Summary of Studies Supporting USDA Product Licensure

Establishment Name	Boehringer Ingelheim Animal Health USA Inc.
USDA Vet Biologics Establishment Number	124
Product Code	44C9.24
True Name	Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza 3-Respiratory Syncytial Virus Vaccine, Modified Live Virus, Haemophilus Somnus Bacterin
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	Express FP 5-HS - No distributor specified Express FP 5/Somnugen - Boehringer Ingelheim (Canada) Ltd.
Date of Compilation Summary	April 16, 2019

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

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	Demonstration of efficacy against persistent infection of calves with BVD Type 1
Product Administration	Pregnant heifers
Study Animals	Bovine
Challenge Description	BVD Type 1a isolate BJ
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	September 19, 2003

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	Demonstration of efficacy against BVD Type 1 (respiratory disease)
Product Administration	
Study Animals	Bovine
Challenge Description	BVD Type 1 isolate NY-1
Interval observed after challenge	
Results	Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	November 9, 1998

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	Demonstration of efficacy against persistent infection of calves with BVD Type 1
Product Administration	
Study Animals	Bovine
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	January 2, 2002; September 25, 2002

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	Demonstration of efficacy against BVD Type 2 (persistently infected calves)
Product Administration	Pregnant heifers
Study Animals	Bovine
Challenge Description	BVD Type 2a isolate PA131
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	August 24, 2006

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	Demonstration of efficacy against BVD Type 2 (respiratory disease)
Product Administration	
Study Animals	Bovine
Challenge Description	BVD Type 2a isolate BVD 890
Interval observed after challenge	
Results	Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	November 9, 1998

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	Demonstration of efficacy against persistent infection of calves with BVD Type 2
Product Administration	Pregnant heifers
Study Animals	Bovine
Challenge Description	BVD Type 2 isolate PA131
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	September 19, 2003

Study Type	Efficacy
Pertaining to	Bovine Virus Diarrhea (BVD)
Study Purpose	Demonstration of efficacy against persistent infection of calves with BVD Type 2
Product Administration	Pregnant heifers
Study Animals	Bovine
Challenge Description	BVD Type 2a isolate NY-93
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	January 2, 2002; September 25, 2002

Study Type	Efficacy
Pertaining to	Infectious Bovine Rhinotracheitis (IBR)
Study Purpose	Demonstration of efficacy against IBR (respiratory disease)
Product Administration	
Study Animals	Bovine
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	May 4, 1994

Study Type	Efficacy
Pertaining to	*Haemophilus somnus*
Study Purpose	Demonstration of efficacy against *Haemophilus somnus*
Product Administration	
Study Animals	Bovine
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	May 5, 1981

Study Type	Efficacy
Pertaining to	Bovine Parainfluenza Type 3 (PI_3)
Study Purpose	Demonstration of efficacy against PI_3
Product Administration	
Study Animals	Bovine
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	September 8, 1994; January 16, 2001

Study Type	Efficacy
Pertaining to	Bovine Parainfluenza Type 3 (PI_3)
Study Purpose	Demonstration of efficacy against PI_3
Product Administration	
Study Animals	Bovine
Challenge Description	
Interval observed after challenge	
Results	Study data were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance at the time of submission. No data are published because this study was submitted to USDA-APHIS prior to January 1, 2007, and APHIS only requires publication of data submitted after that date.
USDA Approval Date	November 3, 2000

Study Type	Efficacy
Pertaining to	Bovine Respiratory Syncytial Virus (BRSV)
Study Purpose	Demonstration of efficacy against BRSV
Product Administration	
Study Animals	Bovine
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	September 19, 2003

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Bovine Respiratory Syncytial Virus (BRSV)</td></tr>
<tr><td>Study Purpose</td><td>Demonstration of efficacy against BRSV</td></tr>
<tr><td>Product Administration</td><td>Two doses, 26 days apart, subcutaneously</td></tr>
<tr><td>Study Animals</td><td>29 bovine (14 vaccinates, 15 controls), 29 – 37 days old</td></tr>
<tr><td>Challenge Description</td><td>Challenged with BRSV at 40 - 41 days after final vaccination</td></tr>
<tr><td>Interval observed after challenge</td><td>Observed daily for 9 days after challenge. Nasal swabs were collected from cattle on days 3, 4, 5, 6, 7, 8 and 9 after challenge. The lungs of cattle were examined on 9 days after the second challenge.</td></tr>
<tr><td>Results</td><td>Results of the study are summarized as follows:

Nasal swabs were evaluated for BRSV shedding. An animal was considered positive if shedding was detected on at least one day:
<table>
<tr><th>Group</th><th>Positive</th><th>Negative</th></tr>
<tr><td>Vaccinates</td><td>2/14 (14%)</td><td>12/14 (86%)</td></tr>
<tr><td>Controls</td><td>13/15 (87%)</td><td>2/15 (13%)</td></tr>
</table>

Lung lesions were evaluated visually and by palpation. An animal was considered positive if its lungs had any visual or palpable abnormality:
<table>
<tr><th>Group</th><th>Positive</th><th>Negative</th></tr>
<tr><td>Vaccinates</td><td>5/13 (38%)</td><td>8/13 (62%)</td></tr>
<tr><td>Controls</td><td>15/15 (100%)</td><td>0/15 (0%)</td></tr>
</table>
Note: calf #17 was removed from analysis of the lungs due to a difference in treatment during humane euthanasia that potentially affected the gross appearance of the lungs.

BRSV was isolated from the lungs using virus isolation and lung tissue was evaluated by fluorescent antibody testing.

See tables on the following pages for data.</td></tr>
<tr><td>USDA Approval Date</td><td>February 12, 2010</td></tr>
</table>

Nasal Swab Results for BRSV by Virus Isolation:

Group	Animal ID	Outcome	Days Post-Challenge						
			3	4	5	6	7	8	9
Vaccinates (14 bovine)	2	Negative	-	-	-	-	-	-	-
	4	Negative	-	-	-	-	-	-	-
	8	Negative	-	-	-	-	-	-	-
	9	Negative	-	-	-	-	-	-	-
	10	Positive	-	-	-	+	-	+	-
	15	Negative	-	-	-	-	-	-	-
	16	Negative	-	-	-	-	-	-	-
	17	Negative	-	-	-	-	-	-	-
	26	Negative	-	-	-	-	-	-	-
	27	Positive	-	-	-	-	+	-	-
	29	Negative	-	-	-	-	-	-	-
	33	Negative	-	-	-	-	-	-	-
	39	Negative	-	-	-	-	-	-	-
	41	Negative	-	-	-	-	-	-	-
Controls (15 bovine)	1	Positive	-	-	-	+	+	-	-
	3	Positive	-	-	-	-	+	-	-
	5	Negative	-	-	-	-	-	-	-
	6	Positive	-	-	-	-	+	-	-
	7	Positive	-	-	-	-	+	-	-
	12	Positive	-	-	-	-	+	+	-
	14	Positive	-	-	-	+	-	-	-
	18	Positive	-	-	-	-	+	+	-
	19	Positive	-	-	-	+	+	-	-
	20	Positive	-	-	-	-	+	-	-
	22	Positive	-	-	-	+	+	-	-
	28	Positive	-	-	+	+	+	-	-
	31	Positive	-	-	-	+	+	-	-
	35	Positive	-	-	+	-	+	-	-
	37	Negative	-	-	-	-	-	-	-

Outcome =

- Positive if any day was positive (+) for BRSV virus isolation
- Negative if all days were negative (-) for BRSV virus isolation

Nasal swab results =

- + if BRSV was detected by virus isolation
- - if BRSV was not detected by virus isolation

Summary of Results for Lung Lesions and Virus Isolation

Group	Animal ID	Outcome (Overall) for Lungs	Total Score for Lungs		BRSV from Lungs	
			Visual	Palpable	Virus Isolation (VI)	Fluorescent Antibody (FA) Testing
Vaccinates (13 bovine)	2	Negative	0	0	Negative	Negative
	4	Negative	0	0	Negative	Negative
	8	Negative	0	0	Negative	Negative
	9	Positive	1	0	Negative	Negative
	10	Positive	2	0	Negative	Negative
	15	Negative	0	0	Negative	Negative
	16	Negative	0	0	Negative	Negative
	26	Positive	1	0	Negative	Negative
	27	Negative	0	0	Negative	Negative
	29	Negative	0	0	Negative	Negative
	33	Positive	0	5	Negative	Negative
	39	Positive	3	0	Negative	Negative
	41	Negative	0	0	Negative	Negative
Controls (15 bovine)	1	Positive	6	2	Positive	Negative
	3	Positive	6	0	Negative	Negative
	5	Positive	8	0	Negative	Negative
	6	Positive	8	3	Negative	Negative
	7	Positive	19	3	Negative	Negative
	12	Positive	8	0	Negative	Negative
	14	Positive	9	0	Positive	Positive
	18	Positive	6	0	Positive	Negative
	19	Positive	6	2	Negative	Negative
	20	Positive	4	0	Negative	Negative
	22	Positive	4	0	Positive	Negative
	28	Positive	6	3	Positive	Negative
	31	Positive	7	4	Positive	Negative
	35	Positive	17	11	Negative	Positive
	37	Positive	6	1	Negative	Negative

Outcome (Overall) for Lungs =

- Positive if any parameter is positive (visual lesions, palpable lesions, VI, FA)
- Negative if all parameters are negative (visual lesions, palpable lesions, VI, FA)

Total Score for Lungs =

- Sum of scores for all lung lobes (see following pages for each lung lobe).
- Scores range from 0 (negative / normal) to 32. Any score of 1 or higher is considered positive.

BRSV Virus Isolation (VI) =

- Positive if BRSV was isolated from lung tissue
- Negative if BRSV was not isolated from lung tissue

Fluorescent Antibody (FA) Testing =

- Positive if BRSV specific staining was observed in lung tissue
- Negative if BRSV specific staining was not observed in lung tissue

Visual Lung Lesions for Each Lung Lobe:

Group	Animal ID	Visual								
		Total Score (Sum)	Left cranial	Left middle	Left caudal	Right cranial	Right posterior cranial	Right middle	Right caudal	Inter-mediate
Vaccinates (13 bovine)	2	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0
	8	0	0	0	0	0	0	0	0	0
	9	1	0	0	0	0	1	0	0	0
	10	2	0	0	2	0	0	0	0	0
	15	0	0	0	0	0	0	0	0	0
	16	0	0	0	0	0	0	0	0	0
	26	1	0	0	0	0	0	1	0	0
	27	0	0	0	0	0	0	0	0	0
	29	0	0	0	0	0	0	0	0	0
	33	0	0	0	0	0	0	0	0	0
	39	3	0	1	0	1	0	1	0	0
	41	0	0	0	0	0	0	0	0	0
Controls (15 bovine)	1	6	0	1	1	1	1	0	1	1
	3	6	1	1	1	1	0	1	0	1
	5	8	1	1	1	1	1	1	1	1
	6	8	1	2	1	0	1	2	0	1
	7	19	2	2	3	2	2	2	3	3
	12	8	1	1	1	1	0	1	1	2
	14	9	1	1	1	2	0	1	1	2
	18	6	0	1	1	2	0	1	1	0
	19	6	0	1	0	2	1	1	0	1
	20	4	0	1	0	0	1	1	0	1
	22	4	0	1	0	2	0	1	0	0
	28	6	1	2	0	1	1	1	0	0
	31	7	0	0	1	3	0	1	1	1
	35	17	2	2	2	2	2	2	3	2
	37	6	0	1	1	1	0	1	1	1

Scoring System for Lung Lobes (Visual)

	Description
0	Normal
1	Slight multifocal or diffuse congestion
2	Moderate congestion with visible lobular pattern (+/- mild edema)
3	Multiple consolidated lobules; minimal to mild pleuritis
4	Most of all of the lobe consolidated; moderate to severe pleuritis

\

Palpable Lung Lesions for Each Lung Lobe:

Group	Animal ID	Palpable								
		Total Score (Sum)	Left cranial	Left middle	Left caudal	Right cranial	Right posterior cranial	Right middle	Right caudal	Inter-mediate
Vaccinates (13 bovine)	2	0	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0	0
	8	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	0	0	0
	10	0	0	0	0	0	0	0	0	0
	15	0	0	0	0	0	0	0	0	0
	16	0	0	0	0	0	0	0	0	0
	26	0	0	0	0	0	0	0	0	0
	27	0	0	0	0	0	0	0	0	0
	29	0	0	0	0	0	0	0	0	0
	33	5	0	1	1	0	0	1	1	1
	39	0	0	0	0	0	0	0	0	0
	41	0	0	0	0	0	0	0	0	0
Controls (15 bovine)	1	2	0	0	0	1	0	0	1	0
	3	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0
	6	3	0	1	0	0	1	1	0	0
	7	3	0	0	0	0	0	1	1	1
	12	0	0	0	0	0	0	0	0	0
	14	0	0	0	0	0	0	0	0	0
	18	0	0	0	0	0	0	0	0	0
	19	2	0	0	1	0	0	0	1	0
	20	0	0	0	0	0	0	0	0	0
	22	0	0	0	0	0	0	0	0	0
	28	3	0	0	1	0	0	1	1	0
	31	4	0	1	1	0	0	0	1	1
	35	11	0	1	1	2	1	3	2	1
	37	1	0	0	0	0	0	1	0	0

Scoring System for Lung Lobes (Palpable)

	Description
0	Normal
1	Slight or mild diffuse firmness within lobe
2	Moderate diffuse firmness within lobe
3	Non-homogeneous firmness throughout lobe, with palpable solid areas
4	Most or all of lobe palpably solid

Study Type	Safety
Pertaining to	All fractions
Study Purpose	To demonstrate safety under field conditions
Product Administration	
Study Animals	Bovine
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	July 6, 1999

<table>
<tr><td>Study Type</td><td>Safety</td></tr>
<tr><td>Pertaining to</td><td>All fractions</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate safety in pregnant heifers/cows and nursing calves</td></tr>
<tr><td>Product Administration</td><td>Two doses, administered subcutaneously. First vaccination given 1 – 2 months prior to breeding. Second vaccination given during a specified trimester of pregnancy.</td></tr>
<tr><td>Study Animals</td><td><u>Site 1:</u>
2,063 cows and heifers received vaccine prior to breeding.
1,586 cows and heifers received vaccine or a placebo during pregnancy and are included in this summary.
<u>Site 2:</u>
120 calves from dams that received vaccine in the 2nd or 3rd trimester.</td></tr>
<tr><td>Challenge Description</td><td>Not applicable</td></tr>
<tr><td>Interval observed after challenge</td><td>Not applicable</td></tr>
<tr><td>Results</td><td>All cows and heifers were observed from pre-breeding vaccination through calving and calves were observed for 4 weeks postpartum. Results of the study are summarized as follows:

Fetal Loss (Site 1):
<table>
<tr><th rowspan="2">Trimester</th><th colspan="2">Vaccinates</th><th colspan="2">Controls (Placebo)</th></tr>
<tr><th>Enrolled</th><th>Fetal Loss (%)</th><th>Enrolled</th><th>Fetal Loss (%)</th></tr>
<tr><td>1st</td><td>306</td><td>7 (2.3%)</td><td>274</td><td>6 (2.2%)</td></tr>
<tr><td>2nd</td><td>237</td><td>1 (0.4%)</td><td>235</td><td>3 (1.3%)</td></tr>
<tr><td>3rd</td><td>267</td><td>5 (1.9%)</td><td>267</td><td>6 (2.2%)</td></tr>
</table>
The number of animals during pregnancy was reduced due to normal losses including dystocia, lameness, and non-study related causes (as affirmed by licensee).
Fetal loss was due to abortion or open (non-pregnant). For all three trimesters, no cows or heifers (0.0%) in either group were diagnosed as having aborted due to Infectious Bovine Rhinotracheitis (IBR) or Bovine Virus Diarrhea Virus (BVDV). All tests for viral detection and isolation of IBR and BVDV on all fetal tissues were negative.

<u>Fetal Infection (Site 2):</u>
Serum samples were collected from calves prior to receiving colostrum. 61 calves were from cows vaccinated in the 2nd trimester and 59 calves were from cows vaccinated in the 3rd trimester. 6 serum samples were removed from the study due to equipment malfunction or concerns that colostrum was received. All valid samples tested negative for antibodies to IBR, BVD1 and BVD2. Serum samples were also negative for IBR by virus isolation and negative for BVD1 and BVD2 by PCR.</td></tr>
</table>

USDA Approval Date	January 11, 2008