Summary of Studies Supporting USDA Product Licensure

Establishment Name	Intervet Inc.
USDA Vet Biologics Establishment Number	165A
Product Code	1861.02
True Name	Mannheimia Haemolytica-Pasteurella Multocida Vaccine, Avirulent Live Culture
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	Bovilis Once PMH IN - Merck Animal Health Bovilis Once PMH IN - No distributor specified Once PMH - No distributor specified Once PMH IN - Merck Animal Health Once PMH IN - No distributor specified
Date of Compilation Summary	October 30, 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.

<table>
<tr><td>Study Type</td><td>EfficacyEfficacyEfficacy</td></tr>
<tr><td>Pertaining to</td><td>Mannheimia haemolytica</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate effectiveness against M. haemolytica.</td></tr>
<tr><td>Product Administration</td><td>1 dose administered by the intranasal route</td></tr>
<tr><td>Study Animals</td><td>40, 3- to 8-day-old calves; 20 controls/placebo, 20 vaccinates</td></tr>
<tr><td>Challenge Description</td><td>All calves were challenged with M. haemolytica 23 days after vaccination.</td></tr>
<tr><td>Interval observed after challenge</td><td>All calves were monitored daily for 7 days post-challenge for clinical signs of respiratory disease then tissues were examined.</td></tr>
<tr><td>Results</td><td>
<u>Lung Lesions</u>:
The percent of the affected lung tissue was determined.
<table>
<tr><th>Group</th><th>n*</th><th>Min</th><th>Q1</th><th>Median</th><th>Q3</th><th>Max</th></tr>
<tr><td>Placebo</td><td>13</td><td>1.2</td><td>24.9</td><td>33.0</td><td>34.4</td><td>68.7</td></tr>
<tr><td>Vaccinates</td><td>15</td><td>0.0</td><td>0.9</td><td>3.0</td><td>7.1</td><td>32.4</td></tr>
</table>
*Two placebo calves and three vaccinated calves died between vaccination and challenge and were excluded from analysis. Another five placebo calves and two vaccinated calves died post-challenge. Only surviving animals are summarized in the table.

<u>Respiratory Rate</u>:
Maximum post-challenge respiratory rate was compared to the median pre-challenge respiratory rate and the difference was calculated. Due to five deaths in the placebo group and two deaths in the vaccinated group prior to the end of the observation period, data only through the third post-challenge day were analyzed.
<table>
<tr><th>Group</th><th>n*</th><th>Q1</th><th>Median</th><th>Q3</th></tr>
<tr><td>Placebo</td><td>18</td><td>40.0</td><td>44.0</td><td>60.0</td></tr>
<tr><td>Vaccinates</td><td>17</td><td>8.0</td><td>10.0</td><td>16.0</td></tr>
</table>
*Two placebo calves and three vaccinated calves died between vaccination and challenge and were excluded from analysis.

Raw data shown on attached page.
</td></tr>
<tr><td>USDA Approval Date</td><td>05/04/2009</td></tr>
</table>

Percent Lung Lesion Data

Group	Calf ID	Total	Mortality
Placebo	423	68.729	
Placebo	427	33.675	
Placebo	428	33.000	
Placebo	430	1.186	
Placebo	431	18.556	
Placebo	432	71.033	Dead
Placebo	433	24.855	
Placebo	434	75.782	Dead
Placebo	438	14.358	
Placebo	439	27.253	
Placebo	442	33.959	
Placebo	445	44.051	
Placebo	446	31.400	
Placebo	447	66.485	Dead
Placebo	451	33.390	Dead
Placebo	452	34.422	
Placebo	455	59.802	Dead
Placebo	459	60.462	
Vaccinate	422	19.852	Dead
Vaccinate	424	5.448	
Vaccinate	426	0.701	
Vaccinate	436	1.885	
Vaccinate	437	32.362	
Vaccinate	440	0.000	
Vaccinate	443	14.836	Dead
Vaccinate	444	2.978	
Vaccinate	448	14.219	
Vaccinate	449	0.000	
Vaccinate	450	19.447	
Vaccinate	453	1.673	
Vaccinate	454	0.623	
Vaccinate	456	3.208	
Vaccinate	457	8.722	
Vaccinate	460	2.963	
Vaccinate	461	1.013	

Respiration Rate Data

Group	Calf ID	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Placebo	423	40	32	22	68	76	76	86	74	76	74
Placebo	427	36	36	32	74	80	80	80	70	60	62
Placebo	428	36	36	38	80	74	74	64	60	36	36
Placebo	430	28	28	28	68	72	72	72	68	62	62
Placebo	431	36	28	20	52	54	54	54	56	58	56
Placebo	432	28	36	32	86	90	90	Dead	Dead	Dead	Dead
Placebo	433	28	24	32	66	68	68	72	68	62	54
Placebo	434	40	44	28	70	78	78	90	88	Dead	Dead
Placebo	438	36	32	32	62	66	66	70	66	64	60
Placebo	439	32	32	28	70	68	68	68	62	60	56
Placebo	442	36	32	20	78	70	70	70	66	70	74
Placebo	445	40	32	36	68	80	80	82	74	68	60
Placebo	446	36	32	28	80	74	74	76	70	64	58
Placebo	447	36	28	24	56	86	86	Dead	Dead	Dead	Dead
Placebo	451	32	36	36	48	72	72	Dead	Dead	Dead	Dead
Placebo	452	28	36	24	64	66	66	66	62	58	56
Placebo	455	36	40	32	82	Dead	Dead	Dead	Dead	Dead	Dead
Placebo	459	40	36	24	72	82	82	76	72	76	72
Vaccinate	422	36	40	24	36	38	38	Dead	Dead	Dead	Dead
Vaccinate	424	32	32	28	40	38	38	38	34	30	30
Vaccinate	426	36	36	28	36	36	36	42	40	38	34
Vaccinate	436	32	32	24	38	36	36	38	36	34	32
Vaccinate	437	36	32	20	38	40	40	40	36	36	34
Vaccinate	440	32	28	28	36	38	38	38	34	32	34
Vaccinate	443	36	36	36	50	46	46	Dead	Dead	Dead	Dead
Vaccinate	444	24	32	32	44	42	42	40	36	34	34
Vaccinate	448	36	40	40	52	56	56	54	48	42	38
Vaccinate	449	32	24	24	42	40	40	42	40	40	36
Vaccinate	450	28	32	28	42	44	44	40	36	38	36
Vaccinate	453	36	36	32	42	44	44	40	34	36	32
Vaccinate	454	32	28	20	36	34	34	38	38	34	34
Vaccinate	456	44	36	28	44	40	40	38	36	32	30
Vaccinate	457	40	40	40	50	52	52	52	48	42	40
Vaccinate	460	28	40	28	38	40	40	38	34	36	34
Vaccinate	461	28	40	22	36	38	38	36	38	34	32

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Pasteurella multocida</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate effectiveness against P. multocida.</td></tr>
<tr><td>Product Administration</td><td>1 dose administered by the intranasal route</td></tr>
<tr><td>Study Animals</td><td>32, 3- to 7-day-old calves; 15 controls/placebo, 14 vaccinates</td></tr>
<tr><td>Challenge Description</td><td>All calves were challenged with P. multocida 27 days after vaccination.</td></tr>
<tr><td>Interval observed after challenge</td><td>All calves were monitored daily for 7 days post-challenge for clinical signs of disease, then tissues were examined.</td></tr>
<tr><td>Results</td><td><u>Lung Lesions</u>:
The percent of the affected lung tissue was determined, and a lung lesion score was calculated for each animal.
<table>
<tr><th>Group</th><th>Min</th><th>Q₁</th><th>Median</th><th>Q₃</th><th>Max</th></tr>
<tr><td>Placebo</td><td>4</td><td>20</td><td>24</td><td>35</td><td>43</td></tr>
<tr><td>Vaccinates</td><td>0</td><td>1</td><td>2</td><td>5</td><td>9</td></tr>
</table>
Raw data shown on attached page.</td></tr>
<tr><td>USDA Approval Date</td><td>10/31/2007</td></tr>
</table>

Percent Lung Lesion Data

Calf_ID	Group	LA	LC	LD	RA	RC	RM	RD	Inter	Total
734	INTRA-NASAL	0.000	0.649	0.000	0.000	0.000	0.766	4.151	0.000	5.566
736	INTRA-NASAL	0.000	0.000	0.000	0.000	0.000	0.000	1.929	0.000	1.929
742	INTRA-NASAL	0.000	0.000	0.000	0.311	0.000	0.000	0.000	0.000	0.311
750	INTRA-NASAL	1.337	2.162	1.968	0.311	0.135	1.313	0.000	1.091	8.317
753	INTRA-NASAL	0.117	0.487	0.000	0.000	0.000	0.000	0.000	0.000	0.604
756	INTRA-NASAL	0.930	0.000	0.000	0.156	0.000	0.000	0.000	0.000	1.086
758	INTRA-NASAL	0.465	0.000	0.000	0.701	0.000	0.984	0.000	0.000	2.150
760	INTRA-NASAL	0.000	0.000	0.000	2.494	1.757	0.000	0.000	0.000	4.251
761	INTRA-NASAL	0.000	0.000	0.000	0.311	0.135	0.000	0.000	0.000	0.446
764	INTRA-NASAL	0.582	0.000	7.014	0.000	0.000	0.000	0.000	0.000	7.596
774	INTRA-NASAL	0.000	0.000	0.000	3.974	0.000	0.000	0.000	0.000	3.974
777	INTRA-NASAL	0.000	0.000	0.000	0.000	0.000	0.438	0.000	0.000	0.438
781	INTRA-NASAL	0.000	2.000	0.986	1.091	0.000	4.703	0.000	0.000	8.780
784	INTRA-NASAL	0.000	0.703	0.000	0.000	0.000	0.000	0.000	0.000	0.703
738	CONTROL	1.047	2.432	3.322	2.104	0.406	7.000	4.746	1.939	22.996
739	CONTROL	0.000	0.000	0.000	2.883	0.000	1.532	0.000	0.000	4.415
740	CONTROL	1.105	4.378	2.954	5.455	4.054	4.594	0.445	1.273	24.258
745	CONTROL	1.105	5.513	18.339	0.701	0.000	5.359	1.631	2.788	35.436
746	CONTROL	0.000	2.054	1.232	6.000	0.406	3.282	4.893	1.818	19.685
747	CONTROL	3.430	5.675	4.554	4.831	3.919	6.016	5.488	4.000	37.913
749	CONTROL	0.000	1.297	1.475	6.0.0	5.000	7.000	10.976	2.606	34.354
751	CONTROL	0.349	1.946	1.107	3.273	0.000	5.578	29.068	1.273	42.594
754	CONTROL	0.000	0.000	0.000	3.974	0.000	2.844	1.040	1.030	8.888
768	CONTROL	0.175	4.811	8.122	0.779	1.284	6.672	2.671	4.000	28.514
769	CONTROL	0.814	1.459	1.846	0.000	0.608	0.657	17.647	1.394	24.425
772	CONTROL	1.163	4.649	4.554	0.857	0.676	6.230	2.965	2.788	23.882
776	CONTROL	1.744	2.919	1.846	1.481	1.284	2.188	4.151	1.454	17.067
779	CONTROL	2.907	6.000	11.568	2.727	2.095	6.234	7.861	3.030	42.422
783	CONTROL	1.337	0.811	2.339	3.740	2.906	3.391	3.560	2.727	20.811

*INTRA-NASAL is the vaccinate group

**LA = Left Apical, LC = Left Cardiac, LD = Left Diaphragm, RA = Right Apical, RC = Right Cardiac, RM = Right Middle, RD = Right Diaphragm, Inter = Intermediate

<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 typical field conditions</td></tr>
<tr><td>Product Administration</td><td>One dose administered by the intranasal route</td></tr>
<tr><td>Study Animals</td><td>1833 calves (914 vaccinates & 919 controls) ranging in age from 1 day to 5 months, located at 3 different sites. 33% of calves were of 3 days of age or younger.</td></tr>
<tr><td>Challenge Description</td><td>N/A</td></tr>
<tr><td>Interval observed after challenge</td><td>All calves were individually observed once between 2- and 6-hours following vaccination and then daily through 14 to 21 days post-vaccination, depending on site.</td></tr>
<tr><td>Results</td><td>
<u>Adverse Event (AE) Summary</u>
<table>
<tr><th rowspan="2">Group</th><th rowspan="2"># Calves Enrolled</th><th colspan="2">Calves with AE's</th></tr>
<tr><th>No.</th><th>%</th></tr>
<tr><td>Vaccinates</td><td>914</td><td>139</td><td>15.2</td></tr>
<tr><td>Controls (Placebo)</td><td>919</td><td>96</td><td>10.4</td></tr>
</table>
<table>
<tr><th rowspan="2">AE Type</th><th colspan="2">Vaccinates</th><th colspan="2">Controls (Placebo)</th></tr>
<tr><th>No.</th><th>%*</th><th>No.</th><th>%*</th></tr>
<tr><td>Diarrhea</td><td>65</td><td>7.1</td><td>50</td><td>5.4</td></tr>
<tr><td>Eye</td><td>13</td><td>1.4</td><td>12</td><td>1.3</td></tr>
<tr><td>Ear</td><td>10</td><td>1.1</td><td>5</td><td>0.5</td></tr>
<tr><td>Respiratory</td><td>3</td><td>0.3</td><td>2</td><td>0.2</td></tr>
<tr><td>Joint</td><td>4</td><td>0.4</td><td>-</td><td>-</td></tr>
<tr><td>Omphalitis</td><td>4</td><td>0.4</td><td>2</td><td>0.2</td></tr>
<tr><td>Non-Specific</td><td>26</td><td>2.8</td><td>15</td><td>1.6</td></tr>
<tr><td>Other</td><td>3</td><td>0.3</td><td>-</td><td>-</td></tr>
<tr><td>Mortality**</td><td>4</td><td>0.4</td><td>4</td><td>0.4</td></tr>
</table>
* % of total animals vaccinated with respective vaccine/control group.
** Affirmed by licensee to have a cause other than product administration.
</td></tr>
<tr><td>USDA Approval Date</td><td>07/12/2012</td></tr>
</table>