Efficacy Review

Date: January 6, 2010

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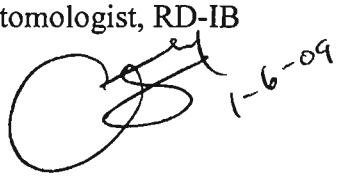

Risk Manager Rev.: Kevin Sweeney

Product: RF 2042 (CDSO)

EPA Reg. #: 2724-796

A.I.'s: Etofenprox (30.0%), S-Methoprene (3.6%), Piperonyl Butoxide (5.0%)

Decision #: 419448

DP #: 369329

Submission: R340, Amendment

MRIDs: Submitted: 47844002

GLP: No

MRID 47844002

Title: RF2042 (CDSO), EPA Reg. No. 2724-796 Summary of Efficacy Data

Guideline: OPPTS 810.3300

Materials and Methods: Various; a summary response to prior efficacy reviews and clarification on new pet dosing proposal

Study Summary of the Results:

1. Adequate flea kill was demonstrated by study 3344 within 15 minutes (i.e., speed of kill claims)
2. Tick control for ADT and BDT exceeded 80% for 30 days
3. Flea control was greater than 90% for 23 days
4. Inhibition of flea development exceeding 98% lasted for 100 days
5. Inhibition of mosquito blood feeding lasted for 28 days for all 3 species of mosquitoes.
6. *Ixodes* tick mortality was greater than 95% for 45 days (*in vitro*).

7. A new dosing scheme is proposed with volume of treatment based on the animal's surface area rather than body weight, for 4 new proposed weight ranges.
8. An argument is presented regarding the placement of parasites from a previous study (along the dorsal midline of the animal rather than anatomically distributed, per the 810.3300 guideline).

Entomologist's Observations/Discussion:

Flea data was reviewed and supports the new proposed speed of kill claim.

While the new dosing scheme (based on a matrix of surface area to weight conversions) is adequate to support the reshuffling of dog weight classes and the addition of a 4.5 mL dosing option, the open-ended top classification still runs the risk of under-treating exceptionally large dogs. While open-ended dosing may be present on other labels, this has been a recurring issue that the Agency seeks to rectify, especially in situations where the top group includes animals as small as 50 lbs. While a 150 lb animal might not require triple the dose of a 50 pound animal (using your proposed dosing scheme as an example, and based on the nature of the surface area to weight relationship you describe), it certainly would require a significantly higher dose than what would be applied to even a median sized animal in what would become a large and highly variable weight class (e.g., certainly dosing for an 80-100 lb dog is not adequate for a 140-150 dog). There must still be adequate dosing classification for dogs weighing greater than 80 pounds on this product label, unless the dosing matrix (comparing weight to surface area) can be extended to show how dosing for animals would calculate out, up to 150 lbs. As currently listed (and presented in the April 1 meeting), the dosing based on surface area for very large dogs was not supported by the presented matrix, and presumably 125-150 lb dogs would receive less than ~1500 g AI/BSA square meter, which is the lowest concentration shown to be efficacious in your studies. Therefore, in that prior meeting, it was decided that dosing could be listed on the label up to the point where the matrix showed that an adequate dose was delivered. It was determined based on the matrix you presented that an 8 mL dose was minimally adequate for dogs weighing up to 125 pounds.

Given the new dosing proposal, and given the desire by the company to have an open ended dosing statement for the largest class of dogs, which would now again include dogs over 125 lbs, a 9 mL dose and dispenser must be included for those dogs 81 lbs and higher (i.e., 'exceptionally large dogs') with appropriate directions for use. A 9 mL dose would ensure adequate a.i. dosing for animals up to a reasonable maximum size encountered in the pet market of 150 lbs. Alternatively, the company would be allowed to revert to the agreement reached at the 1 April meeting, whereby an 8 mL dispenser could be included with a notation on the label indicating that an 8 mL application is adequate to treat dogs between 81 and 125 lbs.

The tick data from Study Number 3268 were reviewed and the data supports the aids in control claim for ticks up to 30 days.

While the registrant argues that placement of ticks along the dorsal midline is common for efficacy studies (to decrease the loss of ticks due to scratching), the 810.3300 guideline is clear in stating that arthropods are to be placed with sufficient anatomical distribution. In addition to

better simulation of natural infestations, this also helps avoid bias in the studies that could occur by placing insects in areas of highest a.i. concentration (especially important for spot-ons, which according to label directions and study protocols, were applied along the dorsal midline). While parasite losses due to scratching are a possible issue, this effect would have been seen in both the treated and control animals and could be addressed by the addition of more parasites. Numerous studies have been submitted to the Agency using the proper anatomical distributions as listed in the guideline without any compromise to the integrity of study statistics or efficacy measurement. This issue is one of the reasons that animals are prequalified for tick and flea infestations, so that study animals can be chosen based upon having high rates of parasite retention. While the flea and tick claims were not and should not be denied outright due to this study shortcoming, the registrant should submit some sort of conditional data demonstrating efficacy to parasites that are properly placed elsewhere on the animal's body. This study would not need to be a full-sized study with animals of all size groups, etc. Instead, the data requirement could be a smaller 2 treatment study (i.e., treatment and control only) on a population of animals in the middle of the company's dosage matrix (i.e., medium sized dogs where the dosage per animal surface area is lowest, e.g. ~1500 g AI/BSA in square meters). Furthermore, such data could be taken from a randomly selected subset of data from another efficacy study being conducted, perhaps for a parallel or future submission.

Overall Review of Efficacy Label Claims and Directions:

1. New dosing as listed on the submitted amended label is acceptable only if an additional classification is made for exceptionally large dogs (81 lbs and up) to be dosed with 9 mL of product. Alternatively, the labeling may revert back to the agreement from the 4-1-09 meeting with the Agency, whereby the old dosing scheme would be used, and an 8 mL treatment would be put in place for dogs between 81 and 125 lbs.

2. The "Aids in control of ticks for up to 30 days" claim is acceptable.

3. "Kills more than 50% of fleas in 2 hours" is acceptable.

4. "[Water resistant][to keep killing fleas and ticks in humid and wet conditions]" is acceptable.