Summary of Studies Supporting USDA Product Licensure

Establishment Name	Diamond Animal Health, Inc.
USDA Vet Biologics Establishment Number	213
Product Code	1551.02
True Name	Escherichia Coli Vaccine, Avirulent Live Culture
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	Coliprotec F4 - Prevtec Microbia, Inc.
Date of Compilation Summary	December 28, 2017

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 2007

Study Type	Efficacy
Pertaining to	K88 (F4)-positive enterotoxigenic *Escherichia coli* (*E. coli*)
Study Purpose	Demonstrate efficacy against Post-weaning diarrhea (PWD).
Product Administration	One dose administered orally.
Study Animals	20 vaccinated and 20 control commercial crossbred pigs, 18 days at vaccination, castrated male andfemale. 5 vaccinated and 8 non-vaccinated were F4-*E. coli* susceptible pigs. Pigs from farms without PWD episodes in the last 6 months.
Challenge Description	F4-positive enterotoxigenic *E. coli* administered 7 days after vaccination.
Interval observed after challenge	Pigs observed twice daily for 3 days after challenge
Results	An animal was considered having diarrhea if the pig showed diarrhea (score ≥2 on a scoring system ranging from (0) normal to (4) totally liquid) at least for 1 day post-challenge. Results of F4-*E. coli* susceptible pigs are presented. Results Frequency of pigs with diarrhea at any day post-challenge: Controls: 16/20 (80%) Vaccinates: 8/20 (40%) Raw data shown on next page.
USDA Approval Date	February 18, 2015

Study 2007. Table below presents fecal consistency scores and presence/absence of diarrhea at any day after challenge.

Control							
Animal ID	RF4 status	Fecal Score[1]					Diarrhea[2]
		DPC 1	DPC 2	DPC 3			
204	-	0	2	0			Yes
208	-	0	0	0			No
209	-	0	0	0			No
221	-	0	0	3			Yes
229	-	0	1	3			Yes
238	-	4	2	1			Yes
243	-	2	0	3			Yes
245	-	2	0	2			Yes
247	-	0	4	0			Yes
421	-	0	0	0			No
448	-	0	0	3			Yes
234	NA	0	0	3			Yes
201	+	2	0	0			Yes
217	+	3	4	NC			Yes
222	+	0	0	2			Yes
233	+	0	2	3			Yes
239	+	0	0	NC			No
240	+	3	4	2			Yes
244	+	2	0	3			Yes
447	+	0	1	4			Yes

Vaccinate							
Animal ID	RF4 status	Fecal Score[1]					Diarrhea[2]
		DPC 1	DPC 2	DPC 3			
205	-	0	0	NA			No
206	-	2	1	NA			Yes
213	-	0	0	0			No
216	-	0	0	0			No
220	-	0	1	NC			No
223	-	0	1	1			No
224	-	0	0	2			Yes
236	-	1	0	1			No
237	-	0	0	0			No
242	-	0	0	3			Yes
248	-	0	0	0			No
250	-	3	0	2			Yes
423	-	0	3	2			Yes
449	-	0	0	0			No
218	NA	0	0	0			No
202	+	0	0	2			Yes
212	+	NC	2	2			Yes
214	+	0	0	0			No
226	+	0	0	3			Yes
230	+	0	0	0			No

[1] The fecal consistency was evaluated on a continuous scale with 5 levels: (0) normal, (1) pasty, (2) presence of liquid but more solid particles than liquid, (3) presence of more liquid than solid particles, and (4) totally liquid.

[2] An animal was considered having diarrhea if the pig showed score ≥2 for at least one day post-challenge.

DPC: Day post-challenge

NC: No content in the intestinal segment

NA: Not Available

Study PREV-08-004

Study Type	Efficacy
Pertaining to	K88 (F4)-positive enterotoxigenic *Escherichia coli* (*E. coli*)
Study Purpose	Demonstrate efficacy against Post-weaning diarrhea (PWD).
Product Administration	One dose administered orally
Study Animals	18 vaccinated and 20 control commercial crossbred F4-*E. coli* susceptible pigs, 18 days at vaccination, castrated male and female. Pigs from farms without PWD episodes in the last 6 months.
Challenge Description	F4-positive enterotoxigenic *E. coli* administered 7 days after vaccination.
Interval observed after challenge	Pigs observed twice daily for 3 days after challenge
Results	An animal was considered having diarrhea if the pig showed diarrhea (score ≥2 on a scoring system ranging from (0) normal to (4) watery diarrhea) at least for 1 day post-challenge. <u>Results</u> Frequency of pigs with diarrhea at any day post-challenge: Controls: 16/20 (80%) Vaccinates: 7/18 (39%) Raw data shown on next page.
USDA Approval Date	February 18, 2015

Study PREV-08-004. Table below presents fecal consistency scores and presence/absence of diarrhea at any day after challenge.

Control						
Animal ID	Fecal Score[1]					Diarrhea[2]
	DPC 1	DPC 2	DPC 3			
42	3	2	NA			Yes
44	2	3	3			Yes
48	2	2	3			Yes
50	1	0	0			No
75	3	2	4			Yes
79	2	3	3			Yes
80	3	3	1			Yes
81	3	3	0			Yes
82	1	1	2			Yes
85	1	3	1			Yes
86	0	1	0			No
88	1	1	0			No
90	1	3	0			Yes
91	1	1	3			Yes
92	2	3	3			Yes
94	1	2	1			Yes
96	1	0	2			Yes
97	1	1	1			No
98	2	2	2			Yes
Blue	0	2	2			Yes

Vaccinate						
Animal ID	Fecal Score[1]					Diarrhea[2]
	DPC 1	DPC 2	DPC 3			
46	1	2	0			Yes
47	1	2	0			Yes
49	2	0	0			Yes
71	2	1	0			Yes
72	1	1	0			No
73	1	1	0			No
74	0	2	0			Yes
76	0	1	0			No
77	1	1	0			No
78	0	2	0			Yes
83	0	0	1			No
84	0	0	0			No
87	0	0	0			No
89	0	1	0			No
93	1	3	0			Yes
95	0	1	0			No
99	0	0	0			No
100	0	0	0			No

[1] Fecal consistency score: 0 for normal; 1 for pasty; 2 for presence of liquid but more solid particles than liquid (mild diarrhea); 3 for presence of more liquid than solid particles (moderate diarrhea); and 4 for totally liquid (severe diarrhea).

[2] An animal was considered having diarrhea if the pig showed score ≥2 for at least one day post-challenge.

DPC: Day post-challenge

NA: Not Available

Study PEX-AR-000-1

Study Type	Efficacy
Pertaining to	K88 (F4)-positive enterotoxigenic *Escherichia coli* (*E. coli*)
Study Purpose	Demonstrate efficacy against post-weaning diarrhea (PWD).
Product	One dose administered orally.
Study Animals	18 vaccinated and 18 control commercial crossbred F4-*E. coli* susceptible pigs, 16-17 days at vaccination, castrated male and female. Pigs from farms without PWD episodes in the last 6 months
Challenge Description	F4-positive enterotoxigenic *E. coli* administered 7 days after vaccination.
Interval observed after	Pigs observed for 3 days after challenge.
Results	An animal was considered having diarrhea if the pig showed diarrhea (score ≥2 on a scoring system ranging from (0) normal to (4) totally liquid) at least for 1 day post-challenge. Results Frequency of pigs with diarrhea at any day post-challenge: Controls: 7/18 (39%) Vaccinates: 2/18 (11%) Raw data shown on next page.
USDA Approval	February 18, 2015

Study PEX-AR-000-1. Table below presents fecal consistency scores and presence/absence of diarrhea at any day after challenge.

Control					
Animal ID	Fecal Score[1]			Diarrhea[2]	
	DPC 1	DPC 2	DPC 3		
45	0	2	2	Yes	
46	0	0	0	No	
53	0	0	0	No	
54	2	0	0	Yes	
83	0	0	2	Yes	
90	0	0	0	No	
129	4	0	4	Yes	
137	0	0	0	No	
154	0	0	0	No	
159	0	0	0	No	
200	0	0	1	No	
202	0	0	0	No	
208	0	0	0	No	
216	0	0	0	No	
263	0	0	0	No	
271	3	4	3	Yes	
276	0	0	2	Yes	
277	2	2	1	Yes	

Vaccinate					
Animal ID	Fecal Score[1]			Diarrhea[2]	
	DPC 1	DPC 2	DPC 3		
41	0	0	0	No	
44	0	0	0	No	
49	0	0	0	No	
55	0	1	1	No	
92	0	1	1	No	
93	0	0	0	No	
135	0	0	1	No	
138	0	0	0	No	
161	0	1	1	No	
163	0	1	0	No	
199	0	1	0	No	
207	2	2	2	Yes	
210	0	0	0	No	
213	0	0	0	No	
265	1	2	1	Yes	
269	0	0	0	No	
273	0	0	0	No	
275	0	0	0	No	

[1] The fecal consistency was evaluated on an ordinal scale with 5 levels: (0) normal, (1) pasty, (2) presence of liquid but more solid particles than liquid, (3) presence of more liquid than solid particles, and (4) totally liquid.

[2] An animal was considered having diarrhea if the pig showed score ≥2 for at least one day post-challenge.

DPC: Day post-challenge

NA: Not Available

Study SRP-RA-0004

Study Type	Efficacy
Pertaining to	K88 (F4)-positive enterotoxigenic *Escherichia coli* (*E. coli*)
Study Purpose	Demonstrate efficacy against Post-weaning diarrhea (PWD).
Product	One dose administered orally.
Study Animals	16 vaccinated and 16 control commercial crossbred F4-*E. coli* susceptible pigs, 18-20 days at vaccination, castrated male and female. Pigs from farms without PWD episodes in the last 6 months.
Challenge Description	F4-positive enterotoxigenic *E. coli* administered 7 days after vaccination. Control and vaccinated pigs were commingled in a single pen for the challenge and evaluation of the efficacy criteria.
Interval observed after challenge	Pigs observed for 9 days after challenge.
Results	An animal was considered having diarrhea if the pig showed diarrhea (score ≥2 on a scoring system ranging from (0) normal to (4) totally liquid, watery, projectile) at least for 1 day post-challenge. Results Frequency of pigs with diarrhea at any day post-challenge: Controls: 7/15 (75%) Vaccinates: 2/16 (12%) Raw data shown on next page.
USDA Approval Date	February 18, 2015

Study SRP-RA-0004. Table below presents fecal consistency scores and presence/absence of diarrhea at any day after challenge.

Control												
Animal ID	**Fecal Score[1]**											**Diarrhea[2]**
	DPC 1	**DPC 2**	**DPC 3**	**DPC 4**	**DPC 5**	**DPC 6**	**DPC 7**	**DPC 8**	**DPC 9**			
8	0	3	3	2	2	3	3	2	1			Yes
10	0	D	D	D	D	D	D	D	D			No
35	1	2	2	2	0	0	0	0	0			Yes
36	0	4	2	1	0	0	0	0	0			Yes
74	0	0	0	0	0	0	0	0	0			No
75	3	4	D	D	D	D	D	D	D			Yes
84	1	2	2	1	0	0	0	0	2			Yes
88	3	0	3	0	2	0	0	0	0			Yes
97	2	0	0	0	0	1	0	0	0			Yes
98	1	1	1	0	1	1	0	0	2			Yes
102	2	1	3	3	2	0	0	0	0			Yes
105	1	3	0	1	0	0	0	D	D			Yes
151	0	1	0	0	0	1	0	0	0			No
159	0	2	3	3	0	0	0	0	0			Yes
161	0	0	0	2	0	0	0	1	0			Yes
165	0	0	1	1	0	0	0	0	0			No

[1] The fecal consistency was evaluated on a continuous scale with 5 levels: (0) normal, (1) soft moulded pasty feces, (2) moist cow-dung appearance, (3) presence of liquid mixed with solid particles, and (4) totally liquid, watery, projectile.

[2] An animal was considered having diarrhea if the pig showed score ≥2 for at least one day post-challenge.

D: Dead

DPC: Day post-challenge

NA: Not Available

Study SRP-RA-0004. Table below presents fecal consistency scores and presence/absence of diarrhea at any day after challenge.

Vaccinates												
Animal ID	Fecal Score[1]											Diarrhea[2]
	DPC 1	DPC 2	DPC 3	DPC 4	DPC 5	DPC 6	DPC 7	DPC 8	DPC 9			
1	0	0	0	0	0	0	0	0	0			No
5	0	0	1	1	0	0	0	0	0			No
37	1	0	0	0	0	0	0	0	0			No
39	1	0	0	0	1	0	0	0	0			No
76	0	0	0	0	0	0	0	0	1			No
77	0	0	0	0	0	0	0	0	0			No
86	0	0	0	0	0	0	0	0	0			No
90	0	0	2	0	1	0	0	2	0			Yes
96	1	0	0	0	1	0	0	0	1			No
100	0	0	0	0	0	0	0	0	0			No
106	0	0	2	0	0	1	1	3	2			Yes
107	0	0	0	0	0	0	0	0	0			No
152	0	0	0	0	0	0	0	1	0			No
158	0	0	1	0	0	0	0	0	0			No
160	0	2	0	3	2	1	1	2	0			Yes
167	1	0	0	2	0	1	2	0	0			Yes

[1] The fecal consistency was evaluated on a continuous scale with 5 levels: (0) normal, (1) soft moulded pasty feces, (2) moist cow-dung appearance, (3) presence of liquid mixed with solid particles, and (4) totally liquid, watery, projectile.
[2] An animal was considered having diarrhea if the pig showed score ≥2 for at least one day post-challenge.
DPC: Day post-challenge
NA: Not Available

<table>
<tr><td>Study Type</td><td>Safety</td></tr>
<tr><td>Pertaining to</td><td>ALL</td></tr>
<tr><td>Study Purpose</td><td>Demonstrate safety of product under field conditions.</td></tr>
<tr><td>Product Administration</td><td>One oral dose administered by either individual administration (drench) or through the drinking water (bowl or water line).</td></tr>
<tr><td>Study Animals</td><td>• 1,851 pigs from the three sites, ranging in age from 16-37 days at vaccination. Site 1: 611 pigs. Site 2: 640 pigs. Site 3: 600 pigs.
• 1/3 of the animals were of minimum age recommended for product administration.
• 1/2 of each site were vaccinated individually (drench) and 1/2 of each site through the drinking water (bowl or water line).</td></tr>
<tr><td>Challenge Description</td><td>Not applicable (N/A).</td></tr>
<tr><td>Interval observed after treatment</td><td>• Animals were observed daily for 14 days after vaccination and observations were recorded four (4) hours after the vaccination and then at 1, 5, 10 and 14 days after the vaccination.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Adverse Event</th><th colspan="2">Total Number of Adverse Events</th></tr>
<tr><td></td><td>Individual administration (drench)</td><td>Drinking water</td></tr>
<tr><td>Anorexia</td><td>2</td><td>0</td></tr>
<tr><td>Decreased Appetite</td><td>1</td><td>0</td></tr>
<tr><td>Loss of condition</td><td>1</td><td>2</td></tr>
<tr><td>Lameness</td><td>2</td><td>8</td></tr>
<tr><td>Suspected Fever</td><td>1</td><td>0</td></tr>
<tr><td>Unable to Walk/Depression</td><td>0</td><td>1</td></tr>
<tr><td>Deaths</td><td>2</td><td>4</td></tr>
<tr><td>Total Number of Adverse Event</td><td>9 (all AE’s determined not due to vaccination by investigating veterinarians or trained observers)</td><td>15 (all AE’s determined not due to vaccination by investigating veterinarians or trained observers)</td></tr>
<tr><td>No Adverse Event</td><td>912</td><td>915</td></tr>
</table>
Note: Rare instances of sneezing was observed in 3 pens (total 153 pigs) within 4 hours post-vaccination, all recovered without treatment, which the investigator determined may have been vaccine related. This observation was not recorded on an individual animal basis.
</td></tr>
<tr><td>USDA Approval Date</td><td>May 25, 2017</td></tr>
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