Summary of Studies Supporting USDA Product Licensure

Establishment Name	Zoetis Inc.
USDA Vet Biologics Establishment Number	190
Product Code	2799.20
True Name	Lawsonia Intracellularis Bacterin
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	Lawsotek Ileitis - No distributor specified
Date of Compilation Summary	July 29, 2022

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>Lawsonia intracellularis</td></tr>
<tr><td>Study Purpose</td><td>Demonstrate efficacy against Lawsonia intracellularis</td></tr>
<tr><td>Product Administration</td><td>One dose administered intramuscularly</td></tr>
<tr><td>Study Animals</td><td>40 vaccinated and 40 control piglets, three weeks of age</td></tr>
<tr><td>Challenge Description</td><td>Lawsonia intracellularis administered 21 days post-vaccination</td></tr>
<tr><td>Interval observed after challenge</td><td>20 vaccinates and 20 control animals were observed for 21 days after challenge. Tissues were evaluated 21 days after challenge for L. intracellularis disease (ileitis).
An additional 20 vaccinates and 20 control animals were observed for 51 days post-challenge to assess duration of fecal shedding.</td></tr>
<tr><td>Results</td><td><u>L. intracellularis disease (ileitis):</u>

L. intracellularis disease was defined as whether an animal had an intestinal lesion (gross or microscopic) score >1.

Controls: 17/20 (85%)
Vaccinates: 5/20 (25%)

<u>L. intracellularis colonization:</u>

L. intracellularis colonization was defined as whether an animal had and an intestinal infection (confirmed by immunohistochemistry) score >1.

Controls: 17/20 (85%)
Vaccinates: 6/20 (30%)

<u>Duration of fecal shedding:</u>

Duration of fecal shedding (days) was assessed in 20 vaccinated animals and 20 control animals. Samples were collected three times weekly post-challenge. Animals followed for duration of fecal shedding were considered affected if they had a qPCR value ≥ limit of detection for Lawsonia in fecal swabs.

<table>
<tr><th></th><th>Minimum</th><th>25th Percentile</th><th>Median</th><th>75th Percentile</th><th>Maximum</th></tr>
<tr><td>Controls</td><td>21</td><td>30</td><td>31</td><td>40</td><td>50</td></tr>
<tr><td>Vaccinates</td><td>21</td><td>23</td><td>26</td><td>28</td><td>42</td></tr>
</table>

See individual data attached.</td></tr>
<tr><td>USDA Approval Date</td><td>August 12, 2019</td></tr>
</table>

Summary of *L. intracellularis* disease (ileitis) and colonization by Treatment and Animal

Controls

Animal	IHC Score	Gross Lesion Score	Microscopic Lesion Score	Ileitis
100	2	0	2	Yes
106	2	0	2	Yes
127	3	1	3	Yes
128	3	1	3	Yes
131	3	3	3	Yes
136	3	2	3	Yes
139	3	2	3	Yes
145	3	0	3	Yes
153	2	1	2	Yes
169	1	1	1	No
173	1	0	0	No
183	3	1	3	Yes
190	3	1	3	Yes
198	2	0	2	Yes
32	3	0	3	Yes
35	2	1	2	Yes
46	3	1	3	Yes
84	3	0	3	Yes
93	3	0	3	Yes
96	1	0	1	No

Vaccinates

Animal	IHC Score	Gross Lesion Score	Microscopic Lesion Score	Ileitis
121	0	0	0	No
125	2	1	2	Yes
135	0	0	0	No
137	2	0	2	Yes
140	0	0	0	No
156	1	1	1	No
170	2	0	2	Yes
171	0	0	0	No
186	2	0	2	Yes
195	0	0	0	No
199	1	0	1	No
30	1	0	1	No
40	3	0	3	Yes
43	0	0	0	No
47	0	0	0	No
78	0	0	0	No
80	2	0	0	No
90	0	0	0	No
91	0	0	0	No
98	0	0	0	No

Scoring definitions

Colonization (Immunohistochemistry (IHC))
0 = 0%
1 = 1-25%
2 = 26-50%
3 = 51-75%
4 = 76-100%

Microscopic lesions
0 = No lesions
1 = Focal crypt hyperplasia and dilation. Reduced number of goblet cells.
2 = Multifocal crypt hyperplasia and dilation. Reduced number of goblet cells.
3 = Diffuse crypt hyperplasia and dilation. Reduced number of goblet cells.

Gross lesions

0 = No gross lesions.
1 = Mild edema and hyperemia of the mucosa or serosa.
2 = Edema and hyperemia, and reticulated serosa and/or mucosa (thickening).
3 = Edema and/or hyperemia, and/or reticulated serosa and/or mucosa with gross thickening of the mucosa with necrosis.

Summary of Fecal Shedding by Treatment and Animal

Controls

Animal	Day 0	Day 21	Day 23	Day 25	Day 28	Day 30	Day 32	Day 35	Day 37	Day 39	Day 42	Day 44	Day 46	Day 49	Day 51	Day 53	Day 56	Day 58	Day 60	Day 63	Day 65	Day 67	Day 70	Day 72
102	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-
124	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-
132	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
141	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	-	-	-
142	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
149	-	-	-	-	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
154	-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-
172	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-			-	-	-	-	-
178	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			-	-	-	-	-
180	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	-	-
184	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-
197	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-
26	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	-	-	-
48	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-
49	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-
85	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-
86	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-
88	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
92	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-
99	-	-	+	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-

Vaccinates

Animal	Day 0	Day 21	Day 23	Day 25	Day 28	Day 30	Day 32	Day 35	Day 37	Day 39	Day 42	Day 44	Day 46	Day 49	Day 51	Day 53	Day 56	Day 58	Day 60	Day 63	Day 65	Day 67	Day 70	Day 72
101	-	-	+	-	+	+	+	+	+	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-
103	-	-	-	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
120	-	-	+	+	+	+	+	-	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-
122	-	-	-	-	-	+	+	-	+	+	+	+	+	+										
130	-	-	+	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
138	-	-	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	-	-	-	-	-
143	-	-	-	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-
144	-	-	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	+	-	-	-	-
150	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
152	-	-	+	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-
176	-	-	+	+	+	+	+	+	-	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-
181	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
185	-	-	+	-	-	-	+	+	+	+	+	+	+	+	-	-	-	-	-	+	-	-	-	-
191	-	-	+	+	-	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
192	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-
28	-	-	+	+	-	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-
33	-	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
44	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
82	-	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
97	-	-	-	+	+	+	+	+	+	+	-	+	+	-	-	-	-	-	-	-	-	-	-	-

Study Type	Efficacy
Pertaining to	*Lawsonia intracellularis*
Study Purpose	Demonstrate duration of immunity of at least 23 weeks against *Lawsonia intracellularis*
Product Administration	One dose administered intramuscularly
Study Animals	30 vaccinated and 30 control piglets, three weeks of age
Challenge Description	*Lawsonia intracellularis* administered 23-weeks post-vaccination
Interval observed after challenge	Animals were observed for 21 days after challenge. Tissues were evaluated 21 days after challenge and evaluated for *L. intracellularis* disease (ileitis).
Results	<u>*L. intracellularis* disease (ileitis):</u> *L. intracellularis* disease was defined as whether an animal had an intestinal lesion (microscopic or gross) score ≥1 and an intestinal infection (IHC) score ≥1. Controls: 10/26 (38.5%)* Vaccinates: 2/28 (7.1%)* * Two vaccinated piglets and four control piglets were removed prior to the end of study due to causes unrelated to vaccination. See individual data attached.
USDA Approval Date	February 11, 2021

Summary of *L. intracellularis* disease (ileitis) by Treatment and Animal

Controls

Animal	IHC Score	Gross Lesion Score	Microscopic Lesion Score	Ileitis
206	1	0	1	Yes
208	0	0	0	No
218	0	0	0	No
221	0	0	0	No
222	0	0	0	No
224	0	0	0	No
228	0	0	0	No
229	0	0	0	No
238	0	0	0	No
240	3	1	3	Yes
242	0	0	0	No
243	0	0	0	No
245	0	0	0	No
248	0	0	0	No
250	1	2	1	Yes
256	0	1	0	No
258	1	1	1	Yes
259	1	1	1	Yes
266	0	0	0	No
267	1	1	1	Yes
275	1	2	0	Yes
282	0	0	0	No
285	2	1	2	Yes
289	1	1	0	Yes
290	0	0	0	No
298	3	0	3	Yes

Vaccinates

Animal	IHC Score	Gross Lesion Score	Microscopic Lesion Score	Ileitis
204	0	1	0	No
205	0	1	0	No
207	0	0	0	No
209	0	0	0	No
213	0	0	0	No
220	0	0	0	No
223	3	0	3	Yes
225	0	0	0	No
226	0	0	0	No
227	0	0	0	No
234	0	0	0	No
235	0	1	0	No
236	0	0	0	No
239	0	0	0	No
246	0	0	0	No
249	0	0	0	No
253	0	0	0	No
254	0	0	0	No
257	1	0	1	Yes
268	0	0	0	No
269	0	0	0	No
274	0	0	0	No
283	0	0	0	No
284	0	0	0	No
292	0	1	0	No
293	0	0	0	No
294	0	0	0	No
299	0	0	0	No

Scoring definitions

Colonization (Immunohistochemistry (IHC))
0 = 0%
1 = 1-25%
2 = 26-50%
3 = 51-75%
4 = 76-100%

Microscopic lesions
0 = No lesions
1 = Focal crypt hyperplasia and dilation. Reduced number of goblet cells.
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Gross lesions

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1 = Mild edema and hyperemia of the mucosa or serosa.
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<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 the product under field conditions</td></tr>
<tr><td>Product Administration</td><td>One dose administered intramuscularly</td></tr>
<tr><td>Study Animals</td><td>A total of 750 pigs (600 vaccinates and 150 controls), 18-22 days of age, enrolled at three locations</td></tr>
<tr><td>Challenge Description</td><td>Not applicable</td></tr>
<tr><td>Interval observed after challenge</td><td>Animals were observed approximately four hours post-vaccination and monitored daily for 21 days after vaccination. Injection sites were observed on day 1, any injection site reaction documented on day 1 was assessed on day 3 and then once per week until resolution.</td></tr>
<tr><td>Results</td><td>Clinical Signs*

<table>
<tr><th></th><th>Controls</th><th>Vaccinates</th></tr>
<tr><td>Normal</td><td>141</td><td>570</td></tr>
<tr><td>Cough</td><td>0</td><td>6</td></tr>
<tr><td>Cyanosis</td><td>0</td><td>1</td></tr>
<tr><td>Diarrhea</td><td>3</td><td>12</td></tr>
<tr><td>Emesis (multiple)</td><td>0</td><td>1</td></tr>
<tr><td>Found dead**</td><td>3</td><td>5</td></tr>
<tr><td>Unthrifty</td><td>4</td><td>16</td></tr>
<tr><td>Swollen limb</td><td>1</td><td>0</td></tr>
</table>
*Pigs observed as abnormal may exhibit more than one clinical sign.
**Deaths were unrelated to product use.

Injection Site Reactions

<table>
<tr><th></th><th>Score 0
(normal)</th><th>Score 1
(≤ 1.5 cm)</th><th>Score 2
(≥ 1.6 cm and ≤ 3 cm)</th><th>Score 3
(> 3 cm)</th></tr>
<tr><td>Controls</td><td>150</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Vaccinates</td><td>599</td><td>1</td><td>0</td><td>0</td></tr>
</table>
Injection site swelling resolved within 3 days.</td></tr>
<tr><td>USDA Approval Date</td><td>January 24, 2022</td></tr>
</table>