Summary of Studies Supporting USDA Product Licensure

Establishment Name	Boehringer Ingelheim Animal Health USA Inc.
USDA Vet Biologics Establishment Number	124
Product Code	47K9.R0
True Name	Canine Distemper-Adenovirus Type 2-Parainfluenza-Parvovirus Vaccine, Modified Live Virus, Live Canarypox Vector, Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterin
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	
Date of Compilation Summary	May 17, 2019

Disclaimer: Do not use the following studies to compare one product to another. Slight differences in study design and execution can render the comparisons meaningless.

Study Type	Efficacy
Pertaining to	Canine adenovirus type (CAV-2)
Study Purpose	Demonstrate efficacy against canine adenovirus type 1 (canine hepatitis)
Product Administration	Subcutaneously (SQ)
Study Animals	Dogs
Challenge Description	
Interval observed after challenge	
Results	Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	1987

Study Type	Efficacy
Pertaining to	Canine adenovirus type (CAV-2)
Study Purpose	Demonstrate efficacy against canine adenovirus type 2 (canine respiratory disease complex)
Product Administration	Subcutaneously (SQ)
Study Animals	Dogs
Challenge Description	
Interval observed after challenge	
Results	Study results applicable to subcutaneous (SQ) route of administration Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	July 14, 1989

Study Type	Efficacy
Pertaining to	*Leptospira canicola*
Study Purpose	Demonstrate efficacy against leptospirosis and leptospiruria due to *L. canicola*
Product Administration	Animals received two doses subcutaneously, 3 weeks apart.
Study Animals	Thirty-seven puppies, 47 to 88 days old Vaccinates: 19 Controls: 18
Challenge Description	Challenged 21 days after second vaccination against *Leptospira canicola*
Interval observed after challenge	Urine samples were collected 14 days prior to challenge and 13, 15, 17, 20, 22 and 34 days after challenge. Tissues were examined 35 days after challenge.
Results	**Leptospirosis:** An animal was considered to have leptospirosis *if L. canicola* was isolated from the urine on one or more occasions and if abnormal renal histopathologic changes were observed, or if *L. canicola* was isolated on multiple occasions from the urine. Animals with leptospirosis: Vaccinates: 0/19 Controls: 16/18 **Leptospiruria** was defined as shedding *Leptospira* organisms in the urine on multiple occasions after challenge Animals with leptospiruria: Vaccinates: 0/19 Controls: 14/18 See raw data on attached page.
USDA Approval Date	August 22, 2007

Table 1: Individual Leptospiruria

Group	Puppy ID	Days Post-Challenge (Study Day)						
		-14 (28)	13 (55)	15 (57)	17 (59)	20 (62)	22 (64)	34 (76)
Cont.	13001	-	+	-	+	+	-	-
Cont.	13104	-	+	+	-	-	-	+
Cont.	12607	-	+	+	-	+	-	-
Cont.	12910	-	+	-	-	+	-	-
Cont.	82204	-	+	+	-	+	-	-
Cont.	12903	-	-	+	-	+	+	-
Cont.	82106	-	+	+	+	+	+	+
Cont.	13106	-	-	+	+	+	-	-
Cont.	82201	-	-	+	-	+	-	+
Cont.	82704	-	-	-	-	-	+	-
Cont.	12606	-	+	+	+	+	+	+
Cont.	82105	-	+	+	+	+	-	-
Cont.	12907	-	+	-	-	-	-	-
Cont.	82206	-	-	-	-	-	-	-
Cont.	82302	-	+	+	-	-	+	-
Cont.	13003	-	+	-	+	+	+	+
Cont.	82703	-	-	-	-	-	-	-
Cont.	12905	-	-	+	-	+	-	+
Vacc.	**82203**	-	-	-	-	-	-	-
Vacc.	**12909**	-	-	-	-	-	-	-
Vacc.	**82702**	-	-	-	-	-	-	-
Vacc.	**12908**	-	-	-	-	-	-	-
Vacc.	**13103**	-	-	-	-	-	-	-
Vacc.	**82303**	-	-	-	-	-	-	-
Vacc.	**82601**	-	-	-	-	-	-	-
Vacc.	**12902**	-	-	-	-	-	-	-
Vacc.	**82701**	-	-	-	-	-	-	-
Vacc.	**82202**	-	-	-	-	-	-	-
Vacc.	**12906**	-	-	-	-	-	-	-
Vacc.	**12904**	-	-	-	-	-	-	-
Vacc.	**82107**	-	-	-	-	-	-	-
Vacc.	**13105**	-	-	-	-	-	-	-
Vacc.	**82205**	-	-	-	-	-	-	-
Vacc.	**13002**	-	-	-	-	-	-	-
Vacc.	**12602**	-	-	-	-	-	-	-
Vacc.	**82705**	-	-	-	-	-	-	-
Vacc.	**12604**	-	-	-	-	-	-	-

+ indicates *Leptospira* organisms were re-isolated from the urine
- indicates no *Leptospira* organisms were re-isolated from urine

Table 2: Individual Renal Histopathology Results

Histopathological findings	Score
No histopathological changes; normal	0
Presence of rare and discrete clusters of inflammatory cells (lymphocytes, plasma cells) within cortical interstitium; no tubular or glomerular abnormalities noted	1
Multiple clusters of inflammatory cells (lymphocytes, plasma cells) lymphocytes within cortical interstitium; clusters are large enough that they obliterate some tubules	2
More than one of the following criteria: ▪ Extensive mononuclear cells inflammatory infiltrates throughout cortex, may also include neutrophils ▪ Renal function is visibly impaired as evidenced by protein within tubules or tubular degeneration, or glomerular senescence ▪ Cortical fibrosis with pitting may be present	3

A score of ≥1 is considered abnormal.

Treatment group	ID	Kidney A	Kidney B
Cont.	12606	0	1
Cont.	12607	0	1
Cont.	12903	2	1
Cont.	12905	0	0
Cont.	12907	2	2
Cont.	12910	1	1
Cont.	13001	2	2
Cont.	13003	1	1
Cont.	13104	2	1
Cont.	13106	1	0
Cont.	82105	1	1
Cont.	82106	1	1
Cont.	82201	1	0
Cont.	82204	2	1
Cont.	82206	0	0
Cont.	82302	1	0
Cont.	82703	1	0
Cont.	82704	0	1

Treatment group	ID	Kidney A	Kidney B
Vacc.	12602	0	0
Vacc.	12604	0	0
Vacc.	12902	0	0
Vacc.	12904	0	0
Vacc.	12906	0	0
Vacc.	12908	0	0
Vacc.	12909	0	0
Vacc.	13002	0	0
Vacc.	13103	0	0
Vacc.	13105	0	0
Vacc.	82107	0	0
Vacc.	82202	0	0
Vacc.	82203	0	0
Vacc.	82205	0	0
Vacc.	82303	0	0
Vacc.	82601	0	0
Vacc.	82701	0	0
Vacc.	82702	0	0
Vacc.	82705	0	0

Study Type	Efficacy
Pertaining to	*Leptospira grippotyphosa*
Study Purpose	Demonstrate efficacy against leptospirosis and leptospiruria due to *L. grippotyphosa*
Product Administration	Animals received two doses subcutaneously, 3 weeks apart.
Study Animals	Thirty-seven puppies, 60 to 70 days old Vaccinates: 18 Controls: 19
Challenge Description	Challenged 17 days after second vaccination against *Leptospira grippotyphosa*
Interval observed after challenge	Urine samples were collected 10 days prior to challenge and 14, 16, 18, 20, 27 and 31 days after challenge. Tissue samples were examined 31 days after challenge.
Results	**Leptospirosis:** An animal was considered to have leptospirosis *if L. grippotyphosa* was isolated from the urine on one or more occasions and if abnormal renal histopathologic changes were observed, or if *L. grippotypho*sa was isolated on multiple occasions from the urine. Animals with leptospirosis: Vaccinates: 0/18 Controls: 16/19 **Leptospiruria** was defined as shedding *L. grippotyphosa* organisms in the urine on multiple occasions after challenge Animals with leptospiruria: Vaccinates: 0/18 Controls: 16/19 See raw data on attached page.
USDA Approval Date	July 17, 2007

Table 1: Individual Leptospiruria

Group	Puppy ID	Days Post-Challenge (Study Day)						
		-10 (28)	14 (52)	16 (54)	18 (56)	20 (58)	27 (65)	31 (69)
Cont.	85001	-	+	-	-	+	+	-
Cont.	15001	-	-	-	-	-	-	-
Cont.	15205	-	+	-	+	+	+	-
Cont.	85204	-	-	+	+	-	-	-
Cont.	15102	-	-	-	-	-	-	-
Cont.	14903	-	+	+	+	+	-	-
Cont.	85202	-	+	+	+	+	+	-
Cont.	85203	-	+	+	+	+	-	-
Cont.	14902	-	-	+	+	-	+	-
Cont.	85304	-	-	-	-	-	+	-
Cont.	85005	-	+	+	+	+	+	-
Cont.	15206	-	+	+	+	-	+	-
Cont.	85103	-	+	-	+	+	+	-
Cont.	85003	-	+	-	+	+	+	-
Cont.	15103	-	-	-	+	-	+	-
Cont.	85303	-	+	+	+	+	+	-
Cont.	85104	-	+	+	+	+	+	-
Cont.	85306	-	+	-	+	+	+	-
Cont.	15203	-	+	+	+	+	+	-
Vacc.	**85006**	-	-	-	-	-	-	-
Vacc.	**15201**	-	-	-	-	-	-	-
Vacc.	**85201**	-	-	-	-	-	-	-
Vacc.	**85205**	-	-	-	-	-	-	-
Vacc.	**85106**	-	-	-	-	-	-	-
Vacc.	**85102**	-	-	-	-	-	-	-
Vacc.	**15202**	-	-	-	-	-	-	-
Vacc.	**85002**	-	-	-	-	-	-	-
Vacc.	**85302**	-	-	-	-	-	-	-
Vacc.	**85004**	-	-	-	-	-	-	-
Vacc.	**85305**	-	-	-	-	-	-	-
Vacc.	**15204**	-	-	-	-	-	-	-
Vacc.	**85105**	-	-	-	-	-	-	-
Vacc.	**15207**	-	-	-	-	-	-	-
Vacc.	**15002**	-	-	-	-	-	-	-
Vacc.	**15101**	-	-	-	-	-	-	-
Vacc.	**15104**	-	-	-	-	-	-	-
Vacc.	**14901**	-	-	-	-	-	-	-

+ indicates *Leptospira* organisms were re-isolated from the urine
- indicates no *Leptospira* organisms were re-isolated from urine

Table 2: Individual Renal Histopathology Results

Histopathological findings	**Score**
No histopathological changes; normal	0
Presence of rare and discrete clusters of inflammatory cells (lymphocytes, plasma cells) within cortical interstitium; no tubular or glomerular abnormalities noted	1
Multiple clusters of inflammatory cells (lymphocytes, plasma cells) lymphocytes within cortical interstitium; clusters are large enough that they obliterate some tubules	2
More than one of the following criteria: ▪ Extensive mononuclear cells inflammatory infiltrates throughout cortex, may also include neutrophils ▪ Renal function is visibly impaired as evidenced by protein within tubules or tubular degeneration, or glomerular senescence ▪ Cortical fibrosis with pitting may be present	3

A score of $\geq$1 is considered abnormal.

Treatment group	ID	Kidney A	Kidney B
Cont.	14902	0	1
Cont.	14903	2	1
Cont.	15001	0	0
Cont.	15102	0	0
Cont.	15103	0	0
Cont.	15203	1	2
Cont.	15205	2	1
Cont.	15206	2	2
Cont.	85001	2	2
Cont.	85003	2	2
Cont.	85005	1	0
Cont.	85103	2	2
Cont.	85104	1	1
Cont.	85202	1	1
Cont.	85203	2	1
Cont.	85204	1	2
Cont.	85303	2	1
Cont.	85304	0	0
Cont.	85306	1	2

Treatment group	ID	Kidney A	Kidney B
Vacc.	**14901**	**0**	**0**
Vacc.	**15002**	**0**	**0**
Vacc.	**15101**	**0**	**0**
Vacc.	**15104**	**0**	**0**
Vacc.	**15201**	**0**	**0**
Vacc.	**15202**	**0**	**0**
Vacc.	**15204**	**0**	**0**
Vacc.	**15207**	**0**	**0**
Vacc.	**85002**	**0**	**1**
Vacc.	**85004**	**0**	**0**
Vacc.	**85006**	**0**	**0**
Vacc.	**85102**	**0**	**0**
Vacc.	**85105**	**0**	**0**
Vacc.	**85106**	**0**	**0**
Vacc.	**85201**	**0**	**0**
Vacc.	**85205**	**0**	**0**
Vacc.	**85302**	**0**	**0**
Vacc.	**85305**	**0**	**0**

Study Type	Efficacy
Pertaining to	*Leptospira grippotyphosa*
Study Purpose	Demonstrate efficacy against leptospirosis and leptospiruria due to *L. grippotyphosa* 15 months after vaccination to establish a minimum duration of immunity
Product Administration	Animals received two doses subcutaneously, 3 weeks apart.
Study Animals	Forty-one puppies, 47 to 73 days old Vaccinates: 20 Controls: 21
Challenge Description	Challenged 15 months after second vaccination against *Leptospira grippotyphosa*
Interval observed after challenge	Urine samples were collected prior to challenge and 15, 18, 20, 22, 25, 29 and 33 days after challenge. Tissues were examined 34 days after challenge.
Results	**Leptospirosis:** An animal was considered to have leptospirosis *if L. grippotyphosa* was isolated from the urine on one or more occasions and if abnormal renal histopathologic changes were observed, or if *L. grippotypho*sa was isolated on multiple occasions from the urine. Animals with leptospirosis: Vaccinates: 0/20 Controls: 16/21 **Leptospiruria** was defined as shedding *Leptospira* organisms in the urine on any day sampled after challenge. Animals with leptospiruria: Vaccinates: 1/20 Controls: 16/21 See raw data on attached page.
USDA Approval Date	June 16, 2008

Table 1: Individual Leptospiruria and Renal Histopathology Score

Group	Dog ID	Leptospiruria - Days Post-challenge (Study Day)								Individual Renal Histopathology Score[b]
		-1 (490)	15 (506)	18 (509)	20 (511)	22 (513)	25 (516)	29 (520)	33 (524)	
Cont.	17901	-	-	-	-	-	-	-	-	0
Cont.	18103	-	-	-	-	+	-	-	-	2
Cont.	87403	-	-	-	-	-	-	-	-	0
Cont.	87504	-	+	-	+	+	+	+	-	2
Cont.	18403	-	+	-	-	+	-	+	-	2
Cont.	87405	-	+	-	+	+	+	+	-	1
Cont.	87503	-	-	-	-	-	-	-	-	0
Cont.	18303	-	+	+	+	+	-	+	+	2
Cont.	87603	-	-	-	-	-	+	+	-	0
Cont.	18204	-	-	-	+	-	+	-	+	2
Cont.	18504	-	-	-	-	-	+	+	-	3
Cont.	87702	-	+	-	+	+	+	+	+	3
Cont.	18101	-	+	+	+	+	+	+	+	3
Cont.	18401	-	-	-	+	+	+	-	-	3
Cont.	87606	-	+	+	-	+	+	-	+	3
Cont.	18201	-	-	-	-	-	-	-	-	0
Cont.	87501	-	-	-	-	-	-	-	-	0
Cont.	18505	-	-	-	+	+	+	+	-	0
Cont.	87604	-	+	+	+	-	+	+	-	1
Cont.	18302	-	-	+	-	-	+	+	+	0
Cont.	17904	-	-	-	+	-	-	-	+	3
Vacc.	**18102**[a]	-	-	-	-					0
Vacc.	**18104**	-	-	-	-	-	-	-	-	0
Vacc.	**87703**	-	-	-	-	-	-	-	-	0
Vacc.	**18501**	-	-	-	-	-	-	-	-	0
Vacc.	**87701**	-	-	-	-	-	-	-	-	0
Vacc.	**87506**	-	-	-	-	-	-	-	-	2
Vacc.	**18402**	-	-	-	-	-	-	+	-	0
Vacc.	**18503**	-	-	-	-	-	-	-	-	0
Vacc.	**18603**	-	-	-	-	-	-	-	-	0
Vacc.	**18404**	-	-	-	-	-	-	-	-	0
Vacc.	**18304**	-	-	-	-	-	-	-	-	0
Vacc.	**18604**	-	-	-	-	-	-	-	-	1
Vacc.	**87505**	-	-	-	-	-	-	-	-	0
Vacc.	**17902**	-	-	-	-	-	-	-	-	0
Vacc.	**87404**	-	-	-	-	-	-	-	-	0
Vacc.	**18202**	-	-	-	-	-	-	-	-	0
Vacc.	**18301**	-	-	-	-	-	-	-	-	0
Vacc.	**87605**	-	-	-	-	-	-	-	-	1
Vacc.	**87607**	-	-	-	-	-	-	-	-	0
Vacc.	**18203**	-	-	-	-	-	-	-	-	0

[a]Dog #18102 (vaccinate) was euthanized on Study Day 512 due to an acute painful abdomen with transudate fluid-filled peritoneal cavity thought to be due to uroperitoneum based on necropsy histopathology reports.
[b]From the 2 kidneys the highest histopathologic score was taken to classify the dog

Leptospiruria
+ indicates *Leptospira* organisms were re-isolated from the urine
- indicates that no *Leptospira* organisms were re-isolated from the urine

Renal histopathology score
Renal histopathology scoring chart found in Table 2.

Table 2: Renal Histopathology Scoring Chart

Histopathological findings	**Score**
No histopathological changes; normal	0
Presence of rare and discrete clusters of inflammatory cells (lymphocytes, plasma cells) within cortical interstitium; no tubular or glomerular abnormalities noted	1
Multiple clusters of inflammatory cells (lymphocytes, plasma cells) lymphocytes within cortical interstitium; clusters are large enough that they obliterate some tubules	2
More than one of the following criteria: ▪ Extensive mononuclear cells inflammatory infiltrates throughout cortex, may also include neutrophils ▪ Renal function is visibly impaired as evidenced by protein within tubules or tubular degeneration, or glomerular senescence ▪ Cortical fibrosis with pitting may be present	3

A score of $\geq$1 is considered abnormal.

Study Type	Efficacy
Pertaining to	*Leptospira icterohaemorrhagiae*
Study Purpose	Demonstrate efficacy against leptospirosis and leptospiruria due to *L. icterohaemorrhagiae*
Product Administration	Animals received two doses subcutaneously, 3 weeks apart.
Study Animals	Thirty-six puppies, 9-12 weeks of age Vaccinates: 18 Controls: 18
Challenge Description	Challenged 7 weeks after second vaccination against *Leptospira icterohaemorrhagiae*
Interval observed after challenge	Urine samples were collected 7 days prior to challenge and 12, 14, 16, 20, 24 and 36 days after challenge. Tissues were examined 36 days after challenge.
Results	**Leptospirosis:** An animal was considered to have leptospirosis *if L. icterohaemorrhagiae* was isolated from the urine on one or more occasions and if abnormal renal histopathologic changes were observed, or if *L. icterohaemorrhagiae* was isolated on multiple occasions from the urine, or if an animal was euthanized for clinical signs of leptospirosis. Animals with leptospirosis: Vaccinates: 0/18 Controls: 17/18 **Leptospiruria** was defined as shedding *Leptospira* organisms in the urine on any day sampled after challenge Animals with leptospiruria: Vaccinates: 0/18 Controls: 16/18 See raw data on attached page.
USDA Approval Date	May 1, 2007

Table 1: Individual Leptospiruria

Group	Puppy ID	Days Post-Challenge (Study Day)						
		- 7 (63)	12 (82)	14 (84)	16 (86)	20 (90)	24 (94)	36 (106)
Cont.	418503	-	+	+	+	-	+	-
Cont.	580105	-	+	+	+	+	+	-
Cont.	580201	-	+	+	+	+	+	-
Cont.	510107	-	+	+	+	+	+	-
Cont.	487205	-	+	+	+	+	+	-
Cont.	418505	-	+	+	+	-	+	-
Cont.	418506	-	+	+	+	+	+	-
Cont.	487001	-	-	+	+	+	+	-
Cont.	*487003*	-	+*	E	E	E	E	E
Cont.	580102	-	+	+	+	+	+	-
Cont.	510101	-	+	+	+	+	-	-
Cont.	*510103*	-	+	+	+	+	E	E
Cont.	487201	-	+	+	+	+	+	-
Cont.	*418601*	-	-*	E	E	E	E	E
Cont.	418501	-	+	+	+	-	+	-
Cont.	487103	-	+	+	+	+	+	-
Cont.	418401	-	+	+	+	-	+	-
Cont.	418402	-	+	+	+	-	-	-
Vacc.	**510106**	-	-	-	-	-	-	-
Vacc.	**580106**	-	-	-	-	-	-	-
Vacc.	**418603**	-	-	-	-	-	-	-
Vacc.	**487204**	-	-	-	-	-	-	-
Vacc.	**418504**	-	-	-	-	-	-	-
Vacc.	**418606**	-	-	+	-	-	-	-
Vacc.	**487105**	-	-	+	-	-	-	-
Vacc.	**486907**	-	-	-	-	-	-	-
Vacc.	**487002**	-	-	-	-	-	-	-
Vacc.	**580101**	-	-	-	-	-	-	-
Vacc.	**580104**	-	-	-	-	-	-	-
Vacc.	**510102**	-	-	-	-	-	-	-
Vacc.	**487202**	-	-	-	-	-	-	-
Vacc.	**487203**	-	-	-	-	-	-	-
Vacc.	**418602**	-	-	-	-	-	-	-
Vacc.	**418502**	-	-	-	-	-	-	-
Vacc.	**487104**	-	-	-	-	-	-	-
Vacc.	**418403**	-	-	-	-	-	-	-

* Actual sample collected on Day 6 post-challenge prior to euthanasia.
E indicates no data as Control Dogs 418601 and 487003 were euthanized on Study Day 76 and control Dog 510103 was euthanized on Study Day 94 due to severe clinical signs (hyperthermia, icterus, dehydration and prostration).
+ indicates *Leptospira* organisms were re-isolated from the urine
- indicates no *Leptospira* organisms were re-isolated from urine

Table 2: Individual Renal Histopathology Results

Histopathological findings	**Score**
No histopathological changes; normal	0
Presence of rare and discrete clusters of inflammatory cells (lymphocytes, plasma cells) within cortical interstitium; no tubular or glomerular abnormalities noted	1
Multiple clusters of inflammatory cells (lymphocytes, plasma cells) lymphocytes within cortical interstitium; clusters are large enough that they obliterate some tubules	2
More than one of the following criteria: ▪ Extensive mononuclear cells inflammatory infiltrates throughout cortex, may also include neutrophils ▪ Renal function is visibly impaired as evidenced by protein within tubules or tubular degeneration, or glomerular senescence ▪ Cortical fibrosis with pitting may be present	3

A score of $\geq$1 is considered abnormal.

Treatment group	ID	Kidney Score
Cont.	418401	2
Cont.	418402	2
Cont.	418501	2
Cont.	418503	2
Cont.	418505	2
Cont.	418506	2
Cont.	418601	2
Cont.	487001	2
Cont.	487003	3
Cont.	487103	2
Cont.	487201	2
Cont.	487205	2
Cont.	510101	2
Cont.	510103	3
Cont.	510107	2
Cont.	580102	2
Cont.	580105	2
Cont.	580201	2

Treatment group	ID	Kidney Score
Vacc.	418403	0
Vacc.	418502	0
Vacc.	418504	0
Vacc.	418602	0
Vacc.	418603	0
Vacc.	418606	0
Vacc.	486907	0
Vacc.	487002	0
Vacc.	487104	0
Vacc.	487105	0
Vacc.	487202	0
Vacc.	487203	0
Vacc.	487204	0
Vacc.	510102	0
Vacc.	510106	0
Vacc.	580101	0
Vacc.	580104	0
Vacc.	580106	0

Study Type	Efficacy
Pertaining to	*Leptospira pomona*
Study Purpose	Demonstrate efficacy against leptospirosis and leptospiruria due to *L. pomona*
Product Administration	Animals received two doses subcutaneously, 3 weeks apart.
Study Animals	Thirty-seven puppies, 49 to 61 days old Vaccinates: 19 Controls: 18
Challenge Description	Challenged 14 days after second vaccination against *Leptospira pomona*
Interval observed after challenge	Urine samples were collected 7 days prior to challenge and 12, 14, 17, 19, 21, 35 and 47 days after challenge. Tissues were examined 47 days after challenge.
Results	**Leptospirosis:** An animal was considered to have leptospirosis *if* *L. pomona* was isolated from the urine on one or more occasions and if abnormal renal histopathologic changes were observed, or if *L. pomona* was isolated on multiple occasions from the urine. Animals with leptospirosis: Vaccinates: 1/19 Controls: 14/18 **Leptospiruria** was defined as shedding *Leptospira* organisms in the urine on any day sampled after challenge Animals with leptospiruria: Vaccinates: 1/19 Controls: 17/18 See raw data on attached page.
USDA Approval Date	August 23, 2007

Table 1: Individual Leptospiruria

Group	Puppy ID	Days Post-Challenge (Study Day)							
		-7 (28)	12 (47)	14 (49)	17 (52)	19 (54)	21 (56)	35 (70)	47 (82)
Cont.	87205	-	-	+	-	+	-	-	-
Cont.	17604	-	-	-	-	-	-	-	-
Cont.	17505	-	-	-	-	+	+	-	-
Cont.	17509	-	-	-	+	-	-	-	-
Cont.	17507	-	+	-	+	+	+	-	-
Cont.	17504	-	-	+	-	+	-	+	-
Cont.	87301	-	-	-	-	+	+	-	-
Cont.	17409	-	-	+	-	-	+	-	-
Cont.	87206	-	+	-	+	+	+	-	-
Cont.	87201	-	-	-	-	-	+	-	-
Cont.	87202*	-	-	-	+	-	-	-	
Cont.	17702	-	+	+	+	+	+	-	-
Cont.	17501	-	-	+	-	-	-	-	-
Cont.	17603	-	-	-	+	-	+	-	-
Cont.	17402	-	+	-	+	+	+	-	-
Cont.	17404	-	-	-	-	-	+	-	-
Cont.	17405	-	-	+	+	+	-	-	-
Cont.	87302	-	-	+	+	-	+	-	-
Vacc.	**87207**	-	-	-	-	-	-	-	-
Vacc.	**17401**	-	-	-	-	-	-	-	-
Vacc.	**17701**	-	-	-	-	-	-	-	-
Vacc.	**17508**	-	-	-	-	-	-	-	-
Vacc.	**17403**	-	-	-	-	-	-	-	-
Vacc.	**87303**	-	-	-	-	-	-	-	-
Vacc.	**17506**	-	-	-	-	-	+	-	-
Vacc.	**17602**	-	-	-	-	-	-	-	-
Vacc.	**17704**	-	-	-	-	-	-	-	-
Vacc.	**17408**	-	-	-	-	-	-	-	-
Vacc.	**17503**	-	-	-	-	-	-	-	-
Vacc.	**17605**	-	-	-	-	-	-	-	-
Vacc.	**17502**	-	-	-	-	-	-	-	-
Vacc.	**87203**	-	-	-	-	-	-	-	-
Vacc.	**17407**	-	-	-	-	-	-	-	-
Vacc.	**17406**	-	-	-	-	-	-	-	-
Vacc.	**17601**	-	-	-	-	-	-	-	-
Vacc.	**87204**	-	-	-	-	-	-	-	-
Vacc.	**17703**	-	-	-	-	-	-	-	-

*There is a missing urine sample on Day 82 as no urine was in the bladder at the time of collection immediately post euthanasia.

\+ indicates *Leptospira* organisms were re-isolated from the urine
\- indicates no *Leptospira* organisms were re-isolated from urine

Table 2: Individual Renal Histopathology Results

Histopathological findings	Score
No histopathological changes; normal	0
Presence of rare and discrete clusters of inflammatory cells (lymphocytes, plasma cells) within cortical interstitium; no tubular or glomerular abnormalities noted	1
Multiple clusters of inflammatory cells (lymphocytes, plasma cells) lymphocytes within cortical interstitium; clusters are large enough that they obliterate some tubules	2
More than one of the following criteria: ▪ Extensive mononuclear cells inflammatory infiltrates throughout cortex, may also include neutrophils ▪ Renal function is visibly impaired as evidenced by protein within tubules or tubular degeneration, or glomerular senescence ▪ Cortical fibrosis with pitting may be present	3

A score of ≥1 is considered abnormal.

Treatment group	ID	Kidney A	Kidney B
Cont.	17402	0	0
Cont.	17404	0	0
Cont.	17405	1	0
Cont.	17409	0	0
Cont.	17501	0	0
Cont.	17504	2	1
Cont.	17505	1	0
Cont.	17507	0	0
Cont.	17509	0	0
Cont.	17603	3	3
Cont.	17604	3	3
Cont.	17702	0	1
Cont.	87201	0	1
Cont.	87202	1	0
Cont.	87205	0	0
Cont.	87206	0	0
Cont.	87301	2	2
Cont.	87302	0	0

Treatment group	ID	Kidney A	Kidney B
Vacc.	17401	0	0
Vacc.	17403	0	0
Vacc.	17406	0	0
Vacc.	17407	0	0
Vacc.	17408	0	0
Vacc.	17502	0	0
Vacc.	17503	0	0
Vacc.	17506	0	1
Vacc.	17508	0	0
Vacc.	17601	1	3
Vacc.	17602	3	0
Vacc.	17605	3	3
Vacc.	17701	0	0
Vacc.	17703	0	0
Vacc.	17704	0	0
Vacc.	87203	0	0
Vacc.	87204	0	0
Vacc.	87207	0	0
Vacc.	87303	0	0

Study Type	Efficacy
Pertaining to	Canine parainfluenza virus
Study Purpose	Demonstrate efficacy against canine parainfluenza virus
Product Administration	Subcutaneously (SQ)
Study Animals	Dogs
Challenge Description	
Interval observed after challenge	
Results	Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	April 27, 1998

Study Type	Efficacy
Pertaining to	Canine distemper virus
Study Purpose	Demonstrate efficacy against canine distemper virus
Product Administration	Subcutaneously (SQ)
Study Animals	Dogs
Challenge Description	
Interval observed after challenge	
Results	Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	November 6, 1995

Study Type	Efficacy
Pertaining to	Canine parvovirus
Study Purpose	Demonstrate efficacy against canine parvovirus
Product Administration	Subcutaneously (SQ)
Study Animals	Dogs
Challenge Description	
Interval observed after challenge	
Results	Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	April 12, 1994

Study Type	Safety
Pertaining to	Canine Adenovirus Type-2 (CAV-2)
Study Purpose	Development of corneal opacity is not associated with the use of this product
Product Administration	
Study Animals	
Challenge Description	
Interval observed after challenge	
Results	Study data are not available.

Study Type	Safety
Pertaining to	ALL
Study Purpose	To evaluate safety under field conditions
Product Administration	Animals received two doses subcutaneously, approximately 3-4 weeks apart.
Study Animals	A total of 686 dogs: ≤ 9 weeks of age: 225 > 9 weeks of age: 461
Challenge Description	Not applicable
Interval observed after challenge	Dogs were observed by veterinarian for 30 minutes post vaccination and examined at least once within 7 days. Owners monitored the dogs for 14 days after each vaccination. Any injection site reactions were monitored every 7 days until resolution.
Results	Twenty-two dogs received the first vaccination but did not receive the second vaccination. Most systemic adverse events resolved within 24-72 hours without treatment. Most local adverse events resolved within 4-8 days without treatment. The same event may have been reported by both the owner and veterinarian. Data on following page.
USDA Approval Date	November 24, 2015

Table 1: Veterinarian-Reported Adverse Events

Clinical sign classification	Number of events[a] in 1350 doses	Percentage of 1350 doses with event
Abscess[b]	1	0.1%
Anorexia	10	0.7%
Ataxia[c]	1	0.1%
Bloating	1	0.1%
Death[d]	1	0.1%
Decreased appetite	2	0.1%
Dehydration	1	0.1%
Depression	14	1.0%
Diarrhea	18	1.3%
Elevated temperature	1	0.1%
Enteritis	1	0.1%
Fever	2	0.1%
Injection Site Edema	15	1.1%
Injection site NOS[e]	1	0.1%
Injection Site Pain	48	3.6%
Injection Site Swelling (<1.5 cm)	7	0.5%
Injection Site Swelling (1.5-5 cm)	29	2.1%
Injection Site Swelling (>5 cm)	6	0.4%
Lethargy	3	0.2%
Limping	3	0.2%
Listless	1	0.1%
Localized Itching	1	0.1%
Nausea	1	0.1%
Other[f]	23	1.7%
Periorbital edema	1	0.1%
Reluctant to move	1	0.1%
Stiffness	1	0.1%
Vomiting	21	1.6%
Welts	1	0.1%

[a]Dogs may be counted in more than one clinical sign category.
[b]Abscess was on ventral abdomen, not injection site
[c]Ataxia resolved within 3 hours
[d]Affirmed by licensee to have cause other than vaccination
[e]NOS = not otherwise specified
[f]Other events include aggression, ear mite otitis, enlarged salivary gland, grumpy, hot spot, kennel cough, loose stool – hookworms, nasal discharge, panting, ringworm, salivation, scooting, sniffing, wheeze, wound

Table 2: Owner-Reported Adverse Events

Clinical sign classification	Number of events[a] in 1350 doses	Percentage of 1350 doses with event
Doses associated with no clinical signs	966	No event - 71.6%
Anorexia	8	0.6%
Breathing difficulty	2	0.1%
Coughing	2	0.1%
Decreased activity	4	0.3%
Depression	61	4.5%
Diarrhea	61	4.5%
Facial swelling	1	0.1%
Fever	3	0.2%
Frequent urination	4	0.3%
Generalized pain	3	0.2%
Hyperactivity	4	0.3%
Inappetence	9	0.7%
Increased respiratory rate	1	0.1%
Increased temperature	1	0.1%
Increased thirst	1	0.1%
Injection site itching	1	0.1%
Injection site pain	193	14.3%
Injection site swelling	166	12.3%
Injection site warmth	1	0.1%
Irritable	3	0.2%
Itching	5	0.4%
Lethargy	15	1.1%
Limping	6	0.4%
Listless	2	0.1%
Malaise	1	0.1%
Mucus stool	1	0.1%
Musculoskeletal pain	1	0.1%
Nausea	1	0.1%
Not drinking	1	0.1%
Other[b]	13	1.0%
Pain	2	0.1%
Panting	1	0.1%
Papules	1	0.1%
Pustules	1	0.1%
Rash	1	0.1%
Restless	2	0.1%
Self-trauma	1	0.1%
Shaking	4	0.3%
Soft stool	10	0.7%
Stiff gait	1	0.1%
Straining to defecate	1	0.1%
Swelling	1	0.1%
Swollen paws	1	0.1%
Tiredness	16	1.2%
Vocalization	4	0.3%
Vomiting	63	4.7%
Warm to touch	1	0.1%

[a]Adverse events are only counted once per vaccination, even if they were observed on more than one day post-vaccination. Dogs may be counted in more than one clinical sign category.

[b]Includes bee sting, decreased frequency of bowel movement/urination, discolored feces, dry mouth, eating grass, eating stool, eye infection, inappropriate urination, increased time for bowel movement/urination, noted abnormal with no sign reported, scooting, sleep disturbance not otherwise specified, intestinal worms