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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

**MEMORANDUM:**

**From**: Kevin Sweeney, Senior Entomologist

**Date**: January 8, 2015

**Subject**: PRODUCT PERFORMANCE DATA EVALUATION RECORD

**This is a primary review.**

**DP barcodes: 423693 and 423696**
**Decision Nos.: 494678 and 494679**
**Submission Nos: 956753 and 956754**
**Action code: R340**
**Product Names: Hartz Reference #143 and #144**
**EPA Reg. Nos: 2596-178 and 2596-179**
**Formulation Type: pet spot-ons**
**Ingredients statement from the label with PC codes includes:**
2596-178 = 9.8% fipronil, pc code 129121; 0.25% pyriproxyfen, pc code 129032; and 11.80% (S)-methoprene, pc code 105402.
2596-179 = 9.8% fipronil, pc code 129121; 0.25% pyriproxyfen, pc code 129032; and 11.80% (S)-methoprene, pc code 105402.
**Application rate(s) of product:** linear dose increments depending upon the weight range as directed by the label.
2596-178 = product dose range from lowest weight class is 0.67 ml (0.023 fl. oz.) (5 lbs) to 4.02 ml (0.136 fl. oz.) (132 lbs.) for the highest weight class.
2596-179 = 1.5 ml (0.051 fl. oz.) applied to cats weighing 3 lbs or more.
**Use pattern:**
2596-178 is a spot-on for dogs. Apply in a continuous band along the dorsal midline from head to tail.
2596-179 is a spot-on for cats. Apply in a single spot between the shoulder blades on the back of the cat.
**OCSPP/OPPTS Guidelines: OPPTS 810.3300.**

**I. Action Requested:** Review cited public literature in support of a label amendment. Registrant has requested that the following claims be added to the labels of both products:

**"Controls flea infestations on treated cats (and kittens) (&kittens) and prevent infestations in the home."**
**"Prevents fleas on treated cats (and kittens) (&kittens) from infesting (reinfesting) your home"**

**II. Background**: The cited literature presents data on a variety of insecticide combinations applied as a spot on to pets. Hartz wishes to use these data to support the above claims, which indicate that applying their product to a pet will control /prevent flea infestations in the home/indoor premises. EPA and Hartz met on October 14, 2014 to discuss these claims and the data needed to support them. Hartz presented a discussion on a new study to EPA and EPA provided input on study design. Concurrently, Hartz advised EPA that the subject amendment was pending and included claims that will be tested in the proposed study. Instead of relying on the proposed study results, they requested EPA to review and rely only on cited published literature to support the claims. EPA advised Hartz that public literature does not stand-alone, but may be used as part of a weight of the evidence approach to supplement a study testing the label claims for control and prevention of fleas in the home.

**III. Study Review:**

**No product specific data were submitted to review. Instead, the registrant submitted a list of public literature citations.**

**MRID49455301. Volume 1: Supplemental Information - White Paper. "Submission of Laboratory and Field Studies to Confirm Topical Parasiticide Applications Control Pre-Existing In-Home Flea Infestations and Specific Support of In-Home Infestation Control Claims for EPA Reg. Nos. 2596-178 and -179."**

The white paper included the following citations. I included the registrants' explanations from their white paper.

**"1. Jacobs, D. E., M. J. Hutchinson, D. Ewald-Hamm. 2000. Inhibition of immature Ctenocephalides felis felts (Siphonaptera: Pulicidae) development in the immediate environment of cats treated with imidacloprid. Journal of Medical Entomology 37 (2): 228-230.**

Jacobs et al. (2000) showed that treated cats had transferred sufficient imidacloprid residues to blankets after a 6 hour contact per day, for 5 days. A new blanket was used each week for 4 weeks. Pre-adult flea viability on blankets was reduced by 100%, 84%, 60% and 74% in the 1st, 2nd, 3rd, and 4th week after treatment, respectively.

**Entomologist's Conclusion: Unacceptable. The product tested was not similar to the subject product.**

**2. Jacobs, D. E., M. J. Hutchinson, D. Stanneck. 2001. Accumulation and persistence of flea larvicidal activity in the immediate environment of cats treated with imidacloprid. Medical and Veterinary Entomology 15: 342-345.**

In another study, Jacobs et al. (2001) used the same test design except for increasing the contact periods to 10 or 20 6-hour blanket contact periods over 2 and 4 weeks, respectively. Results showed that the degree of control was significantly higher after 26 days achieving pre-adult flea control of 100% and 97.4% after 10 or 20 days of blanket exposure, respectively.

**Entomologist's Conclusion: Unacceptable. This study was conducted with an imidacloprid based formulation that was not similar to the subject product.**

**3. Ross, D. H., R. G. Arther, C. von Simson, V. Doyle, M. W. Dryden. 2012. Evaluation of the efficacy of topically administered imidacloprid + pyriproxyfen and orally administered spinosad against cat fleas (Ctenocephalides felis): Impact of treated dogs on flea life stages in a simulated home environment. Parasites & Vectors 5:192.**

Ross et al. (2012) evaluated pre-adult flea control of an orally administered ectoparasiticide versus a topical imidacloprid/pyriproxyfen application. Dogs were housed in pens with floor mats that could be sampled for flea development. Flea infestations were established on-animal 1, 16 and 21 days prior to ectoparasiticide administration. Results showed topical application of the imidacloprid/pyriproxyfen formula resulted in transfer of active ingredients to floor matting. After only 1 week of exposure to treated dogs, floor mat samples provided better than 95% control of adult flea emergence.

While laboratory studies have shown the ability of treated pets to transfer effective amounts of active ingredient within simulated home environments, the same transfer of parasiticide active ingredients under in-home conditions has been demonstrated through field testing.

**Entomologist's Conclusion: Unacceptable. This study was conducted with a formulation that contained spinosad.**

**4. Dryden, M. W., H. Perez, and D. Ulitchny. 1999. Control of fleas on pets and in homes by use of imidacloprid or lufenuron and a pyrethrin spray. JAVMA 215 (I):39-39.**

Dryden et al. (1999) investigated existing household flea infestations. The ability for topical parasiticides and oral parasiticides to control in-home infestations was evaluated. It is critical to note that other flea treatments, either applied to the pets or their surrounds, were not used during the study. As well, no restrictions were made regarding exposure of pets to rain, swimming and outdoor activity. Results showed the incidence of fleas on pets and pre-adult flea populations living in the home were reduced by the topical parasiticide application containing imidacloprid. On-animal flea control was achieved within 1 week and in-home infestation was reduced by 86.8% after 4 weeks.

**Entomologist's Conclusion: Unacceptable. The product tested was not similar to the subject product as it contained an IGR and adulticides not present in this formulation.**

**5. Dryden, M. W., J, M: Denehberg, S. Bunch. 2000. Control of fleas on naturally infested dogs and cats and in private residences with topical spot applications of fipronil or imidacloprid. Vet Parasitol. 93: 69-75.**

In a follow up study, both fipronil and imidacloprid were evaluated for on-animal and infestation control potential. The same conditions existed for no other pesticide treatments being during the test as well as no restrictions on pets' activities or movement. Results showed on-animal control was achieved for both active ingredients after 1 week. In-home infestation control was as well achieved for both active ingredients exceeding 89.0% after 4 weeks. (Dryden et al. 2000).

Infestation control for both of these studies confirms transfer of active ingredients from treated the in-home environment to control pre-adult flea infestations.

**Entomologist's Conclusion: Supplemental. One of the adulticides, fipronil, is present in the formulation at the same level but a complete data set was not provided. Furthermore, the author relied on visual hand counts for assessing flea infestation levels on the animal instead of comb counts.**

**6. Maynard, L. P. Houffschmitt, and B. Lebreux. 2001. Field efficacy of a 10 percent pyriproxyfen spot-on for the prevention of flea infestations on cats. Journal of Small Animal Practice 42: 491-494.**

Maynard et al. (2001) evaluated an IGR only application and the effects it had on in-home flea infestations. Topical application of a 10% pyriproxyfen formula resulted in flea infestation control, measured by 'zero-flea' cats, increasing through the study from 49% control on day 30 to 88% control on day 180. In this study, no restrictions were placed on pets' activities including movement outdoors. It was concluded that appropriately timed topical applications of pyriproxyfen offer a method of flea control in the domestic environment.

**Entomologist's Conclusion: Unacceptable. The formulation is not similar to the subject product and amount of pyriproxyfen applied to the cats is not equivalent to the dose to be delivered by the subject product.**

**7. Dryden, M. W., P. Payne, v. Smith, B. Riggs, J. Davenport, and D. Kobuszewski. 2011a. Efficacy of dinotefuran-pyriproxyfen-permethrin and fipronil-(S)-methoprene topical spot-on formulations to control flea populations in naturally infested pets and private residences in Tampa, FL. Vet. Parasitol. 182:281-286.**

Dryden et al. (2011a) repeated an in-home field trial methodology to investigate a dinotefuran/pyriproxyfen/permethrin topical formula versus topically applied fipronil/(S)-methoprene. The fipronil/(S)-methoprene formula provided in-home pre-adult infestation control greater than 88% after 4 weeks. Greater than 96% was achieved after 6 and 8 weeks showing progressive in-home infestation control over time with monthly treatments.

**Entomologist's Conclusion: Supplemental. The data from the dinotefuran-pyriproxyfen-permethrin formulation are not relevant to this amendment. The data from the fipronil-methoprene combination products provide supporting data that may be useful in a weight of the evidence approach as the concentration of fipronil and methoprene are similar to the subject product. However, these data cannot stand-alone as they are not complete data sets. The % control at 30 days is less than 90% (Study Table 1).**

**8. Dryden, M.W., D. Carithers, A. McBride, B. Riggs, L Smith, J. Davenport, V. Smith, P. Payne, S. Gross. 2011b. A comparison of flea control measurement methods for tracking flea populations in highly infested private residences in Tampa FL, following topical treatment of pets with Frontline® Plus(Fipronil/(S)-Methoprene). Intern J. Appl. Res. Vet. Med. 9:356-367.**

Dryden et al. (2011b) made an assessment of extremely high in-home flea populations with reinfestation pressure from outside environments. A fipronil/(S)-methoprene formula was tested. Significant flea populations existed in the homes studied. Heavy pressure from outdoor wild animal sources existed. With this constant pressure, over the 60 day study, the percent reduction in unfed adult flea emergence from Day 0 and from maximum trap counts in all homes studied were 85.4% and 92.5%, respectively. Under these excessive test conditions, reduction in flea egg production and the transfer of ectoparasiticide active ingredients in the home by treated pets provided significant infestation control.

**Entomologist's Conclusion: Supplemental. The product tested a Merial product containing a similar level of methoprene and fipronil. The data were not collected with the subject product and**

**complete data sets are not available. This citation may be useful in a weight of the evidence approach to supplement a product specific study.**

**9. Dryden, M. W., P. Payne, V. Smith, M. Chwala, E. Jones, J. Davenport, G. Fadl, M. F. Martinez-Perez de Zeiders, K. Heaney, P. Ford, F. Sun. 2013. Evaluation of indoxacarb and fipronil (S)-methoprene topical spot-on formulations to control flea populations in naturally infested dogs and cats in private residences in Tampa FL. USA. Parasites & Vectors 6:366.**

Dryden et al. (2013) also made comparison of formulas containing fipronil/(S)-methoprene versus indoxacarb. The study was done in naturally infested homes. Infestations were noted as the highest ever recorded in Tampa, Florida. Over 2 months, results showed the in-home pre-adult flea infestation control achieved for indoxacarb and fipronil/(S)-methoprene formulas were 97.7% and 84.6%, respectively.

**Entomologist's Conclusion: Supplemental for reasons stated for the previous study.**

**Hartz Conclusions:**
"All studies, both laboratory as well as field studies, document in-home pre-adult flea infestation control can be achieved by topical ectoparasiticide treatments. Specifically, laboratory testing under simulated home conditions have substantiated that effective residues of ectoparasiticide formulas do transfer from treated pets to surrounding surfaces. As seen from field trials, those residues in addition to the reduction in viable eggs being laid on-animal are sufficient to provide pre-adult flea infestation control in the home even under severe adult flea re-infestation pressure.

As for the three field trials discussed above evaluating fipronil/(S)-methoprene topical formulas, and cats were treated with fipronil (9.8% w/w)-(S)-methoprene (8.8% w/w) and fipronil (9.8% w/w) –(S)-methoprene (11.8% w/w), respectively. Results showed flea infestations in the home environment were reduced by over 88% in 4 weeks, by over 92% from peak population counts over 2 months and by over 84% in 2 months. Even with constant heavy pressure from the outside environment, monthly re-applications of a fipronil/(S)-methoprene formula, and no secondary environmental pesticide applications, in-home flea infestations that existed prior to test product application were controlled over a 1 to 2 month period (Dryden et al. 2011a, 2011b, 2013).

These 3 field studies are submitted specifically in support of the claims,

"Controls flea infestations on treated (insert pet) and prevent infestations in the home."

"Prevents fleas on treated (insert pet) from infesting (reinfesting) your home." for EPA registration 2596-178 and 2596-179."

**Entomologist's Conclusion: The Dryden et al. studies provide supplemental evidence that transfer of S-methoprene and fipronil may take place in the home. Light trap data were used to survey for fleas but visual hand-counts on the animal were also used. These studies do not meet GLP requirements and were not conducted under an Experimental Use Permit.**

**IV. Entomologist's Recommendations:**

**1. The cited literature provides supplemental information on the ability of pet spot-on products to control/prevent fleas in the home environment. However, these citations do not stand alone. A GLP experiment must be conducted to show that this product performs as claimed. Therefore, the proposed claims are not acceptable based on citation of literature.**

**The last three studies by Dryden were the most relevant citations but this published literature did not provide the raw data or meet the requirements of GLP. Furthermore, the studies were not**

**conducted with the subject product or with a product that is substantially similar to the subject product.**