Summary of Studies Supporting USDA Product Licensure

Establishment Name	Zoetis Inc.
USDA Vet Biologics Establishment Number	190
Product Code	2863.07
True Name	Campylobacter Fetus-Leptospira Canicola-Grippotyphosa-Hardjo-Icterohaemorrhagiae-Pomona Bacterin
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	Spirovac VL5 - No distributor specified Spirovac VL5 - Zoetis Argentina
Date of Compilation Summary	June 16, 2022

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	*Campylobacter fetus* (*C. fetus*)
Study Purpose	Demonstrate efficacy against campylobacteriosis caused by *C. fetus*
Product Administration	
Study Animals	
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	07/09/1981

Study Type	Efficacy
Pertaining to	*Leptospira interrogans* serovar c*anicola* (*L canicola*)
Study Purpose	Demonstration of efficacy against leptospirosis caused by *L. canicola*
Product Administration	One dose administered intramuscularly
Study Animals	15 Calves approximately 6 months of age; 10 vaccinates and 5 controls. All animals were seronegative for *Leptospira canicola, icterohaemorrhagiae, hardjo, grippotyphosa, pomona*.
Challenge Description	Animals were challenged 3 weeks following vaccination.
Interval observed after challenge	Animals were observed post challenge for 8 days. Body temperatures and blood samples were collected daily.
Results	Leptospira Isolation Results in Blood: Controls: 5/5 (100%) positive Vaccinates: 0/10 (0%) positive Temperature Results: Controls: 5/5 (100%) positive Vaccinates: 0/10 (0%) positive See the following tables for individual raw data
USDA Approval Date	09/13/1977

Blood culture for isolation of Leptospires:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)							
		1	2	3	4	5	6	7	8
CONTROLS	45	+	+	+	-	-	-	-	-
	68	+	+	-	-	-	-	-	-
	75	+	+	+	-	-	-	-	-
	86	+	+	-	-	-	-	-	-
	106	+	+	+	-	-	-	-	-
VACCINATES	39	-	-	-	-	-	-	-	-
	57	-	-	-	-	-	-	-	-
	63	-	-	-	-	-	-	-	-
	67	-	-	-	-	-	-	-	-
	82	-	-	-	-	-	-	-	-
	85	-	-	-	-	-	-	-	-
	92	-	-	-	-	-	-	-	-
	99	-	-	-	-	-	-	-	-
	103	-	-	-	-	-	-	-	-
	104	-	-	-	-	-	-	-	-

+: Leptopires detected; -: Leptopires not detected

Temperature in ºF:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)								
		0	1	2	3	4	5	6	7	8
CONTROLS	45	102.4	101.0	104.4	107.2	106.2	103.6	103.8	101.6	100.8
	68	102.2	102.0	106.6	106.8	103.6	101.2	102.8	101.0	100.6
	75	102.0	102.0	102.0	106.6	106.4	101.4	101.6	101.6	101.8
	86	102.4	103.4	105.6	106.4	105.2	101.8	102.4	102.0	102.0
	106	102.0	102.0	104.0	104.8	104.4	102.8	101.6	101.4	101.0
VACCINATES	39	102.2	101.6	102.0	102.0	102.0	102.0	102.6	103.0	102.2
	57	101.2	102.0	101.4	101.0	101.0	100.2	100.8	100.8	100.2
	63	101.6	101.0	101.0	100.8	100.6	100.4	101.0	101.0	101.4
	67	102.0	102.0	101.6	101.0	101.4	101.8	101.8	101.6	102.0
	82	102.4	102.4	101.6	100.8	101.4	101.0	101.8	102.2	100.2
	85	100.8	102.8	101.4	100.4	100.6	100.2	100.6	101.0	100.8
	92	102.0	101.6	101.0	100.6	100.8	100.0	101.4	101.6	101.2
	99	102.0	102.0	101.4	101.8	102.0	101.4	101.6	101.6	100.6
	103	102.8	102.0	102.0	101.4	100.8	100.0	101.0	101.0	100.8
	104	101.8	101.6	102.0	101.2	101.2	101.2	101.4	101.4	100.6

Temperature >103 ºF was considered as pyrexia

Study Type	Efficacy
Pertaining to	*Leptospira interrogans* serovar *grippotyphosa* (*L Grippotyphosa*)
Study Purpose	Demonstration of efficacy against leptospirosis caused by *L. Grippotyphosa*
Product Administration	One dose
Study Animals	15 Calves; 10 vaccinates and 5 controls. All animals were seronegative for *Leptospira Grippotyphosa, hardjo, pomona*.
Challenge Description	Animals were challenged 8 weeks following vaccination.
Interval observed after challenge	Animals were observed for 8 days post challenge. Body temperatures and blood samples were collected daily.
Results	Leptospira Isolation Results in Blood: Controls: 5/5 (100%) positive Vaccinates: 0/10 (0%) positive Temperature Results: Controls: 5/5 (100%) positive Vaccinates: 0/10 (0%) positive See the following tables for individual raw data
USDA Approval Date	12/09/1975

Blood culture for isolation of Leptospires:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)							
		1	2	3	4	5	6	7	8
CONTROLS	161	+	+	+	+	+	-	-	-
	164	+	+	+	+	-	-	-	-
	165	+	+	+	+	-	-	-	-
	241	+	+	-	-	-	-	-	-
	248	+	+	+	-	-	-	-	-
VACCINATES	130	-	-	-	-	-	-	-	-
	137	-	-	-	-	-	-	-	-
	143	-	-	-	-	-	-	-	-
	145	-	-	-	-	-	-	-	-
	155	-	-	-	-	-	-	-	-
	247	-	-	-	-	-	-	-	-
	250	-	-	-	-	-	-	-	-
	255	-	-	-	-	-	-	-	-
	260	-	-	-	-	-	-	-	-
	261	-	-	-	-	-	-	-	-

+: Leptospires detected; -: Leptospires not detected

Temperature in ºF:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)								
		0	1	2	3	4	5	6	7	8
CONTROLS	161	101.6	102.4	102.2	105.4	104.8	104.4	99.4	100.6	102.8
	164	101.4	101.8	105.8	104.6	106.4	103.6	101.4	101.4	101.4
	165	102.0	102.6	102.2	104.0	104.4	104.8	101.8	102.2	102.0
	241	102.2	101.8	101.2	105.4	103.8	104.2	100.4	101.0	101.2
	248	101.6	100.4	101.8	106.0	104.4	103.6	101.0	101.2	101.6
101.4VACCINATES	130	102.0	102.0	102.0	102.4	101.6	101.4	100.2	101.4	101.8
	137	101.6	101.8	101.8	102.0	101.8	101.4	100.6	100.8	101.0
	143	102.0	101.8	101.8	101.8	102.4	101.8	100.4	99.8	101.2
	145	102.0	101.4	101.4	101.8	102.4	101.6	99.6	101.2	101.4
	155	102.2	102.0	102.0	102.4	102.2	101.2	100.0	100.4	100.8
	247	101.4	100.8	101.6	101.6	101.6	101.8	100.0	100.6	100.8
	250	101.8	102.0	102.2	101.4	101.6	101.6	101.2	101.4	101.8
	255	102.4	101.8	101.8	102.6	102.2	102.4	101.8	102.0	101.4
	260	102.0	102.6	102.8	102.4	102.0	101.6	100.0	101.2	101.2
	261	102.2	100.6	101.2	101.4	101.4	101.0	100.2	100.4	100.6

Temperature >103.5 ºF was considered as pyrexia

Study Type	Efficacy
Pertaining to	*Leptospira borgpetersenii* serovar *hardjo* isolate (*L. Hardjo*)
Study Purpose	Demonstration of efficacy against *L. hardjo* in calves.
Product Administration	Two doses administered 28 days apart subcutaneously.
Study Animals	Calves between 8-9 months of age, 10 controls and 11 vaccinates with two doses (28-42 days apart). All animals were seronegative for *Leptospira* serovars *hardjo, pomona, canicola, icterohaemorrhagiae, and grippotyphosa*.
Challenge Description	Animals were challenged with *L. hardjo* 35 days after the second vaccination.
Interval observed after challenge	Urine cultures collected weekly following 14 days after challenge until the study finalized. Kidney tissues were examined 36 days following the challenge.
Results	Animals were considered positive for *L. hardjo* if at least one urine sample was positive for L. hardjo, left kidney culture result was positive for *L. hardjo*, or a gross lesion was present on the left or right kidney. Urine Culture Results: Controls: 10/10 (100%) positive Vaccinates: 0/11 (0%) positive PCR identity testing confirmed the presence of *L. hardjo* in all culture positive urine samples. Kidney Culture Results: Controls: 10/10 (100%) positive Vaccinates: 0/11 (0%) positive Kidney Gross Lesion Results: Controls: 6/10 (60%) positive Vaccinates: 6/11 (55%) positive See the following tables for the raw data.
USDA Approval Date	05/29/2009

Urine Culture Data

Control ID	Day 14	Day 21	Day 28	Day 35
5892	-	+	+	+
5895	+	+	+	+
5896	-	+	+	+
5903	+	+	+	+
5910	-	+	+	+
5911	+	+	+	+
5917	+	+	+	+
5920	-	+	+	+
5927	-	+	+	+
5929	+	+	+	+
All vaccinates were negative at all sampling points.				

Kidney Gross Lesion Data

Control ID	Left Kidney	Right Kidney
5892	+	+
5895	+	+
5896	+	-
5903	+	+
5910	-	-
5911	-	-
5917	-	-
5920	+	+
5927	-	+
5929	-	-
Vaccinate ID	Left Kidney	Right Kidney
5884	-	+
5886	-	-
5890	-	-
5899	+	+
5905	-	-
5907	-	+
5915	-	-
5922	+	+
5925	-	-
5931	+	+
5935	+	+

Study Type	Efficacy
Pertaining to	*Leptospira borgpetersenii* serovar hardjo type hardjo bovis (*Leptospira interrogans* serovar hardjo, *L. Hardjo*)
Study Purpose	Demonstration of duration of immunity against kidney infection and leptospiuria caused by *L. hardjo* in calves.
Product Administration	Two doses administered 4 weeks apart subcutaneously.
Study Animals	Cattle 7-10 months of age, 9 controls and 9 vaccinates with two doses. All animals were seronegative for *Leptospira* serovar hardjo.
Challenge Description	Animals were challenged with *L. interrogans* serovar hardjo bovis, strain 033, 54 weeks following first vaccination.
Interval observed after challenge	Urine samples were collected weekly from day of challenge for 4 weeks for culture and dark field microscopy testing. Kidneys from cattle and from hamsters inoculated with concentrated urine (5 and 10 fold) from the study animals were collected for culture.
Results	Animals were considered positive for *L. hardjo* if at least one urine or kidney sample yielded positive per the following tests: - Urine: Culture and darkfield microscope - Kidney Tissue: Culture. Only one control cattle was included in culture in kidney. <u>Urine Results</u>: Controls: 9/9(100%) positive Vaccinates: 0/9 (0%) positive <u>Kidney Results</u>: Controls: 1/1 (100%) positive Vaccinates: 0/9 (0%) positive See the following tables for individual raw data.
USDA Approval Date	05/10/2000

Analysis of Urine for detection of Leptospires:

Treatment Group	Animal ID	Weeks Post-Challenge							
		Dark Field Microscopy Results				Culture Results			
		2	3	4	5	2	3	4	5
CONTROLS	11	-	-	-	-	+	+	+	+
	12	-	+	+	+	+	+	+	+
	13	-	-	-	-	+	+	+	+
	14	+	+	+	+	+	+	+	+
	15	-	+	+	+	+	+	+	+
	16	-	-	-	-	+	+	+	+
	17	-	+	+	+	+	+	+	+
	18	-	+	+	+	+	-	+	+
	19	-	-	+	+	+	+	+	+
VACCINATES	1	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-	-
	6	-	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-	-
	9	-	-	-	-	-	-	-	-
	10	-	-	-	-	-	-	-	-

+: Leptopires detected; -: Leptopires not detected

Culture Results of Kidney in Cattle for detection of Leptospires

Treatment Group	Animal ID	Kidney Section		
		1	2	3
CONTROL*	14	+	+	+
VACCINATES	1	-	-	-
	3	-	-	-
	4	-	-	-
	5	-	-	-
	6	-	-	-
	7	-	-	-
	8	-	-	-
	9	-	-	-
	10	-	-	-

* Only one control animal was included in culture in kidney.
+: Leptopires detected; -: Leptopires not detected

Culture Results of Kidney in Hamsters inoculated with concentrated urine for detection of Leptospires:

Treatment Group	Cattle ID	Hamster ID	Cattle Urine Concentrated x Fold	Hamster Kidney Result
CONTROL*	14	19	10	+
VACCINATES	1	1	10	-
		2	5	-
	3	3	10	-
		4	5	-
	4	5	10	-
		6	5	-
	5	7	10	-
		8	5	-
	6	9	10	-
		10	5	-
	7	11	10	-
		12	5	-
	8	13	10	-
		14	5	-
	9	15	10	-
		16	5	-
	10	17	10	-
		18	5	-

* Only one control cattle was included in culture in kidney in hamsters and test was conducted with urine concentrated at 10 fold only.
+: Leptopires detected; -: Leptopires not detected

Study Type	Efficacy
Pertaining to	*Leptospira borgpetersenii* serovar hardjo type hardjo bovis (*Leptospira interrogans* serovar hardjo, *L. Hardjo*)
Study Purpose	Demonstration of efficacy against fetal infection
Product Administration	Two doses administered 4 weeks apart subcutaneously.
Study Animals	Heifers between 12-15 months of age, 16 vaccinates and 8 that were seronegative for *Leptospira* serovar hardjo and were bred post-vaccination.
Challenge Description	Animals were challenged at 4.5 to 5.5 months of gestation by vaginal and conjunctival inoculation for 3 consecutive days with *L. borgpetersenii* serovar hardjo mixed strains 203 and 197.
Interval observed after challenge	Urine samples were collected every 2 weeks beginning 2 weeks post challenge. Maternal kidney and placenta, and calf kidney, liver and lung tissues were collected at calving time (or abortion if happened).
Results	Urine or tissue sample evaluated per the following tests: - Urine: Leptospiral culture and immunofluorescence - Tissue: Leptospiral culture, immunofluorescence, and histologic examination <u>Urine Results from Heifers</u>: Controls: 8/8 (100%) positive Vaccinates: 0/16 (0%) positive <u>Tissue Results for Maternal Kidneys</u>: Controls: 8/8 (100% positive) Vaccinates: 0/16 (0%) positive <u>Tissue Results for placental and/or fetal infection (calf kidney, liver, or lung)</u>: Controls: 5/8 (62.5 %) positive Vaccinates: 0/16 (0%) positive Individual raw data is not available.
USDA Approval Date	September 12, 2002

Study Type	Efficacy
Pertaining to	*Leptospira borgpetersenii* serovar hardjo type hardjo bovis (*Leptospira interrogans* serovar hardjo, *L. Hardjo*)
Study Purpose	Efficacy against renal infection and leptospiuria caused by *L. borgpetersenii* serovar hardjo bovis in calves.
Product Administration	Two doses administered 4 weeks apart subcutaneously.
Study Animals	Twenty-two (22) vaccinated and 13 control seronegative calves included in 2 trials: - Trial 1: 10 vaccinates; 6 controls - Trial 2: 12 vaccinates; 7 controls
Challenge Description	In Trial 1, calves were challenged 13 weeks post first vaccination, and in Trial 2, calves were challenged 6 weeks post vaccination with *L. interrogans* serovar hardjo type hardjo bovis.
Interval observed after challenge	In Trial 1, urine samples were collected on days 28, 34 and 41 post-challenge. Kidney were cultured. In Trial 2, urine samples were collected on days 14, 21, 28, and 35 post-challenge. Kidneys were cultured. Kidneys (4 sections) were cultured from calves with negative leptospiuria only.
Results	Summary of results are as follows: <u>Urine Culture Results Trial 1</u>: Controls: 4/6 (67 %) positive Vaccinates: 0/10 (0 %) positive <u>Urine Culture Results Trial 2</u>: Controls: 7/7 (100 %) positive Vaccinates: 0/11*(0 %) positive * Only 11 vaccinates from trial 2 were tested <u>Kidney Culture Results Trial 1*</u>: Controls: 2/2 (100 %) positive Vaccinates: 0/12 (0%) positive *kidneys were only collected from leptospiuria negative animals <u>Kidney Culture Results Trial 2*</u>: Vaccinates: 0/12 (0%) positive *kidneys were only collected from leptospiuria negative animals <u>Combined Urine and Kidney Culture Results for both Trial 1 and Trial 2</u>: Controls: 13/13 (100 %) positive Vaccinates: 0/22 (0 %) positive See the following tables for individual raw data

USDA Approval Date	05/10/2000

Results from Urine Culture for detection of Leptospires (Trial 1):

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)		
		28	34	41
CONTROLS	62	+	-	+
	64	-	-	-
	67	+	+	+
	69	+	-	+
	77	-	-	-
	78	-	-	+
VACCINATES	49	-	-	-
	50	-	-	-
	52	-	-	-
	65	-	-	-
	68	-	-	-
	71	-	-	-
	74	-	-	-
	75	-	-	-
	76	-	-	-
	79	-	-	-

+: Leptospires detected; -: Leptospires not detected

Results from Urine Culture for detection of Leptospires (Trial 2):

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)			
		14	21	28	35
CONTROLS	1	-	+	+	+
	2	-	+	+	+
	3	-	-	+	+
	4	-	-	+	+
	5	-	+	+	+
	6	-	-	-	+
	7	-	-	-	+
VACCINATES	3	-	-	-	-
	10	-	-	-	-
	11	-	-	-	-
	2	ND	ND	ND	ND
	8	-	-	-	-
	14	-	-	-	-
	5	-	-	-	-
	12	-	-	-	-
	15	-	-	-	-

	4	-	ND	-	-
	7	-	-	-	-
	9	-	-	-	-

+: Leptospires detected; -: Leptopires not detected
ND: Not Done

Results from Kidney Culture for detection of Leptospires (Trial 1):

Treatment Group*	Animal ID	Kidney Section			
		1	2	3	4
CONTROLS	64	-	-	+	+
	77	+	+	+	+
VACCINATES	49	-	-	-	-
	50	-	-	-	-
	52	-	-	-	-
	65	-	-	-	-
	68	-	-	-	-
	71	-	-	-	-
	74	-	-	-	-
	75	-	-	-	-
	76	-	-	-	-
	79	-	-	-	-

*: Only calves with negative leptospiuria were tested
+: Leptospires detected; -: Leptospires not detected

Results from Kidney Culture for detection of Leptospires (Trial 2):

Treatment Group	Animal ID	Kidney Section			
		1	2	3	4
VACCINATES*	3	-	-	-	-
	10	-	-	-	-
	11	-	-	-	-
	2	-	-	-	-
	8	-	-	-	-
	14	-	-	-	-
	5	-	-	-	-
	12	-	-	-	-
	15	-	-	-	-
	4	-	-	-	-
	7	-	-	-	-
	9	-	-	-	-

*: Only calves with negative leptospiuria were tested
+: Leptospires detected; -: Leptospires not detected

Study Type	Efficacy
Pertaining to	*Leptospira borgpetersenii* serovar hardjo type hardjo bovis (*Leptospira interrogans* serovar hardjo, *L. Hardjo*)
Study Purpose	Demonstration of efficacy against renal infection and leptospiuria caused by *L. hardjo*.
Product Administration	Two doses administered 4 weeks apart subcutaneously.
Study Animals	Heifers between 8-12 months of age, 8 controls and 8 vaccinates received two doses of vaccine. All animals were seronegative for *Leptospira* serovar hardjo.
Challenge Description	Animals were challenged 16 weeks following second vaccination by intraperitoneal or conjunctival inoculation for 3 consecutive days with *L. borgpetersenii* serovar hardjo strain type 203.
Interval observed after challenge	Urine samples collected once or twice weekly from day of challenge to necropsy day. Kidney tissues were obtained between 11 and 14 weeks after challenge.
Results	Urine or tissue sample evaluated per the following tests: - Urine: Culture, immunofluorescence, and darkfield microscope - Kidney Tissue: Culture, immunofluorescence, histology and silver staining or immunochemistry <u>Urine Results</u>: Controls: 6/8 (75%) positive Vaccinates: 0/8 (0%) positive <u>Kidney Results</u>: Controls: 8/8 (100%) positive Vaccinates: 0/8 (0%) positive See the following tables for individual raw data.
USDA Approval Date	03/29/2000

Analysis of Urine for detection of Leptospires:

Treatment Group	Animal ID	Study Day Post Challenge (Challenge was on Day 193)																
		2	4	6	8	10	12	14	17	21	24	28	35	42	45	49	51	56	63*
CONTROLS	15	-	-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
	23	-	-	-	+	-	-	-	-	+	+	+	+	+	+	+	+	+	+
	24	-	-	+	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+
	28	-	-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+
	16	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+
	22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
VACCINATES	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*Results for urine samples are available until Day 63 post challenge and on necropsy day (see table below) only.

Analysis of Kidney and Urine at Necropsy:

Treatment Group	Animal ID	Detection of leptospires		Kidney Lesion Score *
		Urine	Kidney	
CONTROLS	15	+	+	1
	23	+	+	0
	24	+	+	1.5
	28	+	+	2
	2	-	+	0
	7	+	+	3.5
	16	+	+	1.5
	22	-	+	2.5
VACCINATES	11	-	-	1
	13	-	-	2
	14	-	-	2
	20	-	-	0
	12	-	-	0
	17	ND	-	0.5
	18	ND	-	2.5
	19	-	-	1

* Lesion Score: 0= no lesions detected; 1=focal or multi focal 1- to 2-mm pale foci of lymphocytic interstitial nephritis in renal cortex; 2=multiple 2- to 5-mm foci of lymphocytic interstitial nephritis in renal cortex; 3=multiple 5- to 10-mm foci in renal cortex and medulla, with extensive lymphocytic interstitial nephritis and tubular degeneration; 4=pale foci > 10 mm foci in renal cortex and medulla, with severe lymphocytic interstitial nephritis, tubular degeneration, and fibrosis

** ND: Not Done

Study Type	Efficacy
Pertaining to	*Leptospira borgpetersenii* serovar hardjo type hardjo bovis (*Leptospira interrogans* serovar hardjo, *L. Hardjo*)
Study Purpose	Demonstration of efficacy against renal and reproductive tract infection and leptospiuria caused by *L. hardjo* in heifers.
Product Administration	Two doses administered 4 weeks apart subcutaneously.
Study Animals	Heifers 12 months of age, 12 controls and 12 vaccinates that received two doses of vaccine. All animals were seronegative for *Leptospira* serovar hardjo.
Challenge Description	Animals were challenged 19 weeks following second vaccination by conjunctival and vaginal inoculation for 3 consecutive days with *L. borgpetersenii* serovar *hardjo* strain 203 type A or 197 type B.
Interval observed after challenge	Urine samples were collected weekly from two weeks post-challenge to necropsy day. Tissues (kidney, uterus, oviduct) were obtained at necropsy between 10 and 12 weeks after challenge.
Results	Urine or tissue sample evaluated per the following tests: - Urine: Culture, immunofluorescence, PCR, and darkfield microscopy - Tissue: Culture, immunofluorescence, histopathology and immunochemistry **Summary of results** <u>Urine Results</u> Controls: 12/12 (100%) positive Vaccinates: 0/11* (0%) positive <u>Kidney Results (leptospires and/or lesion score ≥1)</u> : Controls: 12/12 (100%) positive Vaccinates: 4/11* (36%) positive <u>Reproductive Tract Results</u>: Controls: 10/12 (83%) positive Vaccinates: 0/11* (0%) positive * One heifer from vaccinated group died of unrelated causes (bloat) before the end of study. See the following tables for individual raw data
USDA Approval Date	03/29/2000

Analysis of Urine for detection of Leptospires:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)								
		0	14	21	28	35	42	49	56	63¥
CONTROLS	123	-	-	+	+	+	+	+	+	+
	124	-	-	+	+	+	+	+	+	+
	131	-	+	+	+	+	+	+	+	+
	132	-	+	+	+	+	+	+	+	+
	138	-	-	+	+	+	+	+	+	+
	143	-	+	+	+	+	+	+	+	+
	144	-	-	+	+	+	+	+	+	+
	146	-	-	+	+	+	+	+	+	+
	150	-	+	+	+	+	+	+	+	+
	128*	-	+	+	+	+	+	+	+	+
	135*	-	-	+	+	+	+	+	+	+
	148*	-	-	-	-	+	+	+	+	+
VACCINATES	125	-	-	-	-	-	-	-	-	-
	127	-	-	-	-	-	-	-	-	ND**
	130	-	-	-	-	-	-	-	-	-
	133	-	-	-	-	-	-	-	-	-
	136	-	-	-	-	-	-	-	-	-
	139	-	-	-	-	-	-	-	-	-
	142	-	-	-	-	-	-	-	-	-
	145	-	-	-	-	-	-	-	-	-
	149	-	-	-	-	-	-	-	-	-
	129*	-	-	-	-	-	-	-	-	-
	137*	-	-	-	-	-	-	-	-	-
	140*	-	-	-	-	-	-	-	-	-

+: Leptospires detected; -: Leptospires not detected
*: Heifers with * were challenged with *L. borgpetersenii* serovar *hardjo* strain type A 203. The other animals were challenged with *L. borgpetersenii* serovar *hardjo* strain type B 197.
¥: Results for urine samples are available until Day 63 post challenge and on necropsy day (see table below) only.
** Heifer 127 died of unrelated causes (bloat) before the end of study.
ND: Not Done

Analysis of Kidney, Urine, and Reproductive Tract at Necropsy:

Treatment Group	Animal ID	Detection of leptospires				Kidney Lesion Score €
		Urine	Kidney	Uterus	Oviduct	
CONTROLS	123	+	+	+	+	0
	124	+	+	-	+	3
	131	+	+	-	+	0
	132	+	+	+	-	0
	138	+	+	-	+	1
	143	+	+	+	+	0
	144	-	+	-	-	0
	146	+	+	+	+	2
	150	+	+	+	-	0
	128*	+	+	-	+	ND
	135*	+	+	-	-	0

	148*	+	+	+	+	3
VACCINATES	125	-	-	-	-	0
	127**	ND	ND	ND	ND	ND
	130	-	-	-	-	0
	133	-	-	-	-	0
	136	-	-	-	-	0
	139	ND	-	-	-	1
	142	-	-	-	-	0
	145	-	-	-	-	0
	149	-	-	-	-	1
	129*	-	-	-	-	0
	137*	-	-	-	-	0
	140*	-	-	-	-	3

+: Leptospires detected; -: Leptospires not detected
* Heifers with * were challenged with *L. borgpetersenii* serovar *hardjo* strain type A 203. The other animals were challenged3 with *L. borgpetersenii* serovar *hardjo* strain type B 197.
** Heifer 127 died of unrelated causes (bloat) before the end of study.
€ Lesion Score: 0= no lesions detected; 1=focal or multi focal 1- to 2-mm pale foci of lymphocytic interstitial nephritis in renal cortex; 2=multiple 2- to 5-mm foci of lymphocytic interstitial nephritis in renal cortex; 3=multiple 5- to 10-mm foci in renal cortex and medulla, with extensive lymphocytic interstitial nephritis and tubular degeneration; 4=pale foci > 10 mm foci in renal cortex and medulla, with severe lymphocytic interstitial nephritis, tubular degeneration, and fibrosis
ND: Not Done

Summary Table for Kidney, Urine, and Reproductive Tract (Consolidation results from urine samples and samples from necropsy day):

Treatment Group	Animal ID	Detection of leptospires		
		Urine	Kidney	Reproductive Tract
CONTROLS	123	+	+	+
	124	+	+	+
	131	+	+	+
	132	+	+	+
	138	+	+	+
	143	+	+	+
	144	+	+	-
	146	+	+	+
	150	+	+	+
	128*	+	+	+
	135*	+	+	-
	148*	+	+	+
VACCINATES	125	-	-	-
	127**	ND	ND	ND
	130	-	-	-
	133	-	-	-
	136	-	-	-
	139	ND	-	-
	142	-	-	-
	145	-	-	-
	149	-	-	-
	129*	-	-	-

	137*	-	-	-
	140*	-	-	-

* Reproductive tract includes oviduct and uterus.
** Heifer 127 died of unrelated causes (bloat) before the end of study.

Study Type	Efficacy
Pertaining to	*Leptospira interrogans* serovar icterohaemorrhagiae (*L. icterohaemorrhagiae*)
Study Purpose	Demonstration of efficacy against leptospirosis caused by *L. icterohaemorrhagiae*
Product Administration	One dose administered intramuscularly
Study Animals	15 Calves approximately 6 months of age; 10 vaccinates and 5 controls. All animals were seronegative for *Leptospira canicola, icterohaemorrhagiae, hardjo, grippotyphosa, pomona*.
Challenge Description	Animals were challenged 7 weeks following vaccination.
Interval observed after challenge	Animals were observed for 8 days post challenge. Body temperatures and blood samples were collected daily.
Results	Leptospira Isolation Results in Blood: Controls: 4/5 (80 %) positive Vaccinates: 0/10 (0 %) positive Temperature Results: Controls: 5/5 (100 %) positive Vaccinates: 0/10 (0 %) positive See the following tables for individual raw data
USDA Approval Date	09/13/1977

Blood culture for isolation of Leptospires:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)							
		1	2	3	4	5	6	7	8
CONTROLS	66	+	+	-	-	-	-	-	-
	71	+	+	-	-	-	-	-	-
	79	+	+	+	-	-	-	-	-
	113	+	+	-	-	-	-	-	-
	120	-	-	-	-	-	-	-	-
VACCINATES	58	-	-	-	-	-	-	-	-
	69	-	-	-	-	-	-	-	-
	80	-	-	-	-	-	-	-	-
	102	-	-	-	-	-	-	-	-
	107	-	-	-	-	-	-	-	-
	114	-	-	-	-	-	-	-	-
	121	-	-	-	-	-	-	-	-
	122	-	-	-	-	-	-	-	-
	124	-	-	-	-	-	-	-	-
	128	-	-	-	-	-	-	-	-

+: Leptopires detected; -: Leptopires not detected

Temperature in ºF:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)								
		0	1	2	3	4	5	6	7	8
CONTROLS	66	101.0	103.6	104.8	101.0	100.8	101.2	100.0	100.4	101.0
	71	101.0	104.0	102.0	102.2	101.8	101.4	100.4	102.0	101.4
	79	101.6	103.0	104.8	103.0	102.4	102.0	102.0	101.8	102.4
	113	101.4	104.4	104.2	102.8	100.8	100.2	101.0	101.2	101.4
	120	100.0	105.4	103.0	102.6	102.0	101.2	100.6	101.0	100.8
VACCINATES	58	99.8	101.6	101.4	101.4	101.8	101.6	101.0	101.2	102.4
	69	101.0	100.2	102.4	102.4	102.0	101.2	101.2	101.2	101.6
	80	101.4	101.8	101.4	101.0	102.0	101.6	100.6	101.0	101.6
	102	101.2	101.6	101.4	102.0	102.0	100.6	101.4	101.0	102.0
	107	101.2	102.0	101.8	99.8	101.8	101.0	100.8	101.6	101.4
	114	101.0	101.8	101.6	101.6	101.6	102.0	101.0	101.4	101.4
	121	101.4	101.8	102.0	101.8	101.8	101.4	102.0	101.2	102.2
	122	101.2	100.4	101.8	102.0	101.6	101.6	101.8	101.8	101.4
	124	101.4	101.4	101.4	101.0	101.6	100.8	101.0	101.2	101.8
	128	101.2	101.4	101.2	101.4	102.4	101.4	100.8	102.2	101.2

Temperature >103 ºF was considered as pyrexia

Study Type	Efficacy
Pertaining to	*Leptospira interrogans* serovar p*omona* (*L pomona*)
Study Purpose	Demonstration of efficacy against leptospirosis caused by *L. Pomona*
Product Administration	One dose
Study Animals	15 Calves; 10 vaccinates and 5 controls. All animals were seronegative for *Leptospira grippotyphosa, hardjo, pomona*.
Challenge Description	Animals were challenged 5 weeks following vaccination.
Interval observed after challenge	Animals were observed for 8 days post challenge. Body temperatures and blood samples were collected daily.
Results	Leptospira Isolation Results in Blood: Controls: 5/5 (100%) positive Vaccinates: 0/10 (0%) positive Temperature Results: Controls: 5/5 (100%) positive Vaccinates: 0/10 (0%) positive See the following tables for individual raw data
USDA Approval Date	12/09/1975

Blood culture for isolation of Leptospires:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)							
		1	2	3	4	5	6	7	8
CONTROLS	159	+	+	+	+	-	-	-	-
	163	+	+	+	-	-	-	-	-
	244	+	+	+	-	-	-	-	-
	252	+	+	+	-	-	-	-	-
	265	+	+	+	-	-	-	-	-
VACCINATES	134	-	-	-	-	-	-	-	-
	135	-	-	-	-	-	-	-	-
	142	-	-	-	-	-	-	-	-
	149	-	-	-	-	-	-	-	-
	151	-	-	-	-	-	-	-	-
	242	-	-	-	-	-	-	-	-
	245	-	-	-	-	-	-	-	-
	246	-	-	-	-	-	-	-	-
	257	-	-	-	-	-	-	-	-
	262	-	-	-	-	-	-	-	-

+: Leptospires detected; -: Leptospires not detected

Temperature in ºF:

Treatment Group	Animal ID	Study Day (Challenge was on Day 0)								
		0	1	2	3	4	5	6	7	8
CONTROLS	159	102.6	102.2	104.6	105.8	106.2	103.4	100.8	102.0	102.8
	163	102.6	102.2	105.6	106.0	106.6	103.2	101.0	103.0	102.6
	244	101.6	102.2	103.2	104.6	103.8	102.4	101.8	101.8	102.4
	252	102.6	102.4	103.0	107.4	104.6	103.0	102.2	103.0	103.0
	265	101.8	102.8	103.6	106.4	105.6	103.0	102.0	103.8	102.0
101.4VACCINATES	134	102.2	101.4	101.6	101.6	102.0	102.2	101.4	102.0	103.0
	135	102.6	102.6	102.6	102.4	103.2	102.8	102.0	102.8	102.4
	142	102.6	102.6	101.6	102.0	102.0	102.8	99.8	102.2	102.6
	149	102.4	102.0	102.6	102.0	101.6	102.0	101.6	102.0	102.4
	151	101.6	101.4	102.0	101.4	101.4	101.6	101.4	102.2	101.8
	242	101.6	101.2	101.6	102.0	101.6	102.0	100.8	101.4	101.0
	245	102.8	102.6	102.4	102.0	101.8	102.6	101.0	102.6	102.8
	246	102.4	101.6	102.0	102.0	102.2	102.6	101.0	102.0	102.6
	257	102.2	101.6	101.0	101.6	102.0	101.6	101.2	101.6	101.0
	262	102.6	102.0	101.0	102.0	101.6	101.8	101.0	102.6	101.4

Temperature >103.5 ºF was considered as pyrexia

<table>
<tr><td>Study Type</td><td>Safety</td></tr>
<tr><td>Pertaining to</td><td>ALL</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate safety under field conditions</td></tr>
<tr><td>Product Administration</td><td>2 doses administered either intramuscularly (IM) or subcutaneously (SQ) 28 days apart.</td></tr>
<tr><td>Study Animals</td><td>The study was conducted at 3 locations with 300 head of cattle, including pregnant cows, that ranged in age from less than 4 weeks to 14 years. The animals were allotted to non-vaccinated control (100), SQ vaccination (100), and IM vaccination (100) treatment groups.</td></tr>
<tr><td>Challenge Description</td><td>Not applicable</td></tr>
<tr><td>Interval observed after challenge</td><td>Animals were observed for 1 hour after each injection, weekly for injection site reactions, and daily for 59 days after the first injection.</td></tr>
<tr><td>Results</td><td>Adverse Events (AEs) were recorded
<table>
<tr><th colspan="2">Number of animals</th><th>Animal with no AE (%)</th><th>Animals with AE (%)</th></tr>
<tr><td>Enrolled</td><td>300</td><td rowspan="4"></td><td rowspan="4"></td></tr>
<tr><td>Completed the study</td><td>298</td></tr>
<tr><td>Did not Complete the study</td><td>2</td></tr>
<tr><td>Total</td><td>300</td></tr>
</table>
<table>
<tr><td></td><td>293 (98.3)</td><td>5 (1.7)</td></tr>
<tr><td></td><td>1 †</td><td>1</td></tr>
<tr><td></td><td>294 (98.0)</td><td>6 (2.0)</td></tr>
</table>
†Removed due to aggressive behavior.
<table>
<tr><th rowspan="3">Abnormal Health Events (VeDDRA Code)</th><th colspan="6">Number of Adverse Event Observations</th></tr>
<tr><th colspan="2">Pregnant</th><th colspan="2">Minimum Age calves (≤ 4 weeks)</th><th colspan="2">Older Calves (≥2 months)</th></tr>
<tr><td>Control</td><td>Vaccinate</td><td>Control</td><td>Vaccinate</td><td>Control</td><td>Vaccinate</td></tr>
<tr><td>Death</td><td>0/50</td><td>0/100</td><td>0/20</td><td>1^/40</td><td>0/30</td><td>0/60</td></tr>
<tr><td>Depression</td><td>0/50</td><td>0/100</td><td>0/20</td><td>0/40</td><td>1#/30</td><td>0/60</td></tr>
<tr><td>Laceration</td><td>0/50</td><td>1/100</td><td>0/20</td><td>0/40</td><td>0/30</td><td>0/60</td></tr>
</table>
^Calf died on Day 8 due to diarrhea.
Calf slightly depressed on final observation (Day 59).
None of these Adverse Events were considered by the study Investigator to be related to vaccination.

Injection Site Reactions
No animals on this study had visually observable injection site reactions following SQ or IM vaccination.</td></tr>
</table>

Pregnant cows

150 cows were confirmed to be pregnant on the day of the first vaccination of which 138 were in the second semester and 12 were in the third trimester.

Abnormal Health Events (VeDDRA Code)	**Pregnant**	
	Control	Vaccinate
Abortion	0/50	2*/100
Stillbirth	1**/50	0/100
Metritis	1**/50	0/100

*Cows aborted before conclusion of the study. Fetuses were not recovered.
**Same cow observed to have premature delivery with stillborn calf on Day 45; cause of stillborn calf undetermined. Cow diagnosed with metritis in Day 59.

USDA Approval Date	05/14/2008

<table>
<tr><td>Study Type</td><td>Safety</td></tr>
<tr><td>Pertaining to</td><td>ALL</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate safety under field conditions</td></tr>
<tr><td>Product Administration</td><td>IBR-BVD-PI3-BRSV-VL5 or IBR-BVD-PI3-BRSV-L5 was administered either intramuscularly (IM) or subcutaneously (SQ), followed by a second vaccination 28 days later with BRSV-VL5 or BRSV-L5, respectively</td></tr>
<tr><td>Study Animals</td><td>The study was conducted at 3 locations with 990 head of cattle (661 vaccinates and 329 controls). The animals were allotted to non-vaccinated control (329), subcutaneous (SQ) vaccination with IBR-BVD-PI3-BRSV-VL5 (210), SQ vaccination with IBR-BVD-PI3-BRSV-L5 (120), intramuscular (IM) vaccination with IBR-BVD-PI3-BRSV-VL5 (211) and IM vaccination with IBR-BVD-PI3-BRSV-L5 (120) treatment groups.</td></tr>
<tr><td>Challenge Description</td><td>Not applicable</td></tr>
<tr><td>Interval observed after challenge</td><td>Animals were observed for 1 to 3 hours after each vaccination, then once weekly for injection site reactions until day 49 after first injection or until resolution. Animals were also observed daily for general health observations for 49 days after the first injection.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Cattle Enrolled by Age</th><th>Vaccinate</th><th>Control</th></tr>
<tr><td>17-43 days</td><td>198</td><td>101</td></tr>
<tr><td>10-11 months</td><td>40</td><td>20</td></tr>
<tr><td>13 months</td><td>60</td><td>30</td></tr>
<tr><td>Pregnant 14-27 months</td><td>200</td><td>98</td></tr>
<tr><td>Pregnant 1-6 years</td><td>163</td><td>80</td></tr>
</table>
Adverse Events (AEs)
<table>
<tr><th colspan="2">Number of animals</th><th rowspan="2">Animal with no AE (%)</th><th rowspan="2">Animals with AE (%)</th></tr>
<tr><td>Enrolled</td><td>990</td></tr>
<tr><td>Completed the study</td><td>989</td><td>959 (96.9)</td><td>30 (3.0)</td></tr>
<tr><td>Did not Complete the study</td><td>1*</td><td>1</td><td>0</td></tr>
</table>
* Died from punctured abomasum before second vaccination.
</td></tr>
</table>

Frequency of Adverse Event observations per category of calves:

Observations	**Minimum age calves (17 to 43 days of age) Number of animals**				
	Controls	Vaccinates			
		SQ (1)	IM (1)	SQ (2)	IM (2)
Bloat	1	0	0	0	1
Ear drop	0	0	0	1	1
Depression	1	0	0	0	0
Diarrhea	1	0	0	0	0
Death*	0	0	0	0	1
Depression with ear drop	0	0	0	1	1
Lameness	2	0	0	0	0
Enterotoxemia	1	0	0	0	0
Draining ear	1	0	0	0	0

* Animal died from complications from bloat.
(1) Vaccination with IBR-BVD-PI3-BRSV-L5 and BRSV-L5
(2) Vaccination with IBR-BVD-PI3-BRSV-VL5 and BRSV-VL5
These Adverse Events were considered by the Regional Investigator not to be related to the use of the vaccine.

Observations	**Older calves (10-13 months of age) Number of animals**				
	Controls	Vaccinates			
		SQ (1)	IM (1)	SQ (2)	IM (2)
Foot Rot	1	1	1	0	0

(1) Vaccination with IBR-BVD-PI3-BRSV-L5 and BRSV-L5
(2) Vaccination with IBR-BVD-PI3-BRSV-VL5 and BRSV-VL5
These Adverse Events were considered by the Regional Investigator not to be related to the use of the vaccine.

Frequency of Adverse Event observations per category of pregnant heifers and cows:
Cattle were confirmed pregnant on day of first vaccination.

Cattle Enrolled by Trimeser	**Vaccinate**	**Control**
1	108	53
2	155	77
3	100	48

Observations	Pregnant cattle Number of animals				
	Controls	Vaccinates			
		SQ (1)	IM (1)	SQ (2)	IM (2)
Abortion	4*	2**	1	0	0
Metritis	0	1**	0	0	0

*Cause of abortions was undetermined.
** One animal was observed with abortion and metritis; cause undetermined.
(1) Vaccination with IBR-BVD-PI3-BRSV-L5 and BRSV-L5
(2) Vaccination with IBR-BVD-PI3-BRSV-VL5 and BRSV-VL5

Observations	Pregnant cattle Number of animals				
	Controls	Vaccinates			
		SQ (1)	IM (1)	SQ (2)	IM (2)
Foot rot	2	1	0	0	0
Keratitis	1	0	0	1	0
Cracked hoof	1	0	0	0	0
Lameness/edema	0	0	0	0	1

(1) Vaccination with IBR-BVD-PI3-BRSV-L5 and BRSV-L5
(2) Vaccination with IBR-BVD-PI3-BRSV-VL5 and BRSV-VL5

These Adverse Events were considered by the Regional Investigator not to be related to the use of the vaccine.

Injection Site Reactions per category of age:

Pregnant Cattle													
Controls*		SQ (1)			IM (1)			SQ (2)			IM (2)		
1st Injection													
0.5-2 cm	2-5 cm	0.5-2 cm	2-5 cm	>5 cm	0.5-2 cm	2-5 cm	>5 cm	0.5-2 cm	2-5 cm	>5 cm	0.5-2 cm	2-5 cm	>5 cm
1	1	10	1	0	1	0	0	0	0	0	3**	0	0
2nd injection													
2	0	0	0	0	0	0	0	2	0	0	4	2	0

Minimum Age Calves													
Controls*		SQ (1)			IM (1)			SQ (2)			IM (2)		
1st Injection													
0.5-2 cm	2-5 cm	0.5-2 cm	2-5 cm	>5 cm	0.5-2 cm	2-5 cm	>5 cm	0.5-2 cm	2-5 cm	>5 cm	0.5-2 cm	2-5 cm	>5 cm
0	0	n/a	n/a	n/a	n/a	n/a	n/a	0	0	0	0	0	0
2nd injection													
3	0	n/a	n/a	n/a	n/a	n/a	n/a	15	2	0	5	0	0

	Older Calves Controls* SQ (1) IM (1) SQ (2) IM (2) 1st Injection 0.5-2 cm | 2-5 cm | 0.5-2 cm | 2-5 cm | >5 cm | 0.5-2 cm | 2-5 cm | >5 cm | 0.5-2 cm | 2-5 cm | >5 cm | 0.5-2 cm | 2-5 cm | >5 cm 1 | 0 | 2** | 0 | 4** | 5** | 5** | 0 | 0 | 0 | 0 | 0 | 0 | 0 2nd injection 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 * Controls did not have Injection Site Reactions greater than 2-5 cm ** In the case where an individual animal had an injection site reaction present on multiple weekly observations, only the largest reaction score is represented in the Table. n/a: Minimum age calves were vaccinated only with IBR-BVD-PI3-BRSV-VL5 and BRSV-VL5 (1): Vaccination with IBR-BVD-PI3-BRSV-L5 and BRSV-L5 (2): Vaccination with IBR-BVD-PI3-BRSV-VL5 and BRSV-VL5 The Injection Sites Reactions resolved without incident within 30 days following each vaccination with the exception of one pregnant cow, vaccinated IM with IBR-BVD-PI3-BRSV-VL5 and BRSV-VL5, which was completely resolved on day 58.
USDA Approval Date	05/14/2008

<table>
<tr><td>Study Type</td><td>Safety</td></tr>
<tr><td>Pertaining to</td><td>ALL</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate safety under field conditions.</td></tr>
<tr><td>Product Administration</td><td>Two doses administered either subcutaneously (SQ) or intramuscularly (IM) 28 days apart. Second dose of vaccine consisted of Bacterin product only</td></tr>
<tr><td>Study Animals</td><td>307 beef calves, approximately 7 weeks (104 calves) or 9 months of age (203 calves), at each of 3 sites: Control (103 calves), SC administration of product (102 calves) and IM administration of product (102 calves) treatment groups.</td></tr>
<tr><td>Challenge Description</td><td>Not Applicable</td></tr>
<tr><td>Interval observed after challenge</td><td>Calves were observed daily for 48 days.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th colspan="2">Animals Total</th><th>Animals with no Adverse Event Observations (%)</th><th>Animals with Adverse Event Observations (%)</th></tr>
<tr><td>Completed the study</td><td>306</td><td>301 (98.4)</td><td>5 (1.6)</td></tr>
<tr><td>Did not Complete the study</td><td>1</td><td>0</td><td>1</td></tr>
<tr><td>Total</td><td>307</td><td>301 (98.0)</td><td>6 (2)</td></tr>
</table>
<table>
<tr><th rowspan="2">Abnormal Health Events (VeDDRA Code)</th><th colspan="2">Number of Adverse Event Observations</th></tr>
<tr><td>Controls</td><td>Vaccinates</td></tr>
<tr><td>Abnormal Breathing</td><td>0</td><td>1</td></tr>
<tr><td>Lameness</td><td>0</td><td>2*</td></tr>
<tr><td>Depression</td><td>1**</td><td>0</td></tr>
<tr><td>Dyspnea</td><td>1**</td><td>0</td></tr>
<tr><td>Death</td><td>1**</td><td>0</td></tr>
<tr><td>Anorexia</td><td>0</td><td>2</td></tr>
<tr><td>Cough</td><td>0</td><td>1</td></tr>
</table>
*: Same calf observed on 2 different days. This calf had a lame right hind (physical injury). After appearing to resolve, the lameness was observed again and did not resolve by the end of the study.
**Same calf observed on 3 different days (diagnosed post necropsy with fibronecrotizing bronchopneumonia).
</td></tr>
</table>

	<table><tr><th rowspan="2">Adverse Event Observations</th><th colspan="2">Number of Animals (%)</th></tr><tr><td>Controls</td><td>Vaccinates</td></tr><tr><td>Normal</td><td>102</td><td>199</td></tr><tr><td>Abnormal</td><td>1 (0.97)</td><td>5 (2.45)</td></tr></table> None of the Adverse Events were considered by the study Investigator to be related to vaccination. <table><tr><th rowspan="3">Treatment Group</th><th rowspan="3">Total Number of Animals</th><th colspan="4">Number of Animals with Injection Site Reactions (%)</th></tr><tr><th rowspan="2">7-week-old calves</th><th rowspan="2">9-month-old calves</th><th colspan="2">Injection Site Reaction in cm</th></tr><tr><th>< 1.5</th><th>1.5 to 5</th></tr><tr><td>Controls</td><td>103</td><td>0</td><td>0</td><td>0</td><td>0</td></tr><tr><td>SQ</td><td>102</td><td>7 (6.93)</td><td>1 (0.99)</td><td>7</td><td>1</td></tr><tr><td>IM</td><td>102</td><td>1 (0.98)</td><td>0 (0)</td><td>1</td><td>0</td></tr></table> All injection site reactions were resolved by day 48.
USDA Approval Date	06/17/2009