mucous membranes, horizontal nystagmus, lethargy	≤30 mins
Inactivated Leptospira canicola, at least 40 hamster protective doses and inactivated Leptospira icterohaemorrhagiae, at least 40 hamster protective doses. *≥$10^{8.0}$ and ≤$10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥$10^{3.0}$ and ≤$10^{5.8}$ $TCID_{50}$[2] of live canine parainfluenza virus strain Cornell*	SC Intranasal	1	1	0	Vomiting, urticaria, face and neck swelling, pyrexia	≤6 hr
Inactivated Leptospira canicola, at least 40 hamster protective doses and inactivated Leptospira icterohaemorrhagiae, at least 40 hamster protective doses.	SC	1	1	0	Anaphylaxis, vomiting, anorexia, sickness	≤6 hr

≥$10^{8.0}$ and ≤$10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥$10^{3.0}$ and ≤$10^{5.8}$ $TCID_{50}$[2] of live canine parainfluenza virus strain Cornell	Intranasal					
Inactivated Leptospira interrogans serogroups: Canicola; serovar Portland-vere, strain Ca-12-000 >957-1,676 Units/ml, Icterohaemorrhagiae; serovar Copenhageni, strain 820K > 625-1,335 Units/ml*	SC	1	1	0	Lethargy, facial oedema	≤6 hr
Inactivated Leptospira interrogans serogroups: Canicola; serovar Portland-vere, strain Ca-12-000 >957-1,676 Units/ml, Icterohaemorrhagiae; serovar Copenhageni, strain 820K > 625-1,335 Units/ml*	SC	1	1	0	Dull, facial oedema	≤6 hr
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Urticaria, dull, vomiting, diarrhoea, facial oedema	≤30 mins
Live attenuated Bordetella bronchiseptica, strain 92B 1.4 x 10^{8} - 5.5 x 10^{9} CFU/dose*	SC	1	1	0	Lethargy, injection site pain	≤24 hr
Lyophilisate (live attenuated): Minimum Maximum						

Canine distemper virus, strain CDV Bio 11/A $10^{3.1}$ $TCID_{50}$ $10^{5.1}$ $TCID_{50}$* *Canine adenovirus Type 2, strain CAV-2 Bio 13 $10^{3.6}$ $TCID_{50}$* $10^{5.3}$ $TCID_{50}$* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B $10^{4.3}$ $TCID_{50}$* $10^{6.6}$ $TCID_{50}$* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 $10^{3.1}$ $TCID_{50}$* $10^{5.1}$ $TCID_{50}$* *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	Lethargy, retching, generalised weakness, star-gazing	≤2 mins

Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *Canine adenovirus Type 2, strain CAV-2 Bio 13* $10^{3.6}$ *TCID*$_{50}$* $10^{5.3}$ *TCID*$_{50}$ *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B* $10^{4.3}$ *TCID*$_{50}$* $10^{6.6}$ *TCID*$_{50}$ *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *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	Vocalisation, tachypnoea, hypersalivation, collapse	≤2 mins

Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *Canine adenovirus Type 2, strain CAV-2 Bio 13* $10^{3.6}$ *TCID*$_{50}$* $10^{5.3}$ *TCID*$_{50}$ *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B* $10^{4.3}$ *TCID*$_{50}$* $10^{6.6}$ *TCID*$_{50}$ *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *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	Facial oedema, respiratory discomfort, jaw disorder	≤24 hr

Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *Canine adenovirus Type 2, strain CAV-2 Bio 13* $10^{3.6}$ *TCID*$_{50}$* $10^{5.3}$ *TCID*$_{50}$ *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B* $10^{4.3}$ *TCID*$_{50}$* $10^{6.6}$ *TCID*$_{50}$ *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *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	Collapse, hypersalivation, vomiting, generalised weakness, lateral recumbency, reduced responses	≤30 mins

Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *Canine adenovirus Type 2, strain CAV-2 Bio 13* $10^{3.6}$ *TCID*$_{50}$* $10^{5.3}$ *TCID*$_{50}$ *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B* $10^{4.3}$ *TCID*$_{50}$* $10^{6.6}$ *TCID*$_{50}$ *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15* $10^{3.1}$ *TCID*$_{50}$* $10^{5.1}$ *TCID*$_{50}$ *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	1	Unexplained death, sudden death, not eating, injection site swelling	≤7 days

Table 5d: Feline reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
*Inactivated feline leukaemia virus (FeLV) subtypes A, B and C (Kawakami-Theilen strain) including gp70 sub-unit antigen, inducing anti-gp70 antibodies GMT ≥ 8.1 log_2** *As determined by mouse potency test (anti-gp70 antibodies, GMT denotes: geometric mean titre)*	SC	1	1	0	Vomiting, bloody diarrhoea, twitching, not eating	≤6 hr
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	Injection site lump, injection site pain, anorexia, adipsia, lethargy, anxiety, aggression	≤6 hr
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,	SC	1	1	0	Anorexia, lethargy, adipsia, behavioural disorder - hiding.	≤6 hr

strain Cello ≥ 1.69, Inactivated feline leukaemia virus, strain 61E ≥ 1.45						
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	Restlessness, dilated pupils, disorientation, lethargy	≤24 hr
Live attenuated feline calicivirus (strain F9) $10^{4.6}$–$10^{6.1}$ $CCID_{50}$, Live attenuated feline viral rhinotracheitis virus (strain F2) $10^{5.0}$–$10^{6.6}$ $CCID_{50}$*, Live attenuated feline panleucopenia virus (strain LR 72) Live attenuated feline panleucopenia virus (strain LR 72) $10^{3.7}$–$10^{4.5}$ $CCID_{50}$** **Cell culture infectious dose 50%.*	SC	1	1	0	Increased salivation, lethargy, hyperthermia, fever, inappetence	≤24 hr
Live attenuated feline calicivirus, strain F9: ≥4.6 log_{10} PFU[1]; live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log_{10} PFU[1]; live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log_{10} $CCID_{50}$[2] *[1]PFU: Plaque-Forming*	SC					

Units, *[2]$CCID_{50}$: Cell Culture Infective Dose 50%* *Minimum quantity of purified p45 FeLV-envelope antigen 102 µg*	SC	1	1	0	Swollen face, periorbital oedema	≤1 hr
Live attenuated feline calicivirus, strain F9: ≥4.6 log_{10} PFU[1]; live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log_{10} PFU[1]; live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log_{10} $CCID_{50}$[2] *[1]PFU: Plaque-Forming Units,* *[2]$CCID_{50}$: Cell Culture Infective Dose 50%*	SC	1	1	1	Collapse NOS, anaphylaxis, death, fluid from nose, pleural effusion	≤6 hr
Live attenuated feline calicivirus, strain F9: ≥4.6 log_{10} PFU[1]; live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log_{10} PFU[1]; live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log_{10} $CCID_{50}$[2] *[1]PFU: Plaque-Forming Units,* *[2]$CCID_{50}$: Cell Culture Infective Dose 50%*	SC	1	1	0	Lethargy, anorexia, pyrexia, general pain	≤12 hr

Live attenuated feline calicivirus, strain F9: ≥4.6 log_{10} PFU[1]; live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log_{10} PFU[1]; live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log_{10} $CCID_{50}$[2] *[1]PFU: Plaque-Forming Units,* *[2]$CCID_{50}$: Cell Culture Infective Dose 50%*	SC	1	1	0	Dilated pupils, quiet, cloudy eye	≤12 hr
Minimum quantity of purified p45 FeLV-envelope antigen 102 µg	SC					

Table 5e: Rabbit reports

Active substance(s) (Antigen)	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	0	Injection site swelling, lameness	≤12 hr
*Live myxoma vectored RHD virus strain 009: ≥$10^{3.0}$ and ≤$10^{6.1}$ FFU** ******Focus Forming Units*	SC	1	1	1	Lethargy, death	≤12 hr

Table 5f: Ferret Reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Lethargy, unable to stand	≤30 mins
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Emesis (multiple)	≤30 mins