UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

To: Bonaventure Akinlosotu

From: Clayton Myers, Entomologist **Date:** November 8, 2011

11-8-11

Subject: PRODUCT PERFORMANCE DATA EVALUATION RECORD

DP barcode:	391921
Decision no.:	448350
Submission no:	897940
Action code:	R310
Product Name:	Effitix Topical Solution for Dogs
EPA Reg. No or File Symbol:	2382-RIT
Formulation Type:	Pet Spot-On

Ingredients statement from the label with PC codes included: Permethrin, 44.88% PC: 109701; Fipronil, 6.01% PC: 129121

Application rate(s) of product and each active ingredient (lbs. or gallons/1000 square feet or per acre as appropriate; and g/m^2 or mg/cm^2 as appropriate): Rate not provided on label. States one bottle (sizes not listed in net contents) will treat a surface up to [360][500] square feet.

I. Action Requested: Data was submitted to support pest claims for a pet spot-on product.

II. Background: The registrant seeks to register a fipronil/permethrin combo spot-on product for control of fleas, ticks, and other pests on dogs. The registrant has submitted 9 studies to support efficacy claims, in addition to selective citations.

III. MRID Summaries: (Primary Review attached)

a. MRID 48510701: Efficacy Study Against Fleas (Ctenocephalides) on Dogs: Onset of Action.

1. GLP Study
2. A laboratory study was conducted to test the speed of effectiveness of a fipronil/permethrin combination product with equivalent concentrations as the submitted product (on a w/w % basis). Dogs were qualified for flea retention and allocated into 2 groups, a treatment and a control group (10 dogs each in the treated groups and 6 in the control group). Dogs were infested with fleas on day -6 and day -1. After treatment on day 0, dogs were kept in individual pens. Flea comb counts were conducted on day -5 and on day 0 at 2, 6, and 12 hours after treatment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Mean flea reduction efficacy at 6 hours after treatment was 94.4% (88.6% if the regular arithmetic mean was used). Flea efficacy exceeded 99% by 12 hours after treatment.
4. The primary reviewer agrees that the study is adequate to support killing claims against fleas within 6 hours of treatment. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the

concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of killing fleas within 6 hours of treatment are adequately supported.

b. MRID 48467122: Efficacy Study Against Rhipicephalus sanguineus in Dogs: Duration of Action.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of Brown Dog Ticks on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 50 ticks on day -6, and days 0, 7, 14, 21, 28, 35, 42, 29, 56, and 63. Tick counts and mortality assessment was conducted on day -4, 1, 2, 9, 16, 23, 30, 37, 44, 51, 58, and 65. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 86.6%, but efficacy then exceeded 90% after each subsequent reinfestation through day 51. The study author states that efficacy should be adequately supported for 7 weeks after treatment.
4. The primary reviewer agrees that the study is adequate to support claims against BDT through 7 weeks after treatment. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of killing BDT are supported for 7 weeks after treatment.

c. MRID 48467123: Efficacy Study Against Dermacentor variabilis on Dogs: Duration of Action.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of American Dog Ticks on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 50 ticks on day -6, and days 0, 7, 14, 21, 28, 35, 42, 29, 56, and 63. Tick counts and mortality assessment was conducted on day -4, 1, 2, 9, 16, 23, 30, 37, 44, 51, 58, and 65. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 49.4%, but efficacy then exceeded 90% after each subsequent reinfestation through day 44. The study author states that efficacy should be adequately supported for 6 weeks after treatment.
4. The primary reviewer agrees that the study is adequate to support claims against ADT through 6 weeks after treatment. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of killing ADT are supported for 6 weeks after treatment.

d. MRID 48467124: Efficacy Study Against the Brown Dog Tick (Rhipicephalus sanguineus) and the Cat Flea (Ctenocehpalides felis) on Dogs: Effects of Shampooing and Periodic Water Immersions.

1. GLP Study
2. A laboratory study was conducted to to evaluate the efficacy and duration of control of a fipronil/permethrin combination product against fleas and ticks after shampooing and water immersion, in support of waterproof claims. 24 dogs were blocked within gender and weight groups in 6 blocks of 4 dogs in descending order of pre-treatment flea counts, and assigned to 3 treatment groups: Group 1 was a control group that was shampooed and water immersed, 6 dogs. Group 2 was treated with the test

substance, 6 dogs. Group 3 was treated with the test substance and shampooed, 6 dogs. Group 4 was treated with the test substance and water immersed, 6 dogs. Dogs were infested with fleas (100) on days -4, 0, 7, 14, 21, and 28. Dogs were also infested with ticks (50) on days -5, -1, 6, 13, 20, and 27. Shampooing occurred on day 12. Water immersion on days 12 and 26. Flea and Tick counts were conducted on days -2, 2, 9, 16, 23, and 30. For water immersion and shampooing, animals were rinsed using a shower head for 5 minutes at a flow rate of 2 gallons/minute. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Tick efficacy at 2 days was variable, but at days 9-30, tick efficacy exceeded 99% for all treatment groups, including dogs that were shampooed or water immersed. Flea efficacy exceeded 90% at 2 days, and was at 100% at days 9-10, for all treatment groups, including dogs that were shampooed or water immersed. The study author states that efficacy is adequately supported for fleas and ticks after water immersion and shampooing.
4. The primary reviewer agrees that the study is adequate to support claims against ticks and fleas through 1 month after treatment, with shampooing and water immersion. The reviewer comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and claims of fleas and ticks for 1 month after treatment, with water immersion and shampooing, i.e., 'waterproof' claims.

e. MRID 48467125: The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artificially Induced Infestations of Ticks (Amblyoma americanum) on Dogs.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of Amblyoma americanum on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 50 ticks on day -7, and days 0, 7, 14, 21, 28, 35, and 42. Tick counts and mortality assessment was conducted on day -4, 1, 2, 9, 16, 23, 30, 37, and 44. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 70%, but efficacy then exceeded 90% after each subsequent reinfestation through day 23. Efficacy was 88% at day 37. The study author states that efficacy should be adequately supported for 23 days after treatment, with some residual control of ticks through 30 and 37 days.
4. The primary reviewer agrees that the study is adequate to support claims against BDT through 3 weeks after treatment, but that one month control claims were not adequately supported, as the 90% efficacy threshold was not met for day 30. The reviewer also comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is unacceptable and claims of killing Amblyoma americana for one month, but is partially acceptable and is adequate to support claims for 3 weeks after treatment.

f. MRID 48467126: Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7% w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artificially Induced Infestations of Ticks (Ixodes scapularis) on Dogs.

1. GLP Study
2. A laboratory study was conducted to test the efficacy and duration of control of Black Legged Ticks on dogs for a fipronil/permethrin combination product with equivalent concentrations as the submitted product on a w/w % basis). Dogs were infested with adult ticks for the study. 6 dogs were placed in a treatment group and 6 others in a control group. Each dog received 40 ticks on day -7, and with 50 ticks on days 0, 7, 14, 21, 28, 35, and 42, and with 35 ticks on day 49. Tick counts and mortality assessment was conducted

on day -5, 2, 9, 16, 23, 30, 37, 44 and 51, at 48 hours after infestation. The ticks were categorized as being alive or dead, and also in 3 subgroups: free, attached and unengorged, or attached and engorged. Ticks were counted and removed during the 48 h assessment. Efficacy calculations were based on geometric means and percent efficacy was calculated using Abbott's Formula.
3. Efficacy at 2 days after treatment was 94%, and efficacy then exceeded 90% after each subsequent reinfestation through day 37. The study author states that efficacy should be adequately supported for 37 days after treatment, with some residual control of ticks through 44 and 51 days.
4. The primary reviewer agrees that the study is adequate to support claims against BLT through 30 days after treatment. The reviewer also comments that the weight/volume 'concentrations' used in the study do not exactly match those on the submitted product CSF, but notes that another study validates the concentrations, when converted to a weight/weight ratio to calculate the active ingredient concentrations. This study is acceptable and one month claims against BLT are adequately supported.

g. MRID 48467127: Determination of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs.

1. GLP Study
2. A laboratory study was conducted to test the efficacy of a fipronil/permethrin product against mosquitoes for repellence (preventing feeding) and killing of A. aegypti. Dogs were qualified as mosquito hosts, with dogs allowing a feeding rate of 40% were considered acceptable for the study. 12 dogs were randomly assigned into 2 groups, a treatment and control group. The product was applied on day 0. Dogs were exposed for 28-35 minutes to unfed female mosquitoes in exposure cages on days 1, 7, 14, 21/22, 28, and 35-37. Dogs were sedated during infestations. Afterwards, the mosquitoes were collected and dogs were removed from the exposure cages and returned to normal housing. At 50-90 minutes after exposure, dead and alive mosquitoes were counted. The mosquitoes were frozen and crushed to determine if a blood meal had been taken. Mortality was calculated for both feeding efficacy (repellence) and killing efficacy. Efficacy calculations were made using Abbott's Formula.
3. Short-haired dogs were more susceptible to mosquitoes than long hair dogs. The test product has a more effective repellence efficacy than killing efficacy. Killing efficacy never exceeded 59.5%. Repellence efficacy was 91.7% efficacy at 7 days after treatment.
4. The primary reviewer concludes that the study is not acceptable to support claims against mosquitoes, as no killing efficacy was demonstrated and repellence was only adequate at 7 days after application. The study is not acceptable to support any claims against mosquitoes.

h. MRID 48467128: Repellence Efficacy Study of 104.05 Against Ticks (Dermacentor variabilis and Rhipicephalus sanguineus) on Dogs Under Laboratory Conditions.

1. GLP Study
2. A laboratory study was conducted to evaluate the repellence of ticks for a fipronil/permethrin combination product. 12 dogs were used in the study, with 6 dogs given treatment and 6 dogs left as an untreated control group. Adult BDT and ADT were used in artificial infestations. Dogs were infested with 30 unfed ticks on day -6 (R. sanguineus only), and days 1, 2, 7, 14, 21, 22, and 28. Tick assessments were conducted on days 1, 2, 7, 14, 21, 22, and 28 at 3 hours after infestation/reinfestation. Tick counts with removal were conducted on days -5, 2, 4, 8, 15, 22, 23, and 29, 24 hours after the infestations. Ticks were categorized as being alive or killed and in 3 subgroups: free, attached and engorged, or attached and unengorged. Ticks found in the infestation chamber after removal of the dogs were categorized as live, moribund or dead. % mortality was calculated using Abbott's Formula.
3. BDT repellence efficacy was 90-95% for the 3 hour assessments through 14 days. Efficacy was 99% or greater for the 24 hour assessment through 29 days. For ADT, repellence efficacy was 90-97% for the 3 hour assessments through 22 days. Efficacy was 97% or greater for the 24 hour assessment through 29 days. The author concludes that repellence efficacy for ticks is supported through up to 29 days after treatment.
4. The primary reviewer concurs that basic tick repellence claims are supported for up to one month after application. The study is acceptable to support claims of tick repellence for up to one month.

i. MRID 48467129: Summary of Efficacy Data for Effitix™ Topical Solution for Dogs End Use Product.

This MRID was a summary of selectively cited and submitted studies in support of label claims. The submission is supplemental.

j. Selective Citations of 60 MRIDs from the fipronil and permethrin efficacy database including the following:
43121114, 43121115, 43121116, 43121119, 43121120, 43121121, 43121122, 43444901, 43577701, 43577712, 43577713, 43951701, 44088901, 44942011, 44942106, 45618501, 45620502, 45620503, 45628104, 45628105, 45866901. 43577712, 43121114, 43121115, 43121117, 43121122, 43121118, 45620504, 45620505, 45620506, 43444901. 43444901, 43577701, 43951701, 45612701, 45620503, 45866901. 45620501, 45618101, 45628102, 45628103, 45628201, 45866902, 46019202, 46019201, 41038802, 41038803, 43137202, 43137203, 43396409, 43396410, 46006002, 41683903, 43111607, 43396409, 43396410, 46978901, 42256901, 43396409, 43396410

These studies support efficacy claims (in various versions) against fleas, ticks, lice (chewing/biting), mites (aids in control of sarcoptic mange), mosquitoes, and repellence of biting flies.

Claims are not supported for sand flies, for killing/control of mites (only 'aids in control'), or sucking lice.

IV. RECOMMENDATIONS:

(1) Labeling:

(a) What pests and site/pest combinations may be added as follows to the label based on the submitted or cited data?

Fleas: Killing within 6 hours and control for up to one month. Also repellence of fleas.
Ticks: Killing and controlling for up to one month. Also repellence of fleas.
Mosquitoes: Killing and controlling for up to one month, also repellence and prevention of blood feeding for up to one month
Biting Flies: Repellence
Lice (chewing/biting): Killing and controlling for up to one month
Mites: Aids in control of sarcoptic mange/mites that may cause sarcoptic mange, etc.

(b) What pests and site/pest combinations must be removed from the label?

Any and all claims against sandflies
Any claims of control of fleas or ticks beyond one month (given that waterproof claims are included)
Killing/controlling claims against mites (only aids in control is supported)
Any and all claims against 'sucking' lice

(c) List changes to the directions for use:

None required

(d) List changes to the optional marketing claims:

<u>The following marketing claims must be deleted from the label (pages 4-7)</u>

All references to sandflies, killing/controlling of mites, and 'sucking' lice must be removed from all marketing claims and from the entire label. References to the word 'effective' are deemed inappropriate, as this implies a heightened comparative efficacy claim (a decision on the suitability of this claim is deferred to the product

manager). Finally, any and all claims of 'breaking the flea life cycle' must be deleted, as this product does not kill flea eggs or larvae. On a line-by-line basis, the claims marked with ~~strikethrough text~~ below must be deleted.

"For convenient, quick-acting, long-lasting ~~effective~~ control of fleas ticks . . ."

". . . (biting, chewing and ~~sucking~~) lice and ~~mites~~ . . ." All variations of these kill claims must be deleted throughout the label. Claims against mites may be expressed as 'aids in control.'

"Kills fleas, ticks, lice, ~~mites~~ and mosquitoes, repels biting flies and mosquitoes"

"Repels fleas, ticks, biting flies, ~~sandflies~~ and mosquitoes"

~~"Research has shown that flea, tick, (sucking, biting, and chewing) lice and mite infestations can be completely controlled with monthly applications of EFFITIX™ Topical Solution for Dogs."~~ The claim 'research has shown' is unacceptable and the claim 'can be completely controlled' implies 100% efficacy, which is also unacceptable.

~~"Effective~~ monthly application against fleas, ticks, and mosquitoes"

"Fleas: EFFITIX™ Topical solution for dogs can kill adult fleas in 6 hours ~~for up to three months~~. Apply monthly if your dog . . ."

"~~Effective~~ monthly application against fleas"

"~~Effective~~ monthly control of fleas"

"Easy to apply ~~(effective)~~ control . . ."

~~"Effectively breaks the flea life cycle"~~

~~"Effective~~ monthly application against ticks"

"Repels and inhibits blood feeding by biting flies, ~~sandflies~~ and mosquitoes" (delete all other references to sandflies)

"Lice: EFFITIX™ Topical Solution for Dogs can kill ~~sucking~~, biting and chewing lice for . . ." (delete all other references to sucking lice)

~~"Mites: When applied monthly, EFFITIX™ Topical Solution for Dogs kills mites"~~

~~"Mites (Cheyletiella yasguri): When applied monthly . . . ."~~

~~"Kills mites (that may cause sarcoptic mange)"~~ Can be revised to 'aids in control of mites that may cause . . ."

~~"Sold by veterinarians"~~

~~"Veterinarian recommended"~~

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 485107-01. Fourie, J.J. Efficacy Study Against Fleas (*Ctenocephalides felis*) on Dogs: Onset of Action. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: Dennis M Opresko
Date: OCT 19 2011

Secondary Reviewers:
Gene Burgess, Ph.D.

Signature: Gene Burgess, AE
Date: OCT 19 2011

Robert Ross, M.S., Program Manager

Signature: Robert H. Ross
Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**485107-01.** Efficacy Study Against Fleas (*Ctenocephalides felis*) on Dogs: Onset of Action. Fourie, J.J. 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	VIRBAC SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	27/05/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution

	PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.
PROPOSED LABEL MARKETING CLAIMS:	...can start killing adult fleas within 6 hr and lasts for up to three months.

STUDY REVIEW

Purpose: To test the speed of effectiveness of 104.05 spot-on formulation against *Ctenocephalides felis* fleas on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.

Test Material(s): 104.05 spot-on formulation (6.7% fipronil and 50% permethrin, w/vol).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) greater than 6 months old.; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment and dewormed and did not harbor fleas at the initiation of the study. Dogs were separated by gender and ranked as follows: dogs weighing <18.14 kg were ranked first and then dogs weighing ≥18.14 kg were ranked in descending order of individual pre-treatment flea counts. Within each gender the dog weighing less than 18.14 kg with the highest pre-treatment flea count and the dog weighing ≥ 18.14 kg with the lowest pre-treatment count were allocated to Group 2 (treatment group). The remaining 12 dogs were blocked into 6 blocks of two animals each and within each block were randomly allocated to Group 1 (control) or Group 2. Laboratory breed strain (ClinVet – 2004, routinely fed on cats) of *Ctenocephalides felis* were used in the artificial infestations. Each dog was infested with 100 fleas on Day -6 and on Day -1. After treatment the dogs were kept in individual pens. Flea counts were conducted on Day -5 and on Day 0 (day of application) at 2, 6, and 12 hours after treatment.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Ten in the treated group; six in the negative control group.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 20±4°C; 12/12 light cycle.

Data or endpoints collected/recorded: Flea counts were conducted on Day -5 and on Day 0 (day of application) at 2, 6, and 12 hours after treatment.

Data analysis: Efficacy calculations were based on geometric means, and specifically on the geometric means of the flea data (count +1). One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live fleas on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live fleas on dogs in the treatment group (Group 2) at a specific time point.
Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on flea counts for the various assessment days were calculated and tabulated.

RESULTS

Raw data were not included in the study report. One protocol deviation was reported; two female dogs with the lowest pre-treatment flea count in the lower weight category (<18.14 kg) were excluded instead of the two female dogs with the lowest pre-treatment count per weight category because no female dog in the heavy weight category could be excluded. Flea counts for the negative control group and the treated group are shown in Table 1. Percent efficacy is shown in Table 2.

Table 1. Mean Flea Counts in the Control and Treated Groups.

Day, hr	Group 1, Negative Control		Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
-5	67.5	67.0	75.3	73.7[a]
0, + 2 hr	71.5	71.3	55.4	48.1[a]
0, + 6 hr	71.0	70.9	8.1	4.0[b]
0, +12 hr	70.7	70.5	0.4	0.3[b]

[a]Not statistically significantly ($p > 0.05$) different from the control group on Day -5 and on Day 0, +2 hr.
[b]Statistically significantly ($p < 0.05$) different from the control group.

Table 2. Percent Efficacy Based on Geometric Means of Product 104.05 Against Fleas.

Day, hr	Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean
0, + 2 hr	22.5	32.5
0, + 6 hr	88.6	94.4
0, +12 hr	99.4	99.6

Study Author's Conclusions

The test product (104.05) killed >90% of the fleas on the treated dogs within 6 hr and >99% within 12 hr following administration.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was met within 6 hr post administration. Note: the reported a.i. concentrations in the product tested (6.7% fipronil and 50% permethrin wt/vol) do not exactly match the label concentration (6.01% fipronil and 44.88% permethrin, presumably on a wt/wt basis). The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis. The use of the geometric means in the data analysis was not adequately explained, although it could be argued that the results for each dog can be considered independent variables.

The study author stated that the application was one spot between the shoulder blades. The body weight of the study animals ranged between 10.2 kg (22.5 lb) and 20.2 kg (44.5 lb). On the label it is stated to apply the product evenly to three spots on the dog's back for medium (22-44.9 lb) or large dogs (45-88.9 lb).

Reviewer's Recommendations

Acceptable if the registrant can verify that the concentrations of the a.i. in the test product are the same as those on the label for "Effitix Topical Solution for Dogs" or are within the certified upper and lower limits of the product as specified on the CSF. Results support the label claim that the product starts killing fleas within 6 hr.

Note: The reported test concentrations (6.7% fipronil and 50% permethrin) were expressed on a wt/vol basis (p. 11 of 36 in MRID 485107-01). Other MRIDs in Task 2-30 30 (e.g., MRID 484671-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, the label concentrations.

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TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-22. Fourie J.J. 104.05: Efficacy Study Against *Rhipicephalus sanguineus* in Dogs: Duration of Action. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

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Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: [signature]
Date: OCT 19 2011

Secondary Reviewers:
Gene Burgess, Ph.D.

Signature: Gene Burgess, AE
Date: OCT 19 2011

Robert Ross, M.S., Program Manager

Signature: [signature]
Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: [signature]
Date: OCT 19 2011

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DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-22.** 104.05: Efficacy Study Against *Rhipicephalus sanguineus* in Dogs: Duration of Action. Fourie, J.J. December 9, 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, Virbac SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	09/12/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specificed by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided

FORMULATION TYPE: Topical solution

PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb
ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.

PROPOSED LABEL MARKETING CLAIM: ...can kill ticks for at least a month.

STUDY REVIEW

Purpose: To test the duration of action of 104.05 spot-on formulation against *Rhipicephalus sanguineus* ticks in dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa

Test Material(s): 104.05 spot-on formulation (6.7% fipronil and 50% permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) older than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment; dewormed and "did not harbor ticks at the initiation of the study." Dogs were kept in individual pens 1.9 m by 2.97 m. Laboratory breed strain (French) of *Rhipicephalus sanguineus* were used in the artificial infestations. Immature ticks were fed on rabbits. Adult ticks at least one week old were used in the infestations (50% male and 50% female). Each dog received 50 unfed adult ticks on Day -6, Day 0 (2 hr ±15 min prior to treatment), and on Days +7, +14, +21, +28, +35, +42, +49, +56 and +63. After treatment, the dogs were kept in individual pens. Tick counts were conducted on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65.

Treatments, including untreated control: 0.1 mL/kg

Number of replicates per treatment: One

Number of individuals per replicate: Six in the treated group and six in the control group.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: ~20 ± 4°C; 12/12 light cycle

Data or endpoints collected/recorded: Tick counts were conducted on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65. The ticks were categorized as being alive or killed and in three subgroups: free, attached and unengorged, or attached and engorged (the latter category was not included during the 24 hr in situ count on Day 1. The ticks counted and removed during the 48 hr assessments were categorized according to gender. Dogs were sedated with medetomidine hydrochloride (1.0 mg/mL) to facilitate tick infestation.

Data analysis: Efficacy calculations were made for each treatment group at each assessment day. Efficacy was based on geometric means of the tick data (count +1). One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live ticks on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks on dogs in the treatment group (Group 2) at a specific time point.

Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on tick counts for the various assessment days were calculated and tabulated.

RESULTS

Raw data sheets were included in the study report. No deviations from the study protocol were reported. Mean tick counts for the negative control group and the treated group are shown in Table 1. Percent efficacy is shown in Table 2. The immediate efficacy assessed after 24 hr was 47.1%; at 48 hr it was 86.6%. Greater than 90% efficacies were recorded up to 51 days post treatment with the exception of Day +37 when it was 87.3%.

Table 1. Mean Tick Counts in the Control and Treated Groups

Day	Group 1, Negative Control		Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
-4	25.5	24.0	25.2	24.8
+1[a]	18.0	17.7	11.3	9.3[b]
+2	18.7	16.9	3.0	2.3[b]
+9	20.2	19.3	0.0	0.0[b]
+16	25.8	23.5	0.0	0.0[b]
+23	27.5	26.8	0.0	0.0[b]
+30	27.0	26.4	1.7	1.5[b]
+37	34.2	32.3	6.2	4.1[b]
+44	25.5	23.3	2.0	1.0[b]
+51	27.2	26.3	3.0	1.6[b]
+58	34.8	34.6	8.2	4.2[b]
+65	29.7	29.2	12.2	7.2[b]

[a]In situ counts
[b]Group 2 differed statistically significantly ($p < 0.05$) from Group 1.

Table 2. Percent Efficacy Based on Geometric Means of Product 104.05 Against Ticks

Day	Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean
+1[a]	37.0	47.1
+2	83.9	86.6
+9	100.0	100.0
+16	100.0	100.0
+23	100.0	100.0
+30	93.8	94.2
+37	82.0	87.3
+44	92.2	95.5
+51	89.0	94.0
+58	76.6	87.8
+65	59.0	75.2

[a]In situ counts

Study Author's Conclusions

A 7-week duration of action (>90%) was recorded against *Rhipicephalus sanguineus* ticks in dogs. No treatment related adverse effects occurred.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was met. The reported a.i. concentrations in the test product (6.7% fipronil and 50% permethrin) do not exactly match the label concentration (6.01% fipronil and 44.88% permethrin). The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis.

Reviewer's Recommendations

Acceptable if the registrant can verify that the concentrations of the a.i. in the test product are the same as those in "Effitix Topical Solution for Dogs" (see NOTE below). Results support the label claim that the product kills ticks for at least a month.

NOTE: Although not specifically stated in the study report, the reported test concentrations (6.7% fipronil and 50% permethrin) may have been based on weight per volume measurements. Other MRIDs in Task 2-30 indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-23. Fourie, J.J. 104.05: Efficacy Study Against *Dermacentor variabilis* on Dogs: Duration of Action. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: [signature]
Date: OCT 19 2011

Secondary Reviewers:
Gene Burgess, Ph.D.

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Date: OCT 19 2011

Robert Ross, M.S., Program Manager

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Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-23.** 104.05: Efficacy Study Against *Dermacentor variabilis* on Dogs: Duration of Action. Fourie, J.J. December 9, 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau,Virbac SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	09/12/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution

PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb
ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.

PROPOSED LABEL MARKETING CLAIMS: ..can kill ticks for at least a month.

STUDY REVIEW

Purpose: To test the duration of action of 104.05 spot-on formulation against *Dermacentor variabilis* ticks on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.

Test Material(s): 104.05 spot-on formulation (6.7% fipronil and 50% permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) greater than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment; dewormed and "did not harbor ticks." Dogs were kept in individual pens 1.9 m by 2.97 m. Dogs were separated by gender and blocked per gender in blocks of animals weighing <18.14 kg and animals weighing ≥18.14 kg in descending order of individual pre-treatment tick counts. Laboratory breed strain of *Dermacentor variabilis* were used in the artificial infestations. Immature ticks were fed on rabbits. Adult ticks at least one week old were used in the infestations (50% male and 50% female). Each dog received 50 unfed adult ticks on Day -6, Day 0 (2 hr prior to treatment), and on Days +7, +14, +21, +28, +35, +42, +49, +56 and +63. Tick counts were conducted on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Six treated and six controls.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: ~20±4°C; 12/12 light cycle; relative humidity 21.4-68.0% in room C of unit 20.

Data or endpoints collected/recorded: Tick counts were made on Day -4, +1 (in situ), +2, +9, +16, +23, +30, +37, +44, +51, +58, and +65. The ticks were categorized as being alive or killed and also in three subgroups: free, or attached and unengorged, or attached and engorged (the latter category was not included during the 24 hr in situ count on Day 0). The ticks counted and removed during the 48 hr assessments were categorized according to gender. Dogs were sedated with Domitor (1.0 mg medetomidine hydrochloride/mL) to facilitate tick infestation.

Data analysis: Efficacy calculations were made for each treatment group at each assessment day. Efficacy was based on geometric means of the tick data (count +1). One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x ($Gm_c - Gm_t$) / Gm_c, where:

Gm_c = Geometric mean number of live ticks on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks on dogs in the treatment group (Group 2) at a specific time point.
Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on tick counts for the various assessment days were calculated and tabulated.

RESULTS

Data sheets with the individual animal results were included in the study report. Mean tick counts for the negative control group and the treated group are shown in Table 1. Percent efficacy is shown in Table 2. The immediate efficacy assessed after 24 hr was 0%; at 48 hr it was 49.4%. Efficacy values (based on geometric means) >90% were recorded from Day +9 to Day +44.

Table 1. Mean Tick Counts in the Control and Treated Groups

Day	Group 1, Negative Control		Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean
-4	27.3	26.3	28.7	27.2
+1[a]	15.5	14.8	25.3	24.4[b]
+2	19.2	15.5	11.7	7.9[b]
+9	26.2	20.3	0.0	0.0[b]
+16	23.8	21.5	0.0	0.0[b]
+23	28.7	24.9	0.2	0.1[b]
+30	23.7	19.8	0.2	0.1[b]
+37	26.0	23.4	2.0	1.4[b]
+44	17.5	14.6	1.8	0.8[b]
+51	13.3	10.9	4.0	2.0[b]
+58	20.0	18.7	5.5	4.4[b]
+65	14.0	12.0	3.5	3.0[b]

[a]In situ counts
[b]Group 2 differed statistically significantly ($p < 0.05$) from Group 1.

Table 2. Percent Efficacy Based on Geometric Means of Product 104.05 Against Ticks

Day	Group 2, Treated Group	
	Arithmetic Mean	Geometric Mean
+1[a]	0.0	0.0
+2	39.1	49.4
+9	100.0	100.0
+16	100.0	100.0
+23	99.4	99.5
+30	99.3	99.4
+37	92.3	94.0
+44	89.5	94.8
+51	70.0	81.3
+58	72.5	76.7
+65	75.0	74.8

[a]In situ counts

Study Author's Conclusions

Efficacy reached 100% at Day +9. A 6-week duration of action (>90%) was recorded against *Dermacentor variabilis* ticks in dogs. No treatment related adverse effects occurred.

Reviewer's Conclusions

Results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was reached at Day 9 post-treatment and lasted to Day +44. The reported a.i. concentrations in the test product (6.7% fipronil and 50% permethrin) do not exactly match the label concentrations (6.01% fipronil and 44.88% permethrin). The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis.

Reviewer's Recommendations

Acceptable, if the registrant can verify that the concentrations of the a.i. in the test product are the same as those in "Effitix Topical Solution for Dogs" or are within the certified upper and lower limits of the product as specified on the CSF.

Note: Although not specifically stated in the study report, the reported test concentrations (6.7% fipronil and 50% permethrin) may have been based on weight per volume measurements. Other MRIDs in Task 2-30 30 (e.g., MRID 484671-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, respectively, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-24. Fourie, J.J. Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus*) and the Cat Flea *(Ctenocephalides felis)* on Dogs: Effects of Shampooing and Periodic Water Immersions. December 9, 2009.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: [signature]
Date: OCT 19 2011

Secondary Reviewers:
Gene Burgess, Ph.D.

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Date: OCT 19 2011

Robert Ross, M.S., Program Manager

Signature: [signature]
Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: [signature]
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**MRID: 484671-24.** Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus)* and the cat Flea *(Ctenocephalides felis*) on Dogs: Effects of Shampooing and Periodic Water Immersions. Fourie, J.J. December 9, 2009.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, Virbac SA
TESTING FACILITY:	ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	09/12/2009
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26^{lh}, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution

	PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.
PROPOSED LABEL MARKETING CLAIMS:	..can kill ticks for at least a month....can start killing adult fleas within 6 hr and lasts for up to three months.

STUDY REVIEW

Purpose: To test the effects of shampooing and periodic water immersion on the efficacy of formulation 104.05 against the brown dog tick (*Rhipicephalus sanguineus)* and the cat flea *(Ctenocephalides felis*) on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitsig Road, Bainsvlei, Bloemfontein, South Africa.

Test Material(s): 104.05 topical spot-on formulation (6.7% fipronil and 50% permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female adult dogs (*Canis familiaris*) greater than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment; dewormed and did not harbor ticks at the initiation of the study. The 24 dogs used in the study were blocked within gender and weight groups (dogs weighing <18.14 kg and dogs weighing ≥18.14 kg) in six subsequent blocks of four dogs each in descending order of individual pre-treatment flea counts. Study groups were assigned to the blocks using randomization through minimization. The block which was not gender balanced was allocated to the control group. The remaining three groups were randomly assigned to the three treatment groups. Group #1 was the negative control (shampooed and water immersed, n=6). Group #2 was treated with the test substance (n = 6). Group #3 was treated with the test substance and shampooed (n = 6). Group #4 was treated with the test substance and water immersed (n = 6). After treatment on Day 0, the dogs were kept in individual pens (1.9 m x 2.97 m). Dogs were infested with 100 fleas on Days -4, 0 (4 hr prior to treatment); +7, +14, +21 and +28. Dogs were also infested with 50 ticks on Days -5, -1, +6, +13, +20, and +27. Shampooing occurred on Day +12; water immersion on Days +12 and +26. Tick and flea counts were conducted on Days -2, +2, +9, +16, +23, and +30. Ticks were categorized as alive or killed, as free or attached, and as engorged or unengorged.

Treatments, including untreated control: 0.1 mL for dogs weighing 2 to 10 kg; 2 mL for dogs weighing >10 kg up to 20 kg; 4 mL for dogs weighing >20 kg up to 40 kg.

Number of replicates per treatment: One per treatment type and one control group.

Number of individuals per replicate: Six.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 20±4°C; 12/12 light cycle

Data or endpoints collected/recorded: Tick and flea counts were conducted on Days -2, +2, +9, +16, +23, and +30. Ticks were categorized as alive or killed, as free or attached, and as engorged or unengorged.

Data analysis: Efficacy calculations were based on geometric means of the tick or flea data (count +1). "One" was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group. Percent efficacy was calculated as follows:

Efficacy (%) = 100 x ($Gm_c - Gm_t$) / Gm_c, where:

Gm_c = Geometric mean number of live fleas (or ticks) on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live fleas (or ticks) on dogs in the treatment groups (Groups 2, 3 and 4) at a specific time point.

Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on tick and flea counts for the various assessment days were calculated and tabulated. The groups were compared pair-wise using ANOVA with a treatment effect after a logarithmic transformation on the tick or flea data (count +1) on each assessment day. In addition, the baseline counts were compared in the same way by an ANOVA across all groups.

RESULTS

Tick counts for the negative control group and the treated groups are shown in Table 1. Percent efficacy for the three treated groups is shown in Table 2.

Table 1. Mean Tick Counts in the Control Group and the Three Treatment Groups

DAY	GROUP 1 - Negative control		GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 – Test substance (104.05); Water impressed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[2]	Arithmetic mean	Geometric mean[2]	Arithmetic mean	Geometric mean[2]
-2	31.5	30.7[1]	29.8	29.5[1]	25.8	25.2[1]	29.7	29.4[1]
+2	27.2	25.7[1]	6.8	6.5[1]	10.3	9.1[1]	4.5	3.8[1]
+9	20.0	18.8[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+16	25.3	22.9[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+23	28.0	27.7[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+30	30.8	30.6[1]	0.0	0.0[1]	0.2	0.1[1]	0.0	0.0[1]

[1]: The groups did not differ statistically significantly (P>0.05) on Day -2
[2]: Treatment Groups 2, 3 and 4 differed statistically significantly (P<0.05) from the negative control Group 1 on all post treatment assessment days
[3]: Groups 4 differed statistically significantly (P<0.05) from Group 3 on Day +2

Table 2. Efficacy Values (%) Against Ticks for the Three Treatment Groups

DAY	EFFICACIES (%)					
	GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 - Test substance (104.05); Water Immersed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean
+2	74.8	75.3	61.3	64.6	79.8	85.4
+9	100.0	100.0	100.0	100.0	100.0	100.0
+16	100.0	100.0	100.0	100.0	100.0	100.0
+23	100.0	100.0	100.0	100.0	100.0	100.0
+30	100.0	100.0	99.5	99.6	100.0	100.0

Flea counts for the negative control group and the treated groups are shown in Table 3. Percent efficacy for the three treated groups is shown in Table 4.

Table 3. Mean Flea Counts in the Control Group and the Three Treatment Groups

DAY	GROUP 1 - Negative control		GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 – Test substance (104.05); Water Immersed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[2]	Arithmetic mean	Geometric mean[2]	Arithmetic mean	Geometric mean[2]
-2	58.2	54.3[1]	48.8	47.7[1]	52.8	51.8[1]	45.3	41.3[1]
+2	51.3	47.9[1]	0.8	0.3[1]	3.7	1.4[1]	1.2	0.8[1]
+9	31.2	26.4[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+16	36.7	35.4[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+23	58.0	56.6[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]
+30	56.0	52.0[1]	0.0	0.0[1]	0.0	0.0[1]	0.0	0.0[1]

[1] The groups did not differ statistically significantly (P>0.05) on Day -2
[2] Treatment Groups 2, 3 and 4 differed statistically significantly (P<0.05) from the negative control Group 1 on all post treatment assessment days

Table 4. Efficacy Values (%) Against Fleas for the Three Treatment Groups

DAY	EFFICACIES (%)					
	GROUP 2 – Test substance (104.05)		GROUP 3 - Test substance (104.05); Shampooed		GROUP 4 – Test substance (104.05); Water Immersed	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean
+2	98.4	99.0	92.9	97.0	97.7	98.4
+9	100.0	100.0	100.0	100.0	100.0	100.0
+16	100.0	100.0	100.0	100.0	100.0	100.0
+23	100.0	100.0	100.0	100.0	100.0	100.0
+30	100.0	100.0	100.0	100.0	100.0	100.0

Study Author's Conclusions

***Ticks*:** Efficacy values based on geometric means were considered primary. Therapeutic efficacies for Groups 2, 3, and 4 were 75.3%, 64.6% and 85.4%, respectively on Day +2. All treatment groups had >90% efficacy against ticks for the duration of the assessment period.

Fleas: Efficacy values based on geometric means were considered primary. Therapeutic efficacies for Groups 2, 3, and 4 were 99.0%, 97.0% and 98.4%, respectively, on Day +2. All treatment groups had 100% efficacy against fleas for all other assessment periods.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when

tested under simulated or actual field conditions." Although the efficacy value for ticks on Day +2 were less than 90%, the recommended performance standard was reached in all three treatment groups by Day +9.

Reviewer's Recommendations

Acceptable, if the registrant can verify that the concentrations of the a.i. in the test product are the same as those in "Effitix Topical Solution for Dogs" or are within the certified upper and lower limits of the product as specified on the CSF. Results for ticks support the label claim that the product "kills ticks for at least a month". Results for fleas do not support the label claim "lasts for three months;" however, they can support a claim of efficacy for up to one month. Label does not have any claims concerning the efficacy against ticks or fleas after treated dogs are shampooed or are immersed in water.

Note: although not specifically stated in the study report, the reported test concentrations (6.7% fipronil and 50% permethrin) may be based on weight per volume measurements. Other MRIDs in Task 2-30 (e.g., MRID 48467I-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-25. Moran, C. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Amblyoma americanum*) on Dogs. October 28, 2010

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-25**. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Amblyoma americanum)* on Dogs. Moran, C. October 28, 2010
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	I. Villard, Virbac SA
TESTING FACILITY:	Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland
STUDY DIRECTOR:	C. Moran, BSc, MAnSc
SUBMITTER:	I. Villard, Virbac SA
STUDY COMPLETED:	28/10/2010
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"The study was conducted in compliance with the OECD Principles of Good Laboratory Practice [ENV/MC/CHEM/(98)17]."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: Fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2

	mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.
PROPOSED LABEL MARKETING CLAIMS:	..can kill ticks for at least a month

STUDY REVIEW

Purpose: To determine the duration of efficacy of a single application of formulation 104.05 against infestations of ticks (*Amblyoma americanum*) on dogs.

MATERIALS AND METHODS

Test Location: Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland

Test Material(s): 104.05 spot-on formulation (nominal 6.7% w/v fipronil and 50% w/v permethrin). Two Certificates of Analysis was included in the study report (actual concentrations: 6.71 and 6.68% w/v fipronil and 50.26% and 50.23% w/v permethrin, respectively).

Test Species Name, Life Stage, Sex and Age: Male and female adult beagle and mixed breed dogs (*Canis familiaris*), ≥ 6 months old.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimatized for seven days. Dogs were grouped within one of two body weight bands; ≤17.9 kg or ≥18.0 kg based on Day -2 body weight measurements. Dogs ≥18.0 kg were ranked in decreasing order of Day -5 tick counts, irrespective of sex. The first two dogs ≥18.0 kg formed a block and were assigned to either the treatment group or the control group using random order numbers. The next two dogs ≥18.0 kg were blocked and assigned to groups in the same way, as was the third two dogs ≥18.0 kg. All remaining dogs were then ranked in decreasing order of Day -5 tick count, within each sex. The first two female dogs were assigned to one of the two groups using the same method as described above, followed by the second and third pair of females and then the remaining males until there were three males and three females in the treatment group and in the control group. Dogs were infested with approximately 50 ±4 viable, unfed adult *Amblyoma americanum* ticks (approximately 50% male and 50% female) on Days -7, 0, 7, 14, 21, 28, 35, and 42. On Day -5, about 48 hr post infestation, ticks were counted and removed from the dogs. On Day 1, ticks were counted, categorized by gender, attachment status, viability and location, but not removed. On Day 2, ticks were counted categorized and removed from the dogs approximately 48 hr after treatment. On Days 9, 16, 23, 30, 37 and 44, ticks were counted, categorized, and removed from the dogs approximately 48 hr post infestation.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One and one control group.

Number of individuals per replicate: Six.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 15-22°C; 53-80% RH

Data or endpoints collected/recorded: On Day 1, ticks were counted, categorized by gender, attachment status, viability and location, but not removed. On Day 2, ticks were counted categorized and removed from the dogs approximately 48 hr after treatment. On Days 9, 16, 23, 30, 37 and 44, ticks were counted, categorized, and removed from the dogs approximately 48 hr post infestation.

Data analysis: Primary efficacy was defined as the geometric mean live tick reduction when compared to the untreated control group. Efficacy was declared at ≥90% tick count reduction compared to the control group.

To calculate efficacy the number of live attached ticks was added to the number of live free ticks. This count was calculated after totaling male and female ticks over all locations from which ticks were collected.

Arithmetic and geometric mean tick counts were calculated for each assessment day and used to calculated percent reduction. The geometric mean was calculated by first applying a natural logarithmic transformation. In cases where the data sets included a zero, geometric means were calculated by adding 1 to all numbers before applying the transformations. The arithmetic mean was calculated for the transformed data. This was then antilogged and 1 was subtracted (if the data sets contained a zero).

Percent efficacy was calculated from Abbott's formula as follows:

Efficacy (% reduction) = 100 x [(Mc – Mt) / Mc], where:

Mc = Geometric mean count in the control group (Group 1) at a specific time point.
Mt = Geometric mean count in the treatment group (Group 2) at a specific time point.

The test and control groups were compared using ANOVA for Days 1, 2, 16, 23, 30, 37, and 44. For study Day 9 the comparisons were on the basis of the numbers of animals with tick present using the non-parametric Fisher's Exact test. All tests were two-tailed with a 5% level of significance.

RESULTS

Results for each individual test animal are included in the study report. Deviations from the study plan are listed below:

1. The Study Plan stated that for the duration of the study the dogs would be housed in Unit 2 at the Glenamoy facilities of Charles River Laboratories Preclinical Services Ireland Ltd. The animals were housed in Unit 1 at the Glenamoy facilities of Charles River Laboratories Preclinical Services Ireland Ltd. The deviation arose due to a mistake in the Study Plan, which was subsequently corrected by amendment. Since the pens used were of the correct size, as stated in Section 8.1 of the Study Plan, and the environmental conditions were the same in Unit 1 and Unit 2, there was no impact on the study.

2. Amendment 1 stated that only four female and five male dogs should weigh ≥18.0 kg on Study Day -7, and that six female and five male dogs should weigh ≤17.9 kg on Study Day -7. In fact four female and four male dogs weighing ≥18.0 kg on Study Day -7 and six female and six male dogs weighing ≤17.9 kg on Study Day -7 were included in the study. The deviation arose due to an oversight on the part of the Study Director. Since the correct number of animals of each weight band were assigned to groups on Study Day -1, there was no impact on the study.

3. The Study Plan stated that for the duration of the study the temperature should remain between 15°C and 21°C and the relative humidity between 30 % and 70 %. On 19AUG09 the temperature reached 22 °C and the relative humidity reached 73 %. On 20AUG09 the relative humidity reached up to 75 % in the morning, and 76% in the afternoon, on 21AUG09 the relative humidity reached 77 % in the morning, and on 25AUG09 the relative humidity reached 75 % in the morning. On 01SEP09 the relative humidity in the study unit reached 80%. Since there was no indication of discomfort or illness in the study animals, and ticks are comfortable in humid conditions there was no impact on the study.

4. As a consequence of the unforeseen occurrence (see Section 14.0 Unforeseen Occurrences above) which took place on 10SEP09 (Study Day 30) some tick count data for animals 15019, 28572, 59347 and 33610 on 03SEP09 (Study Day 23) was lost. As these data had been entered into Excel files and checked and the summary results of all tick counts for all animals are still available, the Study Director is satisfied that there is no impact on the study.

5. The Study Plan stated that during tick infestations all animals would remain in containment boxes for 1 hour (± 5 min) post infestation. On Study Day 7 (18AUG09) animal no. 33610 (Group 2, Test Item) was infested with ticks at 15:27 and removed from the tick containment box at 16:20 – a deviation of 2 minutes. The deviation occurred due to an oversight on the part of the technician who removed the animals from the tick containment boxes. Since the animal was kept in the tick containment box for 53 instead of 55 minutes, and as the attachment rates of ticks in the other animals assigned to Group 2 were similar to those for animal no. 33610, the Study Director is satisfied that this deviation would have had no impact on the study.

6. The Study Plan specified that the ticks would be stored between 85-100% RH at the Entomology Dept. at Charles River Laboratories Preclinical Services Ireland Ltd. While the ticks were stored in the Entomology Dept. at Charles River Laboratories Preclinical Services Ireland Ltd., the relative humidity range was 68% to 99%. As all ticks remained viable and as the attachment rate of the ticks was >25% on 6/8 infestation timepoints (mean % attachment rates were 22.3% and 24.4% on Study Days 1 and 9 respectively), the Study Director is satisfied that the low RH values during the storage period in the Entomology Dept. had no impact on the viability of the ticks or on the study.

7. Blinding was broken on one occasion (Study Day 16: 27AUG09) when the individual who checked the allocation to groups data, and who checked the target volume and dose times and witnessed administration of test item, also performed the tick count of animal no. 54047. As the tick count data from this animal were similar to those recorded for other animals assigned to Group 1 (untreated control) at this timepoint, and similar to the tick counts recorded at other timepoints for this animal, the Study Director is satisfied that the tick count performed on this animal was performed in an unbiased way, that the data are valid and that this deviation had no impact on the integrity of the study.

8. The Study Plan specified that the study would continue only if the efficacy of the test item remained above 80%. On Study Day 30, the efficacy of the test item was 79% but following consultation with the sponsor, it was agreed to continue the study. An amendment was not prepared by the Study Director to allow for the continuation of the study when the efficacy of the test item reached 79%. In the opinion of the Study Director, there was no impact of this deviation on the study as at a timepoint subsequent to Study Day 30 (i.e. Study Day 37, the efficacy of the test item increased to 88%.

Tick counts for the negative control group and the treated group are shown in Table 1.

Table 1. Tick Counts in the Control and Treated Groups

Group No. and Treatment	Animal No.	Study Day							
		1	2	9	16	23	30	37	44
1	54047	13	18	11	19	10	27	17	12
Control	59323	8	11	10	14	12	21	16	15
(No treatment)	87360	6	11	15	24	15	21	15	6
	11786	19	23	17	15	10	24	21	17
	49113	9	11	11	22	18	19	25	25
	24358	12	17	10	18	31	33	32	18
Total		67	91	74	112	102	145	126	93
2	01871	14	5	0	1	1	7	5	9
104.05	22800	20	16	0	4	4	10	8	5
(0.1mL/kg bodyweight)	15019	17	2	0	2	4	13	12	17
	28572	4	3	0	0	0	4	1	2
	59347	9	7	2	0	3	3	0	7
	33510	9	2	0	0	0	0	0	0
Total		73	35	2	7	12	45	26	40

* Figures presented in this table include both Live Attached and Live Free Ticks.

The percent efficacy of the test product against *Amblyoma americanum* ticks, based on geometric and arithmetic means, for each assessment day was as follows:

- -3% (geometric means) and -9% (arithmetic means) on study day 1
- 70% (geometric means) and 62% (arithmetic means) on study day 2
- 98% (geometric means) and 97% (arithmetic means) on study day 9
- 96% (geometric means) and 94% (arithmetic means) on study day 16
- 91% (geometric means) and 88% (arithmetic means) on study day 23
- 79% (geometric means) and 69% (arithmetic means) on study day 30
- 88% (geometric means) and 79% (arithmetic means) on study day 37
- 69% (geometric means) and 57% (arithmetic means) on study day 44

Statistically significant differences between the control and treated group in number of live ticks were seen on Days 2, 16, 23, 30, 37, and 44.

Study Author's Conclusions

The results of this study demonstrate that a single administration of the Test Item (104.05: fipronil 6.7% w/v, permethrin 50% w/v) at a dose rate of 0.1 mL/kg bodyweight, to beagle and mixed breed dogs, was effective (efficacy ≥ 90%) against *A. americanum* on Study Days 9, 16 and 23 post treatment, with some residual control of ticks (efficacy was approximately 80%) on Study Day 30 and Study Day 37.

A single topical application of the Test Item (104.05) was well tolerated.

Reviewer's Conclusions

The results support the conclusions of the study author. Although adequate efficacy against *Amblyoma americanum* ticks was demonstrated on Days 9, 16 and 23, efficacy was only 79% on Day 30. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions."

Reviewer's Recommendations

Unacceptable. The label claim that the product kills ticks for at least a month, is not fully supported.

Note: The reported nominal test concentrations were 6.7% w/v fipronil and 50% w/v permethrin. Other MRIDs in Task 2-30 (e.g., MRID 484671-26) indicate that 6.7% w/v fipronil and 50% w/v permethrin are equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin, respectively, the label concentrations.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-26. Moran, C. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7% w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Ixodes scapularis*) on Dogs. December 1, 2010

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-26.** The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7% w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Ixodes scapularis*) on Dogs. Moran, C. December 1, 2010.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	I. Villard, Virbac SA
TESTING FACILITY:	Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland
STUDY DIRECTOR:	C. Moran, BSc, MAnSc.
SUBMITTER:	I. Villard, Virbac SA
STUDY COMPLETED:	22/03/2010
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"The study was conducted in compliance with the OECD Principles of Good Laboratory Practice [ENV/MC/CHEM/(98)17]."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not

provided.

PROPOSED LABEL MARKETING CLAIMS: ..can kill ticks for at least a month.

STUDY REVIEW

Purpose: To determine the duration of efficacy of a single application of formulation 104.05 against infestations of ticks (*Ixodes scapularis*) on dogs.

MATERIALS AND METHODS

Test Location: Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland

Test Material(s): 104.05 spot-on formulation (Nominal 6.7% w/v fipronil and 50% w/v permethrin w/v; equivalent to 6.01% w/w fipronil and 44.88% w/w permethrin). Actual concentrations of two analyses: 6.75% w/v fipronil w/v and 51.36% w/v permethrin, and 6.68% w/v fipronil w/v and 50.23% w/v permethrin. Certificates of Analysis included in study report.

Test Species Name, Life Stage, Sex and Age: Male and female adult beagle and mixed breed dogs (*Canis familiaris*), ≥ 6 months old.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Animals were housed singly in rooms measuring approximately 2 m x 2 m x 2 m and acclimatized for seven days prior to testing. Animals were grouped within one of two body weight bands; ≤17.9 kg or ≥18.0 kg based on Day -2 body weight measurements. Dogs ≥18.0 kg were ranked in decreasing order of Day -5 tick counts, irrespective of sex. The first two dogs ≥18.0 kg formed a block and were assigned to either the treatment group or the control group, using random order numbers. The next two dogs ≥18.0 kg were blocked and assigned to groups in the same way, as was the third two dogs ≥18.0 kg. All remaining dogs were then ranked in decreasing order of Day -5 tick count, within each sex. The first two female dogs were assigned to one of the two groups using the same method as described above, followed by the second and third pair of females and then the remaining males until there were three male and three females in the treatment group and in the control group. Dogs were infested with approximately 40 ±4 viable, unfed adult ticks *Ixodes scapularis* (25 ± 2 females and 15 ± 2 males) on Day -7, and with 50 ±4 ticks (30 ± 2 females and 20 ± 2 males) on Days 0, 7, 14, 21, 28, 35, and 42, and with 35 ±4 (30 ± 2 females and 5 ± 1 males) on Day 49. On Day 0, the dogs were infested with ticks 2 hr ± 10 min prior to being treated. Dogs were sedated to facilitate tick infestation and tick counting. Group #2 dogs were treated once on Day 0 (2 hr ± 4 min post infestation). Group #1 dogs were not treated. Ticks were counted, categorized and removed from the dogs on Days -5, 2, 9, 16, 23, 30, 37, 44, and 51, approximately 48 hr post infestation. Ticks were counted and categorized but not removed from the dogs on Day 1. The number, sex, attachment status, viability and location on the dog of each tick were recorded at each assessment time.

Treatments, including untreated control: Maximum of 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Three males and three females in the treated group and the same numbe rof each in the control group.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 15-20°C; 25-65% relative humidity.

Data or endpoints collected/recorded: The number, sex, attachment status, viability and location on the dog of each tick were recorded at each assessment time.

Data analysis: Efficacy calculations were based on geometric means, and specifically on the geometric means of the live free and attached female tick counts. The geometric mean was calculated by first applying a natural logarithmic transformation. In cases where the data set contained a zero, a "1" was added to all numbers before applying the transformation. The arithmetic mean was calculated for the transformed data. This was then anti-logged and "1" was subtracted (if the data sets contained a zero).

Efficacy was calculated using Abbott's formula as follows:

Percent reduction (Efficacy = $100 \times (Gm_c - Gm_t) / Gm_c$, where:

Gm_c = Geometric or arithmetic mean count in the control group (Group 1) at a specific time point.
Gm_t = Geometric or arithmetic mean count in the treatment group (Group 2) at a specific time point.
The test and control groups were compared using ANOVA for Study Days 1, 2, 30, 37, 44, and 51. For Study days 9, 16, and 23, comparisons were on the basis of the numbers of animals with ticks present using the non-parametric Fisher's exact Test.

RESULTS

Data for each individual test animal and control are included in the study report. Data were adjusted for control mortality using Abbott's formula. Deviations from the study plan included:

1. On Study Day 37 sedation was reversed in two dogs before the 90 min time period specified in the protocol
2. The minimum relative humidity in the tick storage cabinet on most days was less than the 85% specified in the protocol, but with the exception of 9 data points it was >75% (within 10% of the acceptable range).
3. The maximum relative humidity was below the specified range on two occasions when it was 36 and 84%.

Tick counts for the control group and the treated group for each time interval are shown in Table 1. Percent efficacy for each time interval is shown in Table 2.

Table 1. Total Live Female Tick Counts

Group No. and Treatment	Animal No.	Study Day								
		1	2	9	16	23	30	37	44	51
1	62807	17	19	27	17	22	18	23	21	15
Control	29561	17	21	25	14	20	22	22	7	16
(No treatment)	70872	13	19	20	10	16	12	21	19	21
	44062	23	23	21	12	23	25	20	23	26
	21577	15	16	23	19	22	24	22	16	18
	24313	12	19	26	16	23	14	23	16	24
Total		97	119	142	88	126	115	131	102	120
2	99561	5	0	0	0	0	1	1	5	5
104.05	57619	2	0	0	0	0	2	0	3	5
(0 mL/kg bodyweight)	71865	10	1	0	0	0	0	0	0	1
	29532	0	2	0	0	0	0	0	0	0
	75621	6	2	0	0	1	3	4	5	5
	32705	6	5	0	0	0	0	1	4	1
Total		43	10	0	0	1	6	15	22	24

[1] Figures presented in this table include both Live Attached Female and Live Free Female Ticks.
Each animal was infested with 3x12 female *Ixodes scapularis* on Study Days 0, 7, 14, 21, 28, 35, 42 and 49

Table 2. Percent Efficacy Based on Arithmetic and Geometric Means of 104.05 Against *Ixodes scapularis* Ticks.

Day	Arithmetic Mean (%)	Geometric Mean (%)
1	56	59
2	91	94
9	100	100
16	100	100
23	99	99
30	95	96
37	89	93
44	76	83
51	80	85

Study Author's Conclusions

Analysis of homogenity indicated that there were no differences between the control and test groups in terms of body weight or tick counts on Study Day -5.

The test product was effective (≥90% efficacy) against *Ixodes scapularis* ticks on Study Days 2, 9, 16, 23, 30, and 37, with some residual control on Days 44 (83%) and 51 (85%).

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was reached for over one month.

Reviewer's Recommendations

Acceptable. Results support the label claim that the test product, formulation 104.05, kills ticks for at least one month, although 100% mortality was only achieved at two time intervals.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-27. Monzali, C. 2011. Determination of of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
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Task Order No. 2-30

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DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	484671-27. Determination of of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs. Monzali, C. April 6, 2011.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, Virbac SA
TESTING FACILITY:	Avogadro, Parc de Génibrat, 31470 Fontenilles, France
STUDY DIRECTOR:	C. Monzali.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	06/04/2011
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study... was performed in accordance with....and the principles of Good Laboratory Practices including: EC principles of Good Laboratory Practices (Directive 2004/10/EC of the European Parliament and Council of the 11 FEB 2004)..."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: Fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not

provided.

PROPOSED LABEL MARKETING CLAIMS:	"... (prevents blood feeding by) (and) (kills) (and) (repels) ... mosquitoes for up to 4 weeks (a[one] month). Kills mosquitoes for up to four weeks (a[one] month)."

STUDY REVIEW

Purpose: To test the efficacy of 104.05 topical solution against *Aedes aegypti* mosquitoes on dogs.

MATERIALS AND METHODS

Test Location: Avogadro, Parc de Génibrat, 31470 Fontenilles, France

Test Material(s): 104.05 topical solution (6.7% w/v fipronil and 50% w/v permethrin). A Certificate of Analysis for the test product was included in the study report.

Test Species Name, Life Stage, Sex and Age: Short hair Beagle dogs and long hair Golden retriever cross dogs (10 males, 5 short hair and 5 long hair) and 4 females (short hair); age 8.8-15.3 months; weights 9.0-11.3 kg for the beagles and 20.8-27.4 kg for the retrievers.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 12 days prior to treatment during which time they were tested for ability to host mosquitoes by being exposed for 30 min to 40-67 unfed female mosquitoes (*A. aegypti*) at least 2 days old. Dogs allowing a feeding rate of >40% were considered good hosts. Twelve animals were randomly allocated into two groups: one control group of six animals (2 long hair males, 2 short hair males and 2 short hair females); and one test group of treated animals (2 long hair males; 2 short hair males and 2 short hair females). Six blocks of animals were formed based on body weight, and one animal from each block was randomly assigned to one of the two groups. Two animals were swapped in order to balance the groups with respect to the results of the infestation received during acclimatization. The test product (0.1 mL/kg) was administered to the dogs in the treatment group (between the shoulder blades) on Day 0. After treatment the dogs were kept in individual pens. The dogs in both groups were exposed for 28-35 min to unfed female mosquitoes on Day 1 (91-114 mosquitoes), Day 7 (88-108), Day 14 (51-121), Day 21/22 (44-110), Day 28 (87-111) and Day 35-37 (89-136). Dogs were sedated during infestations. Afterwards, the mosquitoes were collected, the dogs removed from the exposure cages and returned to their housing, and at 52-92 min after the beginning of the exposure, dead and alive mosquitoes were counted. The mosquitoes were frozen, crushed to determine if they had a blood meal and then the number of fed and unfed mosquitoes was determined.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One.

Number of individuals per replicate: Six in the treated group and six in the control group.

Length of exposure to treatment (time in seconds, minutes or hours): Topical application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: 14.4-21.0°C; 16-80% RH; 12/12 light cycle.

Data or endpoints collected/recorded: Mosquito mortality rate (%) as well as mosquito blood feeding rate (%) were determined.

Data analysis: Efficacy calculations were calculated from Abbott's formula, by comparing the geometric mean number of blood fed mosquitoes from the treated group to the geometric mean of the number of blood fed mosquitoes from the control group:

Anti-feeding Efficacy (%) = 100 x [(FC – FT)/FC], where:

FC = geometric mean of the number of blood fed mosquitoes from the control group
FT = geometric mean number of blood fed mosquitoes from the treated group

The killing efficacy was determined by comparing the mortality of mosquitoes between the control and treated groups after the 30-min exposure period:

Killing Efficacy (%) = 100 x [(LC – LT)/LC], where:

LC = geometric mean number of live mosquitoes in the control group.
FT = geometric mean number of live mosquitoes in the treated group.

RESULTS

Individual animal results were presented in the study report. Deviations from the study protocol were as listed below:

- The two animals nos.160612 and 251448 were housed in the treated group room since 09 FEB 2010 but were treated 8 days later, on 17 FEB 2010.

- During acclimatisation: dogs were exposed to 40 – 67 unfed female mosquitoes (*A. aegypti*) of at least 2 days old instead of 50 ± 5. During the other infestations, dogs were exposed to 87 – 136 unfed female mosquitoes instead of 100 ± 10 and 44 – 63 unfed female mosquitoes instead of 50 ± 5 at Day 14, for the 4 dogs nos.251092, 251448, 258217 and 160612 and Day 21 for the 8 dogs nos.251561, 258329, 251819, 258075, X1PAL2, X2PAC9, X1PAC6 and X2PAD2.

- Dog no.258329, from Day 10 to Day 37, received 600g of food daily in two times instead of 300g once daily, because he lost weight. Times of the second food distribution were not recorded in the raw data.

- Dogs were fed between 3 hours 07 minutes and 7 hours 52 minutes instead of about four hours post exposure.

- Some dogs received an anti-parasitic treatment within two months before Day 0: short hair dog no.251092 received an anthelminthic treatment (fenbendazole) on 24 DEC 2009 and the five long hair dogs nos.2CHP252, X1PAL2, X2PAC9, X1PAC6 and X2PAD2 received an ear anti-parasitic treatment (fipronil 10%, approximately 1mg/kg) on 18 JAN 2010. These treatments had no repellent or killing impact on mosquitoes.

- Maximum and minimum temperatures and relative humidity of treated dogs room were not recorded on the last day of the in-life phase (27 MAR 2010).

- The 4 dogs nos.251092, 251448, 258217 and 160612 were infested at Day 22 instead of Day 21 and Day 37 instead of Day 35 because of an insufficient number of unfed female mosquitoes of at least 2 days old. Nevertheless, we can consider that Day 22 was equivalent to Day 21 and Day 37 was equivalent to Day 35.

- For dog no.251819, the test item dose volume was rounded to the nearest 0.05 mL, instead of the nearest 0.1 mL.

- Temperature in the exposition room was maintained between 23.2°C and 31.2°C, instead of 24°C and 30°C, and relative humidity was maintained between 40 and 95%, instead of 40 and 80%.

- Dogs were exposed to female mosquitoes for 28 to 35 minutes instead of 30 minutes and dead and alive mosquitoes were counted at 52 minutes to 1h32 (corresponding to 92 minutes) post beginning of exposure, instead of 60 minutes.

Mosquito mortality rates are shown in Table 1. Mosquito blood feeding rates are shown in Table 2. Mosquito anti-feeding efficacy and mosquito killing efficacy of Product 104.05 are shown in Table 3.

Table 1. Mosquito Mortality Rates (%) in Control and Treated Dogs

Long + short hair dogs		Time						
Group	Mosquito mortality rate (%)	Acclimati-sation	Day 1	Day 7	Day 14	Day 21/22	Day 28	Day 35/37
untreated	arithmetic mean	0.0	0.2	0.2	0.0	0.0	0.0	0.0
	SD	0.0	0.4	0.4	0.0	0.0	0.0	0.0
	geometric mean	0.0	0.1	0.1	0.0	0.0	0.0	0.0
treated	arithmetic mean	0.0	33.5	36.2	34.8	27.9	31.2	22.2
	SD	0.0	25.7	28.1	28.1	21.4	20.8	24.8
	geometric mean	0.0	24.6	19.1	19.4	13.5	22.9	13.0

Table 2. Mosquito Blood Feeding Rates in Control and Treated Groups

Long + short hair dogs		Time						
Group	Mosquito blood feeding rate (%)	Acclimati-sation	Day 1	Day 7	Day 14	Day 21/22	Day 28	Day 35/37
untreated	arithmetic mean	75.9	51.7	68.8	71.4	53.3	72.1	41.0
	SD	23.5	25.4	13.4	17.8	22.8	20.3	24.1
	geometric mean	72.1	43.4	67.6	69.6	49.5	69.4	34.2
treated	arithmetic mean	68.9	10.6	9.1	18.8	11.1	24.1	28.2
	SD	26.5	5.4	8.6	14.4	5.0	9.0	14.8
	geometric mean	63.4	9.3	6.2	13.5	9.7	22.6	25.3

Table 3. Mosquito Anti-Feeding Efficacy and Mosquito Killing Efficacy of Product 104.05

	Efficacy (%)	Day 1	Day 7	Day 14	Day 21/22	Day 28	Day 35/37
Anti-feeding efficacy	Short hair	87.4	96.2	86.1	77.6	77.9	52.5
	Long hair	43.1	65.2	55.9	84.5	39.6	-156.7
	Global	79.2	91.7	79.3	79.8	69.1	17.1
Killing efficacy	Short hair	50.6	59.5	53.9	43.4	43.6	26.0
	Long hair	11.5	6.9	-8.0	-5.5	21.8	-2.5
	Global	40.0	46.5	38.6	30.4	37.1	17.5

Study Author's Conclusions

Short-haired dogs were more susceptible to mosquitoes than long hair dogs. The test product had a more effective anti-feeding (repellency) action than a killing action, especially in short hair dogs. Killing efficacy was no greater than 59.5% (Day 7 for short hair dogs). Anti-feeding efficacy for short and long hair dogs combined was only greater the 90% for one time interval (Day 7).

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard for killing efficacy was not reached in this study. Anti-feeding efficacy (repellency) reached 90% at only one time interval, Day 7.

Reviewer's Recommendations

Unacceptable. The study results do not support the label claim that the product "...(prevents blood feeding by) (and) (kills) (and) (repels) ... mosquitoes for up to 4 weeks (a [one] month). Kills mosquitoes for up to four weeks (a[one] month)."

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-28. Fourie, J.J. Repellence Efficacy Study of 104.05 Against Ticks (*Dermacentor variabilis* and *Rhipicephalus sanguineus*) on Dogs Under Laboratory Conditions. November 3, 2010.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
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Task Order No. 2-30

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Disclaimer

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DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-28.** Repllence Efficacy Study of 104.05 Against Ticks (*Dermacentor variabilis* and *Rhipicephalus sanguineus*) on Dogs Under Laboratory Conditions. Fourie, J.J. November 3, 2010.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	S. Bonneau, MD, Virbac SA
TESTING FACILITY:	ClinVet International, Uitzich Road, Bainsvlei, Bloemfontein, Republic of South Africa
STUDY DIRECTOR:	J.J. Fourie, M.Sc.
SUBMITTER:	S. Bonneau, Virbac SA
STUDY COMPLETED:	21/07/2010
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final]. These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF, and METI)."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: Fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided

FORMULATION TYPE: Topical solution

PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb
ACTIVE INGREDIENT APPLICATION RATE(S): Not provided.

PROPOSED LABEL MARKETING CLAIMS: ..can kill ticks for at least a month.

STUDY REVIEW

Purpose: To test the repellence efficacy, tick killing effect, and tick viability impact of 104.05 spot-on formulation against *Dermacentor variabilis* and *Rhipicephalus sanguineus* ticks on dogs.

MATERIALS AND METHODS

Test Location: ClinVet International, Uitzich Road, Bainsvlei, Bloemfontein, Republic of South Africa

Test Material(s): 104.05 spot-on formulation (6.7% w/v fipronil and 50% w/v permethrin, equivalent to 6.01% w/w firpronil and 44.88% w/w permethrin).

Test Species Name, Life Stage, Sex and Age: Male and female sub adult and adult dogs (*Canis familiaris*) greater than 6 months old; mixed, mainly mongrel.

Test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Dogs were acclimated 7 days prior to treatment (Day -7 to Day -1); dewormed and "did not harbor ticks." Dogs were kept in individual pens 1.9 m by 2.97 m. Twelve dogs were used in the study; 8 dogs <18.14 kg and 4 dogs ≥18.14 kg. The 8 dogs of the smaller weight were blocked into four blocks of two dogs each, and the large dogs were blocked into two blocks of two dogs each. Within each block the dogs were randomly assigned to either Group #1 (negative control) or Group #2 (treated group). Dogs were dosed with 0.1 mL of the test product on Day 0.

Laboratory breed strains of *Dermacentor variabilis* and *Rhipicephalus sanguineus* ticks were used in the artificial infestations. Immature ticks were fed on rabbits. The dogs were infested with 30 unfed adult ticks in an infestation chamber on Day -6 (*R. sanguineus* only), and Days +1, +3, +7, +14, +21, +22, and +28. In situ tick assessments were conducted on Days +1, +3, +7, +14, +21, +22, and +28, 3 hours after infestation. Tick counts, and removals were conducted on Day -5, +2, +4, +8, +15, +22, +23, and +29, 24 hours after the infestations.

Treatments, including untreated control: 0.1 mL/kg.

Number of replicates per treatment: One treated group and one control group.

Number of individuals per replicate: Six treated and six controls.

Length of exposure to treatment (time in seconds, minutes or hours): Spot application between shoulder blades.

Were tested specimens transferred to clean containers? N/A

Experimental conditions: ~20±4°C; 12/12 light cycle.

Data or endpoints collected/recorded: In situ tick assessments were conducted on Days +1, +3, +7, +14, +21, +22, and +28, 3 hours after infestation; tcks were counted but not removed. Ticks were counted and removed on Day -5, +2, +4, +8, +15, +22, +23, and +29, 24 hours after the infestations. The ticks were categorized as being alive or killed and also in three subgroups: free, or attached and unengorged, or attached and engorged (the latter category was not included during the in situ observations). The ticks counted and removed during the 24 hr assessments were categorized according to sex. Ticks found in the infestation chamber after removal of the dogs were categorized as alive, moribund or dead. Dogs were sedated to facilitate tick infestation.

Data analysis: Efficacy calculations were made for each treatment group at each assessment interval. Efficacy was based on geometric means of the tick data (count +1) because of the anticipated low and possibly zero counts at some time period and the likelihood that a normal distribution would not be seen. One was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each treatment group.

In situ tick count efficacy was calculated as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live ticks (alive, free and attached) on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks (alive, free and attached) on dogs in the treatment group (Group 2) at a specific time point.

The groups were compared using an ANOVA with a treatment effect after a logarithmic transformation on the tick data (count +1)

24 hour tick count and removal efficacies were calculated for each species of tick as follows:

Efficacy (%) = 100 x (Gm_c – Gm_t) / Gm_c, where:

Gm_c = Geometric mean number of live ticks (alive, free and attached, unengorged and engorged) on dogs in the negative control group (Group 1) at a specific time point.
Gm_t = Geometric mean number of live ticks (alive, free and attached, unengorged and engorged) on dogs in the treatment group (Group 2) at a specific time point.

The groups were compared using an ANOVA with a treatment effect after a logarithmic transformation on the tick data (count +1)

RESULTS

Data sheets with the individual animal results were included in the study report. Amendments to and deviations from the test protocol are shown below:

Protocol amendment	
Amendment #1:	Effective date 13 July 2010, to the effect that the Day +21 tick (*Dermacentor variabilis* and *Rhipicephalus sanguineus*) infestations and subsequent assessments were repeated on Day +22.
Reason for change:	The attachment of *Dermacentor variabilis* ticks to the dogs were less than expected resulting in low tick counts on the study groups. The low number of ticks which attached could be due to a decrease in tick viability and it was decided to repeat the infestations with a different batch of *Dermacentor variabilis* ticks.
Impact on study:	No foreseen negative impact. Additional results for the week 3 assessments were obtained from the repeated infestation and subsequent assessments.
Protocol deviation	
Deviation #1:	Effective date 20 Aug 2010 to the effect that temperatures in Unit 19 Section E deviated from 01 Jul to 04 Jul 2010 between 0.6 – 1.6 °C from the ranges specified in the protocol.
Reason for deviation:	Air conditioning unit malfunction
Impact on study:	No negative impact
Deviation #2:	Effective date 22 June to 21 July that the maximum temperatures recorded in the temperature controlled room with the humidity containers containing the ticks for viability assessments exceeded the protocol specified maximum temperature of 28°C with up to 1°C on a number of occasions.
Reason for deviation:	Air conditioning unit malfunction
Impact on study:	No negative impact

***Results for Rhipicephalus sanguineus*:**

Twenty-four hour tick counts are shown in Table 1. Twenty-four hour killing efficacy values are shown in Table 2. Three-hour in situ tick counts are shown in Table 3, and 3-hr efficacy values in Table 4. Repellency data for 10-min exposures are shown in Table 5 and tick viability after the 10 min exposures is shown in Table 6.

Table 1. 24-hr Counts of *Rhipicephalus sanguineus* in Control and Treated Groups

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+2	13.2	11.8	0.2	0.1
+4	13.3	12.1	0.0	0.0
+8	12.8	11.3	0.0	0.0
+15	15.2	14.1	0.0	0.0
+22	14.7	13.4	0.0	0.0
+23	18.8	18.2	0.0	0.0
+29	14.2	14.0	0.0	0.0

[1]*Group 2 differed statistically significantly (p<0.05) from the negative control Group 1 on all days.*

Table 2. 24-hr Efficacy of Product 104.05 Against *Rhipicephalus sanguineus*

DAY	EFFICACIES (%)	
	GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+2	98.7	99.0
+4	100.0	100.0
+8	100.0	100.0
+15	100.0	100.0
+22	100.0	100.0
+23	100.0	100.0
+29	100.0	100.0

Table 3. 3-hr Counts of *Rhipicephalus sanguineus* in Control and Treated Groups

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+1	13.2	12.1	3.7	2.8
+3	14.7	14.1	3.2	1.4
+7	14.5	13.7	0.8	0.6
+14	16.2	15.7	1.0	0.6
+21	16.8	15.8	3.0	1.9
+22	17.0	16.6	2.2	1.7
+28	17.3	17.2	3.8	3.7

[1]*Group 2 differed statistically significantly (p<0.05) from the negative control Group 1 on all days.*

Table 4. 3-hr Efficacy of Produet 104.05 Against *Rhipicephalus sanguineus*

DAY	EFFICACIES (%)	
	GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+1	72.2	77.1
+3	78.4	90.3
+7	94.3	95.7
+14	93.8	95.9
+21	82.2	88.2
+22	87.3	90.0
+28	77.9	78.4

Table 5. Repellency Effect of Formulation 104.05 Against *Rhipicephalus sanguineus*

Day	Treatment Group	Mean number of ticks[1]	% Repelled[2]	% Difference vs. Control[3]
+1	Group 1 - Negative control	0.1	0.1	3.1
	Group 2 – IVP (104.05)	1.1	3.2	
+3	Group 1 - Negative control	0.3	0.4	2.5
	Group 2 – IVP (104.05)	1.0	2.9	
+7	Group 1 - Negative control	0.4	0.8	16.7
	Group 2 – IVP (104.05)	5.2	17.5[4]	
+14	Group 1 - Negative control	0.0	0.0	5.4
	Group 2 – IVP (104.05)	1.7	5.4[4]	
+21	Group 1 - Negative control	0.3	0.5	1.1
	Group 2 – IVP (104.05)	0.7	1.6	
+22	Group 1 - Negative control	0.0	0.0	3.3
	Group 2 – IVP (104.05)	1.1	3.3[4]	
+28	Group 1 - Negative control	0.2	0.2	6.4
	Group 2 – IVP (104.05)	1.9	6.6[4]	

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber.*
[2] *Average percent repelled, based on the number of ticks (30) initially infested.*
[3] *Percentage repelled: Difference (Group 2 – Group 1).*
[4] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Table 6. Viability of *Rhipicephalus sanguineus* After 10-min Exposures to Formulation 104.05

Day	Treatment Group	Mean number of ticks[1]	% Ticks dead or moribund[2]			
			10 min	3 Hr	24 Hr	48 Hr
+1	Group 1 - Negative control	0.1	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.1	6.7	17.9	75.0[3]	75.0[3]
+3	Group 1 - Negative control	0.3	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.0	0.0	1.7	60.2[3]	60.2[3]
+7	Group 1 - Negative control	0.4	0.0	0.0	0.4	1.2
	Group 2 – IVP (104.05)	5.2	0.0	62.0[3]	96.6[3]	97.8[3]
+14	Group 1 - Negative control	0.0	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.7	0.0	36.6[3]	65.7[3]	65.7[3]
+21	Group 1 - Negative control	0.3	0.0	0.0	0.0	6.7
	Group 2 – IVP (104.05)	0.7	0.0	8.2	37.1	37.1
+22	Group 1 - Negative control	0.0	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.1	0.0	2.5	6.7	6.7
+28	Group 1 - Negative control	0.2	0.0	0.0	0.0	0.0
	Group 2 – IVP (104.05)	1.9	0.0	0.0	0.0	32.8

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber*
[2] *Cumulative percent of ticks dead or moribund following exposure to treated dogs.*
[3] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Results for Dermacentor variabilis

Twenty-four hour tick counts are shown in Table 7. Twenty-four hour killing efficacy values are shown in Table 8. Three-hour in situ tick counts are shown in Table 9, and 3-hr efficacy values in Table 10. Repellency data for 10-min exposures are shown in Table 11, and tick viability after the 10-min exposures is shown in Table 12.

Table 7. 24-hr Counts of *Dermacentor variabilis* in Control and Treated Groups

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+2	19.8	18.4	0.7	0.4
+4	19.0	17.4	0.0	0.0
+8	14.7	14.0	0.0	0.0
+15	3.2	2.5	0.0	0.0
+22	5.0	4.2	0.0	0.0
+23	3.0	2.7	0.0	0.0
+29	12.3	11.2	0.3	0.3

[1]*Group 2 differed statistically significantly ($p<0.05$) from the negative control Group on all days.*

Table 8. 24-hr Efficacy of Product 104.05 Against *Dermacentor variabilis*

DAY	EFFICACIES (%) GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+2	98.6	97.6
+4	100.0	100.0
+8	100.0	100.0
+15	100.0	100.0
+22	100.0	100.0
+23	100.0	100.0
+29	97.3	97.7

Table 7. 3-hr Counts of *Dermacentor variabilis* in Control and Treated Groups

DAY	EFFICACIES (%) GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean
+1	69.6	76.2
+3	87.3	91.6
+7	91.4	94.3
+14	86.5	91.5
+21	91.2	95.2
+22	94.6	96.6
+28	79.1	80.2

Table 8. 3-hr Efficacy of Product 104.05 Against *Dermacentor variabilis*

DAY	GROUP 1 - Negative control		GROUP 2 – IVP (104.05)	
	Arithmetic mean	Geometric mean	Arithmetic mean	Geometric mean[1]
+1	24.7	24.3	7.5	5.3
+3	22.3	22.0	2.8	1.8
+7	17.5	17.1	1.5	1.0
+14	8.7	8.2	1.2	0.7
+21	5.7	5.4	0.5	0.3
+22	6.2	6.0	0.3	0.2
+28	18.3	17.8	3.8	3.5

[1]*Group 2 differed statistically significantly ($p<0.05$) from the negative control Group 1 on all days.*

Table 9. Repellency Effect of Formulation 104.05 Against *Dermacentor variabilis*

Day	Treatment Group	Mean number of ticks[1]	% Repelled[2]	% Difference vs. Control[3]
+1	Group 1 - Negative control	0.1	0.1	29.1
	Group 2 – IVP (104.05)	7.5	29.2[4]	
+3	Group 1 - Negative control	1.1	3.1	35.8
	Group 2 – IVP (104.05)	10.1	38.9[4]	
+7	Group 1 - Negative control	3.2	11.5	47.4
	Group 2 – IVP (104.05)	16.9	58.9[4]	
+14	Group 1 - Negative control	9.6	40.5	34.6
	GROUP 2 – IVP (104.05)	21.2	75.1	
+21	Group 1 - Negative control	10.2	43.1	26.6
	Group 2 – IVP (104.05)	20.4	69.7	
+22	Group 1 - Negative control	12.8	46.0	29.3
	GROUP 2 – IVP (104.05)	22.0	75.3[4]	
+28	Group 1 - Negative control	2.8	9.8	48.0
	Group 2 – IVP (104.05)	16.0	57.8[4]	

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber.*
[2] *Average percent repelled, based on the number of ticks (30) initially infested.*
[3] *Percentage repelled: Difference (Group 2 – Group 1).*
[4] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Table 10. Viability of *Dermacentor variabilis* After 10-min Exposures to Formulation 104.05

Day	Treatment Group	Mean number of ticks[1]	% Ticks dead or moribund[2]			
			10 min	3 Hr	24 Hr	48 Hr
+1	Group 1 - Negative control	0.1	0.0	0.0	6.7	6.7
	Group 2 – IVP (104.05)	7.5	0.2	52.7[3]	82.5[3]	94.5[3]
+3	Group 1 - Negative control	1.1	0.0	0.0	0.8	0.8
	Group 2 – IVP (104.05)	10.1	0.0	28.4[3]	55.7[3]	58.3[3]
+7	Group 1 - Negative control	3.2	0.0	0.0	0.0	1.7
	Group 2 – IVP (104.05)	16.9	0.0	8.7[3]	45.9[3]	66.7[3]
+14	Group 1 - Negative control	2.21	0.0	0.0	2.1	3.6
	Group 2 – IVP (104.05)	21.2	0.0	0.7	18.2[3]	25.8[3]
+21	Group 1 - Negative control	10.2	0.0	0.0	4.3	12.8
	Group 2 – IVP (104.05)	20.4	0.0	0.1	16.3	33.9
+22	Group 1 - Negative control	12.8	0.0	0.0	0.0	4.6
	Group 2 – IVP (104.05)	22.0	0.0	0.6	2.4[3]	23.3
+28	Group 1 - Negative control	2.8	0.0	0.0	0.0	2.8
	Group 2 – IVP (104.05)	16.0	0.0	0.0	0.0	15.8

[1] *Geometric mean number of total ticks (dead or alive) recovered from the infestation chamber.*
[2] *Cumulative percent of ticks dead or moribund following exposure to treated dogs.*
[3] *Group 2 differed statistically significantly ($p<0.05$) from Group 1.*

Study Author's Conclusions

Results of this study indicate that dogs treated with Formulation 104.05 at a dosage of 0.1 mL/kg were protected from infestations of *Dermacentor variabilis* and *Rhipicephalus sanguineus* for up to 29 days post treatment. Efficacy against *Rhipicephalus sanguineus* was 99% at Day +2 and 100% on all other assessment days. Efficacy against *Dermacentor variabilis* was 97.6% on Day +2 and 100% on every other assessment day except Day +29 when it was 97.7%.

Tick counts conducted 3-hr post treatment indicated that the test product was effective against both species throughout the study. Three-hour efficacy values ranged from 77.1 to 95.9% for *Rhipicephalus sanguineus* and from 78.2 to 96.6% for *Dermacentor variabilis*.

The repellent effect of formulation 104.05 after 10-min exposures was ≤ 16.7% for *Rhipicephalus sanguineus* and 26.6 to 48.0% for *Dermacentor variabilis*.

Unattached *Rhipicephalus sanguineus* tick viability values after the 10-min exposures were very variable due to the small numbers of ticks repelled (mean values of 0.7 to 5.2 were recorded for the treated group); however, a marked difference in the percentage of ticks found dead and moribund was observed between the ticks exposed to the test product and the controls (statistically significant by 3 hr on Days +7 and +14, and by 24 hr on Day +3 and +7). For *Dermacentor variabilis* similar results were obtained, with statistically significant differences from controls seen by 3 hr on Day +1, +3, and +7 and by 24 hour on Day +14.

Reviewer's Conclusions

The results support the conclusions of the study author. OCSPP Test Guideline 810.3300 states that the product should "Provide 90% reduction in pest infestation through a killing action when tested under simulated or actual field conditions." This recommended performance standard was reached for both species of tick for all assessment periods. The concentrations of the active ingredients in the test product were not verified or supported by a Certificate of Analysis.

Reviewer's Recommendations

Acceptable. However, the concentrations of the active ingredients in the test product were not verified by the registrant. Results support the label claim that the test product kills ticks for at least a month.

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID: 484671-29. Villard, I. Summary of Efficacy Data for Effitix™ Topical Solution for Dogs (Fipronil 6.01% and Permethrin 44.88% End Use Product). April 20, 2011.

OCSPP 810.3300. Treatments to Control Pests of Humans and Pets

Product Names: EFFITIX™ TOPICAL SOLUTION FOR DOGS

EPA Reg. No.: 2382-RIT

Decision number: 448350

DP number: 391921

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No. 2-30

Primary Reviewer:
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Date: OCT 19 2011

Quality Assurance:
Jennifer Goldberg, B.S.

Signature: Jennifer Goldberg
Date: OCT 19 2011

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

DATA EVALUATION RECORD

[Primary Reviewer's Name]

STUDY TYPE:	PRODUCT PERFORMANCE
MRID:	**484671-29.** Summary of Efficacy Data for Effitix™ Topical Solution for Dogs (Fipronil 6.01% and Permethrin 44.88% End Use Product). Villard, I. April 20, 2011.
DP BARCODE:	391921
DECISION NO:	448350
SUBMISSION NO:	897940
SPONSOR:	C. Parks, Virbac SA
TESTING FACILITY:	N/A
STUDY DIRECTOR:	N/A
SUBMITTER:	C. Parks, Virbac SA
STUDY COMPLETED:	20/04/2011
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	"This document is a compilation document and is not subject to the requirements of 40 CFR Part 160."
TEST MATERIAL:	PRODUCT NAME: Effitix Topical Solution For Dogs EPA REGISTRATION NO.: 2382-RIT ACTIVE INGREDIENT NAMES: fipronil and permethrin CHEMICAL NAMES: Not provided. A.I %: 6.01% fipronil and 44.88% permethrin PC CODES: 129121 (fipronil) and 109701 (permethrin) CAS NO. Not provided FORMULATION TYPE: Topical solution PRODUCT APPLICATION RATE(S): 1 mL for small dogs and puppies 8 weeks old and older, up to 22.9 lb; 2 mL for dogs 23-44.9 lb; 4 mL for dogs 45-88.9 lb; and 6 mL for dogs 89-132 lb ACTIVE INGREDIENT APPLICATION RATE(S): Not

provided.

PROPOSED LABEL MARKETING CLAIMS:	**Fleas:** ...can start killing adult fleas within 6 hr and lasts for up to three months... **Ticks:** ..can kill ticks for at least a month... **Lice:** can kill sucking biting and chewing lice for a month or longer... **Mites:** ...kills mites... **Biting flies and mosquitoes:** ...(prevents blood feeding by)(and)(kills)(and)(repels) biting flies and mosquitoes for up to 4 weeks (a[one] month). Kills mosquitoes for up to four weeks (a [one] month).

STUDY REVIEW

Purpose: To review the efficacy data for Effitix™ Topical Solution for Dogs against fleas, ticks, mites, lice, mosquitoes, biting flies and sand flies.

BACKGROUND

Effitix™ Topical Solution for Dogs contains two active ingredients: 6.01% w/w fipronil and 44.88% w/w permethrin. The registrant proposes using three types of efficacy data in support of its application for registration of Effitix™ Topical Solution for Dogs: 1) data previously submitted, reviewed and accepted by the Agency for fipronil spot on products and for certain permethrin spot-on products; 2) data published in the open literature on certain permethrin spot on products; and 3) new efficacy studies using Effitix™ Topical Solution for Dogs (MRID numbers were not provided for these studies).

NOTE: In MRID 484671-29 the registrant does not present any of the quantitative data given in the previously submitted and accepted MRIDS for fipronil and permethrin. The published information on permethrin is discussed briefly and copies of the published articles are included in an Appendix to MRID 484671-29. Studies conducted on Effitix™ Topical Solution for Dogs are summarized in MRID 484671-29 in a condensed format.

RESULTS

Data on Efficacy Against Fleas

Data on the efficacy of Effitix™ Topical Solution against fleas on dogs is summarized in Table 1.

Table 1. Summary of Efficacy Data for Effitix™ Topical Solution Against Fleas on Dogs

Test Species	Citation	Result
Cat flea *(Ctenocephalides felis)*	Fourie, J.J. 2009. Efficacy Study Against Fleas (*Ctenocephalides felis*) on Dogs: Onset of Action. December 9, 2009.	Kills >90% of fleas within 6 hr and >99% within 12 hr
Cat Flea *(Ctenocephalides felis)*	Fourie, J.J. 2009. Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus*) and the Cat Flea *(Ctenocephalides felis)* on Dogs: Effects of Shampooing and Periodic Water Immersions.	The use of shampoo or water immersion had no effect on the efficacy of the product; efficacies were 100% after shampooing and

		water immersions.

Data on the efficacy of permethrin against fleas in dogs are summarized in Tables 2 and 3. Data on the efficacy of fipronil against fleas in dogs are summarized in Table 4.

Table 2. Published Data on the Efficacy of Permethrin Against Fleas

EPA Reg. #	Publication	MRID #
773-73	Endris, R. *et al*: Efficacy of two 65% permethrin spot-on formulations against induced infestations of Ctenocephalides felis (Insecta: Siphonaptera) and Amblyomma americanum (Acari: Ixodidae) on beagles. Vet Ther. Spring 2003;4(1):47-55	unknown
773-73	Endris, R. *et al*: Efficacy of three dose volumes of topically applied 65% permethrin against Ctenocephalides felis and Rhipicephalus sanguineus on dogs weighing 30 kg or more. Vet Ther. Winter 2002;3(4):435-40	unknown
773-73	Endris, R. *et al*: Efficacy of two 65 % permethrin spot-on formulations against canine infestations of Ctenocephalides felis and Rhipicephalus sanguineus. Vet Ther. Fall 2002;3(3):326-33	unknown
270-278-43591	Ross, D. *et al*: Efficacy of a permethrin and pyriproxyfen product for control of fleas, ticks and mosquitoes on dogs. Canine Pract. 1997; 22(2):53-58	46006002
Not applicable	Tilley L.P. and Smith W.K.: Tularemia in Blackwell's five-minute veterinary consult: canine and feline, fourth edition, 2007 Blackwell Publishing Professional, p.1365.	Unknown

Table 3. Unpublished Data on the Efficacy of Permethrin Against Fleas

Guideline		MRID #	Claim
810.3300		41038802	Fleas
810.3300		41038803	Fleas
810.3300		43137202	Fleas
810.3300		43137203	Fleas
810.3300		43396409	Fleas
810.3300		43396410	Fleas

Table 4. Unpublished Data on the Efficacy of Fipronil Against Fleas

Guideline	MRID #	Claim
810.3300	43121114	Fleas
810.3300	43121115	Fleas
810.3300	43121116	Fleas
810.3300	43121119	Fleas
810.3300	43121120	Fleas
810.3300	43121121	Fleas
810.3300	43121122	Fleas
810.3300	43444901	Fleas
810.3300	43577701	Fleas
810.3300	43577712	Fleas
810.3300	43577713	Fleas
810.3300	43951701	Fleas
810.3300	44088901	Fleas
810.3300	44942011	Fleas
810.3300	44942106	Fleas
810.3300	45618501	Fleas
810.3300	45620502	Fleas
810.3300	45620503	Fleas
810.3300	45628104	Fleas
810.3300	45628105	Fleas
810.3300	45866901	Fleas

Data on Efficacy Against Ticks

Data on the efficacy of Effitix™ Topical Solution against ticks on dogs are summarized in Table 5.

Table 5. Summary of Efficacy of Effitix™ Topical Solution Against ticks in Dogs

Test Species	Citation	Result
Brown dog tick *(Rhipicephalus sanguineus)*	Fourie J.J. 2009. Efficacy Study Against *Rhipicephalus sanguineus* in Dogs: Duration of Action.	The duration of >90% efficacy was 7 weeks
American dog tick, *(Dermacentor variabilis)*	Fourie, J.J. 2009. Efficacy Study Against *Dermacentor variabilis* on Dogs: Duration of Action.	The duration of efficacy was 6 weeks
Lone star tick, *(Amblyoma americanum)*	Moran, C. 2010. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%, Permethrin 50%) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Amblyoma americanum*) on Dogs.	The duration of efficacy was between 4 and 5 weeks
Deer tick *(Ixodes scapularis)*	Moran, C. 2010. The Duration of Efficacy of a Single Application of 104.05 (Fipronil 6.7%w/v, Permethrin 50% w/v) Compared to a No Treatment Control Against Artifically Induced Infestations of Ticks (*Ixodes scapularis*) on Dogs.	The duration of efficacy was at least 5 weeks
Dog ticks, (*D. variablis and R. sanguineus)*	Fourie, J.J. 2010. Repellence Efficacy Study of 104.05 Against Ticks (*Dermacentor variabilis* and *Rhipicephalus songuineus*) on Dogs Under Laboratory Conditions. November 3, 2010.	Effective for at least one month. 24-hr efficacy against *R. sanguineus* was 100% on day 4, 99% on day 9 and 100% on all other days; 24 hr efficacy against *D. variabilis* was 97.6% on day 2, 100% on day 4, and ≥97.7% on all other days

Brown Dog Tick (*R. sanguineus)*	Fourie, J.J. 2009. Efficacy Study Against the Brown Dog Tick (*Rhipicephalus sanguineus*) and the cat Flea *(Ctenocephalides felis)* on Dogs: Effects of Shampooing and Periodic Water Immersions.	The use of shamopoo or water immersion had no effect on the efficacy of the product; efficacies were ≥99.5% after shampooing and after water immersions.

Data on the efficacy of permethrin against ticks in dogs are summarized in Tables 5 and 6. Data on the efficacy of fipronil against ticks in dogs are summarized in Table 7.

Table 5. Published Data on the Efficacy of Permethrin Against Ticks

EPA Reg. #	Publication	MRID #
773-73	Endris, R. *et al*: Efficacy of two 65% permethrin spot-on formulations against induced infestations of Ctenocephalides felis (Insecta: Siphonaptera) and Amblyomma americanum (Acari: Ixodidae) on beagles. Vet Ther. Spring 2003;4(1):47-55	Unknown
773-73	Endris, R. *et al*: Efficacy of three dose volumes of topically applied 65% permethrin against Ctenocephalides felis and Rhipicephalus sanguineus on dogs weighing 30 kg or more. Vet Ther. Winter 2002;3(4):435-40	Unknown
773-73	Endris, R. *et al*: Efficacy of two 65 % permethrin spot-on formulations against canine infestations of Ctenocephalides felis and Rhipicephalus sanguineus. Vet Ther. Fall 2002;3(3):326-33	Unknown
270-278-43591	Ross, D. *et al*: Efficacy of a permethrin and pyriproxyfen product for control of fleas, ticks and mosquitoes on dogs. Canine Pract. 1997; 22(2):53-58	46006002
773-73	Endris, R. *et al*: Repellency and efficacy of 65% permethrin and selamectin spot-on formulations against *Ixodes ricinus* ticks on dogs. Vet Ther. Spring 2002;3(1):64-71	Unknown

Table 6. Unpublished Data on the Efficacy of Permethrin Against Ticks

Guideline	MRID #	Claim
810.3300	41683903	Ticks
810.3300	43111607	Ticks
810.3300	43396409	Ticks
810.3300	43396410	Ticks

Table 7. Unpublished Data on the Efficacy of Fipronil Against Ticks

Guideline	MRID #	Claim
810.3300	43577712	Ticks
810.3300	43121114	Ticks
810.3300	43121115	Ticks
810.3300	43121117	Ticks
810.3300	43121122	Ticks

Data on Efficacy Against Mosquitoes

Data on the efficacy of Effitix™ Topical Solution against mosquitoes on dogs are summarized in Table 8.

Table 8. Summary of Efficacy Information for Effitix™ Topical Solution Against Mosquitoes in Dogs

Test Species	Citation	Result
Mosquito (*Aedes aegypti*)	Monzali, C. 2011. Determination of a Combination of Fipronil and Permethrin in Topical Solution Against Mosquitoes (*Aedes aegypti*) on Dogs	Anti-feeding efficacy on short hair dogs ranged from 52.5% on day 35/37 to 96.2% on day 7. Anti-feeding efficacy on long hair dogs ranged from -156.7% on day 35/37 to 84.5% on day 21/22. Killing efficacies were 50-60% up to day 21 in short hair dogs, and <12% up to day 28 in long hair dogs.

Data on the efficacy of permethrin against mosquitoes in dogs are summarized in Tables 9 and 10. Data on the efficacy of fipronil against mosquitoes in dogs are summarized in Table 11.

Table 9. Published Data on the Efficacy of Permethrin Against Mosquitoes

EPA Reg. #	Publication	MRID #
773-73	Meyer *et al.*: Repellency and Efficacy of a 65 % Permethrin Spot-on Formulation for dogs against *Aedes aegypti* (Diptera: Culicidae) Mosquitoes. Vet Ther. Summer 2003;4(2):135-143.	Unknown
270-278-43591	Ross, D. et al: Efficacy of a permethrin and pyriproxyfen product for control of fleas, ticks and mosquitoes on dogs. Canine Pract. 1997; 22(2):53-58	46006002

Table 10. Unpublished Data on the Efficacy of Permethrin Against Mosquitoes

Guideline	EPA Reg. #	MRID #	Claims supported
810.3300	773-73	42256901	Kills and repel mosquitoes (4 weeks)
810.3300		43396409	
810.3300		43396410	

Table 11. Unpublished Data on the Efficacy of Fipronil Against Mosquitoes

Guideline	MRID #	Claim
810.3300	45866902	Mosquitoes
810.3300	46019202	Mosquitoes
810.3300	46019201	Mosquitoes

Data on Efficacy Against Mites

Data on the efficacy of Effitix™ Topical Solution against mites on dogs are not available. Permethrin data are summarized in Table 12, fipronil data in Table 13.

Table 12. Published Data on the Efficacy of Permethrin Against Mites

EPA Reg. #	Publication	MRID #
773-73	Endris *et al.*: Efficacy of 65 % Permethrin Applied as a Topical Spot-on Against Walking Dandruff Caused by the Mite, Cheyletiella yasguri in Dogs. Vet Ther. Fall 2000;1(4):273-279	Unknown

Table 13. Unpublished Data on the Efficacy of Fipronil Against Mites

810.3300	43577701	Mites
810.3300	43951701	Mites
810.3300	45612701	Mites
810.3300	45620503	Mites
810.3300	45866901	Mites

Data on Efficacy Against Lice

Data on the efficacy of Effitix™ Topical Solution against lice on dogs are not available. Permethrin data are summarized in Table 14; fipronil data in Table 15.

Table 14. Published Data on the Efficacy of Permethrin Against Lice

EPA Reg. #	Publication	MRID #
773-73	Endris *et al.*: Efficacy of a Topical Spot-on containing 65 % Permethrin against the Dog Louse *Trichodectes canis* (Mallophaga: Trichodectidae). Vet Ther. Spring 2001;2(2):135-139.	Unknown

Table 15. Unpublished Data on the Efficacy of Fipronil Against Mites

Guideline	MRID #	Claim
810.3300	45620501	Lice
810.3300	45628101	Lice
810.3300	45628102	Lice
810.3300	45628103	Lice
810.3300	45628201	Lice

Data on Efficacy Against Biting Flies

Data on the efficacy of Effitix™ Topical Solution against biting flies on dogs are not available. Permethrin data are summarized in Table 16; there are no data for fipronil.

Table 16. Unpublished Data on the Efficacy of Permethrin Against Biting Flies

Guideline	EPA Reg. #	MRID #	Claims supported
810.3300	11556-132, 133, 134, 135	46978901 (2004)	Repels biting flies for three weeks

Data on Efficacy Against Sandflies

Data on the efficacy of Effitix™ Topical Solution against sandflies on dogs are not available. Permethrin data are summarized in Table 17; there are no data for fipronil.

Table 17. Published Data on the Efficacy of Fipronil Against Sand Flies

EPA Reg. #	Publication	MRID #
773-73	Molina *et al.*: Evaluation of a topical solution containing 65 % Permethrin against the Sandfly (*Phlebotomus perniciosus*) in Dogs. Vet Ther. Summer 2001;2(3):261-267.	

Study Author's Conclusions

The study author's conclusions are presented in Table 18.

Table 18. Summary of Data Available on the Efficacy of Effitix™ Topical Solution, Permethrin and Fipronil Against Target Organisms on Dogs

Fleas (*C. felis*)	Repels and kills fleas for up to three months Repel and kills fleas in six hours
Ticks (*R. sanguineus, A. americanum, I. scapularis, I. ricinus, D. variabilis*)	Repels and kills ticks for at least one month Kills 90% of the ticks in 3 hours
Lice	Kills and repels *Trichadectes canis* for up to 4 weeks Kills sucking, biting and chewing lice for a month or longer
Mites (*C. yasguri, S. scabiei* var *canis*)	Kills mites (*C. yasguri*) for up to four weeks Aids in the control of sarcoptic mange mite infestation
Mosquitoes (*A. aegypti*)	Prevents blood feeding, kills, repels mosquitoes for up to one month
Biting flies (*S. calcitrans*)	Prevents blood feeding and repels biting flies for up to three weeks
Sandflies (*P. perniciosus*)	Prevents blood feeding and repels sand flies for up to one month

Reviewer's Conclusions

Information on the efficacy on Effitix™ Topical Solution for Dogs was adequately reviewed. Although the use of permethrin and fipronil efficacy data in support of the registration of Effitix™ Topical Solution for Dogs is justified, the information provided was inadequate. It could not always be determined if the dose rates used in the previously accepted studies were less than or equal to the dose rates proposed for Effitix™ Topical Solution for Dogs. Furthermore, the use of data from products that contain more than one active ingredient was not always clearly justified. For example, data for K9 Advantix is used to support biting fly claims for Effitix™ Topical Solution; however, the presence of imidacloprid in the product, in addition to permethrin, may have affected the results (although the author of MRID 484671-29 claims that imidacloprid "is not itself effective on biting flies"). Study author uses data for a 65% permethrin product to support claims of efficacy against sandflies, and states that the dose rate by kg or lb is equal to or below that for Effitix™ Topical Solution; however, no quantitative data were presented to support this claim.

Reviewer's Recommendations

Unacceptable, but upgradable. The reviewer did not have access to information needed for the supporting permethrin and fipronil studies on lice, mites and biting flies. Sandflies are not listed on the label.