Summary of Studies Supporting USDA Product Licensure

Establishment Name	Elanco US Inc.
USDA Vet Biologics Establishment Number	196
Product Code	4X39.R0
True Name	Bovine Virus Diarrhea Vaccine, Modified Live Virus, Mannheimia Haemolytica Bacterial Extract-Toxoid
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	Elanco US Inc.
Date of Compilation Summary	May 18, 2020

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	Bovine Virus Diarrhea (BVD)
Study Purpose	To demonstrate effectiveness against Bovine Virus Diarrhea Type 1
Product Administration	Subcutaneous
Study Animals	Bovine
Challenge Description	BVD isolate NY-1, BVD Type 1b
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 require publication of data submitted after that date.
USDA Approval Date	July 14, 1998

Study Type	Comparative Serology
Pertaining to	Infectious Bovine Rhinotracheitis (IBR) Virus, Bovine Viral Diarrhea (BVD) Virus Type 1, BVD Type 2, and Parainfluenza 3 (PI3) Virus
Study Purpose	Comparative serology to demonstrate lack of interference between the IBR, BVD Type 1, BVD Type 2, and PI3 viral fractions and the Mannheimia Haemolytica bacterial extract when the antigens are combined to show that combining fractions with satisfactory efficacy studies does not reduce the immune response. Refer to the original efficacy studies in the Product Code Summary for this Product.
Product Administration	One dose of combination test vaccine administered subcutaneously to cattle, followed by a second dose of monovalent Bovine Respiratory Syncytial Virus (BRSV) 21 days later.
Study Animals	9 month old calves were vaccinated twice 21 days apart. Animals were seronegative to BVD Type 1, BVD type 2, IBR and PI3. Forty-five animals were vaccinated with the combination test vaccine (BVD1-BVD2-IBR-PI3-BRSV-M Haem) and 45 animals were vaccinated with the reference vaccine (BVD1-BVD2-IBR-PI3-BRSV).
Challenge Description	NA
Interval observed after challenge	Blood was collected on study days D0, D28, D35
Results	The primary outcome was neutralizing antibody serum titer for the BVD type 1, BVD type 2, PI3, and IBR antigens. The study met the criterion in which the test product Geometric Mean Titer (GMT) must be at least 63% of the reference product GMT. Raw data on pages below
USDA Approval Date	November 18, 2016

BVD Type 1 Serum Neutralization Titers

Combination Test Vaccine		
Calf ID	Study Day 0	Study Day 28
1	<2	362
2	<2	1024
3	<2	362
4	<2	790
5	<2	912
6	<2	1312
7	<2	664
8	<2	1117
9	<2	821
10	<2	664
11	<2	575
12	<2	1149
13	<2	724
14	<2	1448
15	<2	1149
16	<2	2702
17	<2	861
18	<2	1328
19	<2	3158
20	<2	1218
21	<2	724
22	<2	1579
23	<2	1449
24	<2	724
25	<2	821
26	<2	912
27	<2	411
28	<2	1643
29	<2	279
30	<2	1117
31	<2	2435
32	<2	1218
33	<2	2048
34	<2	1825
35	<2	1149
36	<2	323
37	<2	1277
38	<2	319
39	<2	1024
40	<2	512
41	<2	1652
42	<2	1448
43	<2	1117
44	<2	1579
45	<2	1290

Reference Vaccine		
Calf ID	Study Day 0	Study Day 28
1	<2	91
2	<2	724
3	<2	1328
4	<2	2435
5	<2	1328
6	<2	456
7	<2	664
8	<2	342
9	<2	1149
10	<2	575
11	<2	724
12	<2	<2
13	<2	724
14	<2	72
15	<2	790
16	<2	1148
17	<2	638
18	<2	456
19	<2	395
20	<2	664
21	<2	744
22	<2	181
23	<2	1328
24	<2	1448
25	<2	724
26	<2	332
27	<2	458
28	<2	1448
29	<2	456
30	<2	558
31	<2	645
32	<2	664
33	<2	206
34	<2	664
35	<2	724
36	<2	1290
37	<2	1149
38	<2	861
39	<2	889
40	<2	878
41	<2	1579
42	<2	458
43	<2	821
44	<2	2048
45	<2	256

BVD Type 2 Serum Neutralization Titers

Combination Test Vaccine		
Calf ID	Study Day 0	Study Day 28
1	<2	29
2	<2	57
3	<2	14
4	<2	51
5	<2	205
6	<2	197
7	<2	13
8	<2	112
9	<2	114
10	<2	36
11	<2	21
12	<2	203
13	<2	45
14	<2	152
15	<2	160
16	<2	72
17	<2	40
18	<2	41
19	<2	91
20	<2	28
21	<2	10
22	<2	12
23	<2	38
24	<2	166
25	<2	29
26	<2	16
27	<2	36
28	<2	57
29	<2	54
30	<2	45
31	<2	219
32	<2	14
33	<2	51
34	<2	41
35	<2	14
36	<2	20
37	<2	31
38	<2	31
39	<2	83
40	<2	20
41	<2	41
42	<2	45
43	<2	18
44	<2	97
45	<2	37

Reference Vaccine		
Calf ID	Study Day 0	Study Day 28
1	<2	181
2	<2	8
3	<2	128
4	<2	16
5	<2	25
6	<2	51
7	<2	11
8	<2	9
9	<2	5
10	<2	114
11	<2	51
12	<2	40
13	<2	25
14	<2	64
15	<2	11
16	<2	40
17	<2	51
18	<2	27
19	<2	2
20	<2	81
21	<2	40
22	<2	144
23	<2	83
24	<2	10
25	<2	76
26	<2	7
27	<2	128
28	<2	16
29	<2	41
30	<2	102
31	<2	181
32	<2	36
33	<2	3
34	<2	9
35	<2	205
36	<2	11
37	<2	23
38	<2	51
39	<2	80
40	<2	103
41	<2	29
42	<2	140
43	<2	11
44	<2	149
45	<2	29

IBR Serum Neutralization Titers

Combination Test Vaccine		
Calf ID	Study Day 0	Study Day35
1	<2	14
2	<2	26
3	<2	41
4	<2	83
5	<2	36
6	<2	38
7	<2	45
8	<2	29
9	<2	49
10	<2	41
11	<2	35
12	<2	23
13	<2	29
14	<2	36
15	<2	23
16	<2	72
17	<2	29
18	<2	72
19	<2	26
20	<2	41
21	<2	45
22	<2	80
23	<2	41
24	<2	12
25	<2	80
26	<2	49
27	<2	41
28	<2	45
29	<2	29
30	<2	32
31	<2	23
32	<2	80
33	<2	57
34	<2	55
35	<2	41
36	<2	38
37	<2	49
38	<2	51
39	<2	49
40	<2	26
41	<2	25
42	<2	35
43	<2	41
44	<2	76
45	<2	83

Reference Vaccine		
Calf ID	Study Day 0	Study Day 35
1	<2	20
2	<2	11
3	<2	8
4	<2	11
5	<2	20
6	<2	36
7	<2	49
8	<2	18
9	<2	18
10	<2	29
11	<2	21
12	<2	4
13	<2	18
14	<2	14
15	<2	23
16	<2	13
17	<2	11
18	<2	12
19	<2	29
20	<2	18
21	<2	36
22	<2	7
23	<2	21
24	<2	36
25	<2	25
26	<2	12
27	<2	45
28	<2	20
29	<2	29
30	<2	23
31	<2	45
32	<2	29
33	<2	45
34	<2	26
35	<2	91
36	<2	23
37	<2	45
38	<2	18
39	<2	29
40	<2	36
41	<2	14
42	<2	23
43	<2	38
44	<2	23
45	<2	18

PI3 Serum Neutralization Titers

Combination Test Vaccine		
Calf ID	Study Day 0	Study Day 35
1	<2	29
2	<2	114
3	<2	5
4	<2	197
5	<2	49
6	<2	23
7	<2	45
8	<2	181
9	<2	72
10	<2	49
11	<2	23
12	<2	49
13	<2	41
14	<2	91
15	<2	12
16	<2	99
17	<2	144
18	<2	72
19	<2	144
20	<2	72
21	<2	72
22	<2	83
23	<2	57
24	<2	45
25	<2	57
26	<2	9
27	<2	41
28	<2	25
29	<2	45
30	<2	23
31	<2	72
32	<2	45
33	<2	91
34	<2	36
35	<2	72
36	<2	25
37	<2	45
38	<2	83
39	<2	91
40	<2	29
41	<2	49
42	<2	41
43	<2	51
44	<2	83
45	<2	91

Reference Vaccine		
Calf ID	Study Day 0	Study Day 35
1	<2	41
2	<2	<2
3	<2	72
4	<2	45
5	<2	36
6	<2	3
7	<2	5
8	<2	3
9	<2	26
10	<2	49
11	<2	45
12	<2	<2
13	<2	23
14	<2	45
15	<2	8
16	<2	91
17	<2	29
18	<2	3
19	<2	45
20	<2	83
21	<2	36
22	<2	23
23	<2	32
24	<2	10
25	<2	3
26	<2	6
27	<2	36
28	<2	6
29	<2	36
30	<2	6
31	<2	41
32	<2	3
33	<2	29
34	<2	11
35	<2	3
36	<2	18
37	<2	9
38	<2	3
39	<2	36
40	<2	20
41	<2	5
42	<2	41
43	<2	91
44	<2	72
45	<2	45

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	To demonstrate effectiveness against Bovine Virus Diarrhea Type 2
Product Administration	Subcutaneous
Study Animals	Bovine
Challenge Description	BVD isolate 890, BVD Type 2a
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 require publication of data submitted after that date.
USDA Approval Date	July 14, 1998

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Mannheimia Haemolytica</td></tr>
<tr><td>Study Purpose</td><td>Demonstrate the efficacy of a combination product (IBR, BVD Type 1, BVD Type 2, BRSV, and PI3 combined with Mannheimia Haemolytica in Combination test vaccine) in protection against M. haemolytica as a means to demonstrate absence of interference of IBR, BVD Type 1, BVD Type 2, and PI3 to M. Haemolytica immunity to show that combining fractions with satisfactory efficacy studies does not reduce the immune response.</td></tr>
<tr><td>Product Administration</td><td>One dose of combination vaccine administered subcutaneously</td></tr>
<tr><td>Study Animals</td><td>63 Calves, 80-82 days of age, randomly distributed into three treatment groups. One group of 21 Vaccinates (Combination test vaccine), one group of 21 reference vaccinates (Reference vaccine – Viral fractions only), and one group of 21 placebo controls.</td></tr>
<tr><td>Challenge Description</td><td>Mannheimia Haemolytica, administered 10 days after vaccination</td></tr>
<tr><td>Interval observed after challenge</td><td>Lungs evaluated 4 days after challenge</td></tr>
<tr><td>Results</td><td>The percent of the lung mass that was abnormal (consolidated) was calculated for every animal.

5-number summary for lung consolidation (%)

<table>
<tr><th>Treatment</th><th>Minimum</th><th>Q1</th><th>Median</th><th>Q3</th><th>Maximum</th></tr>
<tr><td>Combination Test vaccinates</td><td>0.2</td><td>2.6</td><td>5.6</td><td>8.2</td><td>26</td></tr>
<tr><td>Reference Vaccinates</td><td>2.1</td><td>7.9</td><td>24.1</td><td>24.6</td><td>90.4</td></tr>
<tr><td>Placebo Controls</td><td>1.4</td><td>9.5</td><td>17.6</td><td>32.5</td><td>84.8</td></tr>
</table>

Raw data shown on attached page.</td></tr>
<tr><td>USDA Approval Date</td><td>September 16, 2016</td></tr>
</table>

Lung Consolidation (%), in order of rank:

Combination Test vaccinates	Reference Vaccinates	Placebo Controls
0.21	2.14	1.44
1.8	3.1	2.64
1.94	4.47	3.56
2.18	4.54	4.3
2.29	4.99	7.36
2.57	7.94	9.53
2.81	8.39	9.55
3.49	8.87	10.23
3.51	14.65	15.23
5.4	22.95	15.98
5.57	24.05	17.59
5.64	24.36	17.66
6.51	28.45	23.77
6.51	30.95	23.84
6.67	33.95	26.75
8.15	34.55	32.45
10.99	37.3	34.1
11.35	45.9	37.25
13	48.73	38.4
16.57	58.2	39.05
26.01	90.4	84.75

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Mannheimia haemolytica</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate effectiveness against respiratory disease caused by M. Haemolytica as early as 10 days after administration.</td></tr>
<tr><td>Product Administration</td><td>1 dose subcutaneously</td></tr>
<tr><td>Study Animals</td><td>30 calves, 75-83 days of age. 20 vaccinates and 10 controls.</td></tr>
<tr><td>Challenge Description</td><td>Mannheimia Haemolytica, administered 10 days after second vaccination</td></tr>
<tr><td>Interval observed after challenge</td><td>Lungs evaluated 4 days after challenge</td></tr>
<tr><td>Results</td><td>The percent of the lung mass that was abnormal (consolidated) was calculated for every animal.

5-number summary for lung consolidation (%)

<table>
<tr><th>Treatment</th><th>Minimum</th><th>Q1</th><th>Median</th><th>Q3</th><th>Maximum</th></tr>
<tr><td>Controls</td><td>4.6</td><td>20.6</td><td>23</td><td>52.3</td><td>57.8</td></tr>
<tr><td>Vaccinates</td><td>1.0</td><td>6.5</td><td>9.9</td><td>14.7</td><td>41.3</td></tr>
</table>

Raw data shown on attached page.</td></tr>
<tr><td>USDA Approval Date</td><td>June 5, 2009</td></tr>
</table>

Lung Consolidation scores (%), in order of rank:

Vaccinate	Control
0.97	4.61
1.69	13.35
3.66	20.63
4.45	20.65
5.95	20.66
7.13	25.4
7.2	26.35
7.25	52.25
7.35	55.85
9.48	57.75
10.25	
10.93	
11.21	
12.26	
12.86	
16.45	
16.59	
20.4	
38.25	
41.3	

<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>Demonstrate safety of product under typical use conditions</td></tr>
<tr><td>Product Administration</td><td>One dose administered subcutaneously, followed by a monovalent bovine respiratory syncytial virus (BRSV) injection 2 weeks later.</td></tr>
<tr><td>Study Animals</td><td>627 calves, 18-29 days of age at each of three sites.</td></tr>
<tr><td>Challenge Description</td><td>NA</td></tr>
<tr><td>Interval observed after challenge</td><td>No challenge. Animals were observed at 2 hours after each injection and daily for a minimum of 42 days after vaccination.</td></tr>
<tr><td>Results</td><td>All Adverse Events:

<table>
<tr><th>VeDDRA Term</th><th>Number of Calves</th></tr>
<tr><td>No Adverse Events</td><td>329</td></tr>
<tr><td>Injection Site Swelling</td><td>259</td></tr>
<tr><td>Increased Respiratory Rate</td><td>39</td></tr>
<tr><td>Death*</td><td>8</td></tr>
<tr><td>Anorexia</td><td>4</td></tr>
<tr><td>Fever</td><td>13</td></tr>
<tr><td>Hypothermia</td><td>3</td></tr>
<tr><td>Arthritis</td><td>1</td></tr>
<tr><td>Conjunctivitis</td><td>1</td></tr>
<tr><td>Diarrhea</td><td>14</td></tr>
<tr><td>Labored Breathing</td><td>1</td></tr>
<tr><td>Cough Productive</td><td>1</td></tr>
<tr><td>Respiratory Distress</td><td>5</td></tr>
<tr><td>Lameness</td><td>2</td></tr>
<tr><td>Pink Eye</td><td>11</td></tr>
<tr><td>Bloated</td><td>1</td></tr>
<tr><td>Lethargy</td><td>2</td></tr>
</table>

*Deaths not attributable to vaccine</td></tr>
</table>

Injection Site Reactions, Size:

Site	Total number animals	Vaccination	# of injection site reactions by Size (cm^2)			Injection site reactions not observed
			≤ 2.0 cm^2	2.0-10.0 cm^2	>10 cm^2	
1	207	4X59.R1	4	0	0	203
		BRSV	0	0	0	207
2	210	4X59.R1	1	50	69	90
		BRSV	0	0	0	210
3	210	4X59.R1	95	32	0	83
		BRSV	23	0	0	187

Injection Site Reactions, Duration:

Sites	Total number animals	Total # Animals with Reactions	Vaccination	Five Number Summary (Days)				
				Min	Q1	Med	Q3	Max
1	207	4	4X59.R1	6.0	7.0	8.0	8.0	8.0
			BRSV	NA	-	-	-	-
2	210	120	4X59.R1	1.0	2.0	13.0	21.0	50.0*
			BRSV	NA	-	-	-	-
3	210	127	4X59.R1	1.0	1.0	8.0	14.0	28.0
			BRSV	1.0	1.0	1.0	1.0	8.0

* Six reactions were not resolved by study day 50. All were reported to be less than 2 cm^2 at the end of the study.

USDA Approval Date	April 10, 2020