



## Summary of Studies Supporting USDA Product Licensure

|   |   |
|---|---|
| Establishment Name  | Elanco US Inc.  |
| USDA Vet Biologics Establishment Number                                   | 196   |
| Product Code  | 4X29.R0   |
| True Name   | Bovine Rhinotracheitis-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.**

|  |  |
|--|--|
| <b>Study Type</b>                        | Efficacy   |
| <b>Pertaining to</b>                     | Bovine Virus Diarrhea (BVD)  |
| <b>Study Purpose</b>                     | To demonstrate effectiveness against Bovine Virus Diarrhea Type 1  |
| <b>Product Administration</b>            | Subcutaneous   |
| <b>Study Animals</b>                     | Bovine   |
| <b>Challenge Description</b>             | BVD isolate NY-1, BVD Type 1b  |
| <b>Interval observed after challenge</b> |  |
| <b>Results</b>                           | 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. |
| <b>USDA Approval Date</b>                | July 14, 1998  |

|  |   |
|--|---|
| <b>Study Type</b>                        | Comparative Serology  |
| <b>Pertaining to</b>                     | Infectious Bovine Rhinotracheitis (IBR) Virus, Bovine Viral Diarrhea (BVD) Virus Type 1, BVD Type 2, and Parainfluenza 3 (PI3) Virus  |
| <b>Study Purpose</b>                     | 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. |
| <b>Product Administration</b>            | 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.  |
| <b>Study Animals</b>                     | 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).  |
| <b>Challenge Description</b>             | NA  |
| <b>Interval observed after challenge</b> | Blood was collected on study days D0, D28, D35  |
| <b>Results</b>                           | <p>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.</p> <p>Raw data on pages below</p>  |
| <b>USDA Approval Date</b>                | November 18, 2016   |

### BVD Type 1 Serum Neutralization Titers

| <i>Combination Test Vaccine</i> |             |              | <i>Reference Vaccine</i> |             |              |
|---------------------------------|-------------|--------------|--------------------------|-------------|--------------|
| Calf ID                         | Study Day 0 | Study Day 28 | Calf ID                  | Study Day 0 | Study Day 28 |
| 1                               | <2          | 362          | 1                        | <2          | 91           |
| 2                               | <2          | 1024         | 2                        | <2          | 724          |
| 3                               | <2          | 362          | 3                        | <2          | 1328         |
| 4                               | <2          | 790          | 4                        | <2          | 2435         |
| 5                               | <2          | 912          | 5                        | <2          | 1328         |
| 6                               | <2          | 1312         | 6                        | <2          | 456          |
| 7                               | <2          | 664          | 7                        | <2          | 664          |
| 8                               | <2          | 1117         | 8                        | <2          | 342          |
| 9                               | <2          | 821          | 9                        | <2          | 1149         |
| 10                              | <2          | 664          | 10                       | <2          | 575          |
| 11                              | <2          | 575          | 11                       | <2          | 724          |
| 12                              | <2          | 1149         | 12                       | <2          | <2           |
| 13                              | <2          | 724          | 13                       | <2          | 724          |
| 14                              | <2          | 1448         | 14                       | <2          | 72           |
| 15                              | <2          | 1149         | 15                       | <2          | 790          |
| 16                              | <2          | 2702         | 16                       | <2          | 1148         |
| 17                              | <2          | 861          | 17                       | <2          | 638          |
| 18                              | <2          | 1328         | 18                       | <2          | 456          |
| 19                              | <2          | 3158         | 19                       | <2          | 395          |
| 20                              | <2          | 1218         | 20                       | <2          | 664          |
| 21                              | <2          | 724          | 21                       | <2          | 744          |
| 22                              | <2          | 1579         | 22                       | <2          | 181          |
| 23                              | <2          | 1449         | 23                       | <2          | 1328         |
| 24                              | <2          | 724          | 24                       | <2          | 1448         |
| 25                              | <2          | 821          | 25                       | <2          | 724          |
| 26                              | <2          | 912          | 26                       | <2          | 332          |
| 27                              | <2          | 411          | 27                       | <2          | 458          |
| 28                              | <2          | 1643         | 28                       | <2          | 1448         |
| 29                              | <2          | 279          | 29                       | <2          | 456          |
| 30                              | <2          | 1117         | 30                       | <2          | 558          |
| 31                              | <2          | 2435         | 31                       | <2          | 645          |
| 32                              | <2          | 1218         | 32                       | <2          | 664          |
| 33                              | <2          | 2048         | 33                       | <2          | 206          |
| 34                              | <2          | 1825         | 34                       | <2          | 664          |
| 35                              | <2          | 1149         | 35                       | <2          | 724          |
| 36                              | <2          | 323          | 36                       | <2          | 1290         |
| 37                              | <2          | 1277         | 37                       | <2          | 1149         |
| 38                              | <2          | 319          | 38                       | <2          | 861          |
| 39                              | <2          | 1024         | 39                       | <2          | 889          |
| 40                              | <2          | 512          | 40                       | <2          | 878          |
| 41                              | <2          | 1652         | 41                       | <2          | 1579         |
| 42                              | <2          | 1448         | 42                       | <2          | 458          |
| 43                              | <2          | 1117         | 43                       | <2          | 821          |
| 44                              | <2          | 1579         | 44                       | <2          | 2048         |
| 45                              | <2          | 1290         | 45                       | <2          | 256          |

### BVD Type 2 Serum Neutralization Titers

| <i>Combination Test Vaccine</i> |             |              |
|---------------------------------|-------------|--------------|
| 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           |

| <i>Reference Vaccine</i> |             |              |
|--------------------------|-------------|--------------|
| 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**

| <i>Combination Test Vaccine</i> |             |             | <i>Reference Vaccine</i> |             |              |
|---------------------------------|-------------|-------------|--------------------------|-------------|--------------|
| Calf ID                         | Study Day 0 | Study Day35 | Calf ID                  | Study Day 0 | Study Day 35 |
| 1                               | <2          | 14          | 1                        | <2          | 20           |
| 2                               | <2          | 26          | 2                        | <2          | 11           |
| 3                               | <2          | 41          | 3                        | <2          | 8            |
| 4                               | <2          | 83          | 4                        | <2          | 11           |
| 5                               | <2          | 36          | 5                        | <2          | 20           |
| 6                               | <2          | 38          | 6                        | <2          | 36           |
| 7                               | <2          | 45          | 7                        | <2          | 49           |
| 8                               | <2          | 29          | 8                        | <2          | 18           |
| 9                               | <2          | 49          | 9                        | <2          | 18           |
| 10                              | <2          | 41          | 10                       | <2          | 29           |
| 11                              | <2          | 35          | 11                       | <2          | 21           |
| 12                              | <2          | 23          | 12                       | <2          | 4            |
| 13                              | <2          | 29          | 13                       | <2          | 18           |
| 14                              | <2          | 36          | 14                       | <2          | 14           |
| 15                              | <2          | 23          | 15                       | <2          | 23           |
| 16                              | <2          | 72          | 16                       | <2          | 13           |
| 17                              | <2          | 29          | 17                       | <2          | 11           |
| 18                              | <2          | 72          | 18                       | <2          | 12           |
| 19                              | <2          | 26          | 19                       | <2          | 29           |
| 20                              | <2          | 41          | 20                       | <2          | 18           |
| 21                              | <2          | 45          | 21                       | <2          | 36           |
| 22                              | <2          | 80          | 22                       | <2          | 7            |
| 23                              | <2          | 41          | 23                       | <2          | 21           |
| 24                              | <2          | 12          | 24                       | <2          | 36           |
| 25                              | <2          | 80          | 25                       | <2          | 25           |
| 26                              | <2          | 49          | 26                       | <2          | 12           |
| 27                              | <2          | 41          | 27                       | <2          | 45           |
| 28                              | <2          | 45          | 28                       | <2          | 20           |
| 29                              | <2          | 29          | 29                       | <2          | 29           |
| 30                              | <2          | 32          | 30                       | <2          | 23           |
| 31                              | <2          | 23          | 31                       | <2          | 45           |
| 32                              | <2          | 80          | 32                       | <2          | 29           |
| 33                              | <2          | 57          | 33                       | <2          | 45           |
| 34                              | <2          | 55          | 34                       | <2          | 26           |
| 35                              | <2          | 41          | 35                       | <2          | 91           |
| 36                              | <2          | 38          | 36                       | <2          | 23           |
| 37                              | <2          | 49          | 37                       | <2          | 45           |
| 38                              | <2          | 51          | 38                       | <2          | 18           |
| 39                              | <2          | 49          | 39                       | <2          | 29           |
| 40                              | <2          | 26          | 40                       | <2          | 36           |
| 41                              | <2          | 25          | 41                       | <2          | 14           |
| 42                              | <2          | 35          | 42                       | <2          | 23           |
| 43                              | <2          | 41          | 43                       | <2          | 38           |
| 44                              | <2          | 76          | 44                       | <2          | 23           |
| 45                              | <2          | 83          | 45                       | <2          | 18           |

**PI3 Serum Neutralization Titers**

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

|  |  |
|--|--|
| <b>Study Type</b>                        | Efficacy   |
| <b>Pertaining to</b>                     | Bovine Virus Diarrhea (BVD)  |
| <b>Study Purpose</b>                     | To demonstrate effectiveness against Bovine Virus Diarrhea Type 2  |
| <b>Product Administration</b>            | Subcutaneous   |
| <b>Study Animals</b>                     | Bovine   |
| <b>Challenge Description</b>             | BVD isolate 890, BVD Type 2a   |
| <b>Interval observed after challenge</b> |  |
| <b>Results</b>                           | 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. |
| <b>USDA Approval Date</b>                | July 14, 1998  |



|  |  |
|--|--|
| <b>Study Type</b>                        | Efficacy   |
| <b>Pertaining to</b>                     | Infectious Bovine Rhinotracheitis (IBR) Virus  |
| <b>Study Purpose</b>                     | To demonstrate effectiveness against IBR   |
| <b>Product Administration</b>            | Subcutaneous   |
| <b>Study Animals</b>                     | Bovine   |
| <b>Challenge Description</b>             | IBR Coopers Strain   |
| <b>Interval observed after challenge</b> |  |
| <b>Results</b>                           | 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. |
| <b>USDA Approval Date</b>                | July 13, 1998  |

| <b>Study Type</b>                        | Efficacy   |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
|--|--|------------------|----------------|-----------|----------------|-----------|----------------|-----------------------------|-----|-----|-----|-----|----|----------------------|-----|-----|------|------|------|------------------|-----|-----|------|------|------|
| <b>Pertaining to</b>                     | <i>Mannheimia Haemolytica</i>  |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| <b>Study Purpose</b>                     | 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 <i>M. haemolytica</i> as a means to demonstrate absence of interference of IBR, BVD Type 1, BVD Type 2, and PI3 to <i>M. Haemolytica</i> immunity to show that combining fractions with satisfactory efficacy studies does not reduce the immune response.   |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| <b>Product Administration</b>            | One dose of combination vaccine administered subcutaneously  |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| <b>Study Animals</b>                     | 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.  |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| <b>Challenge Description</b>             | <i>Mannheimia Haemolytica</i> , administered 10 days after vaccination   |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| <b>Interval observed after challenge</b> | Lungs evaluated 4 days after challenge   |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| <b>Results</b>                           | <p>The percent of the lung mass that was abnormal (consolidated) was calculated for every animal.</p> <p>5-number summary for lung consolidation (%)</p> <table border="1"> <thead> <tr> <th><i>Treatment</i></th> <th><i>Minimum</i></th> <th><i>Q1</i></th> <th><i>Median</i></th> <th><i>Q3</i></th> <th><i>Maximum</i></th> </tr> </thead> <tbody> <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> </tbody> </table> <p>Raw data shown on attached page.</p> | <i>Treatment</i> | <i>Minimum</i> | <i>Q1</i> | <i>Median</i>  | <i>Q3</i> | <i>Maximum</i> | Combination Test vaccinates | 0.2 | 2.6 | 5.6 | 8.2 | 26 | Reference Vaccinates | 2.1 | 7.9 | 24.1 | 24.6 | 90.4 | Placebo Controls | 1.4 | 9.5 | 17.6 | 32.5 | 84.8 |
| <i>Treatment</i>                         | <i>Minimum</i>   | <i>Q1</i>        | <i>Median</i>  | <i>Q3</i> | <i>Maximum</i> |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| Combination Test vaccinates              | 0.2  | 2.6              | 5.6            | 8.2       | 26             |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| Reference Vaccinates                     | 2.1  | 7.9              | 24.1           | 24.6      | 90.4           |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| Placebo Controls                         | 1.4  | 9.5              | 17.6           | 32.5      | 84.8           |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |
| <b>USDA Approval Date</b>                | September 16, 2016   |                  |                |           |                |           |                |                             |     |     |     |     |    |                      |     |     |      |      |      |                  |     |     |      |      |      |

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

| Combination Test<br>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            |

| <b>Study Type</b>                        | Efficacy   |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
|--|--|------------------|----------------|-----------|----------------|-----------|----------------|-----------------|-----|------|----|------|------|-------------------|-----|-----|-----|------|------|
| <b>Pertaining to</b>                     | <i>Mannheimia haemolytica</i>  |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <b>Study Purpose</b>                     | To demonstrate effectiveness against respiratory disease caused by <i>M. Haemolytica</i> as early as 10 days after administration.   |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <b>Product Administration</b>            | 1 dose subcutaneously  |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <b>Study Animals</b>                     | 30 calves, 75-83 days of age. 20 vaccinates and 10 controls.   |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <b>Challenge Description</b>             | <i>Mannheimia Haemolytica</i> , administered 10 days after second vaccination  |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <b>Interval observed after challenge</b> | Lungs evaluated 4 days after challenge   |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <b>Results</b>                           | <p>The percent of the lung mass that was abnormal (consolidated) was calculated for every animal.</p> <p>5-number summary for lung consolidation (%)</p> <table border="1"> <thead> <tr> <th><i>Treatment</i></th> <th><i>Minimum</i></th> <th><i>Q1</i></th> <th><i>Median</i></th> <th><i>Q3</i></th> <th><i>Maximum</i></th> </tr> </thead> <tbody> <tr> <td><i>Controls</i></td> <td>4.6</td> <td>20.6</td> <td>23</td> <td>52.3</td> <td>57.8</td> </tr> <tr> <td><i>Vaccinates</i></td> <td>1.0</td> <td>6.5</td> <td>9.9</td> <td>14.7</td> <td>41.3</td> </tr> </tbody> </table> <p>Raw data shown on attached page.</p> | <i>Treatment</i> | <i>Minimum</i> | <i>Q1</i> | <i>Median</i>  | <i>Q3</i> | <i>Maximum</i> | <i>Controls</i> | 4.6 | 20.6 | 23 | 52.3 | 57.8 | <i>Vaccinates</i> | 1.0 | 6.5 | 9.9 | 14.7 | 41.3 |
| <i>Treatment</i>                         | <i>Minimum</i>   | <i>Q1</i>        | <i>Median</i>  | <i>Q3</i> | <i>Maximum</i> |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <i>Controls</i>                          | 4.6  | 20.6             | 23             | 52.3      | 57.8           |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <i>Vaccinates</i>                        | 1.0  | 6.5              | 9.9            | 14.7      | 41.3           |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |
| <b>USDA Approval Date</b>                | June 5, 2009   |                  |                |           |                |           |                |                 |     |      |    |      |      |                   |     |     |     |      |      |

**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      |         |

| <b>Study Type</b>                        | Safety   |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
|--|--|--------------------|-------------------------|-------------------|-----|-------------------------|-----|----------------------------|----|--------|---|----------|---|-------|----|-------------|---|-----------|---|----------------|---|----------|----|-------------------|---|------------------|---|----------------------|---|----------|---|----------|----|---------|---|----------|---|
| <b>Pertaining to</b>                     | All  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| <b>Study Purpose</b>                     | Demonstrate safety of product under typical use conditions   |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| <b>Product Administration</b>            | One dose administered subcutaneously, followed by a monovalent bovine respiratory syncytial virus (BRSV) injection 2 weeks later.  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| <b>Study Animals</b>                     | 627 calves, 18-29 days of age at each of three sites.  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| <b>Challenge Description</b>             | NA   |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| <b>Interval observed after challenge</b> | No challenge. Animals were observed at 2 hours after each injection and daily for a minimum of 42 days after vaccination.  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| <b>Results</b>                           | <p>All Adverse Events:</p> <table border="1"> <thead> <tr> <th><b>VeDDRA Term</b></th> <th><b>Number of Calves</b></th> </tr> </thead> <tbody> <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> </tbody> </table> <p>*Deaths not attributable to vaccine</p> | <b>VeDDRA Term</b> | <b>Number of Calves</b> | No Adverse Events | 329 | Injection Site Swelling | 259 | Increased Respiratory Rate | 39 | Death* | 8 | Anorexia | 4 | Fever | 13 | Hypothermia | 3 | Arthritis | 1 | Conjunctivitis | 1 | Diarrhea | 14 | Labored Breathing | 1 | Cough Productive | 1 | Respiratory Distress | 5 | Lameness | 2 | Pink Eye | 11 | Bloated | 1 | Lethargy | 2 |
| <b>VeDDRA Term</b>                       | <b>Number of Calves</b>  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| No Adverse Events                        | 329  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Injection Site Swelling                  | 259  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Increased Respiratory Rate               | 39   |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Death*                                   | 8  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Anorexia                                 | 4  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Fever                                    | 13   |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Hypothermia                              | 3  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Arthritis                                | 1  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Conjunctivitis                           | 1  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Diarrhea                                 | 14   |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Labored Breathing                        | 1  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Cough Productive                         | 1  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Respiratory Distress                     | 5  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Lameness                                 | 2  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Pink Eye                                 | 11   |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Bloated                                  | 1  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |
| Lethargy                                 | 2  |                    |                         |                   |     |                         |     |                            |    |        |   |          |   |       |    |             |   |           |   |                |   |          |    |                   |   |                  |   |                      |   |          |   |          |    |         |   |          |   |

| <b>Injection Site Reactions, Size:</b>  |                      |                                |  |                            |                     |                                       |      |       |
|---|----------------------|--------------------------------|--|----------------------------|---------------------|---------------------------------------|------|-------|
| Site  | Total number animals | Vaccination                    | # of injection site reactions by Size (cm <sup>2</sup> ) |                            |                     | Injection site reactions not observed |      |       |
|   |                      |                                | ≤ 2.0 cm <sup>2</sup>                                    | 2.0-10.0 cm <sup>2</sup>   | >10 cm <sup>2</sup> |                                       |      |       |
| 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                                   |      |       |
| <b>Injection Site Reactions, Duration:</b>  |                      |                                |  |                            |                     |                                       |      |       |
| 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 <sup>2</sup> at the end of the study. |                      |                                |  |                            |                     |                                       |      |       |
| <b>USDA Approval Date</b>   | April 10, 2020       |                                |  |                            |                     |                                       |      |       |