Summary of Studies Supporting USDA Product Licensure

Establishment Name	Zoetis Inc.
USDA Vet Biologics Establishment Number	190
Product Code	48R5.20
True Name	Encephalomyelitis-Rabies-West Nile Virus Vaccine, Eastern & Western & Venezuelan, Killed Virus, Tetanus Toxoid
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	CORE EQ INNOVATOR + V - No distributor specified
Date of Compilation Summary	January 10, 2023

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	Tetanus Toxoid
Study Purpose	Efficacy against *Clostridum tetani* in horses
Product Administration	
Study Animals	Guinea pigs
Challenge Description	NA
Interval observed after challenge	NA
Results	Efficacy requirements were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance per 9 CFR 113.114.
USDA Approval Date	04/19/1984

Study Type	Efficacy
Pertaining to	Eastern Equine Encephalomyelitis Virus (EEE)
Study Purpose	Efficacy against EEE
Product Administration	Each product serial is tested in accordance with 9 CFR 113.207(b)(2) requirements
Study Animals	Guinea pigs
Challenge Description	NA
Interval observed after challenge	NA
Results	Efficacy requirements were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance per 9 CFR 113.207(b)(2).
USDA Approval Date	NA

Study Type	Efficacy
Pertaining to	Venezuelan Equine Encephalomyelitis Virus (VEE)
Study Purpose	Efficacy against VEE
Product Administration	Each product serial is tested in accordance with 9 CFR 113.207(b)(2) requirements
Study Animals	Guinea pigs
Challenge Description	NA
Interval observed after challenge	NA
Results	Efficacy requirements were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance per 9 CFR 113.207(b)(2).
USDA Approval Date	NA

Study Type	Efficacy
Pertaining to	Western Equine Encephalomyelitis Virus (WEE)
Study Purpose	Efficacy against WEE
Product Administration	Each product serial is tested in accordance with 9 CFR 113.207(b)(2) requirements
Study Animals	Guinea pigs
Challenge Description	NA
Interval observed after challenge	NA
Results	Efficacy requirements were evaluated by USDA-APHIS prior to product licensure and met regulatory standards for acceptance per 9 CFR 113.207(b)(2).
USDA Approval Date	NA

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>Rabies Virus (RV)</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate effectiveness and duration of immunity against rabies disease</td></tr>
<tr><td>Product Administration</td><td>Control Group: A single dose of a commercially licensed serial (LVP), West Nile Virus Vaccine, Eastern & Western & Venezuelan, Killed Virus, Tetanus Toxoid, West Nile Innovator® VEWT.
Vaccinate Group: A single dose of the experimental vaccine (IVP) was administered followed by a second vaccination 3-4 weeks later with the LVP.
All vaccines were administered by the intramuscular route.</td></tr>
<tr><td>Study Animals</td><td>Thirty-nine 3 month old crossbred horses that were rabies sero-negative</td></tr>
<tr><td>Challenge Description</td><td>Challenged 14 months after initial vaccination with RV</td></tr>
<tr><td>Interval observed after challenge</td><td>Horses were observed for 90 days post-challenge for clinical signs.</td></tr>
<tr><td>Results</td><td>An animal was classified as affected if it had any clinical sign post challenge and/or was positive by direct flouresent antibody (dFA) in the brain stem tissue. Clinical signs included: depression, nervousness, restless, walking in circles, hyperresponse (auditory and visual stimuli), disorientation, seizures, salivation, labored breathing, death and other clinical signs.

<u>Table 1. Number of Animals Affected by Rabies Virus</u>

<table>
<tr><th rowspan="2">Treatment</th><th colspan="4">Disease</th><th rowspan="2">Total Animals Challenged Per Group</th></tr>
<tr><th colspan="2">YES</th><th colspan="2">NO</th></tr>
<tr><th></th><th>No. of Animals</th><th>%</th><th>No. of Animals</th><th>%</th><th></th></tr>
<tr><td>Controls</td><td>4</td><td>80.0</td><td>1</td><td>20.0</td><td>5</td></tr>
<tr><td>Vaccinated Animals</td><td>2</td><td>7.4</td><td>25</td><td>92.6</td><td>27</td></tr>
</table>

The requirements of 9 CFR 113.209 were met.

The raw data is shown on the attached page.</td></tr>
<tr><td>USDA Approval Date</td><td>November 05, 2014</td></tr>
</table>

Individual Animal Data:

Treatment	Animal	At Least 1 Clinical Sign?	dFA[1] Result	Affected? [2]
Control	076 538 122	YES	Positive	YES
	076 880 039	YES	Positive	YES
	076 880 526	YES	Positive	YES
	076 881 102	YES	Positive	YES
	076 887 310	NO	Negative	NO
Vaccinated	076 513 039	NO	Negative	NO
	076 517 279	NO	Negative	NO
	076 519 794	NO	Negative	NO
	076 523 267	NO	Negative	NO
	076 523 775	NO	Negative	NO
	076 527 858	YES	Positive	YES
	076 539 080	NO	Negative	NO
	076 543 085	NO	Negative	NO
	076 549 351	NO	Negative	NO
	076 551 273	NO	Negative	NO
	076 555 803	NO	Negative	NO
	076 558 785	NO	Negative	NO
	076 560 848	NO	Negative	NO
	076 561 127	NO	Negative	NO
	076 872 322	NO	Negative	NO
	076 874 029	YES	Positive	YES
	076 877 314	NO	Negative	NO
	076 881 010	NO	Negative	NO
	076 881 514	NO	Negative	NO
	076 886 366	NO	Negative	NO
	077 001 331	NO	Negative	NO
	077 004 324	NO	Negative	NO
	077 008 099	NO	Negative	NO
	077 010 273	NO	Negative	NO
	077 012 045	NO	Negative	NO
	077 013 830	NO	Negative	NO
	077 014 833	NO	Negative	NO

(1) dFA = Direct Flourecent Antibody Test
(2) YES = Positive by dFA in Brain or at least one clinical sign post challenge
NO = Negative by dFA in brain or at least one clinical sign post challenge

<table>
<tr><td>Study Type</td><td>Efficacy</td></tr>
<tr><td>Pertaining to</td><td>West Nile Virus (WNV)</td></tr>
<tr><td>Study Purpose</td><td>To demonstrate effectiveness and duration of immunity against WNV</td></tr>
<tr><td>Product Administration</td><td>Two doses, administered intramuscularly 3 weeks apart</td></tr>
<tr><td>Study Animals</td><td>Thirty-two, 9-11 month (at vaccination) old mixed breed horses that were WNV sero-negative: 19 vaccinates, 11 controls (3 added at challenge)</td></tr>
<tr><td>Challenge Description</td><td>Challenged 12 months after vaccination with WNV</td></tr>
<tr><td>Interval observed after challenge</td><td>After challenge, animals were monitored twice daily for 14 days, and then once daily for an additional week</td></tr>
<tr><td>Results</td><td>The primary outcome was prevention of WNV viremia. Serum samples were collected from each animal twice daily from challenge for 2 weeks, and once thereafter.

Table 1. Virernia detected in vaccinated and control horses after experimental challenge with West Nile Virus

<table>
<tr><th>Treatment group</th><th>Number of viremic horses/horses challenged horses</th></tr>
<tr><td>Vaccinates</td><td>1/19</td></tr>
<tr><td>Controls</td><td>9/11</td></tr>
</table>

The raw data is shown on the attached page.</td></tr>
<tr><td>USDA Approval Date</td><td>August 13, 2002</td></tr>
</table>

Table 2: Number of Viremia incidences detected in vaccinated and control horses after experimental challenge with West Nile virus (WNV)

ID number	Group	Days Post Challenge									
		0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
4271041A29	Controls	-	-	-	-	-	+	-	+	-	-
4273363D4C		-	-	+	+	-	+	+	+	+	+
422C651E1C		-	-	-	-	-	-	-	-	-	+
524A3B6477/5317501016		-	-	-	-	-	-	-	-	-	+
421B355400/53190B764A		-	-	-	-	-	-	-	-	-	+
42735D5E73		-	-	-	-	-	-	-	-	-	-
421A056A0A		-	-	-	-	-	-	-	-	-	-
421E51781D		-	-	-	-	+	-	+	+	+	-
421E4F723F		-	-	-	-	-	+	-	+	+	+
421B2C3C13		-	-	+	-	-	+	+	+	+	-
421E565A55		-	-	-	-	+	-	+	+	-	-
421A002D66	Vaccinates	-	-	-	-	-	-	-	-	-	-
5308581947		-	-	-	-	-	-	-	-	-	-
422C63576B		-	-	-	-	-	-	-	-	-	-
417B242E4D		-	-	-	-	-	-	-	-	-	-
422C301B30		-	-	-	-	-	-	-	-	-	-
422C643F28		-	-	-	-	-	+	-	-	-	-
421E77405A		-	-	-	-	-	-	-	-	-	-
421E712746		-	-	-	-	-	-	-	-	-	-
421E78465C		-	-	-	-	-	-	-	-	-	-
421E5C0856		-	-	-	-	-	-	-	-	-	-
421E6C706F		-	-	-	-	-	-	-	-	-	-
422C74131B		-	-	-	-	-	-	-	-	-	-
52491F2C40		-	-	-	-	-	-	-	-	-	-
422C63330B		-	-	-	-	-	-	-	-	-	-
421945065E		-	-	-	-	-	-	-	-	-	-
422C5A5E36		-	-	-	-	-	-	-	-	-	-
421E606E22		-	-	-	-	-	-	-	-	-	-
421E5B025B		-	-	-	-	-	-	-	-	-	-
421E6A2314		-	-	-	-	-	-	-	-	-	-

+ Positive for WNV
- Negative for WNV

Table 2 (continued)

ID number	Group	Days Post Challenge									
		5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5
4271041A29	Controls	-	-	-	-	-	-	-	-	-	-
4273363D4C		-	-	-	-	-	-	-	-	-	-
422C651E1C		-	-	-	-	-	-	-	-	-	-
524A3B6477/5317501016			+	-	-	-	-	-	-	-	-
421B355400/53190B764A		+	+	-	-	-	-	-	-	-	-
42735D5E73		-	-	-	-	-	-	-	-	-	-
421A056A0A		-	-	-	-	-	-	-	-	-	-
421E51781D		-	-	-	-	-	-	-	-	-	-
421E4F723F		-	+	-	-	-	-	-	-	-	-
421B2C3C13		-	-	-	-	-	-	-	-	-	-
421E565A55		-	-	-	-	-	-	-	-	-	-
421A002D66	Vaccinates	-	-	-	-	-	-	-	-	-	-
5308581947		-	-	-	-	-	-	-	-	-	-
422C63576B		-	-	-	-	-	-	-	-	-	-
417B242E4D		-	-	-	-	-	-	-	-	-	-
422C301B30		-	-	-	-	-	-	-	-	-	-
422C643F28		-	-	-	-	-	-	-	-	-	-
421E77405A		-	-	-	-	-	-	-	-	-	-
421E712746		-	-	-	-	-	-	-	-	-	-
421E78465C		-	-	-	-	-	-	-	-	-	-
421E5C0856		-	-	-	-	-	-	-	-	-	-
421E6C706F		-	-	-	-	-	-	-	-	-	-
422C74131B		-	-	-	-	-	-	-	-	-	-
52491F2C40		-	-	-	-	-	-	-	-	-	-
422C63330B		-	-	-	-	-	-	-	-	-	-
421945065E		-	-	-	-	-	-	-	-	-	-
422C5A5E36		-	-	-	-	-	-	-	-	-	-
421E606E22		-	-	-	-	-	-	-	-	-	-
421E5B025B		-	-	-	-	-	-	-	-	-	-
421E6A2314		-	-	-	-	-	-	-	-	-	-

+ Positive for WNV
- Negative for WNV

Table 2 (continued)

ID number	Group	Days Post Challenge										
		10.0	10.5	11.0	11.5	12.0	12.5	13.0	13.5	14.0	14.5	21.0
4271041A29	Controls	-	-	-	-	-	-	-	-	-	-	-
4273363D4C		-	-	-	-	-	-	-	-	-	-	-
422C651E1C		-	-	-	-	-	-	-	-	-	-	-
524A3B6477/5317501016		-	-	-	-	-	-	-	-	-	-	-
421B355400/53190B764A		-	-	-	-	-	-	-	-	-	-	-
42735D5E73		-	-	-	-	-	-	-	-	-	-	-
421A056A0A		-	-	-	-	-	-	-	-	-	-	-
421E51781D		-	-	-	-	-	-	-	-	-	-	-
421E4F723F		-	-	-	-	-	-	-	-	-	-	-
421B2C3C13		-	-	-	-	-	-	-	-	-	-	-
421E565A55		-	-	-	-	-	-	-	-	-	-	-
421A002D66	Vaccinates	-	-	-	-	-	-	-	-	-	-	-
5308581947		-	-	-	-	-	-	-	-	-	-	-
422C63576B		-	-	-	-	-	-	-	-	-	-	-
417B242E4D		-	-	-	-	-	-	-	-	-	-	-
422C301B30		-	-	-	-	-	-	-	-	-	-	-
422C643F28		-	-	-	-	-	-	-	-	-	-	-
421E77405A		-	-	-	-	-	-	-	-	-	-	-
421E712746		-	-	-	-	-	-	-	-	-	-	-
421E78465C		-	-	-	-	-	-	-	-	-	-	-
421E5C0856		-	-	-	-	-	-	-	-	-	-	-
421E6C706F		-	-	-	-	-	-	-	-	-	-	-
422C74131B		-	-	-	-	-	-	-	-	-	-	-
52491F2C40		-	-	-	-	-	-	-	-	-	-	-
422C63330B		-	-	-	-	-	-	-	-	-	-	-
421945065E		-	-	-	-	-	-	-	-	-	-	-
422C5A5E36		-	-	-	-	-	-	-	-	-	-	-
421E606E22		-	-	-	-	-	-	-	-	-	-	-
421E5B025B		-	-	-	-	-	-	-	-	-	-	-
421E6A2314		-	-	-	-	-	-	-	-	-	-	-

+ Positive for WNV
- Negative for WNV

Study Type	Efficacy
Pertaining to	West Nile Virus (WNV)
Study Purpose	Demonstrate efficacy against West Nile Virus (WNV)
Product Administration	2 doses, administered intramuscularly, 3 weeks apart
Study Animals	30 horses, mixed breeds, male/female, 17-20 months of age. 20 horses in the vaccinated group and 10 horses in the control group.
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 13, 2002

Study Type	Safety
Pertaining to	ALL
Study Purpose	Demonstrate safety of product under typical use conditions
Product Administration	Horses were administered a vaccination series consisting of a single dose of experimental serial (IVP) followed 3-4 weeks later with a single dose of a commercially licensed serial (LVP), West Nile Virus Vaccine, Eastern & Western & Venezuelan, Killed Virus, Tetanus Toxoid, West Nile Innovator® VEWT. Vaccination was given by the intramuscular route.
Study Animals	Six hundred eighty two mixed breed client owned horses; 209 were ≤ 3 months of age and 473 were ≥ 4 months of age
Challenge Description	NA
Interval observed after vaccination	Horses were observed for abnormal health events a minimum of 21 days after each vaccination.
Results	Table 1: Frequency distribution of abnormal health events after vaccination.

Number of Vaccinations	**1st Vac IVP**	**2nd Vac LVP**	**Abnormal Health Event**	**Number of Horses/% Vaccinations**
1359 Vaccinations (682 doses of IVP, 677 doses of LVP)		1	Ataxia	1 (0.15%)
	1		Cough	1 (0.15%)
		1	Fever	1 (0.15%)
		1	Hoof Abscess Left Front/Left Hind Lameness	1 (0.15%)
	1*		Injection Site Swelling (1.5-5cm)	1 (0.15%)
	4		Lameness	4 (0.59%)
	1*		Muscle Pain	1 (0.15%)
	1		Nasal Discharge	1 (0.15%)
	1	1	NOS	2 (0.29%)
	2		Skin Haematoma	2 (0.29%)
	2	3	Skin Lesion NOS**	4 (0.59%)
	2	1	Skin Oedema	3 (0.44%)
	1	1	Ataxia	2 (0.29%)
	1		Blepharoedema	1 (0.15%)
	2		Cough	2 (0.29%)
		1	Depression	1 (0.15%)
		1	Diarrhoea	1 (0.15%)
		3	Fever	3 (0.44%)
	4	3	Lameness	7 (1.03%)
		1	Leukocytosis	1 (0.15%)
	2	1	Nasal Discharge	3 (0.44%)
		1	NOS	1 (0.15%)
		2	Skin Lesion NOS	2 (0.29%)
		1	Skin Oedema	1 (0.15%)

	NOS = Not Otherwise Specified *Attributed to Vaccination by licensee. Swelling resolved within 24 hours. **One horse was recorded with 2 separate abnormal health events both described as Skin Lesion, NOS
USDA Approval Date	May 13, 2016

<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 typical use conditions</td></tr>
<tr><td>Product Administration</td><td>Horses were administered a vaccination series consisting of a single dose of experimental serial (IVP) followed 3-4 weeks later with a single dose of commercial serial (LVP), West Nile Virus Vaccine, Eastern & Western & Venezuelan, Killed Virus, Tetanus Toxoid, West Nile Innovator® VEWT. Vaccination was given by intramuscular route.</td></tr>
<tr><td>Study Animals</td><td>Three hundred and twenty five mixed breed client owned horses; 112 were ≤ 3 months of age and 213 were ≥ 4 months of age</td></tr>
<tr><td>Challenge Description</td><td>NA</td></tr>
<tr><td>Interval observed after vaccination</td><td>Horses were observed for abnormal health events a minimum of 21 days after each vaccination.</td></tr>
<tr><td>Results</td><td>Table 1: Frequency distribution of abnormal health events after vaccination
<table>
<tr><th>Treatment / Number of Vaccinations</th><th>1st Vac. (IVP)</th><th>2nd Vac (LVP)</th><th>Abnormal Health Event</th><th>Number of Horses/% Vaccinations</th></tr>
<tr><td rowspan="4">325 Vaccinations at each time point</td><td>1*</td><td></td><td>Abdominal Pain</td><td>1 (0.15%)</td></tr>
<tr><td></td><td>1*</td><td>Abortion</td><td>1 (0.15%)</td></tr>
<tr><td>3</td><td></td><td>Lameness</td><td>3 (0.46)</td></tr>
<tr><td>1</td><td></td><td>Wheals</td><td>1 (0.15)</td></tr>
</table>
* These events occurred in the same horse. Affirmed by licensee to have a cause other than vaccination.</td></tr>
<tr><td>USDA Approval Date</td><td>January 3, 2018</td></tr>
</table>

<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>To demonstrate safety in pregnant mares in the third trimester under field conditions.</td></tr>
<tr><td>Product Administration</td><td>Single dose administered intramuscularly during the third trimester of pregnancy.</td></tr>
<tr><td>Study Animals</td><td>A total of 282 healthy pregnant mares in their third trimester were enrolled in one of two treatment groups in two distinct geographical locations. The animals were distributed as follows: Controls, n = 57, Vaccinated, n = 225.</td></tr>
<tr><td>Challenge Description</td><td>N/A</td></tr>
<tr><td>Interval observed after last treatment</td><td>Clinical observations were performed on all mares for at least 30 minutes following vaccination. Pregnant mares were also observed at least once daily for general health for 21 days following vaccination and at least once weekly until foaling.

Mares were observed during foaling and foals were observed at least once weekly for general health until they were at least 21 days of age.</td></tr>
<tr><td>Results</td><td>
Mare Abnormal Health Events
<table>
<tr><th colspan="2">Number of Mares</th><th rowspan="2">Mares with no AE* (%)</th><th rowspan="2">Mares with AE* (%)</th></tr>
<tr><th>Total Enrolled</th><td>282</td></tr>
<tr><td>Controls</td><td>57</td><td>54 (94.7%)</td><td>3 (5.3%)</td></tr>
<tr><td>Vaccinated</td><td>225</td><td>214 (95.1%)</td><td>11 (4.9%)</td></tr>
</table>
*AE= Adverse Events
<table>
<tr><th>Treatment / Number of Vaccinations</th><th>Mare Abnormal Health Events</th><th>Number of Mares / Percent of Vaccinations</th></tr>
<tr><td rowspan="4">Controls (57 animals)</td><td>Agalactia</td><td>1 / 1.75%</td></tr>
<tr><td>Death[1]</td><td>1 / 1.75%</td></tr>
<tr><td>Dystocia</td><td>1 / 1.75%</td></tr>
<tr><td>Fracture</td><td>1 / 1.75%</td></tr>
<tr><td rowspan="11">Vaccinated (Product Code 48R5.20; 225 animals)</td><td>Abdominal Pain</td><td>1 / 0.44%</td></tr>
<tr><td>Decreased Appetite</td><td>1 / 0.44%</td></tr>
<tr><td>Dystocia</td><td>3 / 1.33%</td></tr>
<tr><td>Fracture</td><td>1 / 0.44%</td></tr>
<tr><td>Injection Site Swelling</td><td>1 / 0.44%</td></tr>
<tr><td>Laceration</td><td>1 / 0.44%</td></tr>
<tr><td>Lameness</td><td>2 / 0.89%</td></tr>
<tr><td>Nasal Discharge</td><td>1 / 0.44%</td></tr>
<tr><td>Placental Abnormality</td><td>1 / 0.44%</td></tr>
<tr><td>Retained Placenta</td><td>1 / 0.44%</td></tr>
</table>
[1] Mare died due to septic shock as a result of a difficult foaling.
</td></tr>
</table>

<table>
<tr><td></td><td>There was only one adverse event that was attributable to IVP which was an injection site reaction in a vaccinate that was observed the day after vaccination and resolved the following day.

Birth Outcome Summary from Vaccinated Mares
<table>
<tr><th colspan="2">Number of Foals</th><th>Live Foals</th><th>Foal died during or immediately post-parturition</th></tr>
<tr><td>Total Foals</td><td>280[1]</td><td>273 (97.50%)</td><td>7 (2.50%)</td></tr>
<tr><td>Controls</td><td>56</td><td>53 (94.64%)</td><td>3 (5.36%)</td></tr>
<tr><td>Vaccinated</td><td>224</td><td>220 (98.21%)</td><td>4 (1.79%)</td></tr>
</table>
[1] Two mares (one vaccinate and one control) were removed prior to foaling due to fractured legs.</td></tr>
<tr><td>USDA Approval Date</td><td>March 02, 2022</td></tr>
</table>