Summary of Studies Supporting USDA Product Licensure

Establishment Name	Boehringer Ingelheim Animal Health USA Inc.
USDA Vet Biologics Establishment Number	124
Product Code	19P9.R1
True Name	Porcine Reproductive & Respiratory Syndrome-Circovirus Vaccine, Respiratory Form, Type 2, Modifed Live Virus, Killed Baculovirus Vector
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	FLEXCircoPRRS - No distributor specified
Date of Compilation Summary	December 16, 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>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Porcine Circovirus Vaccine, Type 2, Killed Baculovirus Vector</td></tr>
<tr><td>Study Purpose</td><td>Efficacy of Porcine Circovirus Vaccine, Type 2</td></tr>
<tr><td>Product Administration</td><td>Administration of one dose intramuscularly. Product tested contained ORF2 gene of strain PCV2a.</td></tr>
<tr><td>Study Animals</td><td>3 week old caesarian derived, colostrum deprived pigs, divided into 24 vaccinates and 24 controls</td></tr>
<tr><td>Challenge Description</td><td>Challenged with Porcine Circovirus Type 2a at 31 days after vaccination</td></tr>
<tr><td>Interval observed after challenge</td><td>Pigs were observed daily for 25 days. At 25 days, tissues were assessed for lymphoid depletion, lymphoid and lung inflammation and immunohistochemistry (IHC)</td></tr>
<tr><td>Results</td><td>Summary of Results:

Tissues were assessed for lymphoid depletion, lymphoid and lung inflammation, and immunohistochemistry (IHC) for both lymphoid and lung tissue.

An animal was considered positive for lymphoid depletion, lymphoid inflammation, or lymphoid IHC if depletion, inflammation, or PCV2 antigen, respectively, were present in tonsil tissue, mesenteric lymph node (MLN) tissue, iliac lymph node (ILN) tissue, or tracheobronchial lymphoid (TBLN) tissue.

An animal was considered positive for lung inflammation if microscopic lung inflammation was present and Lung IHC positive if PCV2 antigen was detected in lung cells.

<table>
<tr><th>Tissues</th><th>Vaccinates</th><th>Controls</th></tr>
<tr><td>Lymphoid depletion (LyD)</td><td>0/24</td><td>20/24</td></tr>
<tr><td>Lymphoid inflammation (LyI)</td><td>1/24</td><td>21/24</td></tr>
<tr><td>Lung Inflammation</td><td>3/24</td><td>18/24</td></tr>
<tr><td>Lymphoid IHC</td><td>2/24</td><td>22/24</td></tr>
<tr><td>Lung IHC</td><td>0/24</td><td>14/24</td></tr>
<tr><td>Any pig: (LyD or LyI)</td><td>2/24</td><td>22/24</td></tr>
</table>

See tables on the following pages for data.</td></tr>
<tr><td>USDA Approval Date</td><td>June 5, 2008</td></tr>
</table>

Individual Lymphoid Depletion

Group	Animal ID	Tonsil	MLN	ILN	TBLN
Vaccinates (24)	22	-	-	-	-
	23	-	-	-	-
	26	-	-	-	-
	29	-	-	-	-
	31	-	-	-	-
	32	-	-	-	-
	34	-	-	-	-
	39	-	-	-	-
	43	-	-	-	-
	44	-	-	-	-
	45	-	-	-	-
	47	-	-	-	-
	51	-	-	-	-
	53	-	-	-	-
	57	-	-	-	-
	62	-	-	-	-
	67	-	-	-	-
	69	-	-	-	-
	72	-	-	-	-
	74	-	-	-	-
	82	-	-	-	-
	87	-	-	-	-
	88	-	-	-	-
	95	-	-	-	-
Controls (24)	28	+	+	+	+
	30	+	+	+	+
	36	*	+	+	+
	38	-	-	-	-
	40	-	-	-	-
	41	+	-	-	+
	42	-	+	+	+
	46	-	-	-	-
	55	+	+	+	+
	56	-	+	-	-
	58	-	-	-	-
	60	-	-	-	+
	61	-	+	-	-
	64	-	+	+	+
	65	+	+	+	+
	71	-	-	-	+
	75	+	+	+	+
	77	+	+	+	+
	78	+	+	+	+
	79	+	+	+	+
	80	+	+	+	+
	81	+	+	+	+
	86	-	-	-	+
	94	-	-	-	+

(+) = positive
(-) = negative
(*)=missing tissue

Individual Lymphoid Inflammation

Group	Animal ID	Tonsil	MLN	ILN	TBLN
Vaccinates (24)	22	-	-	-	-
	23	-	-	-	-
	26	-	-	-	-
	29	-	-	-	-
	31	-	-	-	-
	32	-	-	-	-
	34	-	-	-	-
	39	-	-	-	-
	43	-	-	-	-
	44	-	-	-	-
	45	-	-	-	-
	47	-	-	-	-
	51	-	-	-	+
	53	-	-	-	-
	57	-	-	-	-
	62	-	-	-	-
	67	-	-	-	-
	69	-	-	-	-
	72	-	-	-	-
	74	-	-	-	-
	82	-	-	-	-
	87	-	-	-	-
	88	-	-	-	-
	95	-	-	-	-
Controls (24)	28	+	+	+	+
	30	+	+	+	+
	36	*	+	+	+
	38	-	-	-	-
	40	-	-	-	-
	41	+	+	+	+
	42	+	+	+	+
	46	+	-	+	-
	55	+	+	+	+
	56	+	+	+	+
	58	-	-	-	-
	60	-	-	+	+
	61	+	+	+	-
	64	+	+	+	+
	65	+	+	+	+
	71	+	-	+	+
	75	+	+	+	+
	77	+	+	+	+
	78	+	+	+	+
	79	+	+	+	+
	80	+	+	+	+
	81	+	+	+	+
	86	+	-	+	+
	94	+	-	+	+

(+) = positive
(-) = negative
(*)=missing tissue

Individual Lymphoid IHC Results

Group	Animal ID	Tonsil	MLN	ILN	TBLN
Vaccinates (24)	22	-	-	-	-
	23	-	-	-	-
	26	-	-	-	-
	29	-	-	-	-
	31	-	-	-	-
	32	-	-	-	-
	34	-	-	-	-
	39	+	+	-	-
	43	-	-	-	-
	44	-	-	-	-
	45	-	-	-	-
	47	-	-	-	-
	51	-	-	-	+
	53	-	-	-	-
	57	-	-	-	-
	62	-	-	-	-
	67	-	-	-	-
	69	-	-	-	-
	72	-	-	-	-
	74	-	-	-	-
	82	-	-	-	-
	87	-	-	-	-
	88	-	-	-	-
	95	-	-	-	-
Controls (24)	28	+	+	+	+
	30	+	+	+	+
	36	*	+	+	+
	38	-	-	-	-
	40	-	+	-	-
	41	+	+	+	+
	42	+	+	+	+
	46	+	-	+	-
	55	+	+	+	+
	56	+	+	+	-
	58	-	-	-	-
	60	-	-	-	+
	61	+	+	+	-
	64	+	+	+	+
	65	+	+	+	+
	71	+	-	+	+
	75	+	+	+	+
	77	+	+	+	+
	78	+	+	+	+
	79	+	+	+	+
	80	+	+	+	+
	81	+	+	+	+
	86	+	-	+	+
	94	+	-	+	+

(+) = positive
(-) = negative
(*)=missing tissue

Individual Lung Inflammation Results

Group	Animal ID	Lung Inflammation Result
Vaccinates (24)	22	-
	23	-
	26	-
	29	-
	31	-
	32	-
	34	-
	39	+
	43	-
	44	-
	45	-
	47	-
	51	+
	53	+
	57	-
	62	-
	67	-
	69	-
	72	-
	74	-
	82	-
	87	-
	88	-
	95	-
Controls (24)	28	+
	30	+
	36	+
	38	-
	40	-
	41	+
	42	+
	46	-
	55	+
	56	+
	58	-
	60	+
	61	-
	64	+
	65	+
	71	+
	75	+
	77	+
	78	+
	79	+
	80	+
	81	+
	86	-
	94	+

(+) = positive
(-) = negative

Individual Lung IHC Results

Group	Animal ID	Lung IHC Result
Vaccinates (24)	22	-
	23	-
	26	-
	29	-
	31	-
	32	-
	34	-
	39	-
	43	-
	44	-
	45	-
	47	-
	51	-
	53	-
	57	-
	62	-
	67	-
	69	-
	72	-
	74	-
	82	-
	87	-
	88	-
	95	-
Controls (24)	28	+
	30	+
	36	+
	38	-
	40	-
	41	+
	42	+
	46	+
	55	+
	56	-
	58	-
	60	+
	61	-
	64	-
	65	+
	71	-
	75	+
	77	+
	78	+
	79	+
	80	-
	81	+
	86	-
	94	-

(+) = positive
(-) = negative

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Porcine Circovirus Vaccine, Type 2, Killed Baculovirus Vector</td></tr>
<tr><td>Study Purpose</td><td>Demonstration of 4 months duration of immunity</td></tr>
<tr><td>Product Administration</td><td>Single intramuscular administration of vaccine. ORF2 gene of strain PCV2a.</td></tr>
<tr><td>Study Animals</td><td>Caesarian-derived colostrum deprived pigs vaccinated at 19 – 23 days of age and randomly divided into 24 vaccinates and 24 controls</td></tr>
<tr><td>Challenge Description</td><td>All pigs were challenged 122 days (4months) following vaccination with Porcine Circovirus, Type 2a challenge virus.</td></tr>
<tr><td>Interval observed after challenge</td><td>Lymphoid tissues were examined 25 days after challenge.</td></tr>
<tr><td>Results</td><td>Summary of Efficacy Results
<table>
<tr><th>Group & Treatment</th><th>Lymphoid Depletion +/total (%)</th><th>Lymphoid Inflammation +/total (%)</th><th>Lymphoid IHC +/total (%)</th></tr>
<tr><td>Group # 1 – PCV2 Vaccine</td><td>0/24 (0%)</td><td>0/24 (0%)</td><td>0/24 (0%)</td></tr>
<tr><td>Group # 2 - Control Group</td><td>13/24 (54.2%)</td><td>20/24 (83.3%)</td><td>20/24 (83.3%)</td></tr>
</table>
Observations of Lymphoid Tissue by Parameter and Tissue:
IHC = Immunohistochemistry
MLN = Mesenteric Lymph Node
ILN = Iliac Lymph Node
TBLN = Tracheobronchial Lymph Node

Lymphoid Depletion Criteria:
Negative (-) = Normal, no lymphoid depletion present
Positive (+) = Mild, moderate or severe depletion

Lymphoid Inflammation Criteria:
Negative (-) = Normal, no lymphoid inflammation
Positive (+) = Mild, moderate or severe histiocytic to granulomatous inflammation

Lymphoid IHC Criteria:
Negative (-) = Zero lymphoid cells observed with PCV2 antigen staining
Positive (+) = Lymphoid follicles have cells with PCV2 antigen staining

Raw data is presented on the following pages.</td></tr>
<tr><td></td><td></td></tr>
</table>

USDA Approval Date	April 17, 2007

Pig ID	Lymphoid Depletion				Lymphoid Inflammation				Lymphoid IHC			
	Tonsil	MLN	ILN	TBLN	Tonsil	MLN	ILM	TBLN	Tonsil	MLN	ILN	TBLN
	Group 1: PCV2 Vaccine											
5	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-	-	-	-	-
26	-	-	-	-	-	-	-	-	-	-	-	-
37	-	-	-	-	-	-	-	-	-	-	-	-
38	-	-	-	-	-	-	-	-	-	-	-	-
39	-	-	-	-	-	-	-	-	-	-	-	-
44	-	-	-	-	-	-	-	-	-	-	-	-
49	-	-	-	-	-	-	-	-	-	-	-	-
56	-	-	-	-	-	-	-	-	-	-	-	-
57	-	-	-	-	-	-	-	-	-	-	-	-
59	-	-	-	-	-	-	-	-	-	-	-	-
66	-	-	-	-	-	-	-	-	-	-	-	-
68	-	-	-	-	-	-	-	-	-	-	-	-
71	-	-	-	-	-	-	-	-	-	-	-	-
80	-	-	-	-	-	-	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-	-	-	-	-
89	-	-	-	-	-	-	-	-	-	-	-	-
99	-	-	-	-	-	-	-	-	-	-	-	-
109	-	-	-	-	-	-	-	-	-	-	-	-
113	-	-	-	-	-	-	-	-	-	-	-	-
114	-	-	-	-	-	-	-	-	-	-	-	-
119	-	-	-	-	-	-	-	-	-	-	-	-

Pig ID	Lymphoid Depletion				Lymphoid Inflammation				Lymphoid IHC			
	Tonsil	MLN	ILN	TBLN	Tonsil	MLN	ILN	TBLN	Tonsil	MLN	ILN	TBLN
	Group 2: Control Group											
1	+	-	+	+	+	+	+	+	+	+	+	+
7	+	-	+	+	+	+	+	+	+	+	+	+
9	-	-	+	-	+	+	+	-	+	-	+	-
13	-	-	-	-	+	-	+	-	-	-	+	-
28	-	-	-	+	+	-	+	+	-	-	-	+
29	-	-	-	-	+	-	-	-	+	-	-	-
31	-	+	+	+	+	+	+	+	+	+	+	+

35	+	+	-	+	+	+	+	+	+	+	+	+
40	+	-	+	+	+	+	+	+	+	+	+	+
41	-	-	-	-	+	+	+	+	+	-	+	+
46	-	-	-	-	-	-	-	-	-	-	-	-
51	+	-	-	-	+	+	-	+	+	+	+	+
60	-	-	+	-	+	+	+	-	+	+	+	-
69	-	-	+	-	+	+	+	-	+	+	+	-
74	-	-	-	+	+	+	-	+	+	-	-	+
75	-	-	-	-	-	-	-	-	-	-	-	-
92	+	-	-	-	+	-	+	+	+	-	-	+
93	-	-	-	-	+	-	-	+	+	-	-	-
98	-	-	-	-	-	-	-	-	-	-	-	-
100	-	-	-	-	+	-	-	-	+	-	-	-
104	-	+	-	-	+	+	+	-	+	+	+	-
110	-	-	-	-	+	-	-	-	+	-	-	-
116	-	-	-	-	+	-	-	-	+	-	-	-
117	-	-	-	-	-	-	-	-	-	-	-	-

Study Type	Efficacy
Pertaining to	Porcine Reproductive and Respiratory Syndrome Virus (PRRS)
Study Purpose	Demonstration of a Duration of Immunity of at least 4 months against the respiratory form of PRRS disease
Product Administration	Administration of one dose intramuscularly to 1 month old pigs
Study Animals	
Challenge Description	Challenged with PRRS 110 days after vaccination
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	March 11, 1994

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Porcine Reproductive and Respiratory Syndrome Virus (PRRSV)</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate efficacy of the PRRSV, respiratory form</td></tr>
<tr><td>Product Administration</td><td>Administration of one dose intramuscularly</td></tr>
<tr><td>Study Animals</td><td>Forty pigs, 22-24 days old, divided into 20 vaccinates and 20 controls</td></tr>
<tr><td>Challenge Description</td><td>Challenged with virulent PRRS virus 28 days after vaccination</td></tr>
<tr><td>Interval observed after challenge</td><td>Pigs were observed for 14 days after challenge, and tissues were examined for lung lesions</td></tr>
<tr><td>Results</td><td>The percentage of lung consolidation was evaluated.

Summary of Results:
<table><tr><th>Treatment Group</th><th>Minimum</th><th>25th Percentile</th><th>Median</th><th>75th Percentile</th><th>Maximum</th></tr><tr><td>Vaccinates</td><td>0</td><td>1</td><td>1</td><td>4</td><td>27</td></tr><tr><td>Controls</td><td>2</td><td>13</td><td>28</td><td>55</td><td>81</td></tr></table>
See tables on the following pages for data. The total percent lung lesion score was defined as the sum of the % lung pathology for the right and left apical, right and left cardiac, right and left diaphragmatic and intermediate lobes.</td></tr>
<tr><td>USDA Approval Date</td><td>June 18, 2009</td></tr>
</table>

Lung Lesions Percent Pathology for Vaccinates

ID#	R. Apical	R. Cardiac	R. Diaphragmatic	L. Apical	L. Cardiac	L. Diaphragmatic	Intermediate	Total
477	0.2	0.5	0	0	0.2	0	0	0.9
482	0	0.2	0	0.2	0	0	0	0.4
485	0	0.2	0	0	0	0	0	0.2
486	0	0.5	0	0	1	0	0	1.5
487	0.2	0.5	0	0.1	0.5	0	0	1.3
488	0.1	0.2	0	0	0.5	0	0.1	0.9
489	0.5	3	0	1	3	0	0.5	8
490	0.2	1	0.5	2	1	1.25	0.5	6.45
491	0	0	0	0	0	0	0	0
492	0	0.5	0	0	0.2	0	0	0.7
505	0	0.2	0	0	0.5	0	0.5	1.2
507	0	0.5	0	0	0.2	0.25	0	0.95
516	0.2	0.1	0.25	0	0	0.25	0	0.8
517	0	0.5	0	0	0.2	0	0	0.7
518	0	1	1.25	0	0.1	0	0.5	2.85
524	0	0.5	0.5	0	0.2	0	0.2	1.4
525	0.2	1.5	0	5	8	12.5	0.2	27.4
526	4	5	2.5	3	3	5	3	25.5
528	0.5	5	2.5	0.2	0.5	0.5	0.5	9.7
529	0	0	0	0	0	0	0	0

Lung Lesions Percent Pathology for Controls

ID#	R. Apical	R. Cardiac	R. Diaphragmatic	L. Apical	L. Cardiac	L. Diaphragmatic	Intermediate	Total
476	0	3	1.25	0	0.5	0.5	1	6.25
478	7	8	15	9	9	15	7	70
483	8	9	17.5	8	9	20	8	79.5
484	9	9	7.5	3	6	5	5	44.5
493	2	5	1.25	1	2	1.25	1	13.5
494	3	6	5	2	6	7.5	5	34.5
495	1	5	0.5	0	1	2.5	5	15
497	0.5	7	1.25	2	3	1.25	6	21
499	7	7	7.5	5	8	12.5	7	54
500	3	6	15	8	8	12.5	6	58.5
503	2.5	6	1.25	3	6	2.5	8	29.25
508	0.5	5	1.25	9.5	10	2.5	0.5	29.25
509	8	8	22.5	9	8	17.5	8	81
513	2	6	2.5	1	3	2.5	5	22
514	0.2	1	0.5	0	2	0.25	0.5	4.45
515	4	8	1.25	5	7	1.25	1	27.5
519	0	0.2	0.5	0.1	0.2	0.5	0.5	2
520	0.2	1	0.5	0.2	0.5	0.5	1.5	4.4
521	6	8	12.5	5	8	15	5	59.5
522	0.2	1.5	0.5	0.2	1.5	0.25	0	4.15

<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 of the product under field conditions</td></tr>
<tr><td>Product Administration</td><td>Adminstration of one dose intramuscularly</td></tr>
<tr><td>Study Animals</td><td>1349 pigs, 18-25 days of age, at three different geographical locations divided into 672 vaccinates and 677 controls</td></tr>
<tr><td>Challenge Description</td><td>Not Applicable</td></tr>
<tr><td>Interval observed after challenge</td><td>Animals were observed for at least 2 hours after vaccination and then daily for 14 days after vaccination</td></tr>
<tr><td>Results</td><td>Results Summary:

No injection site reactions were observed.

The number of pigs by site with specific clinical observations post-vaccination are presented in the following table:

<table>
<tr><th>Clinical Observation</th><th colspan="2">Site 1</th><th colspan="2">Site 2</th><th colspan="2">Site 3</th></tr>
<tr><th></th><th>Vac.</th><th>Cont.</th><th>Vac.</th><th>Cont.</th><th>Vac.</th><th>Cont.</th></tr>
<tr><td>Cough</td><td>1</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Gaunt</td><td>4</td><td>1</td><td>0</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>Lacking vigor / growth</td><td>1</td><td>2</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Red anus</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Red ears</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Swollen joint/foot /leg</td><td>0</td><td>1</td><td>2</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>Inflamed umbilicus</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Greasy pig disease</td><td>0</td><td>0</td><td>0</td><td>0</td><td>8</td><td>14</td></tr>
<tr><td>Pneumonia</td><td>0</td><td>0</td><td>0</td><td>0</td><td>3</td><td>0</td></tr>
<tr><td>Scours</td><td>0</td><td>0</td><td>0</td><td>0</td><td>18</td><td>15</td></tr>
<tr><td>Streptococcus infection</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Lame</td><td>0</td><td>0</td><td>1</td><td>0</td><td>2</td><td>5</td></tr>
</table>
Additional observations were affirmed by licensee to be due to causes other than vaccination.
Vac. is vaccinate; Cont. is control.

The total number of animals exhibiting clinical signs for at least one day at all three sites are as follows:
<table>
<tr><th></th><th>Clinical Signs Present</th><th>Clinical Signs Absent</th><th>Percent with Clincal Signs</th></tr>
<tr><td>Vaccinates</td><td>48</td><td>624</td><td>7%</td></tr>
<tr><td>Controls</td><td>43</td><td>634</td><td>6%</td></tr>
</table>
</td></tr>
<tr><td>USDA Approval Date</td><td>June 18, 2009</td></tr>
</table>