WART SAFETY

FIELD SAFETY STUDY REPORT:

Wart Vaccine, Killed Baculovirus Vector from Cambridge Technologies: Safety of Repeated Subcutaneous Injections in Cattle Under Typical U.S. Field Conditions

INTRODUCTION

Historically, vaccines for bovine papillomas have been a source of frustration for veterinarians and cattlemen alike as existing products have been plagued by inconsistent availability as well as safety concerns. Cambridge Technologies has conducted a field safety study of their Wart Vaccine, Killed Baculovirus Vector, as part of the process of obtaining a conditional product license supporting safety of the production platform. It also supports the following label claim for the vaccine:

"For the vaccination of cattle 60 days of age or older against bovine papillomavirus. This product license is conditional; efficacy and potency have not been fully demonstrated. For more information regarding safety data, see productdata.aphis.usda.gov."

MATERIALS AND METHODS

This report describes a field safety study in cattle conducted at three different locations in the U.S. using two prelicense serials (PLS) of Cambridge Technologies' Wart Vaccine, Killed Baculovirus Vector.

The study was conducted by three cooperating veterinarians in California, Illinois, and Iowa who enrolled bovines from commercial herds in their veterinary practices. A total of 960 healthy bovines were enrolled in the study, all between 2 and 15 months of age on day zero, the date of first vaccination. All vaccinations in this first round were administered on the right side of the neck.

ENROLLMENTS WERE AS FOLLOWS:

California Site: 360 head, consisting of 246 male and female 61 days of age Angus-Holstein calves in hutches and 114 male and female 60 days of age Angus-Holstein calves in hutches. The first animal received a 4mL SQ injection of serial 1, the second received a 4mL SQ injection of serial 2, and the third animal was enrolled as a non-vaccinated control. This continued until all 360 animals were enrolled in the study.

Illinois Site: 363 head, consisting of 244 male Holsteins 8-10 months of age housed in two pens, and 119 female 5-7 months of age dairy/beef cross cattle housed in one pen. The first animal received a 4mL SQ injection of serial 1, the second received a 4mL SQ injection of serial 2, and the third animal was enrolled as a non-vaccinated control. This continued until all 363 animals were enrolled in the study.

Iowa Site: 237 head, consisting of female commercial beef heifers 14-15 months of age housed in one pen. The first animal received a 4mL SQ injection of serial 1, the second received a 4mL SQ injection of serial 2, and the third animal was enrolled as a non-vaccinated control. Due to a smaller study pool, this continued until there were 32 animals in each group, then subsequent animals were enrolled by alternating between serial 1 and serial 2 until all 237 animals were enrolled in the study.

At all three locations, all cattle were ruled healthy at enrollment by the cooperating veterinarians for the testing site. For the Iowa and Illinois testing sites, cattle from all treatment groups were present within each pen, and all cattle remained comingled (without sorting by treatment group) for the duration of the study.

For the California testing site, the calves were housed in individual calf hutches for the first 25 days of the study, with the calves in adjacent hutches receiving the various treatments, i.e., the hutch locations were not clustered to segregate treatment groups from one another. After moving the calves from their individual hutches to large holding pens, calves from all groups were commingled within the two pens.

In total, three hundred forty-five of the enrolled cattle received serial 1,342 serial 2, and the remaining 273 enrolled cattle were left unvaccinated as controls. All animals were observed daily by the Herd Manager with observations recorded. All animals received two booster doses at two and four weeks following the initial dose, on alternating sides of the neck.

The cooperating veterinarian was responsible for administering the vaccines, for observing all enrolled animals for at least one hour immediately following vaccinations, and for palpating injection sites of each vaccinate after each vaccination on the day after administration (days 1, 15, and 29) as well as two weeks after each vaccination (days 14, 28, and 42). On study day 42, an injection site palpation was performed on all injection sites. Animals that still had a palpable injection site reaction at study day 42 were palpated again at day 56, and, if needed, again at day 70.

Table 1. Scheduled activities and study completion (all sites)

STUDY DAY	Activity
0	Animals assigned to vaccination groups as explained above. Animals observed by herd veterinarians for one hour post-vaccination.
1	All animals were palpated by the veterinarian. Veterinarian instructed herd manager on daily observations.
2-13	Daily observations recorded.
14	Veterinarian palpated original injection site on right side of neck and then administered appropriate vaccine into the left side of the neck. Observed cattle for at least one hour post vaccinatin.
15	Veterinarian palpated booster injection site on left side of the neck, herd manager conducted daily observations.
16-27	Herd manager conducted daily observations.
28	Daily observations recorded and veterinarian palpated both injection sites. Booster administered to right neck. Observed cattle for at least one hour post vaccination.
29	Veterinarian palpated booster injection site on right side of the neck, herd manager conducted daily observations.
30-41	Herd manager conducted daily observations.
42	Veterinarian palpated right and left side of neck and general observations recorded. If any injection site reactions were still present, animals were checked in two weeks.
56	Veterinarian palpated both right and left side of neck for any animals with residual ISRs.
70	Veterinarian palpated both right and left side of neck for any animals with residual ISRs. Study concluded.

RESULTS

At the immediate and 24 hours post-injection observation times, palpable injection site reactions (ISR) were recorded in 19 of the 204 vaccinated animals at the Iowa site and 155 of the 241 vaccinates at the Illinois site. All the palpable injection site reactions at these sites had returned to normal by 14 days post primary injection, with the exception of one animal in IL that still had a palpable reaction on the right side on day 14. On day 42 (two weeks after final boost), one animal in IL had a palpable reaction on the right side, but this animal had not had a noted reaction on day 29, and two animals had a palpable reaction on the left side at day 42 (but had not had a detectable reaction on the left side on day 28). All three animals were normal on day 56. In IA, two animals developed a chronic reaction that had not resolved by day 70.

At the California site, where minimum age cattle (60-61 days of age) were enrolled, 174 of 240 vaccinated calves and one non-vaccinated calf had palpable lumps or swellings with no affirmed alternative etiology at the injection site 24 hours post-injection; all but 40 of these had recovered to normal by 14 days post injection, while 2 animals in the non-vaccinated group and 2 vaccinates had measurable ISRs that were not detected on day 1. There was a whole-herd vaccination consisting of several doses of various vaccines administered on study days 5 and 6. There was another round of whole-herd injections consisting of several doses of various vaccines and treatments at days 36-38 and the palpation on day 40 (12 days post 3rd injection of the test articles) showed higher number of palpable reactions than previous doses did at two weeks post vaccination with test articles.

Table 2. Adverse Events and Veterinary Dictionary for Drug Related Affairs (VeDDRA) Designation by Vaccine Serial and Study Site

VeDDRA Term	Vaccine Serial	Site ID					
		CA		IL		IA	
		No. Calves	No. Occurances	No. Calves	No. Occurances	No. Calves	No. Occurances
INJECTION SITE LUMP	SERIAL ONE	120	2120	100	188	35	35
INJECTION SITE MASS NOS		0	0	0	0	2	2
INJECTION SITE SWELLING		83	295	0	0	40	40
INJECTION SITE WARMTH		2	2	0	0	0	0
LETHARGY		2	2	0	0	0	0
INJECTION SITE LUMP	SERIAL TWO	120	2162	115	241	43	43
INJECTION SITE NOS		0	0	0	0	1	1
INJECTION SITE SWELLING		82	247	0	0	44	44
INJECTION SITE WARMTH		1	1	0	0	0	0
LETHARGY		0	0	0	0	0	0
INJECTION SITE LUMP	NO TREATMENT	90	477	4	4	0	0
INJECTION SITE NOS		0	0	0	0	0	0
INJECTION SITE SWELLING		70	172	0	0	0	0
INJECTION SITE WARMTH		2	4	0	0	0	0
LETHARGY		1	1	0	0	0	0

Table 3. Tabulation of Largest Palpable Injection Site Reactions with no attributable alternative etiology by Vaccine Serial as Reported by the Cooperating Veterinarian by Study Day for California Study Site

		LARGEST LOCAL SITE LESION REPORTED				
VACCINE SERIAL	STUDY DAY	NO LESION	<5CM	<5CM TO 10CM	>10CM	SIZE NOT REPORTED
SERIAL 1	1	30	6	69	15	0
SERIAL 2		36	5	65	14	0
NO TREATMENT		119	0	1	0	0
SERIAL 1	14	92	24	1	0	0
SERIAL 2		96	15	2	0	0
NO TREATMENT		118	2	0	0	0
SERIAL 1	15	30	35	43	11	1
SERIAL 2		13	33	69	3	0
NO TREATMENT		107	8	4	0	1
SERIAL 1	28	102	9	6	0	2
SERIAL 2		104	8	4	0	4
NO TREATMENT		101	12	4	1	2
SERIAL 1	29	58	30	14	0	17
SERIAL 2		53	30	14	0	23
NO TREATMENT		106	8	1	0	4
SERIAL 1	40	51	19	25	4	20
SERIAL 2		43	19	32	12	13
NO TREATMENT		55	25	20	6	13
SERIAL 1	54	68	21	5	0	0
SERIAL 2		70	28	4	0	1
NO TREATMENT		55	23	5	1	0
SERIAL 1	70	19	7	0	0	0
SERIAL 2		16	15	0	0	1
NO TREATMENT		19	10	0	0	0

Table 4. Tabulation of Largest Palpable Injection Site Reactions with no attributable alternative etiology by Vaccine Serial as Reported by the Cooperating Veterinarian by Study Day for Illinois Study Site

		LARGEST LOCAL SITE LESION REPORTED				
VACCINE SERIAL	STUDY DAY	NO LESION	<5CM	<5CM TO 10CM	>10CM	SIZE NOT REPORTED
SERIAL 1	1	55	64	3	0	0
SERIAL 2		31	79	9	0	0
NO TREATMENT		120	1	0	0	0
SERIAL 1	14	122	0	0	0	0
SERIAL 2		118	1	0	0	0
NO TREATMENT		121	0	0	0	0
SERIAL 1	15	56	44	22	0	0
SERIAL 2		34	61	23	1	0
NO TREATMENT		120	0	1	0	0
SERIAL 1	28	118	3	0	0	0
SERIAL 2		118	1	0	0	0
NO TREATMENT		120	0	0	1	0
SERIAL 1	29	72	38	11	0	0
SERIAL 2		53	42	24	0	0
NO TREATMENT		118	0	2	0	0
SERIAL 1	42	119	3	0	0	0
SERIAL 2		119	0	0	0	0
NO TREATMENT		121	0	0	0	0
SERIAL 1	56	3	0	0	0	0
SERIAL 2		0	0	0	0	0
NO TREATMENT		0	0	0	0	0

Table 5. Tabulation of Largest Palpable Injection Site Reactions with no attributable alternative etiology by Vaccine Serial as Reported by the Cooperating Veterinarian by Study Day for Iowa Study Site

		LARGEST LOCAL SITE LESION REPORTED				
VACCINE SERIAL	STUDY DAY	NO LESION	<5CM	<5CM TO 10CM	>10CM	SIZE NOT REPORTED
SERIAL 1	1	94	2	6	1	0
SERIAL 2		91	0	6	4	0
NO TREATMENT		32	0	0	0	0
SERIAL 1	14	103	0	0	0	0
SERIAL 2		101	0	0	0	0
NO TREATMENT		32	0	0	0	0
SERIAL 1	15	79	6	17	1	0
SERIAL 2		76	9	16	0	0
NO TREATMENT		32	0	0	0	0
SERIAL 1	28	102	0	0	1	0
SERIAL 2		99	0	1	1	0
NO TREATMENT		32	0	0	0	0
SERIAL 1	29	89	7	7	0	0
SERIAL 2		87	6	7	1	0
NO TREATMENT		32	0	0	0	0
SERIAL 1	42	96	3	4	0	0
SERIAL 2		101	0	0	0	0
NO TREATMENT		32	0	0	0	0
SERIAL 1	56	5	5	0	0	0
SERIAL 2		0	0	0	0	0
NO TREATMENT		0	0	0	0	0
SERIAL 1	70	0	2	0	0	0
SERIAL 2		0	0	0	0	0
NO TREATMENT		0	0	0	0	0

DISCUSSION

This research confirms the safety of Cambridge Technologies' Wart Vaccine, Killed Baculovirus Vector, when used according to label instructions in healthy bovines of minimum age 60 days or more given a maximum 4mL dose and a maximum of 3 repeat doses per the label recommendations.

There were no clear differences in the safety of the two serials; both performed equivalently as was expected in this study.

Transient injection site reactions (ISRs) were observed in all sites, but at a much lower incidence at the Illinois and Iowa sites where older calves were enrolled. None of the ISRs which occurred were severe enough to require surgical intervention nor any other exceptional treatment.

Many later-reported ISRs occurred in the California hutch calf test site, where precise attribution of the ISR to the experimental product was complicated by the unexpected administration of multiple "whole-herd" injections during the study term without notation of the location on the calves where those "whole-herd" injections had been given. The resulting difficulty in specific attribution of alternative etiology to the ISRs from this site is illustrated by the finding that non-treated calves from the CA site had palpable ISRs during the study, despite these calves never having had injections of the experimental vaccines. Regardless of the difficulties in data interpretation posed by this unanticipated injection practice in the California herd, the cooperating veterinarian for that site did not view the ISR incidence and the overall herd health status during the study term as outside what he considered routine and ordinary for this production unit.

All three cooperating veterinarians made favorable assessments of the overall safety of the product.

Both of the serials used as test articles in this study were proven safe under field conditions, with no serious adverse nor any systemic reactions to vaccination. The incidence of ISRs warrants a label warning stating that transient injection site inflammation may occur, but any such ISR should resolve without treatment.

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