



James McFadden, Ph.D.
Regulatory Project Manager

Wellmark International
1501 E. Woodfield Rd
Suite 200W
Schaumburg, IL 60173

847-330-5369 phone
847-330-5393 fax

jmcfadden@central.com
www.centrallifesciences.com

August 15, 2008

George LaRocca, PM13
Registration Division, RD
Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington VA 22202

Subject: Submission of New Product Application Containing (S)-Methoprene,
Etofenprox and PBO; Product Name: RF2042 [CDSO], 2724-XXX
(Contains Confidential Business Information)

Dear Mr. LaRocca:

Enclosed with this cover letter please find our application for a new product containing the pesticide active ingredients (S)-Methoprene, Etofenprox and PBO. The new product name is RF2042 [CDSO], and is a topical (spot-on) treatment for insect pests on dogs (PRIA Category R310, S4360).

This product is expected to be significantly safer than some of the existing permethrin dog topical products, and so it will provide significant benefits to consumers. Although a reduced risk classification is not possible since this product does not represent a new use, Wellmark believes the product does offer significant benefits to consumers:

- **Reduced Risk to non-target animals.** Cat deaths from permethrin dog topicals are a significant issue at the EPA, and even though the EPA has worked to reduce the potential for cat deaths from these products, fatalities still occur. Since testing shows etofenprox is not highly toxic to cats, the dog topical product will be much safer than existing permethrin dog topical products.
- **Reduced Risk to applicators and children.** Etofenprox has acute mammalian toxicity of category IV and is classified as "not likely" to be a human carcinogen. Since Permethrin has an acute oral toxicity classification in Category III and is classified as a likely human carcinogen, an etofenprox topical product for dogs will provide reduced risk to applicators and children. Note (in this submission) that the RF2042 [CDSO] product was classified in Category IV in acute toxicity studies.

Based on our understanding of the submission requirements, this application includes the following components:

Form 8570-27, Application for Pesticide Registration
Proposed Label, 5 copies
Form 8570-4, Confidential Statement of Formula, 2 copies
Form 8570-27, Formulator's Exemption Statement, 1 copy
Form 8570-34 Certification with Respect to Citations of Data
Form 8570-35 Data Matrix for the RF2042 [CDSO]
Transmittal document for all studies submitted with the application

The reduced risk benefits of the RF2042 [CDSO] are described in more detail in the following paragraphs.

1. **Reduced toxicity to non-target animals.** As discussed on page 1 of this cover letter, issues surrounding the exposure of cats to permethrin by direct or indirect exposure from dog spot-on treatments are a major concern at the EPA. In the EPA's Occupational and Residential Exposure Assessment for permethrin¹, some discussion of HED's review of animal incident data is presented. HED performed an animal incident data review in 2002 and reviewed that database again in April 2004 to note any changes or additions. The EPA summarized that:

For Permethrin containing products, there were 18,466 incidents involving domestic animals reported from April 1, 1998 to March 31, 2002.....Severe adverse reactions, including deaths, in cats intentionally or mistakenly exposed directly to concentrated (45 and 65%) permethrin products or secondarily exposed to treated dogs are a major concern. (emphasis added)

Additionally, the EPA notes that:

There is evidence that a majority of the incidents for Hartz Control One Spot for Dogs and Puppies involve cats. Care reports for the incidents recorded for this product show that the majority of domestic animal deaths reported for this product, 59%, involved cats which were accidentally or intentionally treated with the product and some of the deaths of cats (7%) involved exposure to treated dogs. Symptoms in cats reported before death include tremors, seizures and ataxia. Exposure of cats to permethrin can cause life-threatening toxicosis because cats, as compared to other domestic animals, are relatively deficient in their ability to conjugate xenobiotics with glucuronic acid, which is the most important step in the metabolism of certain substances.

These statements from the EPA indicate there is significant agency concern over cat deaths resulting from accidental direct or indirect exposure to dog spot on products. By comparison, our etofenprox based spot-on products should provide significantly reduced risk to cats, and some of the reasons for that claim are discussed in the paragraphs below:

¹ Permethrin. Third Revision of the Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document., EPA-HQ-OPP-2004-0385-0074, page 20.

In part:

A. The acute toxicity of etofenprox technical is significantly less than the acute toxicity of permethrin technical, so reduced metabolism in cats is less likely to cause significant adverse effects. The LD50 for permethrin technical is 2280 mg/kg in female rats², while the LD50 for etofenprox technical is greater than 42,880 mg/kg³, more than 10 times lower toxicity. Since the acute toxicity of etofenprox is lower than permethrin, the likelihood of significant adverse effects in cats is low, even though metabolism in cats may be reduced.

B. The acute oral toxicity of both of Wellmark's etofenprox spot-on products (based on this submission and MRID 46513404) place them in Toxicity Category IV. The oral acute LD50s for both the Cat Spot-On (2724-504) and this new RF2042 [CDSO] for dogs are greater than 5000 mg/kg in rats, and so both products do not show high acute toxicity.

C. Wellmark has an etofenprox-based cat spot on (EPA Reg. No. 2724-504) that contains 40% etofenprox. Wellmark has conducted and submitted a Companion Animal Safety study (in cats) to support this product (MRID 46513409). The results of this study found that:

No treatment-related findings were noted in food consumption, body weight and clinical pathology indices. The test material, RF2004[CCSO], produced no systemic effects when applied dermally to the dorsal neck area of young adult cats. Minimal dermal effects of unknown cause were noted in three cats at the highest doses.

Since direct application of a formulation containing 40% etofenprox to cats does not cause severe adverse reactions, it can be inferred that accidental direct application or indirect exposure of cats to etofenprox from a dog spot-on treatment should not cause severe adverse effects.

2. As noted on page one of this cover letter, this new product should also provide reduced risk to applicators and children. Etofenprox has acute mammalian toxicity of category IV and is classified as "not likely" to be a human carcinogen³. Since Permethrin has an acute oral toxicity classification in Category III and is classified as a likely human carcinogen, an etofenprox topical product for dogs will also provide reduced risk to applicators and children.

The following paragraphs describe the studies submitted with this application in more detail. Note that some reports refer to RF2042B, which is the designation given to the formula used in testing, while some reports refer to RF2042 [CDSO], which is the proposed product name. In all cases except for the companion animal safety study (as described below), the same formula was used for testing.

New product chemistry and a revised analytical method are provided to support this new product:

1. McFadden, T. (2008), RF2042 [CDSO]: Description of Materials and Formulation Process, unpublished, Wellmark international Study Number 3251, 9pp.
(Note: Contains Confidential Business Information)
2. Thornton, K. (2007) Color, Odor, Physical State, Density, Flammability and Viscosity of RF2042 [CDSO], unpublished, Wellmark International Study Number 3257, 25pp.
3. Witte, J. (2007) Validation of a Chemical Analysis Procedure for the Assay of Active Ingredients in RF2042 [CDSO], unpublished, Wellmark International Study Number 3244, 46pp.

² Permethrin Revised RED, http://www.epa.gov/oppsrtd1/REDS/permethrin_amended_red.pdf

³ See Federal Register Notice for EPA's FQPA Rationale for Etofenprox and subsequent revisions

In addition, a series of five acute toxicology studies is being submitted to support this product:

4. Lowe, C. (2008a) RF2042 [CDSO] Acute Oral Toxicity Up and Down Procedure in Rats, unpublished, Wellmark International Study Number 3271, 16p. (LD50 > 5000 mg/kg, CAT IV)
5. Lowe, C. (2008b) Acute Dermal Toxicity in Rats – Limit Test, unpublished, Wellmark International Study Number 3272, 16p. (LD50 > 5000 mg/kg, CAT IV)
6. Lowe, C. (2008c) RF2042 [CDSO] Primary Eye Irritation Study in Rabbits, unpublished, Wellmark International Study Number 3273, 17p. (slightly irritating, CAT IV)
7. Lowe, C. (2008d) RF2042 [CDSO] Primary Skin Irritation Study in Rabbits, unpublished, Wellmark International Study Number 3274, 17p. (slightly irritating, CAT IV)
8. Lowe, C. (2008e) RF2042 [CDSO] Dermal Sensitization Study in Guinea Pigs (Buehler Method), unpublished, Wellmark International Study Number 3275, 25p. (not a sensitizer)
9. Mizens, M. (2008) RF2042 [CDSO] Request for Waiver of Pesticide Data Requirements, unpublished, Wellmark International Study Number 3474, 7pp.

According to our understanding, an acute inhalation study is not required, according to CFR Title 40 Part 158.500 (The product is not a spray or aerosol, and so use will not result in respirable particles.) It is on this basis that we are submitting a specific waiver request (item 9) to formally ask the EPA to waive the requirement for an acute inhalation study for this product.

Since the toxicity test results show the RF2042 [CDSO] to be classified in Toxicity Category IV for toxicity testing, no signal word is required on the label.

We also include a companion animal safety study with this application, to satisfy the data requirements for OPPTS 870.7200. In previous correspondence, the agency agreed that the test article for this study (30.0% etofenprox, 60% PBO and 10% S-Methoprene) would cover not only this product, but anticipated applications for etofenprox shampoos and pet sprays. (DP Barcode D342633)

10. Stone, R. (2008) Safety of an Experimental JM982 Spot-On Administered Topically to Adult Dogs, unpublished, Wellmark International Study Number 3323, 661 pp.

It is important to note that the design of this companion animal study provides support for retreatment of dogs after one week, if necessary.

However, this study only includes studies for adult dogs, while the draft label submitted with this application includes uses on puppies. An additional companion animal safety study that covers the use on puppies will be submitted in October of this year, along with the application for an etofenprox-based pet spray.

We are asking the EPA to approve the RF2042 [CDSO] use on puppies as a conditional use, pending review of the puppy study to be submitted in October. In part, since this product represents a reduced risk product for non-target organisms (cats) and applicators and children, it will be a benefit to the consumer to get this product into channels of trade as rapidly as possible. Since the study conducted with adult dogs (submitted with this application) shows no adverse effects and the study with puppies will be submitted in time to allow some review prior to registration, the EPA should be able to make some evaluation of the safety of the RF2042 [CDSO] to puppies prior to registration.

A total of three efficacy studies are being submitted to support the efficacy on public health pests:

11. Everett, W. (2008a) Evaluate the Speed of Kill of RF-2042B against Ticks and Fleas on Dogs, unpublished, Wellmark International Study Number 3344, 15 p.
12. Everett, W. (2008b) Evaluate Ovicidal and Adult Cat Flea Efficacy and Tick Efficacy of RF2042B on Dogs, unpublished, Wellmark International Study Number 3268, 20p.
13. Everett, W. (2008c), Efficacy of a Combination of Etofenprox and PBO (RF2042B) as a Topical Spot-On for Dogs Experimentally Infected with Adult *Ixodes scapularis* Ticks and Three Species of Adult Mosquitoes, unpublished, Wellmark International Study Number 3362, 22pp.

The results of the efficacy studies submitted with this application provide supports for claims that:

- The killing action of RF2042 [CDSO] begins within minutes (Study 3344)
- The product kills fleas and ticks, and Kills and repels mosquitoes (Study 3268 and 3362)
- The product kills flea eggs and prevents flea emergence for about 90 days.
- In addition, wetting the dogs did not affect product performance

From Study 3344

Results of this trial indicate that the killing effect of RF2042B initiates within minutes of a parasite acquiring a treated host. Within 15 minutes 38% of the infested fleas had died on the treated animals and 3% of the ticks were dead. Within 48 hours all fleas and 85% of the infesting ticks were dead on the treated host animals.

From Study 3268

RF-2042B provided > 88% control of American Dog Ticks and > 94% control of Brown Dog Ticks at 23 days after treatment. Control of fleas was >94% from Day 1 through Day 23. Inhibition of flea egg hatch was >88% through Day 82 and inhibition of adult flea emergence was >91% through Day 14. A separate group of 3 treated dogs were wetted weekly throughout the study. Wetting these dogs did not dramatically affect the efficacy of the treatment.

For Study 3362

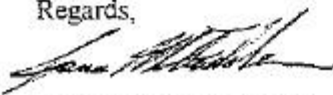
RF2042B provided $\geq 98\%$ in vitro control of Black Leg Ticks through day 45. For *Aedes aegypti* mosquitoes, mortality control was $\geq 95\%$ through day 35 and feeding reduction remained > 94% through Day 42. *Culex quinquefasciatus* mortality control was $\geq 94\%$ only on Day 0 but feeding reduction remained $\geq 95\%$ through Day 28. For *Anopheles quadramaculatus* mortality control was $\geq 98\%$ though day 42 and feeding reduction remained > 83% through Day 35.

Note that *Culex quinquefasciatus* is a species that feeds at night, and so the reduced control with this organism may be an artifact of testing conditions.

Overall, this product provides an effective treatment of fleas and ticks with improved safety for non-target animals and applicators and children. We hope that the EPA will agree that this product would provide significant benefits to consumers, and that registration will be granted as soon as possible.

If you have questions regarding this submission, or require further information, please let me know by e-mail or phone as noted on Page 1.

Regards,



James McFadden, Ph.D.
Regulatory Project Manager