	Inventaris Wob-verzoek W21-04								
		wordt verstrekt				weigeringsgronden			
nr.	Aanvraagdossier 20173724	reeds openbaar	niet	geheel	deels	10.1.c	10.2.e	10.2.g	11.1
1	E-mail van VGH aan CCD inzake verzending stukken, d.d. 16 oktober 2017				x		x	x	
2	Aanvraagformulier, d.d. 16 oktober 2017				x		x	x	
3	Aanvraagformulier (versie 2), d.d. 16 oktober 2017				x		x	x	
4	Projectvoorstel, d.d. 16 oktober 2017				x	x		x	
5	Bijlage 1, d.d. 16 oktober 2017				x	x		x	
6	Bijlage 2, d.d. 16 oktober 2017				x	x		x	
7	Bijlage 3, d.d. 16 oktober 2017				x	x		x	
8	Bijlage 4, d.d. 16 oktober 2017				x	x		x	
9	Interne e-mail met betaalgegevens, d.d. 17 oktober 2017				x			x	
10	Adviesaanvraag van CCD aan DEC, d.d. 17 oktober 2017				x		x	x	
11	Bevestiging van CCD aan VGH, inzake adviesaanvraag DEC, d.d. 17 oktober 2017				x		x	x	
12	E-mail van CCD aan VGH, inzake ontvangstbevestiging Aanvraag Projectvergunning, d.d. 17 oktober 2017				x		x	x	
13	Ontvangstbevestiging Aanvraag Projectvergunning met factuur, d.d. 17 oktober 2017				x		x	x	
14	Interne notificatie - nieuwe aanvraag ontvangen, d.d. 17 oktober 2017				x		x	x	
15	E-mail van DEC, inzake ontvangst verzoek DEC-adviesaanvraag, d.d. 17 oktober 2017				x		x	x	
16	DEC-advies, d.d. 31 oktober 2017				x	x	x	x	
17	E-mail van CCD aan DEC over DEC-advies, d.d. 1 november 2017				x		x	x	
18	E-mail van DEC aan CCD over DEC-advies, d.d. 1 november 2017				x		x	x	
19	E-mail van CCD aan DEC over DEC-advies, d.d. 1 november 2017				x		x	x	

20	Intern advies aan CCD - 15 december 2017				x	x	x	x	x
21	Verzoek CCD aan VGH om aanvullende informatie, d.d. 18 december 2017				x	x	x	x	
22	Notificatie CCD aan DEC inzake verzoek aan VGH om aanvullende informatie, d.d. 18 december 2017				x	x	x	x	
23	E-mail van VGH aan CCD inzake aanvullende informatie, d.d. 20 december 2017				x		x	x	
24	Aanvullende informatie van VGH, d.d. 20 december 2017				x	x	x	x	
25	Bijlage dierproeven 2, versie 2, d.d. 20 december 2017				x	x		x	
26	Bijlage dierproeven 4, versie 2, d.d. 20 december 2017				x	x		x	
27	E-mail CCD aan VGH inzake intentie voor vergunning, d.d. 28 december 2017				x	x	x	x	
28	E-mail CCD aan VGH - gelegenheid tot zienswijze over voorgenomen besluit, d.d. 3 januari 2018				x	x	x	x	
29	Reactie van VGH inzake voorgenomen voorwaarden, d.d. 4 januari 2018				x		x	x	
30	Reactie van CCD op voorstel van VGH voor opschuiving reactie termijn, d.d. 9 januari 2018				x		x	x	
31	E-mail CCD aan DEC - kennisgeving van voorgenomen besluit aan de DEC, d.d. 11 januari 2018				x	x	x	x	
32	Ontvangstbevestiging DEC, d.d. 11 januari 2018				x		x	x	
33	E-mail VGH inzake zienswijze, d.d. 16 januari 2018				x		x	x	
34	E-mail advocaat VGH inzake bezwaar op beslissing, d.d. 16 januari 2018				x		x	x	
35	Zienswijze van VGH, d.d. 16 januari 2018				x	x	x	x	
36	E-mail van CCD aan DEC inzake zienswijze van VGH, d.d. 17 januari 2018				x	x	x	x	

37	E-mail van CCD aan DEC inzake doorsturen stukken ter volledigheid, d.d. 17 januari 2018				x	x	x	x	
38	E-mail van DEC aan CCD inzake haar standpunt, d.d. 17 januari 2018				x		x	x	
39	Interne e-mail - akkoord voor ondertekening aanvraag, d.d. 29 januari 2018				x		x	x	
40	Begeleidende e-mail bij beschikking, d.d. 29 januari 2018				x		x	x	
41	Beschikking, d.d. 29 januari 2018				x	x	x	x	
42	E-mail van VGH inzake NTS, d.d. 29 januari 2018				x		x	x	
43	Interne notitie over de afhandeling van de aanvraag, d.d. 29 januari 2018				x	x		x	
44	Interne e-mail - verzoek om publicatie NTS, d.d. 5 februari 2018				x		x		
45	Terugkoppeling van CCD aan DEC, d.d. 5 februari 2018				x	x	x	x	
46	E-mail van DEC aan CCD, d.d. 5 februari 2018				x		x	x	
47	E-mail van CCD aan DEC, d.d. 5 februari 2018				x		x	x	
48	NTS (versie 1)			x					
49	NTS (versie 2)			x					
50	NTS (versie 3)	x							
51	Aanvraagformulier melding 1, d.d. 26 november 2018				x	x	x	x	
52	Bijlage 1, d.d. 26 november 2018				x	x		x	
53	Bijlage 3, d.d. 26 november 2018				x	x		x	
54	Aanvraagformulier melding 1 (ontvangststempel), d.d. 29 november 2018				x		x	x	
55	Ontvangstbevestiging van melding 1, d.d. 3 december 2018				x	x	x	x	
56	Aanvraagformulier melding 2, d.d. 4 juni 2020				x	x	x	x	
57	Bijlage 2, d.d. 4 juni 2020				x	x		x	
58	E-mail van CCD inzake ontvangstbevestiging, d.d. 5 juni 2020				x		x	x	
59	Ontvangstbevestiging, d.d. 5 juni 2020				x		x	x	

60	Aanvraagformulier melding 2 (gestempeld), d.d. 9 juni 2020				x	x	x	x	
61	Aanvraagformulier melding 3, d.d. 18 januari 2021				x	x	x	x	
62	Bijlage 3, d.d. 18 januari 2021				x	x	x	x	
63	Aanvraagformulier melding 3 (gestempeld), d.d. 22 januari 2021				x	x	x	x	
64	Ontvangstbevestiging melding 3, d.d. 19 januari 2021				x		x	x	

10.2.e

Van: 10.2.e en 10.2.g
Verzonden: maandag 16 oktober 2017 16:40
Aan: Info-zbo
Onderwerp: ingezonden projectaanvraag, DEC advies wordt nog nagezonden [Confidential]

Categorieën: Nieuwe aanvraag (of nummer): 10.2.e

10.2.g

Geachte CCD,

Zojuist zijn er een nieuwe aanvraag via de beveiligde verbinding ingezonden van VGH 10.2.g

- Project: Canine Vaccine Development
-

Het officiele positieve DEC advies wordt nog zo spoedig mogelijk nagezonden. Deze is momenteel in de schrijffase.

Met vriendelijke groeten,
10.2.g

10.2.g

Telnr: 10.2.e en 10.2.g

10.2.g

Aanvraag
Projectvergunning Dierproeven
Administratieve gegevens

- U bent van plan om één of meerdere dierproeven uit te voeren.
- Met dit formulier vraagt u een vergunning aan voor het project dat u wilt uitvoeren. Of u geeft aan wat u in het vergunde project wilt wijzigen.
- Meer informatie over de voorwaarden vindt u op de website www.centralecommissiedierproeven.nl. of in de toelichting op de website.
- Of bel met 0900-2800028 (10 ct/min).

1 Gegevens aanvrager

1.1 Heeft u een deelnemernummer van de NVWA?
Neem voor meer informatie over het verkrijgen van een deelnemernummer contact op met de NVWA.

☐ Ja > *Vul uw deelnemernummer in* 10.2.g

☐ Nee > *U kunt geen aanvraag doen*

1.2 Vul de gegevens in van de instellingsvergunninghouder die de projectvergunning aanvraagt.

Naam instelling of organisatie	10.2.g
Naam van de portefeuillehouder of diens gemachtigde	10.2.e
KvK-nummer	10.2.g
Straat en huisnummer	
Postbus	
Postcode en plaats	

1.3 Vul de gegevens van het postadres in.
Alle correspondentie van de CCD gaat naar de portefeuillehouder of diens gemachtigde en de verantwoordelijke onderzoeker.

IBAN	
Tenaamstelling van het rekeningnummer	

1.4 Vul de gegevens in van de verantwoordelijke onderzoeker.

(Titel) Naam en voorletters	10.2.e 10.2.e
Functie	10.2.e
Afdeling	
Telefoonnummer	
E-mailadres	

1.5 *(Optioneel)* Vul hier de gegevens in van de plaatsvervangende verantwoordelijke onderzoeker.

(Titel) Naam en voorletters	10.2.e 10.2.e
Functie	10.2.e
Afdeling	
Telefoonnummer	
E-mailadres	

1.6	*(Optioneel)* Vul hier de gegevens in van de persoon die er verantwoordelijk voor is dat de uitvoering van het project in overeenstemming is met de projectvergunning.	(Titel) Naam en voorletters	☐ Dhr. ☐ Mw.
		Functie	
		Afdeling	
		Telefoonnummer	
		E-mailadres	
1.7	Is er voor deze projectaanvraag een gemachtigde?	☐ Ja > *Stuur dan het ingevulde formulier Melding Machtiging mee met deze aanvraag*	
		☐ Nee	

2 Over uw aanvraag

2.1	Wat voor aanvraag doet u?	☒ Nieuwe aanvraag > Ga verder met vraag 3
		☐ Wijziging op (verleende) vergunning die negatieve gevolgen kan hebben voor het dierenwelzijn Vul uw vergunde projectnummer in en ga verder met vraag 2.2
		☐ Melding op (verleende) vergunning die geen negatieve gevolgen kan hebben voor het dierenwelzijn Vul uw vergunde projectnummer in en ga verder met vraag 2.3
2.2	Is dit een *wijziging* voor een project of dierproef waar al een vergunning voor verleend is?	☐ Ja > Beantwoord dan in het projectplan en de niet-technische samenvatting alleen de vragen waarop de wijziging betrekking heeft en onderteken het aanvraagformulier
		☐ Nee > Ga verder met vraag 3
2.3	Is dit een *melding* voor een project of dierproef waar al een vergunning voor is verleend?	☐ Nee > Ga verder met vraag 3
		☐ Ja > Geef hier onder een toelichting en ga verder met vraag 6

3 Over uw project

3.1	Wat is de geplande start- en einddatum van het project?	Startdatum	01 - 1 - 2018
		Einddatum	31 - 12 - 2023
3.2	Wat is de titel van het project?	Canine Vaccine Development	
3.3	Wat is de titel van de niet-technische samenvatting?	Onderzoek en ontwikkeling van nieuwe hondenvaccins	
3.4	Wat is de naam van de Dierexperimentencommissie (DEC) aan wie de instellingsvergunninghouder doorgaans haar projecten ter toetsing voorlegt?	Naam DEC	10.2.g
		Postadres	
		E-mailadres	10.2.e

4 Betaalgegevens

4.1 Om welk type aanvraag gaat het?

☒ Nieuwe aanvraag Projectvergunning € 1.684 Lege

☐ Wijziging € Lege

4.2 Op welke wijze wilt u dit bedrag aan de CCD voldoen.
Bij een eenmalige incasso geeft u toestemming aan de CCD om eenmalig het bij 4.1 genoemde bedrag af te schrijven van het bij 1.2 opgegeven rekeningnummer.

☐ Via een eenmalige incasso

☒ Na ontvangst van de factuur

5 Checklist bijlagen

5.1 Welke bijlagen stuurt u mee?

Verplicht

☒ Projectvoorstel

☒ Niet-technische samenvatting

Overige bijlagen, indien van toepassing

☐ Melding Machtiging

☐

6 Ondertekening

6.1 Print het formulier uit, onderteken het en stuur het inclusief bijlagen via de beveiligde e-mailverbinding naar de CCD of per post naar:

Centrale Commissie
Dierproeven
Postbus 20401
2500 EK Den Haag

Ondertekening door de instellingsvergunninghouder of gemachtigde (zie 1.7). De ondergetekende verklaart:

- dat het projectvoorstel is afgestemd met de Instantie voor Dierenwelzijn.
- dat de personen die verantwoordelijk zijn voor de opzet van het project en de dierproef, de personen die de dieren verzorgen en/of doden en de personen die de dierproeven verrichten voldoen aan de wettelijke eisen gesteld aan deskundigheid en bekwaamheid.
- dat de dieren worden gehuisvest en verzorgd op een wijze die voldoet aan de eisen die zijn opgenomen in bijlage III van richtlijn 2010/63/EU, behalve in het voorkomende geval de in onderdeel F van de bijlage bij het bij de aanvraag gevoegde projectvoorstel gemotiveerde uitzonderingen.
- dat door het ondertekenen van dit formulier de verplichting wordt aangegaan de leges te betalen voor de behandeling van de aanvraag.
- dat het formulier volledig en naar waarheid is ingevuld.

Naam	10.2.e
Functie	10.2.e en 10.2.g
Plaats	10.2.g
Datum	16 - 10 - 2017
Handtekening	10.2.e

Aanvraag
Projectvergunning Dierproeven
Administratieve gegevens

- U bent van plan om één of meerdere dierproeven uit te voeren.
- Met dit formulier vraagt u een vergunning aan voor het project dat u wilt uitvoeren. Of u geeft aan wat u in het vergunde project wilt wijzigen.
- Meer informatie over de voorwaarden vindt u op de website www.centralecommissiedierproeven.nl. of in de toelichting op de website.
- Of bel met 0900-2800028 (10 ct/min).

1 Gegevens aanvrager

1.1 Heeft u een deelnemernummer van de NVWA?
Neem voor meer informatie over het verkrijgen van een deelnemernummer contact op met de NVWA.

☐ Ja > *Vul uw deelnemernummer in* 10.2.g

☐ Nee > *U kunt geen aanvraag doen*

1.2 Vul de gegevens in van de instellingsvergunninghouder die de projectvergunning aanvraagt.

Naam instelling of organisatie	10.2.g
Naam van de portefeuillehouder of diens gemachtigde	10.2.e
KvK-nummer	10.2.g
Straat en huisnummer	
Postbus	
Postcode en plaats	

1.3 Vul de gegevens van het postadres in.
Alle correspondentie van de CCD gaat naar de portefeuillehouder of diens gemachtigde en de verantwoordelijke onderzoeker.

IBAN	
Tenaamstelling van het rekeningnummer	

1.4 Vul de gegevens in van de verantwoordelijke onderzoeker.

(Titel) Naam en voorletters	10.2.e 10.2.e
Functie	10.2.e
Afdeling	
Telefoonnummer	
E-mailadres	

1.5 *(Optioneel)* Vul hier de gegevens in van de plaatsvervangende verantwoordelijke onderzoeker.

(Titel) Naam en voorletters	10.2.e 10.2.e
Functie	10.2.e
Afdeling	
Telefoonnummer	
E-mailadres	

1.6	*(Optioneel)* Vul hier de gegevens in van de persoon die er verantwoordelijk voor is dat de uitvoering van het project in overeenstemming is met de projectvergunning.	(Titel) Naam en voorletters	☐ Dhr. ☐ Mw.
		Functie	
		Afdeling	
		Telefoonnummer	
		E-mailadres	
1.7	Is er voor deze projectaanvraag een gemachtigde?	☐ Ja > *Stuur dan het ingevulde formulier Melding Machtiging mee met deze aanvraag*	
		☐ Nee	

2 Over uw aanvraag

2.1	Wat voor aanvraag doet u?	☒ Nieuwe aanvraag > Ga verder met vraag 3
		☐ Wijziging op (verleende) vergunning die negatieve gevolgen kan hebben voor het dierenwelzijn Vul uw vergunde projectnummer in en ga verder met vraag 2.2
		☐ Melding op (verleende) vergunning die geen negatieve gevolgen kan hebben voor het dierenwelzijn Vul uw vergunde projectnummer in en ga verder met vraag 2.3
2.2	Is dit een *wijziging* voor een project of dierproef waar al een vergunning voor verleend is?	☐ Ja > Beantwoord dan in het projectplan en de niet-technische samenvatting alleen de vragen waarop de wijziging betrekking heeft en onderteken het aanvraagformulier
		☐ Nee > Ga verder met vraag 3
2.3	Is dit een *melding* voor een project of dierproef waar al een vergunning voor is verleend?	☐ Nee > Ga verder met vraag 3
		☐ Ja > Geef hier onder een toelichting en ga verder met vraag 6

3 Over uw project

3.1	Wat is de geplande start- en einddatum van het project?	Startdatum	01 - 1 - 2018
		Einddatum	31 - 12 - 2023
3.2	Wat is de titel van het project?	Canine Vaccine Development	
3.3	Wat is de titel van de niet-technische samenvatting?	Onderzoek en ontwikkeling van nieuwe hondenvaccins	
3.4	Wat is de naam van de Dierexperimentencommissie (DEC) aan wie de instellingsvergunninghouder doorgaans haar projecten ter toetsing voorlegt?	Naam DEC	10.2.g
		Postadres	
		E-mailadres	10.2.e

4 Betaalgegevens

4.1 Om welk type aanvraag gaat het?

☒ Nieuwe aanvraag Projectvergunning € 1.684 Lege

☐ Wijziging € Lege

4.2 Op welke wijze wilt u dit bedrag aan de CCD voldoen.
Bij een eenmalige incasso geeft u toestemming aan de CCD om eenmalig het bij 4.1 genoemde bedrag af te schrijven van het bij 1.2 opgegeven rekeningnummer.

☐ Via een eenmalige incasso

☒ Na ontvangst van de factuur

5 Checklist bijlagen

5.1 Welke bijlagen stuurt u mee?

Verplicht

☒ Projectvoorstel

☒ Niet-technische samenvatting

Overige bijlagen, indien van toepassing

☐ Melding Machtiging

☐

6 Ondertekening

6.1 Print het formulier uit, onderteken het en stuur het inclusief bijlagen via de beveiligde e-mailverbinding naar de CCD of per post naar:

Centrale Commissie
Dierproeven
Postbus 20401
2500 EK Den Haag

Ondertekening door de instellingsvergunninghouder of gemachtigde (zie 1.7). De ondergetekende verklaart:

- dat het projectvoorstel is afgestemd met de Instantie voor Dierenwelzijn.
- dat de personen die verantwoordelijk zijn voor de opzet van het project en de dierproef, de personen die de dieren verzorgen en/of doden en de personen die de dierproeven verrichten voldoen aan de wettelijke eisen gesteld aan deskundigheid en bekwaamheid.
- dat de dieren worden gehuisvest en verzorgd op een wijze die voldoet aan de eisen die zijn opgenomen in bijlage III van richtlijn 2010/63/EU, behalve in het voorkomende geval de in onderdeel F van de bijlage bij het bij de aanvraag gevoegde projectvoorstel gemotiveerde uitzonderingen.
- dat door het ondertekenen van dit formulier de verplichting wordt aangegaan de leges te betalen voor de behandeling van de aanvraag.
- dat het formulier volledig en naar waarheid is ingevuld.

Naam	10.2.e
Functie	
Plaats	10.2.g
Datum	16 - 10 - 2017
Handtekening	10.2.e

Form
Project proposal

- This form should be used to write the project proposal for animal procedures.
- The appendix 'description animal procedures' is an appendix to this form. For each type of animal procedure, a separate appendix 'description animal procedures' should be enclosed.
- For more information on the project proposal, see our website (www.centralecommissiedierproeven.nl).
- Or contact us by phone (0900-2800028).

1 General information

1.1	Provide the approval number of the 'Netherlands Food and Consumer Product Safety Authority'.	10.2.g
1.2	Provide the name of the licenced establishment.	
1.3	Provide the title of the project.	Canine Vaccine Development

2 Categories

2.1 Please tick each of the following boxes that applies to your project.

- ☐ Basic research
- ☒ Translational or applied research
- ☒ Regulatory use or routine production
- ☐ Research into environmental protection in the interest of human or animal health or welfare
- ☐ Research aimed at preserving the species subjected to procedures
- ☐ Higher education or training
- ☐ Forensic enquiries
- ☐ Maintenance of colonies of genetically altered animals not used in other animal procedures

3 General description of the project

3.1 Background

Describe the project (motivation, background and context) with respect to the categories selected in 2.

- For legally required animal procedures, indicate which statutory or regulatory requirements apply (with respect to the intended use and market authorisation).
- For routine production, describe what will be produced and for which uses.
- For higher education or training, explain why this project is part of the educational program and describe the learning targets.

Rationale

Companion animal ownership is thought to confer significant psychological as well as physical health benefits. Estimates put dog ownership in the EU at approximately 61 million dogs and worldwide at

approximately 223 million dogs. Vaccination is perhaps the single most important measure that can be taken to ensure these animals remain healthy. Therefore the [redacted]

Disease causing organisms continue to evolve becoming more or perhaps less pathogenic and as new viral and bacterial strains appear it is important to determine whether vaccines continue to provide the necessary protection. The factors which govern how the pathogenicity changes are complex and not completely understood. We therefore need to be able to investigate such concerns when they arise and if necessary develop [redacted]

The two key requirements of any vaccine are (i) that it is safe, and (ii) that it is efficacious. Vaccination is a medical treatment that is administered to healthy individuals. Therefore, apart from perhaps some transient minor discomfort it is important that no harm is done. With regard to efficacy the use of a vaccine can only be justified when significant protection from disease and/or infection is shown. Therefore it is important that vaccines are updated to take account of the changes occurring in circulating field strains resulting in new vaccines or improvement of vaccines already on the market.

Vaccine development

The current project proposal covers the development phase for [redacted] dog vaccines including the [redacted]
The animal studies that are performed during the development phase are necessary to prepare the registration dossier that is submitted to the regulatory authorities. The requirements for these studies are laid down in EU directives, the Pharmacopoeia Europaea (Ph.Eur) and guidelines and regulations of the European Medicines Agency and other international regulatory bodies. Several batches of the new vaccine are produced and full quality control testing is performed in order to meet the requirements of the regulatory authorities by providing efficacy and safety data of these batches.

Once the registration dossier has been submitted, additional studies may be requested by the regulatory authorities during the licensing procedure.

For most vaccines, registration and launch of the product is not necessarily the end of the R&D involvement. In most cases continued development and improvement are needed to update existing product characteristics. [redacted]

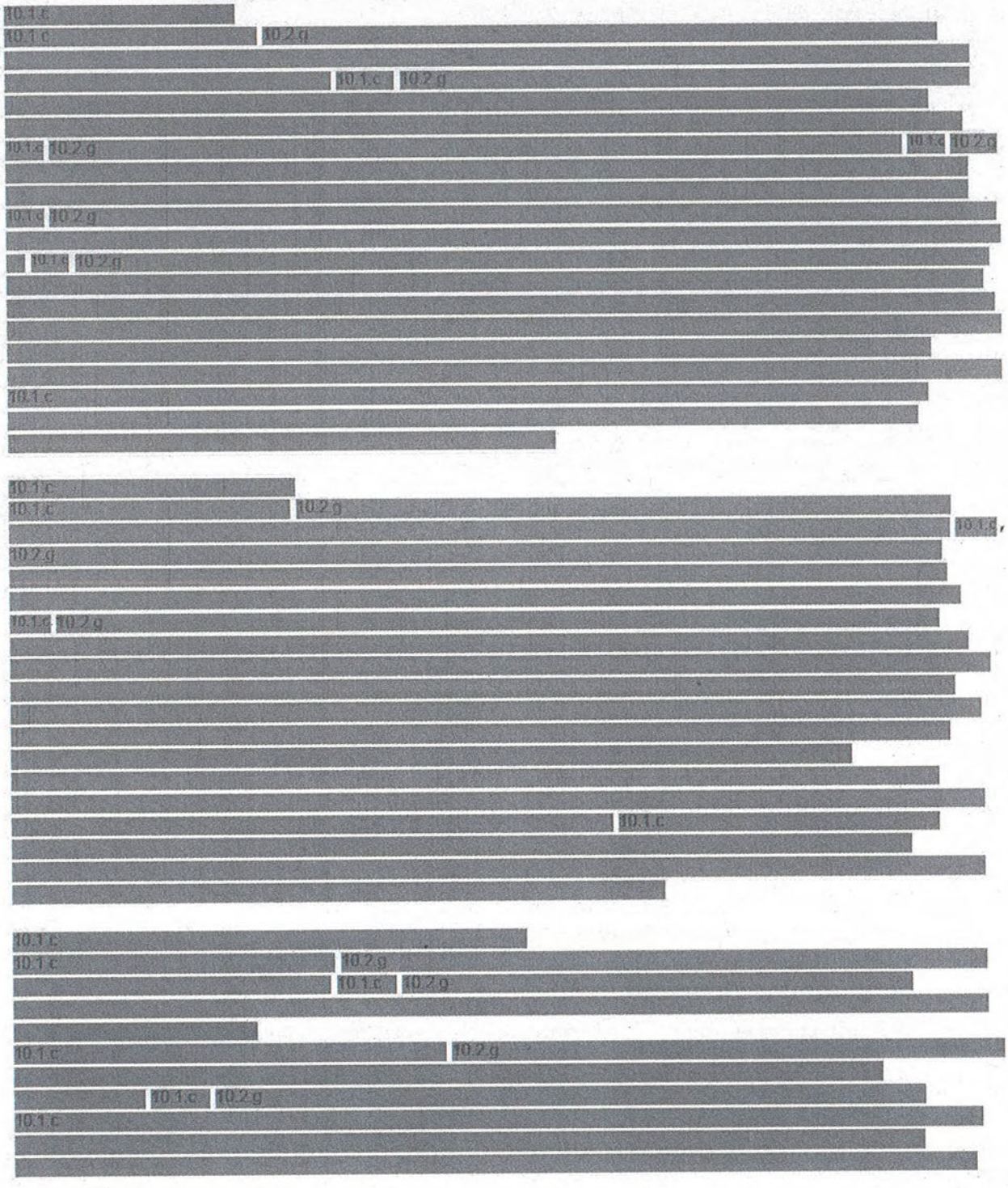
Regulatory Requirements
The requirements for the development of specific veterinary vaccines (i.e., per pathogen and animal species) are set out in a series of monographs published in the European Pharmacopoeia. There are general monographs outlining the studies required to demonstrate safety and efficacy of veterinary vaccines (5.2.6 and 5.2.7). In addition there are specific monographs for a live and inactivated [redacted] vaccine, a live [redacted] vaccine, a live and inactivated [redacted] vaccine, a live [redacted] vaccine, a live and inactivated [redacted] vaccine, an inactivated [redacted] vaccine and a live [redacted] vaccine for dogs, respectively. When there is no specific monograph for a live vaccine, but there is one for an inactivated product or vice versa, regulators will use the existing monograph as a guide when assessing study design, parameters and results. These monographs, together with relevant European Medicines Agency guidelines and regulations, set out the parameters which should be addressed such as reversion to virulence, safety after administration of an overdose and repeated dose of vaccine. They also indicate minimum group sizes, minimum study duration of and in efficacy studies the minimum levels of clinical signs in non-vaccinated control animals.

Canine infectious diseases

There are a number of canine diseases for which 10.2.g has a vaccine development program, as detailed below.

Major pathogens

There are currently 10.1.c important canine pathogens for which vaccination is routinely administered.



10.1.c

10.1.c 10.2.g

10.1.c

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10.1.c 10.2.g

10.1.c 10.2.g 10.1.c

10.1.c

10.1.c 10.2.g

10.2.g

10.2.g

10.1.c

10.1.c

10.2.g 10.1.c 10.2.g

10.1.c 10.2.g 10.1.c

10.2.g 10.1.c 10.2.g

10.1.c

10.2.g

10.1.c 10.2.g

10.1.c 10.2.g 10.1.c

10.1.c

Minor pathogens and emerging diseases

10.2.g

[redacted]

Current products

[redacted] licenses a wide range of vaccines against the [redacted] canine pathogens in multiple combinations, for example: [redacted]

R&D projects and historical progress

Work carried out during the last five years has been successful in bringing a number of [redacted] products to the market [redacted]. Furthermore, a major "alternative for animal testing" achievement was the development and validation of two *in vitro* batch potency tests in order to replace the worldwide used "gold standard" hamster [redacted] test for the existing [redacted]

[redacted]

At first sight it would seem that no further development work is needed once a vaccine against a certain pathogen has been developed and licensed. However, in reality the optimization of the manufacturing of [redacted] vaccine range is a continuous process. The [redacted] aims to improve its products to [redacted]

3.2 Purpose

Describe the project's main objective and explain why this objective is achievable.

- If the project is focussed on one or more research objectives, which research questions should be addressed during this project?
- If the main objective is not a research objective, which specific need(s) does this project respond to?

The goal of the project is the development of [redacted] vaccines. The outcome of the project is the licensing of [redacted] vaccines that fulfil important [redacted] in the field of canine healthcare or a successful [redacted] vaccines.

1) As part of development of [redacted] vaccines: To generate the efficacy and safety data to be included in marketing authorization applications (registration dossiers) for [redacted] canine vaccines. The [redacted] vaccines will have already shown proof of concept (i.e. induction of protection combined with an acceptable safety profile) in the [redacted] of vaccine development, and the efficacy and safety studies to be undertaken in the current development proposal are needed to fulfil the regulatory requirement. The outcome of the objective is the licensing of [redacted] vaccines that fulfil important needs in the field.
2) As part of [redacted] vaccine registrations: To generate new efficacy and/or safety data needed to [redacted] registration dossiers. When [redacted] are made to active ingredients or [redacted] efficacy claims need to be [redacted] to a licensed vaccine or [redacted] of licensed vaccines ([redacted]) needs to be submitted, current registration dossiers may have to be [redacted] by [redacted] of new efficacy and/or safety studies. The outcome of the objective is a successful registration [redacted] vaccines.

3.3 Relevance

What is the scientific and/or social relevance of the objectives described above?

Vaccines are the most effective method for prevention or eradication of diseases. Further [redacted] of the [redacted] vaccine [redacted] will bring safer, more efficacious vaccines, including vaccines against [redacted]. Also, [redacted] diseases can be managed more effectively, [redacted] vaccination [redacted], when vaccines are developed that can be used [redacted] or [redacted] vaccines, or even in [redacted] products. In addition, canine vaccines against [redacted] pathogens like [redacted] will protect dogs as well as [redacted] from infection with the pathogens included in the efficacy claims of these vaccines.
The prospects are that the new vaccines will further reduce animal suffering and the use of antibiotics, and increase animal welfare and healthcare for dogs.

3.4 Research strategy

3.4.1 Provide an overview of the overall design of the project (strategy).

Prior to the development phase a safety and efficacy profile has been generated in feasibility studies during [redacted]. As a result [redacted] vaccines were [redacted].
For licensure of candidate vaccines specific regulatory studies are required. These development studies are broadly split into the following:

1) Efficacy studies. Determination of vaccine efficacy requires that dogs are 'challenged', that is to say that they are exposed to the virulent organism against which the vaccine is targeted. For vaccines against some pathogens the specific efficacy criteria that have to be fulfilled are prescribed in e.g. a monograph of the Ph.Eur. When doing efficacy studies, it is attempted to find an immunological correlate of protection, so that in further studies efficacy can be evaluated on the basis of e.g. the serological response after vaccination instead of challenge.
2) Safety studies: Safety of vaccine candidates has also to be evaluated in dogs to show that systemic and local (injection site) reactions after vaccination, if any, are acceptable. For vaccines against some pathogens, the specific safety criteria that have to be fulfilled are prescribed in e.g. a monograph of the Ph.Eur.

At the start of the development phase of a new vaccine, it is decided in which area(s) of the world the product is intended to be licensed. This will determine in detail which types of studies have to be performed to satisfy local regulatory requirements. Also at that time the minimum vaccination age, the vaccination schedule and the intended label claims are set, which will further determine the types of studies that have to be performed.

Registration dossiers need to contain a comprehensive set of efficacy and safety studies in the target animal to allow regulatory bodies to make a sound risk-benefit analysis that is the basis for their decision on the marketing approval of a [redacted] product. Therefore, all studies have to be performed with the formulation to be marketed and all production and quality controls methods should be finalized before start of the studies. In addition, results of laboratory safety and efficacy studies will have to be provided to authorities in order to be able to obtain a permit for the field studies (which are outside the scope of this project) that are to be included in the dossier. During the evaluation of the registration dossier, additional animal studies may be requested by the regulatory authorities. In addition non target animals are also used in efficacy studies to determine the potency of a candidate vaccine in non-target animals which correlates with the efficacy of a vaccine in the target animal. Also for safety studies, non-target animals are used particularly needed in the framework of a [redacted].

Similarly, when [redacted] the characteristics of a [redacted] vaccine, e.g. for showing [redacted] or protection against a new serotype of the pathogen, the number of studies required depends on the regulations and guidelines for registration variation procedures.

3.4.2 Provide a basic outline of the different components of the project and the type(s) of animal procedures that will be performed.

The development phase of a [redacted] vaccine will consist of one or more of the following types of animal experiments (described in detail in appendices 1 through 5).

1. Efficacy studies using target and non-target animals: Once a challenge model has been established, the efficacy of candidate vaccines against a pathogen can be evaluated. The efficacy of vaccines (of the final product/formulation) should be shown under controlled laboratory conditions as described in Ph.Eur 5.2.7 (Evaluation of efficacy of veterinary vaccines and immunosera) or vaccine specific monographs, EU Directive 2009/9/EC amending Directive 2001/82/EC (Community code relating to veterinary medicinal products) and national guidelines and regulations outside the EU. For all efficacy claims (e.g. protection against infection/disease, reduction of clinical signs, reduction of shedding, onset and duration of immunity) to be made for a [redacted] product, proof should be provided by showing a meaningful and statistical significant difference between vaccinated animals and unvaccinated controls in a challenge model (vaccination-challenge studies). [redacted]

Studies will be performed according to the following basic set-up (challenge will not be performed in case an immunological marker for protection can be monitored):

- Administration of a [redacted] vaccine
- Infection with a pathogen
- Observation of clinical signs post-challenge
- Sampling (e.g. for [redacted])
- Necropsy to investigate [redacted] changes (e.g. [redacted])

2. Safety studies using target and non-target animals: To be able to make a proper risk-benefit analysis for a [redacted] product, all vaccines have to be tested in safety studies in the target animal (Ph.Eur 5.2.6 (Evaluation of safety of veterinary vaccines and immunosera), EU Directive 2009/9/EC amending Directive 2001/82/EC (Community code relating to veterinary medicinal products) and national guidelines and regulations). This generally means observation for abnormal systemic (clinical signs, body temperature etc.) and local (injection site) reactions after administration.
Inactivated and subunit vaccines usually contain an adjuvant that enhances the immune response to the antigen(s) in the vaccine. Unfortunately, although the adjuvant preparations themselves can be considered safe, the combination of antigen and adjuvant sometimes results in unwanted systemic and/or local reactions after vaccination. Therefore, for each new inactivated or subunit vaccine the effect on the animals' general health, determined by observing clinical signs (e.g. general demeanour, body temperature, appetite etc.) and injection site reactions has to be determined.
Live vaccines have to be shown not to induce disease. Therefore live vaccines, [redacted], will have to be evaluated for persistence and dissemination in vaccinated animals and their ability to spread to [redacted] animals. Live vaccines will also be tested for reversion to virulence, i.e. re-isolation of the vaccine from vaccinated animals followed by administration back into other animals up to five times in total. For live vaccines that are derived from a pathogen with a broad host range and/or zoonotic potential, it is necessary to also investigate the safety for non-target species that may come into contact with the vaccine according to Ph.Eur 5.2.6 (Evaluation of safety of veterinary vaccines and immunosera), EU Directive 2009/9/EC amending Directive 2001/82/EC (Community code relating to veterinary medicinal products), national guidelines and regulations [redacted]
For vaccines that are intended to be given to [redacted] animals, also the effect on [redacted] must be investigated.

Studies will be performed according to the following basic set-up:

- Administering the candidate vaccine
- Observation of systemic and local reactions post vaccination
- Monitoring of persistence and excretion of the vaccine by sampling of [redacted]
- Necropsy to investigate [redacted] changes at the injection site and re-isolation of the

vaccine

3.4.3 Describe the coherence between the different components and the different steps of the project. If applicable, describe the milestones and selection points.

At [redacted], all [redacted] projects are subject to regular review by [redacted]. If the [redacted] a vaccine against the specific disease an evaluation will be made as to whether that vaccine [redacted] which in most cases is the preferred situation as [redacted] studies are [redacted] or [redacted] needs to be developed. Only vaccine candidates for which the safety and efficacy data obtained during the [redacted] indicate a high probability of success are approved for further development.

At the start of a development project, the project team agrees on the types of studies required and the sequence of these studies.

[redacted]

The safety of the vaccine is investigated in parallel, but in separate studies, as the dose levels to be tested are different from the levels in the efficacy studies. For live vaccines, the following safety characteristics must be investigated: i) dissemination of the strain in the vaccinated animal, ii) shedding of the strain, iii) the potential to spread to in-contact animals and iv) the potential to revert to virulence by animal-to-animal passage.
Once these criteria are met, the safety of the final product composition (including any excipients such as [redacted] has to be demonstrated in animals of the most susceptible categories: animals of the [redacted] age group intended for vaccination. If a vaccine will be licenced for use during [redacted], the safety has also to be demonstrated in these categories.

All of the above mentioned studies are mandatory for the regulatory approval of companion animal vaccines.

[redacted]

3.4.4 List the different types of animal procedures. Use a different appendix 'description animal procedures' for each type of animal procedure.

Serial number	Type of animal procedure
1	Efficacy studies in dogs
2	Studies in non-target animals to determine efficacy
3	Safety studies in dogs
4	Safety studies in non-target animals

Appendix
Description animal procedures

- This appendix should be enclosed with the project proposal for animal procedures.
- A different appendix 'description animal procedures' should be enclosed for each type of animal procedure.
- For more information, see our website (www.centralecommissiedierproeven.nl).
- Or contact us by phone (0900-2800028).

1 General information

1.1 Provide the approval number of the 'Netherlands Food and Consumer Product Safety Authority'.

10.2.g

1.2 Provide the name of the licenced establishment.

1.3 List the serial number and type of animal procedure.

Use the serial numbers provided in Section 3.4.4 of the Project Proposal form.

Serial number	Type of animal procedure
1	Efficacy studies in dogs

2 Description of animal procedures

A. Experimental approach and primary outcome parameters

Describe the general design of the animal procedures in relation to the primary outcome parameters. Justify the choice of these parameters.

The aim of the work to be carried out under this DAP is to develop canine vaccines that are efficacious in in reducing or preventing one or more parameters of the disease caused by the pathogens(s) involved. Efficacy against different pathogen serotypes may also be evaluated. In the absence of a surrogate (serological) marker, the efficacy of a vaccine is tested based on clinical parameters depending on the disease and/or requirements stated in specific Ph.Eur monographs, or other relevant legislation. Dogs that have received the recommended vaccination schedule (or 10.1.c protection) and unvaccinated control animals will be challenged after a specific interval. A label claim can only be obtained for those aspects of a disease that are measured in the respective challenge model and for which a statistically significant difference between vaccinates and controls are shown. In general, efficacy of a vaccine has to be demonstrated for each of the vaccination routes and schedules and for each category of target animal (e.g. age, biological status) to substantiate the claims made for the product in the registration dossier. When testing compatibility of vaccines 10.1.c , EU guidelines dictate that in principle for all efficacy claims made for the products protection should be proven by challenge for all components, unless an immunological correlate for protection has been established. The types of studies in the target animal that in general need to be undertaken are the following:

1. Confirmation of the 10.1.c study); this study is mostly combined with the study under 2
2. Determination of the minimum interval (between completion basic vaccination and challenge) after which protection can be observed (onset of immunity study)
3. Determination of the maximum interval (between completion basic vaccination and challenge) after which protection can be observed (duration of immunity study)
4. Determination of the effect of 10.1.c on the level of protection (10.1.c study; this study may include 10.1.c)

5. Determination of the effect of a single (yearly or two-yearly or three-yearly) re-vaccination, using the desired interval after the basic vaccination(s).
6. In case of more than one vaccination in the basic vaccination schedule: determination of the minimum and maximum interval between the vaccinations

When challenge (administration of disease agent, i.e. pathogen is required, one or more of the following parameters will be evaluated:

- Clinical signs (e.g. changes in general health)
- Body temperature (rectal temperature, or transponder)• Virus or bacterial shedding or dissemination (swabbing
- Serological response (amnestic response), viraemia or bacteraemia, or changes (blood sampling)
- Post-mortem examination

If an immunological correlate has been established, the evaluation of the immune response (antibody levels) will suffice (blood sampling) and therefore no challenge will be needed.

From a regulatory standpoint animals must be monitored for differing lengths of time following challenge depending on the challenge pathogen. In a successful challenge study control animals generally develop disease well within the stated time period.

During the development of a vaccine, efficacy studies may be run that include group(s) of dogs vaccinated with vaccines. The inclusion of these animals is important for ensuring that any vaccine under development is It allows the vaccine to be properly as it and provides scientifically to support this. Ultimately the data may be published so that veterinarians are able to make informed, scientific, decisions on which vaccines to use in their practice.

Describe the proposed animal procedures, including the nature, frequency and duration of the treatment. Provide justifications for the selected approach.

of the following treatments will be employed depending on the characteristics of the disease involved
and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al.,2016.

1. Application subcutaneous transponder , to measure body temperature
2. Blood sampling
3. Administration of vaccine
4. Challenge
5. Administration of diuretic
6. Cystocentesis: bladder puncture
7. Measurement of rectal temperature
8. Weighing
9. Swabbing
10. Sedation
11. Euthanasia

The duration of all procedures described above are expected to be carried out within a matter of minutes. The length of the observation period after challenge depends on the incubation period of the pathogen, but is generally

10.2.g

10.1.c [redacted]

10.1.c [redacted] one or two small blood samples and/or swabs may be taken. Procedures will be limited and of mild discomfort. If required, antibiotic treatment may be administered on the advice of the attending veterinarian.

Describe which statistical methods have been used and which other considerations have been taken into account to minimise the number of animals.

For some vaccines, the minimum number of animals that must be used are specified in Ph.Eur monographs or EMA guidance papers. In these instances all measures will be taken to meet the mandatory requirements of the regulatory authorities whilst using the minimum possible number of animals.
When animal numbers are not specified, the minimum number of animals required to give a sufficient likelihood of a statistically significant result will be used. In this way it can be demonstrated that the test vaccine is efficacious in comparison with the control group. In particular, the variance in the groups together with the magnitude of effect will be used in power calculations to achieve 80% power at the 95% confidence level (regarded by regulatory authorities as the standard by which such experiments should be designed).

B. The animals

Specify the species, origin, estimated numbers, and life stages. Provide justifications for these choices.

Dogs (Beagles) of both sexes will be used for this type of animal experiment.

Purchase of animals:
Dogs will be derived from SPF breeding facilities or purchased from commercial certified suppliers of laboratory dogs.

Numbers:
Based on the experience over the last 5 years and the current 10.1.c [redacted], the total expected number of dogs is 600. The number of efficacy trials needed for all the projects running over a 5 year time period is 45, with a mean groups size of 8-20 dogs per experiment depending on the project.

Age of animals:
The age of dogs used for vaccine development varies from 10.1.c [redacted] old to 10.1.c [redacted]

The table below specifies the discomfort that is predicted for the different pathogens that might be included in development projects over the next 5 years. 10.1.c [redacted]

10.2.g

Pathogen	Discomfort of disease (% of animals)	Duration of Maximum Discomfort
10.1.c	Mild (≥93%) Moderate (≤7%)	Max. 1 week
	Mild (≥70%) Moderate (≤30%)	Max. 1 week
	Mild (≥70%) Moderate (≤20%) Severe (≤10%)	Max. 1 week
	Mild (≥70%) Moderate (≤30%)	Max. 1 week
	Mild (≥70%) Moderate (≤20%) Severe (≤10%)	Max. 1 day
	Mild (≥70%) Moderate (≤15%) Severe (≤15%)	Max. 1 day
	Mild (≥70%) Moderate (≤15%) Severe (≤15%)	Max. 1 day
	Mild (≥70%) Moderate (≤22%) Severe (≤8%)	Max. 1 day

*Pathogens may be given individually or in combination

10.1.c

C. Re-use

Will the animals be re-used?

☐ No, continue with question D.

☒ Yes > Explain why re-use is considered acceptable for this animal procedure.

Animals may be re-used if they have only experienced mild or moderate discomfort in the preceding experiment, the subsequent study will not exceed moderate, and if veterinarian confirmation of fitness has been given. Re-use will be according to Directive 2010/63/EU, Article 16. In addition, the immunological status should be acceptable for the scientific purpose of the study.

Are the previous or proposed animal procedures classified as 'severe'?

☒ No

☐ Yes> Provide specific justifications for the re-use of these animals during the procedures.

D. Replacement, reduction, refinement

10.2.g

Describe how the principles of replacement, reduction and refinement were included in the research strategy, e.g. the selection of the animals, the design of the procedures and the number of animals.

Replacement:
Animals must be used for these studies because there are no suitable alternatives or models for the induction of immunity in a whole organism or for the colonization of living tissues as complex as those found in the whole animal for which these vaccines are intended to induce protection. The use of the target animal is specified in the Ph.Eur monographs or other legislations.

Reduction:
The number of animals used will be reduced wherever possible without endangering the scientific integrity of the work. Study protocols will be designed to combine the collection of data on as many different parameters as possible within a study in order to minimise the total number of animals used. Where possible the same control group will be used for multiple comparisons in order to reduce the number of animals being required. The minimum numbers of animals required in safety and efficacy studies are set out in the respective European Pharmacopoeia monographs and EMA guidelines. In many cases, the number of animals stipulated by the guidelines is small. From earlier vaccine research work, challenge models have been refined and are robust enough to allow the use of the minimal numbers of animals. According to internal procedures, each study protocol will be reviewed by the Animal Welfare Body and (where applicable) a statistician.

Animals will be re-used where possible, keeping animal welfare in mind without endangering the scientific integrity of the work.

Refinement:
Dogs are the target animal, but if there are [redacted] species that could be a model for the dog diseases that will be studied these species will be used. Regulations and guidelines determine to a large extent what kind of data must be generated and, to a large extent, this determines what form of models and methods should be employed.

The classical method to prove protection of a new vaccine is efficacy in a vaccination-challenge test. However, if immunological correlates of protection (e.g. a serological response) can be used to prove efficacy this will be used rather than challenge tests. When a challenge model is mandated, clearly defined humane endpoints will be applied and staff will be fully trained to recognize animals that are experiencing discomfort. Animals will be closely monitored and frequent checks will be made to ensure that no animal is left suffering.

Where challenge efficacy studies are mandated, clearly defined humane endpoints specific to the pathogen will be described and where more virulent challenge viruses, bacteria, or a novel isolate are used the frequency of observation will be increased during any anticipated critical period. Throughout all challenge phases, the welfare of the animals will be monitored by experienced animal technicians under the care of the attending veterinarian. Animals will be euthanised before reaching the humane endpoint when it is clear that continuation would not provide any additional scientific data. Previous in house experience with the diseases to be studied has led to the refinement of the challenge models. In most cases, they are robust enough to allow control groups to be of the minimal number.

An ongoing assessment of the challenge models used will be undertaken. We will try to find a correlation between changes in relevant parameters and the (start of) clinical signs. If the results are acceptable for regulatory submission, a validated change in [redacted] parameter(s) may be implemented so that an earlier scientific endpoint can be reached with fewer clinical signs (and therefore discomfort).

Explain what measures will be taken to minimise 1) animal suffering, pain or fear and 2) adverse effects on the environment.

In general dogs are always housed socially, but animals may have to be (temporarily) separated due to fighting or because of veterinary concerns. In such cases, the group of dogs will be split up into subgroups to avoid separation of a single dog. Furthermore, to enhance animal welfare, environmental enrichment is provided to all animals. This will enable dogs to express their species-specific behavioural repertoire. Programs are in place for the housing and caring of animals exposed experimentally to pathogens, with emphasis on management and safety practices for containment (according to the

regulations of Biosafety level 1 – 3).

An active approach to providing environmental enrichment will be taken. Appropriate bedding and play materials will be provided, and new ideas for improving the general wellbeing of the animals sought.

For monitoring of the clinical health status of animals, all study animals will be checked at least 10.1.c by a certified person, or more frequently as required. Special attention will be paid to the general health of the animals as well as feed and water consumption. All daily observations are recorded. In case of any unexpected event, a clinical examination of the animal will be performed by an experienced animal technician.

Few if any adverse reactions are expected in the majority of dogs since the procedures that are being carried out are routine vaccinations, and small volumes 10.1.c of blood will be sampled. These procedures are minimally invasive. Efficacy studies using a challenge model however will require that all animals are exposed to the disease agent. This may result in clear clinical symptoms in unprotected animals. When it is clear that continuation would not provide any additional scientific data, every effort will be made to euthanize them before the humane endpoint is reached.

In order to prevent undue stress during a challenge procedure animal may be sedated. Sedation will be carried out using licensed agents and dosing regimens developed under guidance of a veterinary surgeon. Experience has shown that for certain procedures such as 10.1.c Therefore, in certain circumstances, it will be advantageous to both animal welfare and scientific consistency to make the decision to use sedation for certain procedures.

Repetition and duplication

E. Repetition

Explain what measures have been taken to ensure that the proposed procedures have not already been performed. If applicable, explain why repetition is required.

10.2.g. To show that vaccines are compatible 10.1.c a number of the safety and efficacy studies done with the individual products have to be repeated with the vaccines administered together according to international regulations and guidelines.

Accommodation and care

F. Accommodation and care

Is the housing and care of the animals used in experimental procedures not in accordance with Annex III of the Directive 2010/63/EU?

☒ No

☐ Yes > If this may adversely affect animal welfare, describe how the animals will be housed and provide specific justifications for these choices.

G. Location where the animals procedures are performed

Will the animal procedures be carried out in an establishment that is not licenced by the NVWA?

☒ No > Continue with question H.

☐ Yes > Describe this establishment.

Provide justifications for the choice of this establishment. Explain how adequate housing, care and treatment of the animals will be ensured.

Classification of discomfort/humane endpoints

H. Pain and pain relief

Will the animals experience pain during or after the procedures?

☐ No > Continue with question I.

☒ Yes > Will anaesthesia, analgesia or other pain relieving methods be used?

☒ No > Justify why pain relieving methods will not be used.

Blood sampling, swabbing, rectal temperatures, administration of the vaccine and weighing are procedures which may cause mild to moderate discomfort. Blood sampling and other biotechnical procedures have been described in Standard Operating Procedures (SOPs) and only well trained personnel will be responsible for carrying them out (GLP accredited procedures).

10.1.c [redacted]

The administration of the challenge inoculum will only induce short term mild to moderate discomfort, but depending on the nature of the subsequent challenge the discomfort of the challenge can range from mild and the absence of any clinical signs (10.1.c [redacted]), to moderate (10.1.c [redacted]), and severe (10.1.c [redacted]). Vaccination is expected to result in a significant reduction of clinical abnormalities after challenge compared to the unvaccinated control group.

Administration of a diuretic will induce only mild discomfort.
Cystocentesis will result in mild discomfort, but local analgesia may be used if necessary.
Repeated 10.1.c [redacted] is considered to cause mild discomfort.

For monitoring of the clinical health status of animals, all study animals will be checked at least 10.1.c [redacted] by a certified person. Special attention will be paid to the general health of the animals as well as feed and water consumption. All daily observations are recorded.

☒ Yes > Indicate what relieving methods will be used and specify what measures will be taken to ensure that optimal procedures are used.

In consultation with the veterinarian and study director it will be decided whether to apply adequate veterinary care to alleviate unexpected pain and/or distress 10.1.c [redacted] Possible options for analgesia: local analgesia, NSAIDs and opioids.

I. Other aspects compromising the welfare of the animals

Describe which other adverse effects on the animals' welfare may be expected?

10.1.c [redacted]

10.1.c

10.1.c

Explain why these effects may emerge.

10.2.g

These procedures are part of the study design to monitor the course of the disease model and the health and welfare of the animals.

Indicate which measures will be adopted to prevent occurrence or minimise severity.

Procedures (SOPs) and only well trained personnel will be responsible for the execution (GLP accredited procedures). The number of samplings will be done in accordance with the respective guidelines or if no requirements are given, the number of samplings is reduced to a minimum number required to for a valid evaluation of results.

J. Humane endpoints

May circumstances arise during the animal procedures which would require the implementation of humane endpoints to prevent further distress?

☐ No > Continue with question K.

☒ Yes > Describe the criteria that will be used to identify the humane endpoints.

To determine the efficacy of a vaccine it is necessary to challenge animals with the pathogenic organism. The severity of discomfort depends on the nature of the pathogen/disease. However, the duration of severe discomfort will be limited with the application of a humane endpoint if needed.
For each type of experiment test-specific humane endpoints will be described in the corresponding study protocol. Animals will be checked at least 10.1.c or more frequently as required, for general health by a certified animal technician so that any welfare concerns are detected quickly. All daily observations are recorded. Veterinarians and AWB members are on site and can be consulted when necessary.
The description and improvement of specific humane endpoints is an ongoing process in collaboration with the AWB, project leaders, veterinarians and animal animal technicians. During the development of currently licensed canine vaccines humane endpoints were set-up and appplied for most applicable canine pathogens/diseases. These will be used during future vaccine development and improved/adjusted when needed based on findings during the studies.
The following subsections summarise the clinical signs which will be used to determine the humane endpoints for each of the vaccination/challenge pathogens that are currently under investigation for which it is likely that a moderate or severe discomfort limit could be reached. Other pathogens (10.1.c) rarely, if ever, cause clinical signs resulting in moderate or severe discomfort in a laboratory environment. However, in the event that animals do display unexpected clinical signs whether or not these are believed to be study related, the veterinarian will be consulted and the necessary treatment will be administered or the animal will be euthanased.
The disease pathogenesis and expected adverse affects for each challenge organism are described below. Relevant refinements are given, together with specific and unambiguous humane endpoints. If the scientific endpoint is not reached at an earlier timepoint, an animal will be euthanased when it reaches the humane endpoint.

10.1.c
10.2.g 10.2.g

Refinement controls
Severe signs are expected since animals will usually be unvaccinated controls, so monitoring will be three or more times daily so that animals can be rapidly euthanised if the HEP is reached. Animals losing body temperature and shivering will be kept warm by providing heat lamps in certain areas. Treatment using electrolyte replacement may be effective but we regard it as unethical in this situation, where euthanasia is the best method of reducing suffering. Animals will be euthanised earlier if a scientific endpoint has been reached.

Humane endpoints
The humane endpoint will be applied when pathognomonic clinical signs of disease are reached:
10.2.g

10.1.c

10.2.g

[redacted]

Refinement controls

Severe signs are expected in this protocol since animals will usually be unvaccinated controls, so that from day 4 post challenge, monitoring will be three or more times daily so that animals can be rapidly euthanised if the HEP is reached. Animals losing body temperature and shivering will be kept warm by providing heat lamps in certain areas. Suffering can be ameliorated by gently sponging away caked on ocular discharge with cotton wool and warm water. Dogs will be euthanised earlier if a scientific endpoint has been reached.

Humane endpoints

The humane endpoint will be applied when pathognomonic clinical signs of disease are reached:

[redacted]

Refinement controls

Dogs [redacted] very rarely experience severe discomfort and therefore close monitoring at least once a day is considered sufficient unless there is cause for concern in one or more individuals. In this case, monitoring will be increased so that animals can be rapidly euthanised if the HEP is reached. Dogs may be euthanised earlier if a scientific endpoint has been reached or can be re-homed.

Humane endpoints

The humane endpoint will be applied if [redacted]

[redacted]

Refinement controls

[redacted] Severe discomfort may be expected in unvaccinated control animals, so monitoring will be as frequent as necessary so that animals can be rapidly euthanised if the HEP is reached. Animals losing body temperature and shivering will be kept warm by providing heat lamps. Dogs will be euthanised earlier if a scientific endpoint has been reached.

Humane endpoints

The humane endpoint will be applied when pathognomonic clinical signs of disease are reached:

[redacted]

[redacted]

Refinement controls
Dogs challenged with [redacted] rarely experience severe discomfort and therefore close monitoring at least once a day is considered sufficient unless there is cause for concern in one or more individuals. In this case, monitoring will be increased so that animals can be rapidly euthanised if the HEP is reached. Dogs will be euthanised earlier if a scientific endpoint has been reached.
Dogs challenged with [redacted] will be monitored three or more times daily from day 3 post-challenge onwards.

Humane endpoints
The humane endpoint will be applied when pathognomonic clinical signs of disease are reached:
[redacted]

Indicate the likely incidence.

In this type of experiment, up to 10% of the animals are expected to experience severe discomfort and may reach the humane endpoint.

K. Classification of severity of procedures

Provide information on the expected levels of discomfort and indicate to which category the procedures are assigned ('non-recovery', 'mild', 'moderate', 'severe').

For studies without challenge, discomfort will be mild. For vaccination challenge studies, the type and severity of the clinical signs are depending on the type of challenge. Similar to natural field infections they may cause mild to severe pain, distress and suffering. Vaccination is expected to reduce the level of discomfort after challenge, but the non-vaccinated control group will experience the symptoms of the natural infection. The following discomfort score is an estimate based on experience of the previous 3 years:

Mild: 72%
Moderate: 20%
Severe: 8%

End of experiment

L. Method of killing

Will the animals be killed during or after the procedures?

☐ No

☒ Yes > Explain why it is necessary to kill the animals during or after the procedures.

In the majority of cases, it will not be possible to re-use or re-home animals used in efficacy studies. Animals that have been vaccinated with an unlicensed live vaccine and/or animals that have been challenged are not suitable for release for reasons of environmental safety as well as animal welfare. In addition, necropsy may be required at the end of the study for scientific reasons. These animals will be humanely euthanized by experienced personal at the end of the study, or when the humane endpoint is reached. Approved methods of euthanasia are detailed in the relevant SOP and are in line with EU directive 2010/63.

The following animals may be considered for re-homing:

- [redacted]

Re-homing will be in accordance with Directive 2010/63/EU. An animal will only be considered for re-homing if it has been assessed by a veterinarian with knowledge of the lifetime experience of the animal and it is considered to be healthy and not likely to suffer future adverse effects as a result of the regulated procedures. All animals will be suitably socialised for everyday life outside of the facility and fully vaccinated before release.

[redacted]

Is the proposed method of killing listed in Annex IV of Directive 2010/63/EU?
☐ No > Describe the method of killing that will be used and provide justifications for this choice.
☒ Yes

10.2.g

Appendix
Description animal procedures

- This appendix should be enclosed with the project proposal for animal procedures.
- A different appendix 'description animal procedures' should be enclosed for each type of animal procedure.
- For more information, see our website (www.centralecommissiedierproeven.nl).
- Or contact us by phone (0900-2800028).

1 General information

1.1 Provide the approval number of the 'Netherlands Food and Consumer Product Safety Authority'.

10.2.g

1.2 Provide the name of the licenced establishment.

1.3 List the serial number and type of animal procedure.

Use the serial numbers provided in Section 3.4.4 of the Project Proposal form.

Serial number	Type of animal procedure
2	Studies in non-target animals to determine efficacy

2 Description of animal procedures

A. Experimental approach and primary outcome parameters

Describe the general design of the animal procedures in relation to the primary outcome parameters. Justify the choice of these parameters.

For some projects, non-target animals may be used to determine the efficacy of a dog vaccine which can be studied by means of serology or challenge: 10.1.c (mouse), 10.1.c (hamster) and 10.1.c (guinea pigs). The aim of these types of studies is, similar to those in dogs, to show that a vaccine is efficacious against one or more aspects of the relevant disease. Also, efficacy against different serotypes of pathogens may be evaluated. In the development phase of a project efficacy tests in non-target animal species are sometimes used to determine the potency of a vaccine prior to the start of a (large and laborious) study in target animals. This is possible when this in vivo potency test is described in a Pharmacopoeia Europea (Ph Eur) requirement.
For 10.1.c projects it is necessary to 10.1.c challenge strains that do not result in a valid test in dogs (according to Ph Eur Monograph 10.1.c of these 10.1.c through 10.1.c is needed prior to challenge. For strains of 10.1.c (immediately prior to dog challenge) are needed.

In case challenge has to take place, one or more of the following parameters will be evaluated:

- Clinical signs (e.g. changes in general health)
- Body temperature (subcutaneous transponder)
- Virus or bacterial shedding or dissemination 10.1.c
- Viraemia or bacteraemia, or 10.1.c
- Post-mortem examination 10.1.c

From a regulatory standpoint animals must be monitored for different time periods following challenge depending on the challenge agent. Nevertheless in a successful challenge study control animals will develop infection and/or clinical disease well within this time period.

When previously, in the [redacted] phase of a project, a serological correlate of protection was identified in a non-target animal species an alternative for challenge efficacy studies was provided. In this case serological efficacy studies with new candidate vaccines in a non-target animal species can be done without challenge.

In case of serological efficacy studies without challenge the following parameter will be evaluated:

- Serological response to one or more vaccinations

Describe the proposed animal procedures, including the nature, frequency and duration of the treatment. Provide justifications for the selected approach.

In case challenge has to take place [redacted] of the following treatments will be employed depending on the characteristics of the disease involved [redacted] and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al., 2016.

1. Blood sampling [redacted]
2. Administration of vaccine [redacted]
3. Infection/challenge [redacted]
4. Measurement of temperature (by subcutaneous transponder) [redacted]
5. Weighing [redacted]
6. Swabbing [redacted]
7. Euthanasia

The duration of all procedures described above will only be minutes max. The length of the observation period after challenge depends on the incubation period of the disease agent, but is generally [redacted] To rule out that clinical signs are caused by [redacted] with [redacted] may be included in a study.

In case of serological efficacy studies without challenge the following treatments will be employed depending on the characteristics of the disease involved [redacted]

1. Blood sampling [redacted]
2. Administration of vaccine [redacted]

Describe which statistical methods have been used and which other considerations have been taken into account to minimise the number of animals.

For some vaccines, the number of animals to be used is specified in Ph.Eur monographs or national regulations and in these instances all measures will be taken to meet the mandatory requirements of the regulatory authorities while using the minimum possible number of animals.
When animal numbers are not specified, the minimum numbers of animals needed in the groups to give sufficient likelihood of obtaining a statistically significant result by which it can be judged that the treatments have had a real effect are used. In particular, the variance in the groups together with the magnitude of effect will be used in power calculations to achieve 80% power at the 95% confidence level (regarded by regulatory authorities as the standard by which such experiments should be designed).

B. The animals

Specify the species, origin, estimated numbers, and life stages. Provide justifications for these choices.

Based on the experience over the last 5 years and the current [redacted], the total expected number of animals used is:

Mouse: 200
(per [redacted] vaccine potency test a minimum of 10 mice are included, total of 15 vaccine batches are expected to be produced during the 5 year period).

Hamster: 600
(per [redacted] challenge strain 6-12 hamsters are included (4 [redacted] strains in total), 14 challenges are expected

during the 5 year period).

Guinea pig: 100
(per canine 10.1.c vaccine potency test 8 guinea pigs are included, total of 12 vaccine batches are expected to be produced during the 5 year period).

Sex of animals:
For mouse, hamster and guinea tests only female animals will be included in studies because of a higher risk of fighting in male animals. Since these experiments last for ≥ 2 weeks it is not acceptable to use males, because they would need to be single housed which is not recommendable since these are social animals. Moreover, aggression/fighting will cause stress, which is known to have effects on the immune system. In these studies the functioning of the immune system is crucial and variation in the immune response caused by external factors should be avoided as much as possible. In addition, using animals of both sexes will increase the variability and, thereby, increase the number of animals needed.

Age of animals:
The required species and age are usually designated as the most sensitive species or age for the test component in question. 10.1.c [redacted] If such specific knowledge is not available or no requirements are applicable the most practical choices are made, based on possibilities for purchase and housing conditions or opportunities to re-use animals to contribute to Reduction of the 3 R's.

Origin mouse:
All animals are supplied by licensed commercial suppliers. All purchased animals have an SPF status.

Origin guinea pig:
All animals are supplied by licensed commercial suppliers. All purchased animals have an SPF status.

Origin hamster:
All animals are supplied by licensed commercial suppliers. All purchased animals have an SPF status.

C. Re-use

Will the animals be re-used?

☒ No, continue with question D.

☐ Yes > Explain why re-use is considered acceptable for this animal procedure.

Are the previous or proposed animal procedures classified as 'severe'?

☐ No

☐ Yes> Provide specific justifications for the re-use of these animals during the procedures.

D. Replacement, reduction, refinement

Describe how the principles of replacement, reduction and refinement were included in the research strategy, e.g. the selection of the animals, the design of the procedures and the number of animals.

Replacement:
Animals must be used for these studies because there are no suitable alternatives or models for the induction of immunity in a whole organism or for the colonization of living tissues as complex as those found in the whole animal for which these vaccines are tended to induce protection.

Reduction:
For efficacy studies for some vaccines, the number of animals per group is specified in Ph.Eur monographs and in these instances all measures will be taken to meet the enforced requirements of the regulatory authorities as close as possible. The numbers of animals used will be reduced wherever possible without endangering the scientific integrity of the work. This will be achieved through an on-going evaluation of the observations in each study. The number of animals per study will be substantiated in each study protocol. According to internal procedures, each study protocol will be

reviewed by the Animal Welfare Body and a statistician. Also animals will be re-used were possible keeping animal welfare in mind and without endangering the scientific integrity of the work.

Refinement:
Regulations and guidelines determine to a large extent what sort of data must be generated and, to a large extent, this determines what form of models and methods can be employed.
The classic method to prove protection of a new vaccine is efficacy in a vaccination-challenge test. However, if immunological correlates of protection (e.g. a serological response) can be used to prove efficacy this will be used rather than challenge tests. When a challenge model has to be used, humane end-points will be employed and staff will be fully trained to recognize animals that experience discomfort. Animals will be closely monitored and extra checks will be made to ensure that no animal is left suffering.

Explain what measures will be taken to minimise 1) animal suffering, pain or fear and 2) adverse effects on the environment.

In general animals are housed socially, but animals might have to be (temporarily) separated because of veterinary concerns. Furthermore, to enhance animal welfare, environmental enrichment is provided to all animals. This will enable animals to express their species-specific behavioural repertoire. Programs are in place for the housing and caring of animals exposed experimentally to pathogens, with emphasis on management and safety practices for containment (according to the regulations of Biosafety level 1 – 3).

For monitoring of the clinical health status of animals, all study animals will be checked at least 10.1.c by a certified person. Special attention will be paid to the general health of the animals as well as feed and water consumption. All daily observations are recorded. In case of any abnormalities, a clinical examination of the respective animal will be performed.

Pathogen	Animal Category	Test	Discomfort of disease (% of animals)	Duration of Maximum Discomfort
10.1.c	Hamster 10.1.c of age	challenge	Mild (≥30%) Moderate (≤60%) Severe (≤10%)	Max. 1 day
	Hamster 10.1.c of age	challenge	Mild (≥30%) Moderate (≤60%) Severe (≤10%)	Max. 1 day
	Hamster 10.1.c of age	challenge	Mild (≥30%) Moderate (≤60%) Severe (≤10%)	Max. 1 day
	Hamster 10.1.c of age	challenge	Mild (≥60%) Moderate (≤30%) Severe (≤10%)	Max. 1 day
	Mouse 10.1.c gram)	Challenge or serology	Mild (≥55%) Moderate (≤40%) Severe (≤5%)	Max. 1 day
	Guinea pig 10.1.c gram	serology	Mild (100%)	Max 1 day

* Hamster 10.1.c needed in case of 10.1.c strains of 10.1.c

** 10.1.c

Repetition and duplication

E. Repetition

Explain what measures have been taken to ensure that the proposed procedures have not already been performed. If applicable, explain why repetition is required.

10.2.g

Vaccine candidates will be selected on the basis of scientific knowledge within or outside [redacted], but for every [redacted] vaccine animal studies have to be performed. [redacted] has a patent department that checks, worldwide, if a [redacted] vaccine that is being developed is not a copy of a competitor product. The vaccines in development are unique and proprietary to [redacted]. To show that vaccines are compatible [redacted] a number of the safety and efficacy studies done with the individual products has to be repeated with the vaccines administered together according to international regulations and guidelines. In case of in vivo batch potency tests in mice or hamsters this requirement may, apart from the target animal species (dog), also be applicable in the relevant non-target animal species.

Accommodation and care

F. Accommodation and care

Is the housing and care of the animals used in experimental procedures not in accordance with Annex III of the Directive 2010/63/EU?

☒ No

☐ Yes > If this may adversely affect animal welfare, describe how the animals will be housed and provide specific justifications for these choices.

G. Location where the animals procedures are performed

Will the animal procedures be carried out in an establishment that is not licenced by the NVWA?

☒ No > Continue with question H.

☐ Yes > Describe this establishment.

Provide justifications for the choice of this establishment. Explain how adequate housing, care and treatment of the animals will be ensured.

Classification of discomfort/humane endpoints

H. Pain and pain relief

Will the animals experience pain during or after the procedures?

☐ No > Continue with question I.

☒ Yes > Will anaesthesia, analgesia or other pain relieving methods be used?

☒ No > Justify why pain relieving methods will not be used.

Insertion of a subcutaneous transponder, blood sampling (in rodents always under general anaesthesia) and vaccine administration will induce only mild discomfort, with the exception of repeated blood sampling that can cause moderate discomfort. For each species blood sampling and other biotechnical procedures have been described in Standard Operating Procedures and only well trained personnel will be responsible for the execution (GLP accredited procedures).

[redacted]

The administration of the challenge inoculum will only induce short term mild to moderate discomfort. Depending on the nature of the subsequent infection/disease the discomfort of the challenge can range from moderate to severe. Vaccination will result in a significant reduction of clinical abnormalities after challenge compared to the unvaccinated control group. Animals will be euthanized when it is clear that the clinical picture of the challenge pathogen/disease has been established at which point humane endpoints will be applied (see further under J. Humane endpoints).

[redacted]

For monitoring of the clinical health status of animals, all study animals will be checked at least [redacted] by a certified person. Special attention will be paid to the general health of the animals as well as feed and water consumption. All daily observations are recorded. In case of any abnormalities, a clinical examination of the respective animal will be performed by a veterinarian.

☒ Yes > Indicate what relieving methods will be used and specify what measures will be taken to ensure that optimal procedures are used.

In consultation with the veterinarian and study director it will be decided whether to apply adequate veterinary care to alleviate unexpected pain and/or distress [redacted] In case of severe suffering, humane endpoints are applicable. General humane endpoints are described in SOPs and test specific humane endpoints are given in each study protocol.

I. Other aspects compromising the welfare of the animals

Describe which other adverse effects on the animals' welfare may be expected?

Temperature measurement, weighing and taking samples of [redacted] after infection.

Explain why these effects may emerge.

These procedures are part of the study design to monitor the course of the infection model and the health and welfare of the animals.

Indicate which measures will be adopted to prevent occurrence or minimise severity.

Temperature measurement, weighing and taking samples of [redacted] after infection will induce only mild discomfort, with the exception of repeated [redacted], which is considered to cause moderate discomfort. For each species biotechnical procedures have been described in Standard Operating Procedures (SOPs) and only well trained personnel will be responsible for the execution (GLP accredited procedures). The number of samplings will be done in accordance with the respective guidelines or if no requirements are given, the number of samplings is reduced to a minimum number required for a valid evaluation of results.

J. Humane endpoints

May circumstances arise during the animal procedures which would require the implementation of humane endpoints to prevent further distress?

☐ No > Continue with question K.

☒ Yes > Describe the criteria that will be used to identify the humane endpoints.

In potency tests that require challenge with a pathogenic organism, the severity of discomfort is depending on the nature of the pathogen. However, the duration of severe discomfort will be limited due to the application of a humane endpoint. Therefore, pathogen specific humane endpoints are formulated. These contain information about the clinical signs that can be expected and describe when a humane endpoint has been reached for (a combination of) the respective clinical signs.
In case it is difficult to reach a decision based on the pre-defined criteria for an endpoint the designated veterinarian is empowered to decide that a humane endpoint is applied/reached.

General humane endpoints are described in an SOP. These endpoints are applicable to all animals, irrespectively of the type of experiment.
Examples of situations where this is applicable:

- The animal experiences more than minor additional discomfort as a consequence of conditions resulting in long term or non-reversible inability to eat and or drink autonomously, fast or long lasting loss of weight, diseases or conditions that cause severe pain, suffering or discomfort such as bone fractions, force unnatural positioning and / or movements, open wounds or abscesses.
- Scientific endpoints: The target of the study reached / all planned samplings have been performed.
- Reliable and useful) results cannot be reached for reasons unrelated to the study.

Indicate the likely incidence.

In this type of challenge experiments, for [redacted] ≤10% and for [redacted] ≤5% of the animals is expected to have severe discomfort that could be a cause for euthanasia.

K. Classification of severity of procedures

Provide information on the expected levels of discomfort and indicate to which category the procedures are assigned ('non-recovery', 'mild', 'moderate', 'severe').

Mild: 51%
Moderate: 42%

Severe: 7%

End of experiment

L. Method of killing

Will the animals be killed during or after the procedures?

☐ No

☒ Yes > Explain why it is necessary to kill the animals during or after the procedures.

In challenge studies all animals will be euthanized at the end of the study or when a humane endpoint is reached. [redacted]

For each animal species methods have been described in an SOP that follows the approved methods as described in the EU directive 2010/63.

Is the proposed method of killing listed in Annex IV of Directive 2010/63/EU?

☐ No > Describe the method of killing that will be used and provide justifications for this choice.

☒ Yes

[redacted]

Appendix
Description animal procedures

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- For more information, see our website (www.centralecommissiedierproeven.nl).
- Or contact us by phone (0900-2800028).

1 General information

1.1 Provide the approval number of the 'Netherlands Food and Consumer Product Safety Authority'.

10.2.g

1.2 Provide the name of the licenced establishment.

1.3 List the serial number and type of animal procedure.

Use the serial numbers provided in Section 3.4.4 of the Project Proposal form.

Serial number	Type of animal procedure
3	Safety studies in dogs

2 Description of animal procedures

A. Experimental approach and primary outcome parameters

Describe the general design of the animal procedures in relation to the primary outcome parameters. Justify the choice of these parameters.

The following parameters must be assessed in order to confirm the safety of live and inactivated vaccines:

1. The effect on general health

With live vaccines particular attention should be paid to those signs typical of infection with the virulent organism. General safety parameters are assessed after a 10.1 c vaccination. After vaccination, one or more of the following parameters will be evaluated:

- Clinical signs (e.g. changes in general health)
  - 10.1 c changes (blood samples)
  - Body Weight
- Injection site reactions (measurement and palpation)
- Body temperature (subcutaneous transponder), or rectal temperature
- Post-mortem examination

Specific studies for a particular pathogen may also be required by the Ph.Eur monograph, for example; 10.1 c

For live, particularly 10.1 c vaccines, a number of additional studies are required:

2. Spreading and dissemination of the vaccine strain.

Spread from the vaccinated animal is determined by looking for the vaccine strain in bodily secretions. Consequently, swabs 10.1 c are taken. 10.1 c should be investigated.

10.2.g

3. Reversion to virulence.
To test for reversion to virulence the vaccine should be given by the route most likely to make the vaccine strain revert. It should then be re-isolated from the animal and passaged by administration back into subsequent animals up to a total of five times. The safety profile of the passaged material should then be compared with the starting material.

4. Ecotoxicity
The ecotoxicological effects that the vaccine candidate may have on the environment need to be assessed. In terms of *in vivo* work, this includes the potential for recombination with other vaccines/vectors and the potential to [redacted] in the [redacted]. Methods of [redacted] that prevent the spread of the vaccine candidate from [redacted] need to be investigated.

During the development of a vaccine, a basic safety study may be run that includes group(s) of dogs vaccinated with [redacted] vaccines. The inclusion of these animals is important for ensuring that any vaccine under development has a safety profile that is [redacted] It allows the vaccine to be properly [redacted] as it [redacted] and provides scientifically [redacted] to support this. Ultimately the data may be published so that veterinarians are able to make informed, scientific, decisions on which vaccines to use in their practice.

Describe the proposed animal procedures, including the nature, frequency and duration of the treatment. Provide justifications for the selected approach.

[redacted] of the following procedures will be employed depending on the characteristics of the pathogen/disease involved [redacted]
and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al.,2016.

1. Application of a subcutaneous transponder for body temperature [redacted]
2. Blood sampling [redacted]
3. Administration of vaccine [redacted]
4. Measurement of rectal temperature [redacted]
5. Palpation of the injection site [redacted]
6. Weighing [redacted]
7. Swabbing [redacted]
8. Administration of diuretic [redacted]
9. Cystocentesis: bladder puncture [redacted]
10. Euthanasia

The duration of all procedures described above are expected to be carried out within a matter of minutes. The length of the observation period after vaccination is in principle [redacted] after each vaccination, unless specified otherwise in a vaccine-specific Ph.Eur monograph, but will be longer in case of [redacted] that have to be followed up until [redacted] Also, in case of injection site reactions that have not resolved after 14 days or a persistent live vaccine strain a longer observation period will be needed.

[redacted] one or two small blood samples and/or swabs may be taken. Procedures will be limited and of mild discomfort. If required, antibiotic treatment may be administered on the advice of the attending veterinarian.

Describe which statistical methods have been used and which other considerations have been taken into account to minimise the number of animals.

For some vaccines, the number of animals to be used is specified in Ph.Eur monographs or national regulations and in these instances all measures will be taken to meet the mandatory requirements of the regulatory authorities while using the minimum possible number of animals.

10.2.g

B. The animals

Specify the species, origin, estimated numbers, and life stages. Provide justifications for these choices.

Dogs (Beagles) of both sexes will be used for this type of animal experiment.

Purchase of animals:
Dogs will be derived from a certified SPF breeding unit or purchased from commercial certified suppliers of laboratory dogs.

Age of animals:
The age of dogs used for vaccine development varies from [redacted] old [redacted]

Numbers:
Based on the experience over the last 5 years and the current [redacted] the total expected number of dogs is 400. The number of safety trials needed for all the projects running over a 5 year time period is 30, [redacted]

C. Re-use

Will the animals be re-used?

☐ No, continue with question D.

☒ Yes > Explain why re-use is considered acceptable for this animal procedure.

Animals may be re-used if they have only experienced mild or moderate discomfort in the preceding experiment and if veterinarian confirmation of fitness has been given. Re-use will be according to Directive 2010/63/EU, Article 16. In addition, the immunological status should be acceptable for the scientific purpose of the study.

Are the previous or proposed animal procedures classified as 'severe'?

☒ No

☐ Yes> Provide specific justifications for the re-use of these animals during the procedures.

D. Replacement, reduction, refinement

Describe how the principles of replacement, reduction and refinement were included in the research strategy, e.g. the selection of the animals, the design of the procedures and the number of animals.

Replacement:
Dogs must be used for these studies in accordance with international regulations. For these safety investigations, the number animals to be used are mostly specified and all measures will be taken to meet the mandatory requirements of the regulatory authorities.

Reduction:
If the number of animals required is not specified in the relevant legislation, they will be reduced wherever possible without endangering the scientific integrity of the work. This will be achieved through an on-going evaluation of the observations in each study. The number of animals per study will be detailed in each study protocol. According to internal procedures, each study protocol will be reviewed by the Animal Welfare Body and (where applicable) a statistician.

Animals will be re-used where possible, keeping animal welfare in mind without endangering the scientific integrity of the work.

Refinement:
International regulations determine to a large extent what sort of data must be generated and this determines which methods have to be employed.

Explain what measures will be taken to minimise 1) animal suffering, pain or fear and 2) adverse effects on the environment.

In general dogs are housed socially, but animals might have to be (temporarily) separated due to fighting or because of veterinary concerns. In such cases, the group of dogs will be split up into subgroups to avoid separation of a single dog. Furthermore, to enhance animal welfare, environmental enrichment is provided to all animals. This will enable dogs to express their species-specific behavioural repertoire. Programs are in place for the housing and caring of animals exposed experimentally to pathogens, with emphasis on management and safety practices for containment (according to the regulations of Biosafety level 1 – 3).

Few adverse reactions are expected in the majority of dogs since the procedures that are being carried out are routine vaccinations [redacted] These procedures are minimally invasive. Consequently the level of severity for the safety studies will be mild.

Repetition and duplication

E. Repetition

Explain what measures have been taken to ensure that the proposed procedures have not already been performed. If applicable, explain why repetition is required.

Vaccine candidates will be selected on the basis of scientific knowledge within or outside [redacted], but for every [redacted] vaccine dog studies have to be performed. [redacted] has a patent department that checks, worldwide, if a [redacted] vaccine that is being developed is not a copy of a patented competitor product.
To show that vaccines are compatible ([redacted]), a number of the safety and efficacy studies done with the individual products has to be repeated with the vaccines administered together according to international regulations and guidelines.

Accommodation and care

F. Accommodation and care

Is the housing and care of the animals used in experimental procedures not in accordance with Annex III of the Directive 2010/63/EU?

☒ No

☐ Yes > If this may adversely affect animal welfare, describe how the animals will be housed and provide specific justifications for these choices.

G. Location where the animals procedures are performed

Will the animal procedures be carried out in an establishment that is not licenced by the NVWA?

☒ No > Continue with question H.

☐ Yes > Describe this establishment.

Provide justifications for the choice of this establishment. Explain how adequate housing, care and treatment of the animals will be ensured.

Classification of discomfort/humane endpoints

10.2.g

H. Pain and pain relief

Will the animals experience pain during or after the procedures?

☐ No > Continue with question I.

☒ Yes > Will anaesthesia, analgesia or other pain relieving methods be used?

☒ No > Justify why pain relieving methods will not be used.

10.1.c [redacted] are part of normal veterinary care and will induce only mild discomfort. For each species blood sampling and other biotechnical procedures have been described in Standard Operating Procedures and only well trained personnel will be responsible for the execution (GLP accredited procedures).

10.1.c [redacted]

For monitoring of the clinical health status of animals, all study animals will be checked at least 10.1.c [redacted] by a certified person. Special attention will be paid to the general health of the animals as well as feed and water consumption. All daily observations are recorded. In case of any abnormalities, a clinical examination of the respective animal will be performed by a veterinarian.

☒ Yes > Indicate what relieving methods will be used and specify what measures will be taken to ensure that optimal procedures are used.

In consultation with the veterinarian and study director it will be decided whether to apply adequate veterinary care to alleviate unexpected pain and/or distress 10.1.c [redacted]. In case of severe suffering, humane endpoints are applicable. However, severe discomfort in safety studies is not experiment related and will only occur as a result of congenital disease, trauma or an infectious disease.

I. Other aspects compromising the welfare of the animals

Describe which other adverse effects on the animals' welfare may be expected?

10.1.c [redacted]

- [redacted]
- [redacted]

[redacted]

10.2.g

10.1.c

[redacted]

Explain why these effects may emerge.

These procedures are part of the study design to monitor the safety of the vaccination schedule.

Indicate which measures will be adopted to prevent occurrence or minimise severity.

Procedures (SOPs) and only well trained personnel will be responsible for the execution (GLP accredited procedures).

J. Humane endpoints

May circumstances arise during the animal procedures which would require the implementation of humane endpoints to prevent further distress?

☒ No > Continue with question K.

☐ Yes > Describe the criteria that will be used to identify the humane endpoints.

Indicate the likely incidence.

It is not expected that euthanasia needs to be applied because of severe discomfort.

K. Classification of severity of procedures

Provide information on the expected levels of discomfort and indicate to which category the procedures are assigned ('non-recovery', 'mild', 'moderate', 'severe').

Mild: 100%

End of experiment

L. Method of killing

Will the animals be killed during or after the procedures?

☐ No

☒ Yes > Explain why it is necessary to kill the animals during or after the procedures.

If an animal cannot be re-used or rehomed or animals have to be necropsied they will be euthanized at the end of the study. Methods have been described – for each species – in an SOP that follows the approved methods as described in the EU directive 2010/63.

In many cases, it will not possible to re-use or re-home animals used in safety studies. Animals that have been vaccinated with an unlicensed live vaccine are not suitable for release for reasons of environmental safety. In addition, necropsy may be required at the end of the study for scientific

reasons. These animals will be humanely euthanized by experienced personal at the end of the study. Approved methods of euthanasia are detailed in the relevant SOP and are in line with EU directive 2010/63.

The following animals may be considered for re-homing:

- [redacted]

Re-homing will be in accordance with Directive 2010/63/EU. An animal will only be considered for re-homing if it has been assessed by a veterinarian with knowledge of the lifetime experience of the animal and it is considered to be healthy and not likely to suffer future adverse effects as a result of the regulated procedures. All animals will be suitably socialised for everyday life outside of the facility and fully vaccinated and/or wormed before release.

Is the proposed method of killing listed in Annex IV of Directive 2010/63/EU?

☐ No > Describe the method of killing that will be used and provide justifications for this choice.

☒ Yes

10.2.g

Appendix 8
Description animal procedures

- This appendix should be enclosed with the project proposal for animal procedures.
- A different appendix 'description animal procedures' should be enclosed for each type of animal procedure.
- For more information, see our website (www.centralecommissiedierproeven.nl).
- Or contact us by phone (0900-2800028).

1 General information

10.2.g

1.1 Provide the approval number of the 'Netherlands Food and Consumer Product Safety Authority'.

1.2 Provide the name of the licenced establishment.

1.3 List the serial number and type of animal procedure.

Use the serial numbers provided in Section 3.4.4 of the Project Proposal form.

Serial number	Type of animal procedure
4	Safety studies in non-target animals

2 Description of animal procedures

A. Experimental approach and primary outcome parameters

Describe the general design of the animal procedures in relation to the primary outcome parameters. Justify the choice of these parameters.

For live, 10.1.c vaccine strains that are shed from the target species after vaccination, it is a regulatory requirement to perform safety experiments in relevant non-target species that share the same environment. These studies are designed to assess any adverse effects that the vaccine strain may have on domestic/wild animals that are likely to come into contact with the vaccinated animal. In the case of dogs, non-target species are often cats, chickens, rodents, rabbits, and may also include other species that are known to be susceptible to the vector and/or pathogen, for example; ferrets 10.1.c, and mink 10.1.c. Other non-target species may be requested by the authorities during the licensing procedure. 10.1.c Two or more of the following parameters will be evaluated:

- Clinical signs (e.g. changes in general health)
- Assessment of injection site reactions
- Body temperature (rectal temperature, subcutaneous transponder)
- Body Weight
- Virus or bacterial shedding or dissemination 10.1.c
- Viraemia or bacteraemia, 10.1.c (blood sampling)
- Post-mortem examination

Describe the proposed animal procedures, including the nature, frequency and duration of the treatment. Provide justifications for the selected approach.

10.2.g

10.1.c of the following treatments will be employed depending on the characteristics of the disease involved 10.1.c
and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al.,2016.

1. Application subcutaneous transponder 10.1.c
2. Blood sampling 10.1.c
3. Administration of vaccine 10.1.c
4. 10.1.c
5. Weighing 10.1.c
6. Swabbing 10.1.c
7. Sedation *(1-2x)*, 10.1.c
8. Euthanasia

The duration of all procedures described above is expected to take a matter of minutes. The length of the observation period after vaccine administration is in principle 10.1.c unless specified otherwise in a vaccine-specific Ph.Eur monograph, but will be longer in case of a persistent live vaccine strain.

Describe which statistical methods have been used and which other considerations have been taken into account to minimise the number of animals.

As the number of non-target animals required are not detailed in the European monographs, the minimum number of vaccinates and controls required for statistical significance are used. This is normally in the region of 10.1.c

B. The animals

Specify the species, origin, estimated numbers, and life stages. Provide justifications for these choices.

Species to be used are domestic or wild species other than dogs that can come into contact with the vaccine strain. Based on the experience over the last 5 years and the current 10.1.c, the total expected number of animals used will be:

Mouse: 90
Rabbit: 90
Chickens: 90
Cats: 50
Ferrets: 50
Mink: 50

The number of safety trials needed for all the projects running over a 5 year time period can be 2 per species, with a mean group size from 10-40 per experiment depending on the project. Based on the nature of a vaccine it will be decided which non-target species is needed to perform safety trials.

Sex of animals:
Animals of both sexes will be used, with the exception of mice, rats and rabbits.
For mice, rats and rabbits, depending on the age only female animals will be included in studies because of the high risk of fighting in male animals. Since these experiments last for ≥ 2 weeks, it is not acceptable to use males due to the animal welfare implications. Single housing would be required to avoid injury (sometimes fatal or requiring euthanasia) and this is not recommended since these are social animals and it would be contrary to the refinement principles of the 3R's. The sex of the animals to be tested is not specified in the scientific guidance and it is therefore not a regulatory requirement to test safety in both male and female animals.

Age of animals:
The required species and age is usually designated as the most sensitive species or age for the test component in question. As such, 10.1.c if appropriate. For example, cats, rabbits, mink and ferrets from 10.1.c of age, rodents and chickens from 10.1.c of age.

Origin Rodents:
All animals are supplied by licensed breeding establishments. All purchased animals have an SPF status.

Origin Mouse:
All animals are supplied by licensed breeding establishments. All purchased animals have an SPF status.

Origin chicken:
All animals are supplied by own SPF poultry breeding unit or licensed breeding establishments. All animals have an SPF status.

Origin cat:
All animals are supplied by certified commercial breeders. All purchased animals have an SPF status.

Origin ferrets:
All animals are supplied by certified commercial breeders. All purchased animals have an SPF status.

Origin mink:
All animals are supplied by certified commercial breeders.

C. Re-use

Will the animals be re-used?

☒ No, continue with question D.

☐ Yes > Explain why re-use is considered acceptable for this animal procedure.

Are the previous or proposed animal procedures classified as 'severe'?

☒ No

☐ Yes> Provide specific justifications for the re-use of these animals during the procedures.

D. Replacement, reduction, refinement

Describe how the principles of replacement, reduction and refinement were included in the research strategy, e.g. the selection of the animals, the design of the procedures and the number of animals.

Replacement:
It is a regulatory requirement that the safety of a 10.1.c vaccine is assessed in non-target species that share the same ecosystem as dogs and may come into contact with the vaccine strain. . For these studies, the number of animals used will be the minimum number required to demonstrate a statistical difference between the vaccinates and control groups. 10.1.c

Reduction:
The number of animals used will be the minimum number required to demonstrate a statistical difference between the vaccinates and control groups. According to internal procedures, each study protocol will be reviewed by the Animal Welfare Body and a statistician.

Refinement:
European regulations determine to a large extent what sort of data must be generated and this determines which methods have to be employed.

Explain what measures will be taken to minimise 1) animal suffering, pain or fear and 2) adverse effects on the environment.

In general animals are always housed socially, but male animals might have to be (temporarily) separated due to fighting or because of veterinary concerns. In such cases, however, when possible the group of animals is split up into subgroups to avoid separation of a single animal. When possible female animals will be used instead of male animals to avoid animal suffering due to fighting. Furthermore, to

10.2.g

enhance animal welfare, environmental enrichment is provided to all animals. This will enable animals to express their species-specific behavioural repertoire.

For monitoring of the clinical health status of animals, all study animals will be checked at leas 10.1.c by a certified person. Special attention will be paid to the general health of the animals as well as feed and water consumption. All daily observations are recorded. In case of any abnormalities, a clinical examination of the respective animal will be performed by a veterinarian.

Few if any adverse reactions are expected in the majority of animals since the procedures that are being carried out are routine vaccinations and small volumes of blood 10.1.c will be sampled. These procedures are minimally invasive. Consequently the level of severity for the studies will be mild.

Repetition and duplication

E. Repetition

Explain what measures have been taken to ensure that the proposed procedures have not already been performed. If applicable, explain why repetition is required.

Vaccine candidates will be selected on the basis of scientific knowledge within or outside 10.2.g, but for every 10.1.c vaccine animal studies have to be performed. 10.2.g has a patent department that checks, worldwide, if a 10.1.c vaccine that is being developed is not a copy of a competitor product. Therefore, the vaccines in development are unique and proprietary to 10.2.g.

Accommodation and care

F. Accommodation and care

Is the housing and care of the animals used in experimental procedures not in accordance with Annex III of the Directive 2010/63/EU?

☒ No

☐ Yes > If this may adversely affect animal welfare, describe how the animals will be housed and provide specific justifications for these choices.

With exception of mink, for which we follow the guidelines of the supplier.

G. Location where the animals procedures are performed

Will the animal procedures be carried out in an establishment that is not licenced by the NVWA?

☒ No > Continue with question H.

☐ Yes > Describe this establishment.

Provide justifications for the choice of this establishment. Explain how adequate housing, care and treatment of the animals will be ensured.

Classification of discomfort/humane endpoints

H. Pain and pain relief

Will the animals experience pain during or after the procedures?

☐ No > Continue with question I.

☒ Yes > Will anaesthesia, analgesia or other pain relieving methods be used?

☒ No > Justify why pain relieving methods will not be used.

Insertion of a subcutaneous transponder, infrequent blood sampling (when necessary, under

10.2.g

sedation) and vaccine administration will induce only mild discomfort. For each species blood sampling and other biotechnical procedures have been described in Standard Operating Procedures and only well trained personnel will be responsible for the execution (GLP accredited procedures).

As the vaccines to be tested have already been found to be safe in the target species (dogs) it is very unlikely that they will cause disease in non-target animals. However, vaccination can result sometimes in 10.1.c following vaccination and in addition they may be 10.1.c during this period. Vaccination with a live attenuated vaccine could induce 10.1.c 10.1.c but this is very unlikely.

For monitoring of the clinical health status of animals, all study animals will be checked at least 10.1.c by a certified person. Special attention will be paid to the general health of the animals as well as feed and water consumption. All daily observations are recorded.

☐ Yes > Indicate what relieving methods will be used and specify what measures will be taken to ensure that optimal procedures are used.

I. Other aspects compromising the welfare of the animals

Describe which other adverse effects on the animals' welfare may be expected?

Temperature measurement, weighing and taking samples of 10.1.c after vaccination when applicable.

Explain why these effects may emerge.

These procedures are part of the study design to monitor the course of the infection model and the health and welfare of the animals.

Indicate which measures will be adopted to prevent occurrence or minimise severity.

Temperature measurement, weighing and taking samples of 10.1.c after vaccination will induce only mild discomfort. For each species biotechnical procedures have been described in Standard Operating Procedures (SOPs) and only well trained personnel will be responsible for the execution (GLP accredited procedures). The number of samplings will be done in accordance with the respective guidelines or if no requirements are given, the number of samplings is reduced to a minimum number required for a valid evaluation of results.

J. Humane endpoints

May circumstances arise during the animal procedures which would require the implementation of humane endpoints to prevent further distress?

☒ No > Continue with question K.

☐ Yes > Describe the criteria that will be used to identify the humane endpoints.

Indicate the likely incidence.

It is not expected that euthanasia needs to be applied because of severe discomfort.

K. Classification of severity of procedures

Provide information on the expected levels of discomfort and indicate to which category the procedures are assigned ('non-recovery', 'mild', 'moderate', 'severe').

Mild: 100%

End of experiment

L. Method of killing

Will the animals be killed during or after the procedures?

☐ No

☒ Yes > Explain why it is necessary to kill the animals during or after the procedures.

10.1.c Animals that have been vaccinated with an unlicensed live vaccine are not suitable for release for reasons of environmental safety, and animals bred in captivity will not be adapted for life in the wild. In addition, necropsy may be required at the end of the study for scientific reasons. These animals will be humanely euthanized by experienced personal at the end of the study, or when the humane endpoint is reached. Approved methods of euthanasia are detailed in the relevant SOP and are in line with EU directive 2010/63.

Re-homing will be considered for cats. The following animals may be considered for re-homing:

- 10.1.c

Re-homing will be in accordance with Directive 2010/63/EU. An animal will only be considered for re-homing if it has been assessed by a veterinarian with knowledge of the lifetime experience of the animal and it is considered to be healthy and not likely to suffer future adverse effects as a result of the regulated procedures. All animals will be suitably socialised for everyday life outside of the facility and fully vaccinated and/or wormed before release.

Is the proposed method of killing listed in Annex IV of Directive 2010/63/EU?

☐ No > Describe the method of killing that will be used and provide justifications for this choice.

☒ Yes

10.2.g

From: info@zbo-ccd.nl
To: Kasbeheer
Subject: Betaalgegevens AVD10.2.g20173724
Date: dinsdag 17 oktober 2017 15:08:53

Er is een nieuwe aanvraag ontvangen. Hiervoor is een factuur verstuurd. Hieronder de gegevens t.b.v. het opboeken van de factuur.

NAW-gegevens:
10.2.g

Factuurdatum: 17-10-2017
Factuurnummer: 173724
Aanvraagnummer: AVD10.2.g20173724
Factuurbedrag: EUR 1.684,00

Met vriendelijke groet,

Centrale Commissie Dierproeven
www.centralecommissiedierproeven.nl

.....
Postbus 20401 | 2500 EK | Den Haag
.....
T: 0900 2800028
E: info@zbo-ccd.nl

10.2.e

Van: info@zbo-ccd.nl
Verzonden: dinsdag 17 oktober 2017 15:13
Aan: 10.2.e
Onderwerp: Verzoek om advies over projectvergunningsaanvraag AVD10.2.g20173724
Bijlagen: Aanvraag_projectvergunning_Dog_development_10.2.g.pdf; NTS_Dog_development_10.2.g.pdf; Project_proposal_Development_of_new_dog_vaccines_10.2.g.pdf; DAP_4_safety_studies_non_target_animals_10.2.g.pdf; DAP_1_efficacy_studies_dogs_10.2.g.pdf; DAP_3_safety_studies_dogs_10.2.g.pdf; Aanvraag_projectvergunning_Dog_development_10.2.g_1.pdf; DAP_2_efficacy_studies_non_target_animals_10.2.g.pdf

Geachte leden van 10.2.g

De Centrale Commissie Dierproeven (hierna: CCD) verzoekt u in het kader van vergunningverlening (of wijziging van een vergunning) advies te geven over het project met als titel: "Canine Vaccine Development" en aanvraagnummer: AVD10.2.g20173724.

Uw commissie wordt verzocht op grond van artikel 10.a.2 van de Wet op de dierproeven de aanvraag te beoordelen en een ethische toetsing uit te voeren waarbij wordt afgewogen of de doelstelling van het project, de verwachte voordelen voor mens, dier of milieu en de haalbaarheid van de doelstellingen, het gebruik van dieren en de schade die zal worden toegebracht aan de dieren in de vorm van lijden, pijn en angst kan rechtvaardigen.

Graag ontvangen wij van u bericht dat deze e-mail goed is ontvangen en wanneer u dit advies in de vergadering gaat bespreken.

Voor het in te dienen advies dient de DEC gebruik te maken van de meest actuele versie van het op de website van de CCD gepubliceerde Format DEC-advies en de toelichting daarbij. U dient deze aanvraag vertrouwelijk te behandelen. Voor de communicatie met de CCD dient u gebruik te maken van de beveiligde verbinding.

De CCD verzoekt u uiterlijk binnen 20 werkdagen, na 17-10-2017, uw advies bij de CCD in te dienen. Indien de aanvraag door uw commissie niet in behandeling kan worden genomen, dient u dit per ommegaande per e-mail aan de CCD te melden.

Ingeval uw commissie tussentijds aanvullende informatie wil inwinnen bij de aanvrager kan de termijn worden opgeschort. U dient de CCD zo spoedig mogelijk op de hoogte te stellen van deze opschorting. Zodra de opschortende termijn is beeindigd, stelt u de CCD hiervan onverwijld op de hoogte. Opschorting van de adviestermijn vindt niet plaats ingeval u ten behoeve van uw advies een onafhankelijk extern expert raadpleegt.

Met vriendelijke groeten,

CCD

10.2.e

Van: info@zbo-ccd.nl
Verzonden: dinsdag 17 oktober 2017 15:14
Aan: 10.2.e
CC: 10.2.e
Onderwerp: Verzoek om advies AVD10.2.g20173724 verstuurd aan DEC

Geachte meneer, mevrouw,

Op 16-10-2017 hebben wij uw aanvraag voor een projectvergunning dierproeven ontvangen. Het gaat om uw project "Canine Vaccine Development" met aanvraagnummer AVD10.2.g20173724.

Uw aanvraag is naar 10.2.g gestuurd. Zij zal hierover advies aan de CCD uitbrengen. Als de DEC vragen heeft, zal zij contact met u opnemen.

Mocht u vragen hebben, dan kunt u uiteraard contact met ons opnemen.

Met vriendelijke groet,

Centrale Commissie Dierproeven
www.centralecommissiedierproeven.nl

.....
Postbus 20401 | 2500 EK | Den Haag
.....
T: 0900 2800028
E: info@zbo-ccd.nl

10.2.e

Van: Info-zbo
Verzonden: dinsdag 17 oktober 2017 15:17
Aan: 10.2.g
CC: 10.2.e
Onderwerp: OntvangstBevestiging
Bijlagen: OntvangstBevestiging.pdf

Geachte 10.2.e

In de bijlage treft u het besluit op uw digitaal ontvangen aanvraag voor een projectvergunning. Gedurende de behandeling van uw aanvraag hebben wij hierover met u per e-mail gecorrespondeerd.
Met deze email sturen wij u hierbij het besluit. Op uw verzoek hebben de verantwoordelijk onderzoeker uit uw organisatie in de CC gezet.

Graag maken wij u erop attent dat vergunningen en andere besluiten van de Centrale Commissie Dierproeven met ingang van 1 september 2017 uitsluitend nog per e-mail zullen worden toegezonden.

Met vriendelijke groet,

10.2.e

Centrale Commissie Dierproeven www.centralecommissiedierproeven.nl
Nationaal Comité advies dierproevenbeleid www.ncadierproevenbeleid.nl
.....
Bezuidenhoutseweg 73 | 2594 AC | Den Haag Postbus 20401 | 2500 EK | Den Haag
.....
T: 0900 2800028
E: info@zbo-ccd.nl

Centrale Commissie Dierproeven

13

> Retouradres Postbus 20401 2500 EK Den Haag

10.2.g
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10.2.g

Centrale Commissie Dierproeven
Postbus 20401
2500 EK Den Haag
centralecommissiedierproeven.nl
0900 28 000 28 (10 ct/min)
info@zbo-ccd.nl

Onze referentie
Aanvraagnummer
AVD10.2.g20173724
Bijlagen
2

Datum 17 oktober 2017
Betreft Ontvangstbevestiging aanvraag projectvergunning Dierproeven

Geachte 10.2.e

Wij hebben uw aanvraag voor een projectvergunning dierproeven ontvangen op 16 oktober 2017. Het gaat om uw project "Canine Vaccine Development". Het aanvraagnummer dat wij aan deze aanvraag hebben toegekend is AVD10.2.g20173724. Gebruik dit nummer wanneer u contact met de CCD opneemt.

Wacht met de uitvoering van uw project
Als wij nog informatie van u nodig hebben dan ontvangt u daarover bericht. Uw aanvraag is in ieder geval niet compleet als de leges niet zijn bijgeschreven op de rekening van de CCD. U ontvangt binnen veertig werkdagen een beslissing op uw aanvraag. Als wij nog informatie van u nodig hebben, wordt deze termijn opgeschort. In geval van een complexe aanvraag kan deze termijn met maximaal vijftien werkdagen verlengd worden. U krijgt bericht als de beslisperiode van uw aanvraag vanwege complexiteit wordt verlengd. Als u goedkeuring krijgt op uw aanvraag, kunt u daarna beginnen met het project.

Factuur
Bijgaand treft u de factuur aan voor de betaling van de leges. Wij verzoeken u de leges zo spoedig mogelijk te voldoen, zodat we uw aanvraag in behandeling kunnen nemen. Is uw betaling niet binnen dertig dagen ontvangen, dan kan uw aanvraag buiten behandeling worden gesteld. Dit betekent dat uw aanvraag niet beoordeeld wordt en u uw project niet mag starten.

Meer informatie
Heeft u vragen, kijk dan op www.centralecommissiedierproeven.nl. Of neem telefonisch contact met ons op: 0900 28 000 28 (10 ct/minuut).

Datum:
17 oktober 2017
Aanvraagnummer:
AVD[redacted]20173724

Met vriendelijke groet,

Centrale Commissie Dierproeven

Deze brief is automatisch aangemaakt en daarom niet ondertekend.

Bijlagen:
- Gegevens aanvraagformulier
- Factuur

Datum:
17 oktober 2017
Aanvraagnummer:
AVD[redacted]20173724

Gegevens aanvrager

Uw gegevens

Deelnemersnummer NVWA: [redacted]
Naam instelling of organisatie: [redacted]
Naam portefeuillehouder of diens gemachtigde: [redacted]
Straat en huisnummer: [redacted]
Postcode en plaats: [redacted]

Gegevens plaatsvervangende verantwoordelijke onderzoeker

Naam: [redacted]
Functie:
Afdeling:
Telefoonnummer:
E-mailadres:

Over uw aanvraag

Wat voor aanvraag doet u?

[x] Nieuwe aanvraag
[ ] Wijziging op een (verleende) vergunning die negatieve gevolgen kan hebben voor het dierenwelzijn
[ ] Melding op (verleende) vergunning die geen negatieve gevolgen kan hebben voor het dierenwelzijn

Datum:
17 oktober 2017
Aanvraagnummer:
AVD[redacted]20173724

Over uw project

Geplande startdatum:	1 januari 2018
Geplande einddatum:	31 december 2023
Titel project:	Canine Vaccine Development
Titel niet-technische samenvatting:	Onderzoek en ontwikkeling van nieuwe hondenvaccins
Naam DEC:	[redacted]
Postadres DEC:	
E-mailadres DEC:	

Betaalgegevens

De leges bedragen:	€ 1.684,-
De leges voldoet u:	na ontvangst van de factuur

Checklist bijlagen

Verplichte bijlagen:

[x] Projectvoorstel
[x] Beschrijving Dierproeven
[x] Niet-technische samenvatting

Ondertekening

Naam:	[redacted]
Functie:	
Plaats:	
Datum:	16 oktober 2017

Centrale Commissie Dierproeven

> Retouradres Postbus 20401 2500 EK Den Haag

10.2.g
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10.2.g

Centrale Commissie Dierproeven
Postbus 20401
2500 EK Den Haag
centralecommissiedierproeven.nl
0900 28 000 28 (10 ct/min)
info@zbo-ccd.nl

Onze referentie
Aanvraagnummer
AVD10.2.g20173724
Bijlagen
2

Datum 17 oktober 2017
Betreft Factuur aanvraag projectvergunning Dierproeven

Factuur
Factuurdatum: 17 oktober 2017
Vervaldatum: 16 november 2017
Factuurnummer: 173724

Omschrijving	Bedrag
Betaling leges projectvergunning dierproeven Betreft aanvraag AVD10.2.g20173724	€ 1.684,00

Wij verzoeken u het totaalbedrag vóór de gestelde vervaldatum over te maken op rekening NL29INGB 070.500.1512 onder vermelding van het factuurnummer en aanvraagnummer, ten name van Centrale Commissie Dierproeven, Postbus 93144, 2509 AC te 's Gravenhage.

From: Info-zbo
To: 10.2.e
Cc: 10.2.e
Subject: Nieuwe aanvraag
Date: dinsdag 17 oktober 2017 15:23:45

Hoi,
Betreft AVD10.2.g20173724
DEC nee
Met vriendelijke groet,

10.2.e

Namens,

Centrale Commissie Dierproeven www.centralecommissiedierproeven.nl
Nationaal Comité advies dierproevenbeleid www.ncadierproevenbeleid.nl
.....
Bezuidenhoutseweg 73 | 2594 AC | Den Haag
Postbus 20401 | 2500 EK | Den Haag
.....
T: 0900 2800028
E: info@zbo-ccd.nl

15

10.2.e

Van: 10.2.e
Verzonden: dinsdag 17 oktober 2017 16:48
Aan: info@zbo-ccd.nl
Onderwerp: RE: Verzoek om advies over projectvergunningsaanvraag AVD10.2.g20173724

Categorieën: Nieuwe aanvraag (of nummer): 10.2.e (DEC)

Geachte CCD,
Deze e-mail is in goede orde ontvangen en het project is door onze DEC al besproken. Een DEC advies wordt momenteel geschreven. Wel merk ik als secretaris op dat alle documenten als niet versleuteld zijn opgestuurd.
Met vriendelijke groet,
10.2.e
10.2.g

From: info@zbo-ccd.nl [mailto:info@zbo-ccd.nl]
Sent: dinsdag 17 oktober 2017 15:13
To: 10.2.e
Subject: Verzoek om advies over projectvergunningsaanvraag AVD10.2.g20173724

11

Geachte leden van 10.2.g

De Centrale Commissie Dierproeven (hierna: CCD) verzoekt u in het kader van vergunningverlening (of wijziging van een vergunning) advies te geven over het project met als titel: "Canine Vaccine Development" en aanvraagnummer: AVD10.2.g20173724.

Uw commissie wordt verzocht op grond van artikel 10.a.2 van de Wet op de dierproeven de aanvraag te beoordelen en een ethische toetsing uit te voeren waarbij wordt afgewogen of de doelstelling van het project, de verwachte voordelen voor mens, dier of milieu en de haalbaarheid van de doelstellingen, het gebruik van dieren en de schade die zal worden toegebracht aan de dieren in de vorm van lijden, pijn en angst kan rechtvaardigen.

Graag ontvangen wij van u bericht dat deze e-mail goed is ontvangen en wanneer u dit advies in de vergadering gaat bespreken.

Voor het in te dienen advies dient de DEC gebruik te maken van de meest actuele versie van het op de website van de CCD gepubliceerde Format DEC-advies en de toelichting daarbij. U dient deze aanvraag vertrouwelijk te behandelen. Voor de communicatie met de CCD dient u gebruik te maken van de beveiligde verbinding.

De CCD verzoekt u uiterlijk binnen 20 werkdagen, na 17-10-2017, uw advies bij de CCD in te dienen. Indien de aanvraag door uw commissie niet in behandeling kan worden genomen, dient u dit per ommegaande per e-mail aan de CCD te melden.

Ingeval uw commissie tussentijds aanvullende informatie wil inwinnen bij de aanvrager kan de termijn worden opgeschort. U dient de CCD zo spoedig mogelijk op de hoogte te stellen van deze opschorting. Zodra de opschortende termijn is beeindigd, stelt u de CCD hiervan onverwijld op de hoogte. Opschorting van de adviestermijn vindt niet plaats ingeval u ten behoeve van uw advies een onafhankelijk extern expert raadpleegt.

Met vriendelijke groeten,

CCD

14 juli 2016

16

Format DEC-advies

Maak bij de toepassing van dit format gebruik van de Praktische Handreiking: Ethisch Toetsingskader voor proefdiergebruik. Voor voorbeelden, zie bijlage I.

Herhaling van antwoorden is niet nodig. Indien van toepassing kan verwezen worden naar een bij een eerdere vraag verstrekt antwoord.

A. Algemene gegevens over de procedure

1. Aanvraagnummer **AVD[redacted] 2017**
2. Titel van het project *Canine Vaccine Development*

3. Titel van de NTS *Onderzoek en ontwikkeling van nieuwe hondenvaccins*

4. Type aanvraag: **nieuwe aanvraag projectvergunning**

5. Contactgegevens DEC:
   - naam DEC [redacted]
   - telefoonnummer contactpersoon [redacted]
   - e-mailadres contactpersoon [redacted]

6. Adviestraject (data dd-mm-jjjj):
   - ☐ ontvangen door DEC **06-09-2017 , aangehouden, 2e versie 11-10-2017**
   - ☐ aanvraag compleet ja
   - ☐ in vergadering besproken **14 september en 12 oktober 2017**
   - ☐ anderszins behandeld
   - ☐ termijnonderbreking(en) van / tot
   - ☐ besluit van CCD tot verlenging van de totale adviestermijn met maximaal 15 werkdagen
   - ☐ aanpassing aanvraag
   - ☐ advies aan CCD

7. Geef aan of de aanvraag is afgestemd met de IvD en deze de instemming heeft van de IvD. Ja, de aanvraag is afgestemd met de IvD en heeft ook de instemming van de IvD.

Bij de punten 8 t/m 10 kan worden volstaan met 'n.v.t.' wanneer de betreffende acties niet aan de orde zijn geweest.

8. Eventueel horen van aanvrager**:** NvT

9. Correspondentie met de aanvrager
   - Datum **27-09-2017, 09-10-2017, 13-10-2017, 17-10-2017 en 27-10-2017**
   - Gestelde vraag/vragen zie hieronder de vragen vanuit de DEC over het projectvoorstel (in rood de reactie van de aanvrager, met in italic de gewijzigde tekst in de aanvraag)
   - Datum antwoord
   - Verstrekt(e) antwoord(en)

De antwoorden hebben geleid tot aanpassing van de aanvraag.

14 juli 2016

Correspondentie met de aanvrager:
Graag ontvangen wij van u de antwoorden op de volgende vragen in een aparte brief/memo en de aangepaste aanvraag zo spoedig in verband met de grote drukte bij de CCD.

Proposal:

1. *Kunt u aangeven wat al in de* [redacted] *fase bekend is geworden en of er op basis daarvan al keuzes zijn gemaakt?*

Afhankelijk van de vragen in het document komen we hierop terug op een aantal verschillende pagina's: **Pagina 2:**
The current project proposal covers the development phase for [redacted] *dog vaccines including the updating and improvement of vaccines already on the market.* [redacted]

Pagina 5: 1) *As part of development of* [redacted] *vaccines: To generate the efficacy and safety data to be included in marketing authorization applications (registration dossiers) for* [redacted] *canine vaccines. The* [redacted] *vaccines will have already shown proof of concept (i.e. induction of protection combined with an acceptable safety profile) in the* [redacted] *phase of vaccine development, and the efficacy and safety studies to be undertaken in the current development proposal are needed to fulfil the regulatory requirement. The outcome of the objective is the licensing of* [redacted] *vaccines that fulfil important needs in the field.*
Pagina 6: *Prior to the development phase a safety and efficacy profile has been generated in feasibility studies during* [redacted] *phase.* [redacted]*. For licensure of candidate vaccines specific regulatory studies are required. These development studies are broadly split into the following: Efficacy and Safety.*

2. *Kunt een strategie aangeven voor het development traject? Waar start u mee, en wat zijn go-no go momenten waarop besloten wordt door te gaan of te stoppen met een vaccin?*

De strategie wordt beschreven onder het hoofdstuk "3.4. Research strategy" pagina 6-8 (deze is onze "development strategy") een aantal zaken werden verduidelijkt:
[redacted]
For licensure of [redacted] *vaccines specific regulatory studies are required. These development studies are broadly split into the following:*

1. *Efficacy studies:.....*
2. *Safety studies:....*

....In addition non target animals are also used in efficacy studies to determine the potency of a candidate vaccine in non-target animals which correlates with the efficacy of a vaccine in the target animal. Also for safety studies, non-target animals are used particularly needed in the framework of a [redacted]

We hebben de onderverdeling aangepast:

1. *Efficacy studies using target and non-target animals;.....*
2. *Safety studies using target and non-target animals:.....*

.....[redacted]
Titel van DAP 2 werd aangepast:
Studies in non-target animals to determine efficacy.

3. *Gaat u eerst efficacy testen en dan safety en waarom in die volgorde?*

Omdat de efficacy en safety 10.2.g verwachten wij geen resultaten die leiden tot het stopzetten van het project tijdens de development fase daarom lopen efficacy en safety studies parallel.

Bijlage 1:

4. *Wat is de belangrijkste parameter waarop efficacy wordt gebaseerd?*

Dit is afhankelijk per project / antigeen waartegen het vaccin wordt ontwikkeld. 10.2.g

5. *Kunt u bij de handelingen aard en frequentie onderbouwen en dat u werkt volgens bepaalde richtlijnen voor afname van de volumina?*

10.1.c of the following treatments will be employed depending on the characteristics of the disease involved *(in italics the frequency of the treatments) and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al.,2016.*

1. Application subcutaneous transponder 10.1.c
1. Blood sampling 10.1.c
2. Administration of vaccine 10.1.c *for vaccination.*
3. Challenge 10.1.c
4. Administration of diuretic 10.1.c *to increase urine production.*
5. Cystocentesis: bladder puncture 10.1.c
6. Measurement of rectal temperature 10.2.g
7. Weighing 10.1.c
8. Swabbing of 10.1.c
9. Sedation 10.1.c
10. Euthanasia

6. *U geeft aan dat* 10.1.c

Dit werd in het hele document aangepast.

7. *Kunt u aangeven hoe u tot een totaal aantal dieren van 600 bent gekomen?*

Based on the experience over the last 5 years 10.1.c, the total expected number of dogs is *600. The number of efficacy trials needed for all the projects running over a 5 year time period is 45, with a mean groups size of 8-20 dogs depending on the project.*

8. *Graag de tabel met 'pathogen animal category...' etc aanpassen voor* 10.1.c *omdat in meerdere gevallen* 10.1.c *dieren gebruikt gaan worden?*

Pathogen	*Discomfort of disease (% of animals)*	*Duration of Maximum Discomfort*
10.1.c	*Mild (≥93%) Moderate (≤7%)*	*Max. 1 week*
	Mild (≥70%) Moderate (≤30%)	*Max. 1 week*
	Mild (≥70%) Moderate (≤20%) Severe (≤10%)	*Max. 1 week*
	Mild (≥70%) Moderate (≤30%)	*Max. 1 week*
	Mild (≥70%) Moderate (≤20%) Severe (≤10%)	*Max. 1 day*
	Mild (≥70%) Moderate (≤15%) Severe (≤15%)	*Max. 1 day*
	Mild (≥70%) Moderate (≤15%) Severe (≤15%)	*Max. 1 day*
	Mild (≥70%) Moderate (≤22%) Severe (≤8%)	*Max. 1 day*

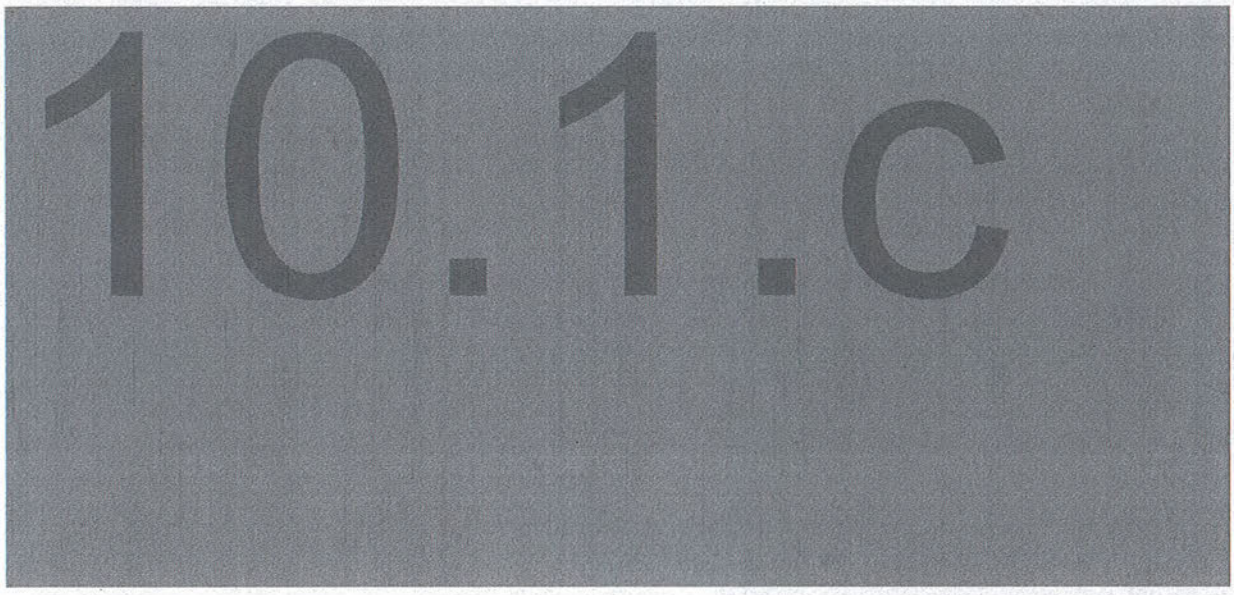
10.1.c

9. *Bij replacement zou u voorgaand werk kunnen opnemen?*

Wij veronderstellen dat wordt bedoeld dat het voorgaande werk meegenomen kan worden bij reductie van het aantal dieren aangezien wij geen onverwachte resultaten verwachten 10.2.g Dit werd aangepast in het document:

Reduction:

The number of animals used will be reduced wherever possible without endangering the scientific integrity of the work. Study protocols will be designed to combine the collection of data on as many different parameters as possible within a study in order to minimise the total number of animals used. Where possible the same control group will be used for multiple comparisons in order to reduce the number of animals being required. The minimum numbers of animals required in safety and efficacy studies are set out in the respective European Pharmacopoeia monographs and EMA guidelines. In many cases, the number of animals stipulated by the guidelines is small. From 10.2.g *have been refined and are robust enough to allow the use of the minimal numbers of animals. According to internal procedures, each study protocol will be reviewed by the Animal Welfare Body and (where applicable) a statistician.*



11. *Graag de % dieren met severe discomfort nalopen, er zitten inconsistenties bij classification en toepassing humaan eindpunt?*

Mild: 72%
Moderate: 20%
Severe: 8%

Bijlage 2:

12. *Algemeen de vragen die voor bijlage 1 van toepassing zijn op deze bijlage graag overnemen.*

Dit werd aangepast:
In case challenge has to take place 10.1.c of the following treatments will be employed depending on the characteristics of the disease involved 10.1.c *and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al., 2016.*

1. Blood sampling 10.1.c
2. Administration of vaccine 10.1.c
3. Infection/challenge 10.1.c
4. Measurement of temperature 10.1.c
5. Weighing 10.1.c
6. Swabbing 10.1.c
7. Euthanasia

Based on the experience over the last 5 years 10.1.c, the total expected number of animals used is:
Mouse: 200 *(per* 10.1.c *vaccine potency test a minimum of 10 mice are included, total of 15 vaccine batches are expected to be produced during the 5 year period).*
Hamster: 600 *(per* 10.1.c *challenge strain 6-12 hamsters are included* 10.1.c *14 challenges are expected during the 5 year period).*
Guinea pig: 100 *(per* 10.1.c *vaccine potency test 8 guinea pigs are included, total of 12 vaccine batches are expected to be produced during the 5 year period).*

13. *Kunt u aangeven wat u bedoeld met batch potency testing en waarom dat onder deze aanvraag moet vallen?*

Met batch potency wordt bedoeld 10.1.c vaccines die tijdens de ontwikkelings fase worden gemaakt om te onderzoeken welke hoeveelheid antigeen overeenkomt met de efficacy.

Om dit te verduidelijken werd zowel de titel van DAP 2 als de tekst de tekst aangepast in het voorstel:
Titel: Studies in non-target animals to determine efficacy.
For some projects, non-target animals may be used to [redacted] *The aim of these types of studies is,* [redacted] *This is possible when this in vivo potency test is described in a Pharmacopoeia Europea (Ph Eur) requirement.*
For [redacted] *projects it is necessary to* [redacted] *that do not result in a valid test in dogs (according to Ph Eur Monograph* [redacted]

14. *Kunt u duidelijker maken dat de hamsters grotendeels bedoeld zijn om de virulentie van de* [redacted] *te verhogen?*
Aangepast in bovenstaande.

15. *Classificatie ongerief graag bij K vermelden of copieren.*
Mild: 51%
Moderate: 42%
Severe: 7%

Bijlage 3:
16. *Algemeen de vragen die voor bijlage 1 van toepassing zijn op deze bijlage graag overnemen.*
Dit werd aangepast:
[redacted] of the following procedures will be employed depending on the characteristics of the *pathogen/*disease involved [redacted] *and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al.,2016.*

1. Application of a subcutaneous transponder for body temperature (1x)
2. Blood sampling [redacted]
3. Administration of vaccine [redacted]
4. Measurement of rectal temperature [redacted]
5. Palpation of the injection site [redacted]
6. Weighing [redacted]
7. Swabbing [redacted]
8. Administration of diuretic [redacted] to increase urine production.
9. Cystocentesis: bladder puncture [redacted]
10. Euthanasia

Numbers:
Based on the experience over the last 5 years [redacted]*, the total expected number of dogs is 400. The number of safety trials needed for all the projects running over a 5 year time period is 30, with a mean groups size of 10-15 dogs depending on the project.*

Bijlage 4:

17. Algemeen de vragen die voor bijlage 1 van toepassing zijn op deze bijlage graag overnemen.

Dit werd aangepast:

10.1.c of the following treatments will be employed depending on the characteristics of the disease involved 10.1.c *and will be applied in accordance with "handboek proefdierkunde, van Zutphen et al.,2016.*

1. Application subcutaneous transponder *(1x)*, to measure body temperature
2. Blood sampling 10.1.c
3. Administration of vaccine 10.1.c
4. Measurement of rectal temperature 10.1.c
5. Weighing 10.1.c
6. Swabbing 10.1.c
7. Sedation 10.1.c
8. Euthanasia

Mouse: 90
Rabbit: 90
Chickens: 90
Cats: 90
Ferrets: 50
Mink: 50
The number of safety trials needed for all the projects running over a 5 year time period can be 2 per species, with a mean group size from 10-40 depending on the project. Based on the nature of a vaccine it will be decided which non-target species is needed to perform safety trials.

18. Kunt u voor de andere diersoorten die in het kader van veiligheid worden getest, aangeven of dat een besluit moment is? Bv indien er shedding wordt gezien in de muis, gaat u dan verder met andere diersoorten, idem voor ferret en mink?

Voor knaagdieren werd dit aangepast, enkel muizen zullen worden meegenomen, ratten werden verwijderd. Wat betreft fretten en nertsen, 10.1.c moeten beide diersoorten op safety worden onderzocht omdat deze diersoorten andere gevoeligheden laten zien voor 10.1.c

19. Kunt u de verschillende diersoorten onderbouwen en aangeven of u daadwerkelijk per alle soorten gaat gebruiken?

Deze diersoorten worden gekozen op basis van 10.1.c die wordt gebruikt per project: gevoeligheid van het antigeen waarvan 10.1.c werd gemaakt voor bepaalde diersoorten anders dan het target dier of afhankelijk op basis van de mogelijkheid dat een andere diersoort in contact komt met 10.1.c

NTS:

20. NTS: graag aanpassen nav bovenstaande vragen.

Honden: 1000
Muizen: 290
Cavia's: 100
Hamster: 600
Kippen: 90

Fretten: 50
Katten: 50
Konijnen: 90
Nertsen: 50
De genoemde aantallen dieren zijn gebaseerd op het wettelijk aantal benodigde testen welke staan beschreven in de Europese farmacopee voor de ontwikkeling van vaccins voor honden.

21. *In de NTS noemt u andere diersoorten voor de ontwikkeling van laboratorium testen. Dit wordt echter in de aanvraag of bijlagen nergens vermeld. Graag aanpassen waar nodig?*

Non target dieren worden gebruikt om immuniteits testen op te zetten, niet ter vervanging van. Dit wordt duidelijker omschreven in de aangepaste tekst:

In dit project start de ontwikkeling van nieuwe hondenvaccins. Hierbij worden studies gedaan met de nieuwe vaccins om aan eisen voor Europese en internationale productregistratie voor nieuwe vaccins te voldoen. Bij vaccin kandidaten kan het gaan om vaccins tegen nieuwe ziekteverwekkers waar nog geen vaccin voor is, verbetering van bestaande vaccins (bv aanpassing aan veranderde ziekteverwekker in het veld, of een vaccin met nog betere bescherming), een verbeterde toedieningsroute, beter oplosmiddel, of combinatie van bestaande vaccins waarmee het aantal vaccinatiemomenten vermindert. Bij ontwikkeling van vaccins voor honden worden ook andere diersoorten ingezet om o.a. benodigde veiligheid te testen of om immuniteitstesten op te zetten in non-target dieren.

22. *Marketing authorisation van nieuwe of gewijzigde vaccins gebeurt door de European Medicines Agency (EMA). Protocollen voor onderzoek worden vastgesteld in overleg met EMA. De Europese Farmacopee is verantwoordelijk voor de vrijgifte van batches. Uitzondering is als bestaande producten geoptimaliseerd worden of gecombineerd met andere producten. In die gevallen kan de Commissie zich voorstellen dat men wil werken met methoden die in de Ph.Eur. beschreven staan. Verder: zoals het nu beantwoord wordt lijkt het er op dat het totaal aantal dieren gebaseerd is op het aantal testen x een vast aantal dieren per test. Dit staat haaks op 4.2. waar aangegeven wordt dat alles statistisch wordt doorberekend.*

De statistische analyse wordt meestal gebruikt [redacted] en waar mogelijk tijdens de [redacted] maar bij meer dan 90% van [redacted] staan het aantal dieren vastgelegd in de PhEur. Wij hebben de onderstaande tekst hierop aangepast:

Voordat vaccins worden getest in dieren, worden ze eerst uitvoerig getest in vitro in het laboratorium en alleen de meest veelbelovende vaccin kandidaten zullen worden getest in dieren. [redacted] Dit werd per studie berekend waar mogelijk op basis van eerdere observaties. Testen die dienen te worden [redacted], zijn vastgelegd in de Europese farmacopoea of andere regelgeving van overheden met betrekking tot vaccins. Daarnaast worden dieren, indien mogelijk, opnieuw ingezet met in acht neming van dierenwelzijn.

Verder een aanpassing van de totale ongerief score:

Licht: 80%
Matig: 16%
Ernstig: 4%

10. Eventuele adviezen door experts (niet lid van de DEC): nvt

B. Beoordeling (adviesvraag en behandeling)

1. Is het project vergunningplichtig (dierproeven in de zin der wet)? Ja
2. De aanvraag betreft een nieuwe aanvraag.

3. Is de DEC competent om hierover te adviseren? Ja

4. Geef aan of DEC-leden, met het oog op onafhankelijkheid en onpartijdigheid, zijn uitgesloten van de behandeling van de aanvraag en het opstellen van het advies. Indien van toepassing, licht toe waarom. Er zijn geen DEC leden uitgesloten van de behandeling van de aanvraag en het opstellen van het advies.

C. Beoordeling (inhoud)

1. Beoordeel of de aanvraag toetsbaar is en voldoende samenhang heeft *(Zie handreiking 'Invulling definitie project'; zie bijlage I voor toelichting en voorbeeld).*
Deze aanvraag heeft een concrete doelstelling: "*Onderzoek en ontwikkeling van nieuwe hondenvaccins*". Het project heeft betrekking op dierstudies om vaccins voor honden te verbeteren of aan te passen aan andere virulente stammen. De dieren worden gevaccineerd en de kwaliteit van de vaccinatie wordt getest door bij het dier de ziekte te induceren waarvoor de vaccinatie is bedoeld ('challenge'). Verder wordt onderzocht of vaccins welke 10.1 c [redacted] bevat een risico kunnen vormen voor de omgeving van de hond door ook andere diersoorten te onderzoeken ('safety') Voor alle experimenten in dit project geldt dat de wijze van uitvoering ofwel is vastgelegd in richtlijnen die zijn uitgevaardigd door de registratie-autoriteiten ofwel dat er andere reden is naast de richtlijnen. De beschreven dierproeven zijn duidelijk wat betreft de uit te voeren handelingen en daarmee gepaard gaande ongerief voor het individuele dier. De eenvormigheid qua design en uitvoering van de beschreven experimenten, is volgens de DEC één van de redenen waarom dit project als een toetsbare eenheid kan worden beschouwd.

2. Signaleer of er mogelijk tegenstrijdige wetgeving is die het uitvoeren van de proef in de weg zou kunnen staan. Het gaat hier om wetgeving die gericht is op de gezondheid en welzijn van het dier of het voortbestaan van de soort (bijvoorbeeld Wet dieren en Flora- en faunawet). Ja er is tegenstrijdige wetgeving, welke ook wordt benoemt door de aanvrager: 10.1 c [redacted] De DEC heeft dit aspect uitvoerig besproken en in haar afweging meegenomen. Voor zover bekend bij de DEC zijn er geen andere aspecten in de aanvraag die niet in overeenstemming zijn met andere wet- en regelgeving.

3. Beoordeel of de in de projectaanvraag aangekruiste doelcategorie(ën) aansluit(en) bij de hoofddoelstelling. Nevendoelstellingen van beperkt belang hoeven niet te worden aangekruist in het projectvoorstel.
De DEC is van mening dat de genoemde doelcategorie "wettelijk verplicht" aansluit bij de hoofdoelstelling.

Belangen en waarden

4. Benoem zowel het directe doel als het uiteindelijke doel en geef aan of er een directe en reële relatie is tussen beide doelstellingen. Beoordeel of het directe doel gerechtvaardigd is binnen de context van het onderzoeksveld *(Zie Praktische handreiking ETK: Stap 1.C4; zie bijlage I voor voorbeeld).*
Het directe doel van het project is het ontwikkelen en verbeteren van vaccins voor honden om werkzaamheid en veiligheid vast te stellen voor het registratietraject. Het

betreft potentiele vaccins welke in research fase al aan bepaalde eisen van werkzaamheid en veiligheid voldoen, maar waarvoor nu het registratie dossier moet worden samengesteld. Er is een reële relatie tussen het directe doel en het uiteindelijke doel.

5. Benoem de belanghebbenden in het project en beschrijf voor elk van de belanghebbenden welke morele waarden in het geding zijn of bevorderd worden *(Zie Praktische handreiking ETK: Stap 2.B en tabel 1; zie bijlage I voor voorbeeld)*.
De belanghebbenden in dit onderzoeksproject zijn de proefdieren, de aanvrager en de honden waarvoor de vaccins worden ontwikkeld. De proefdieren in het project zullen verschillende niveaus van ongerief ondergaan, waardoor hun welzijn wordt aangetast. De aanvrager heeft een aanzienlijk economisch belang bij het op de markt kunnen brengen van bedoelde vaccins. De doel honden hebben een belangrijke waarde omdat zij [redacted] adequaat kunnen worden gevaccineerd tegen voor hen soms dodelijke infectie ziekten, of maakt een vaccinatie het mogelijk dat zij (tijdelijk) in een professionele kennel kunnen worden ondergebracht of met eigenaren mee kunnen reizen/verhuizen buiten Nederland.

6. Geef aan of er sprake kan zijn van substantiële milieueffecten. Zo ja, benoem deze, leg uit waarom daar sprake van kan zijn en geef aan of deze effecten afgedekt worden door specifieke wet- en regelgeving op het gebied van het omgaan met voor het milieu risicovolle stoffen of organismen.
Er is geen sprake van directe substantiële milieueffecten. Dieren welke afloop van de challenge testen gedood zijn, worden vernietigd door verbranding, daardoor zullen geen pathogene micro-organismen in het milieu terecht komen.

Proefopzet en haalbaarheid

7. Beoordeel of de kennis en kunde van de onderzoeksgroep en andere betrokkenen bij de dierproeven voldoende gewaarborgd zijn. Licht uw beoordeling toe. *(Zie Praktische handreiking ETK: Stap 1.C5)*.
De DEC is ervan overtuigd dat de aanvrager over voldoende expertise en infrastructuur beschikt om de doelstelling van het onderzoek binnen de gevraagde termijn te realiseren. Dit wordt ondersteund door het feit dat de aanvrager al decennia veilig vaccins produceert.

8. Beoordeel of het project goed is opgezet, de voorgestelde experimentele opzet en uitkomstparameters logisch en helder aansluiten bij de aangegeven doelstellingen en of de gekozen strategie en experimentele aanpak kan leiden tot het behalen van de doelstelling binnen het kader van het project. Licht uw beoordeling toe. *Zie Praktische handreiking ETK: Stap 1.C6)*.
De DEC is van mening de gekozen strategie en experimentele aanpak kunnen leiden tot het behalen van de doelstelling binnen het kader van het project. Het behalen van de directe doelstellingen is vooral afhankelijk van het zo strikt mogelijk volgens de richtlijnen en afspraken uitvoeren van de experimenten. [redacted]

Welzijn dieren

9. Geef aan of er sprake is van één of meerdere bijzondere categorieën van dieren, omstandigheden of behandeling van de dieren. Beoordeel of de keuze hiervoor voldoende wetenschappelijk is onderbouwd en of de aanvrager voldoet aan de in de Wet op de Dierproeven (Wod). voor de desbetreffende categorie genoemde beperkende voorwaarden. Licht uw beoordeling toe *(Zie Praktische handreiking ETK: Stap 1.C1; zie bijlage I voor toelichting en voorbeelden)*.

☐ Bedreigde diersoort(en) (10e, lid 4)
☐ Niet-menselijke primaten (10e)
☐ Dieren in/uit het wild (10f)
☐ Niet gefokt voor dierproeven (11, bijlage I richtlijn)
☐ Zwerfdieren (10h)
☐ Hergebruik (1e, lid 2)
☐ Locatie: buiten instelling vergunninghouder (10g)
☐ Geen toepassing verdoving/pijnbestrijding (13)
☐ Dodingsmethode niet volgens bijlage IV richtlijn (13c, lid 3)
NVT

10. Geef aan of de dieren gehuisvest en verzorgd worden op een wijze die voldoet aan de eisen die zijn opgenomen in bijlage III van richtlijn 2010/63/EU. Indien niet aan deze minimale eisen kan worden voldaan, omdat het, om redenen van dierenwelzijn of diergezondheid of om wetenschappelijke redenen, noodzakelijk is hiervan af te wijken, beoordeel of dit in voldoende mate is onderbouwd. Licht uw beoordeling toe.
De dieren worden gehuisvest conform de richtlijn. 10.1.c [redacted]

11. Beoordeel of het cumulatieve ongerief als gevolg van de dierproeven voor elk dier realistisch is ingeschat en geclassificeerd. Licht uw beoordeling toe *(Zie Praktische handreiking ETK: Stap 1.C2)*.
Het ongerief van de dierproeven is realistisch ingeschat en geclassificeerd. Het merendeel van de dieren ondervind mild ongerief omdat het vaccin ze zal beschermen tegen de opgewekte ziekte. Een deel dieren ondervindt matig ongerief ten gevolge van de procedures en er worden op basis van de experimenten voor sommige controle dieren humane eindpunten verwacht. Deze zijn goed beschreven 10.2.g [redacted] in nauwe samenspraak tussen onderzoekers, proefdierdeskundigen/IvD en de DEC strikte criteria voor humane eindpunten ontwikkeld. Bij twijfel heeft de dierenarts altijd het recht de beslissing te nemen.

12. Het uitvoeren van dierproeven zal naast het ongerief vaak gepaard gaan met aantasting van de integriteit van het dier. Beschrijf op welke wijze er sprake is van aantasting van integriteit. *(Zie Praktische handreiking ETK: Stap 1.C2). (zie bijlage I voor voorbeeld).*
Elke dierproef vormt, door de vrijheidsbeperking en de aantasting van de lichamelijke integriteit voor instrumentele doeleinden, een aantasting van de integriteit van het dier. Het vaccineren en de daarop volgende challenge test is een aantasting van de integriteit van de dieren omdat met name de controle dieren ziek worden. Maar omdat deze proeven dienen om de werkzaamheid en veiligheid van honden vaccins aan te tonen om zodoende grote populaties honden effectief tegen voor hen gevaarlijke ziekten te kunnen beschermen is de DEC van oordeel dat de aantasting van integriteit bij deze handeling het ongerief (de welzijnsaantasting) op de voorgrond staat. De aantasting van de integriteit van de dieren is daarmee vergeleken zeer beperkt.

13. Beoordeel of de criteria voor humane eindpunten goed zijn gedefinieerd en of goed is ingeschat welk percentage dieren naar verwachting een humaan eindpunt zal bereiken. Licht uw beoordeling toe *(Zie Praktische handreiking ETK: Stap 1.C3)*.
Er worden voor een beperkt aantal dieren humane eindpunten verwacht. Het aantal dieren en de criteria voor het humane eindpunt is naar het oordeel van de commissie goed ingeschat. Bij de challenge proeven worden ter controle dieren besmet met het

pathogen waartegen de andere groepen ook zijn gevaccineerd. Deze controle groep dient als wettelijk verplichte controle dat de challenge testen goed worden uitgevoerd en daarom onvermijdelijk. Verder zijn in de loop van vele jaren [redacted] in nauwe samenspraak tussen onderzoekers, proefdierdeskundigen/IvD en de DEC strikte criteria voor humane eindpunten ontwikkeld. Voor elk werkprotocol worden de humane eindpunten en de eindverantwoordelijkheid voor het toepassen daarvan, tot in detail afgestemd met de IvD.

3V's

14. Beoordeel of de aanvrager voldoende aannemelijk heeft gemaakt dat er geen geschikte vervangingsalternatieven zijn. Licht uw beoordeling toe *(Zie Praktische handreiking ETK: Stap 1.C3)*. het betreft hier een wettelijk verplicht traject om nieuwe vaccins te kunnen registreren. Er worden alleen vaccins getest welke in de [redacted] al een zekere werkzaamheid en (beperkte) mate van veiligheid hebben laten zien.

15. Beoordeel of het aantal te gebruiken dieren realistisch is ingeschat en of er een heldere strategie is om ervoor te zorgen dat tijdens het project met zo min mogelijk dieren wordt gewerkt waarmee een betrouwbaar resultaat kan worden verkregen. Licht uw beoordeling toe *(Zie Praktische handreiking ETK: Stap 1.C3).)*.
Voor wettelijk vereiste experimenten liggen de aantallen te gebruiken dieren vast. De aanvrager heeft op basis van eerdere ervaring van vaccin ontwikkeling per jaar een realistische inschatting gemaakt van het totaal aantal te gebruiken dieren.

16. Beoordeel of het project in overeenstemming is met de vereiste van verfijning van dierproeven en het project zodanig is opgezet dat de dierproeven zo humaan mogelijk kunnen worden uitgevoerd. Licht uw beoordeling toe *(Zie Praktische handreiking ETK: Stap 1.C3)*.
[redacted]
Deze werkwijze voor werkzaamheid en veiligheid is wettelijk vereist. Daardoor kan de uitvoering van de proef niet meer worden verfijnd.

17. Beoordeel, indien het wettelijk vereist onderzoek betreft, of voldoende aannemelijk is gemaakt dat er geen duplicatie plaats zal vinden en of de aanvrager beschikt over voldoende expertise en informatie om tijdens de uitvoering van het project te voorkomen dat onnodige duplicatie plaatsvindt. Licht uw beoordeling toe.
Het betreft hier het aantonen van werkzaamheid en veiligheid van verbeterde vaccins, de aanvrager heeft een decennia lange expertise in het ontwikkelen van vaccins voor dieren op allerlei gebeid.

Dieren in voorraad gedood en bestemming dieren na afloop proef

18. Geef aan of dieren van beide geslachten in gelijke mate ingezet zullen worden. Indien alleen dieren van één geslacht gebruikt worden, beoordeel of de aanvrager dat in voldoende mate wetenschappelijk heeft onderbouwd. *(Zie Praktische handreiking ETK: Stap 1.C3; zie bijlage I voor voorbeeld).*
Binnen dit project zullen in principe dieren van beide geslachten in de experimenten gebruikt worden.

19. Geef aan of dieren gedood worden in kader van het project (tijdens of na afloop van de dierproef). Indien dieren gedood worden, geef aan of en waarom dit noodzakelijk is voor het behalen van de doelstellingen van het project. Indien dieren gedood

worden, geef aan of er een voor de diersoort passende dodingsmethode gebruikt wordt die vermeld staat in bijlage IV van richtlijn 2010/63/EU. Zo niet, beoordeel of dit in voldoende mate is onderbouwd. Licht uw beoordeling toe. Indien van toepassing, geeft ook aan of er door de aanvrager ontheffing is aangevraagd *(Zie Praktische handreiking ETK: Stap 1.C3).*
In het project zullen dieren worden gedood aan het einde van het experiment. Dit is noodzakelijk omdat de organen moeten worden uitgenomen, geprepareerd en beooordeeld. De DEC is er van overtuigd dat in het kader van de doelstelling noodzakelijk is om na afloop van de proef weefsels te isoleren en te beoordelen op de beschreven parameters. De aanvrager gebruikt methoden die beschreven zijn in bijlage IV van de richtlijn 2010/63/EU.

20. Indien niet-humane primaten, honden, katten of landbouwhuisdieren worden gedood om niet-wetenschappelijke redenen, is herplaatsing of hergebruik overwogen? Licht toe waarom dit wel/niet mogelijk is.
10.1.c [redacted]

NTS

21. Is de niet-technische samenvatting een evenwichtige weergave van het project en begrijpelijk geformuleerd?
De niet-technische samenvatting is een evenwichtige weergave van het project en is duidelijk geformuleerd.

D. Ethische afweging

1. Benoem de centrale morele vraag *(Zie Praktische handreiking ETK: Stap 3.A).*
Rechtvaardigt het belang van de doelstelling van het project het ongerief dat de dieren wordt aangedaan, en is aan alle zorgvuldigheidseisen (3V's) voldaan?

2. Weeg voor de verschillende belanghebbenden, zoals beschreven onder C5, de sociale en morele waarden waaraan tegemoet gekomen wordt of die juist in het geding zijn, ten opzichte van elkaar af. Om dit proces te vergemakkelijken, kunt u de belangrijkste belanghebbenden en de belangrijkste waarden die in het geding zijn waarderen. U kunt dit verwoorden in termen van gering, matig of veel/ernstig voordeel of nadeel. Geef aan waarom de DEC bevordering van waarden (baten) voor de ene belanghebbende prevaleert boven de aantasting van waarden (kosten) voor de andere belanghebbende *(Zie Praktische handreiking ETK: Stap 3.B; zie bijlage I voor voorbeelden).*

Voor het merendeel van de dieren die gebruikt worden in de voorgestelde experimenten leiden de experimenten tot licht ongerief en geen of zeer beperkte aantasting van hun integriteit tijdens het experiment. De vaccins worden toegediend op dezelfde wijze die ook voor honden in de praktijk worden gebruikt. Echter, de challenge testen kunnen heftiger ziekte verschijnselen oproepen dan die welke een dier in de natuurlijke situatie zou vertonen, omdat soms een artificiële route van besmetting moet worden toegepast. Daardoor worden met name de controle dieren ziek met matig tot ernstige aantasting van hun welzijn. 10.1.c [redacted]

10.1.c [redacted]

De aanvrager heeft een groot economisch belang bij het op de markt kunnen brengen van deze vaccins en kan dit alleen doen als hij door middel van de voorgestelde dierproeven aantoont dat ze werkzaam en veilig zijn.
De honden en hun eigenaren hebben baat bij het product omdat honden 10.1.c efficiënt kunnen worden gevaccineerd.
De DEC acht de economische belangen van de aanvrager op zich legitiem en zij leggen zeker enig gewicht in de schaal, maar alleen in combinatie met het maatschappelijk belang van de honden (en hun eigenaren), namelijk voldoende weerstand opbouwen tegen voor de hond ernstige infecties. Daarnaast hebben ander dieren en mensen het belang dat zij niet of veel minder blootgesteld kunnen worden aan 10.1.c . Daarmee acht de DEC het uitvoeren van de voorgestelde experimenten met het gebruik van de beschreven proefdieren gerechtvaardigd.

3. Beantwoord de centrale morele vraag. Maak voor het beantwoorden van deze vraag gebruik van bovenstaande afweging van morele waarden. Maak daarnaast gebruik van de volgende moreel relevante feiten: belang onderzoek (C4), kennis en kunde van betrokkenen (C7), haalbaarheid doelstellingen (C8), categorieën en herkomst dieren (C9), 3V's (C14-C18), ongerief (C10-13 en C19) en relevante wet en regelgeving (C2). Onderbouw hoe al deze elementen zijn meegewogen bij de beantwoording van de centrale morele vraag, zodanig dat het navolgbaar is zonder gedetailleerde kennis te hebben van het projectvoorstel *(Zie Praktische handreiking ETK: Stap 3.C; zie bijlage I voor voorbeeld)*.
De DEC is overtuigd van het belang van de doelstellingen beschreven in het projectvoorstel "*Onderzoek en ontwikkeling van nieuwe hondenvaccins*". Volgens de DEC wegen de voordelen voor de samenleving en de aanvrager zwaarder dan de nadelen voor de gebruikte proefdieren. Het project is goed opgezet. Verder is de DEC van mening dat de aanvrager voldoende kennis en kunde heeft om te kunnen voldoen aan de 3V beginselen en dat de aanvrager ervoor zal zorgen dat het ongerief van de proefdieren zoveel mogelijk beperkt zal worden. Gelet op het bovenstaande is de DEC unaniem van oordeel dat voor het project het gebruik van de proefdieren gerechtvaardigd is.

E. Advies

1. Advies aan de CCD

X **De DEC adviseert de vergunning te verlenen.**

☐De DEC adviseert de vergunning te verlenen onder de volgende voorwaarden

☐ Voor de uitvoering van dit project is tevens ministeriële ontheffing vereist

☐ Overige door de DEC aan de uitvoering verbonden voorwaarden, te weten...

☐ De DEC adviseert de vergunning niet te verlenen vanwege:

☐ De vaststelling dat het project niet vergunningplichtig is om de volgende redenen:...

☐ De volgende doorslaggevende ethische bezwaren:...

☐ De volgende tekortkomingen in de aanvraag:...

2. Het uitgebrachte advies kan unaniem tot stand zijn gekomen dan wel gebaseerd zijn op een meerderheidsstandpunt in de DEC. Indien gebaseerd op een

meerderheidsstandpunt, specificeer het minderheidsstandpunt op het niveau van verschillende belanghebbenden en de waarden die in het geding zijn *(Zie Praktische handreiking ETK: Stap 4.A; zie bijlage I voor voorbeeld).*
Het advies is unaniem tot stand gekomen.

3. Omschrijf de knelpunten/dilemma's die naar voren zijn gekomen tijdens het beoordelen van de aanvraag en het opstellen van het advies zowel binnen als buiten de context van het project *(Zie Praktische handreiking ETK: Stap 4.B)*.

10.1 c