



MEMORANDUM

Via E-Mail

DATE: February 26, 2007

TO: Firm Clients and Friends

FROM: Bergeson & Campbell, P.C.

RE: EPA and FDA Request Information on Insect Repellent-Sunscreen Combination Products

In the February 22, 2007, *Federal Register*, the U.S. Environmental Protection Act (EPA) and Food and Drug Administration (FDA) published separate notices requesting information to determine how they should regulate insect repellent-sunscreen combination products. Both EPA and FDA regulate insect repellent-sunscreen combination products. EPA has regulatory authority because of the insect repellent component, and FDA has regulatory authority because of the sunscreen component.

The issues raised by the notices potentially could be of significance for other products that have dual jurisdiction issues. Both agencies seek comments on issues such as labeling, product performance, and applicable safety standards to determine how these products should be regulated. According to the notices, EPA and FDA will work together to develop a coordinated approach to regulating the combination products. EPA is seeking information to determine how combination products should be regulated so that it can complete the reregistration eligibility decision (RED) for N,N-diethyl-metatoluamide (DEET). FDA is considering amending its monograph for over-the-counter (OTC) sunscreen products to add conditions for marketing combination products. FDA asks interested persons to review and comment on both notices, and submit comments to both agencies. Comments are due **May 23, 2007**.

Background

Currently, there are approximately 20 combination insect repellent-sunscreen products available on the market. Each product contains an insect repellent component (DEET, oil of citronella, or IR3535) and a sunscreen component. The combination products are available in lotion, cream, and spray-on formulations, and are marketed for use by the entire family. When



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EPA issued the RED for DEET, due to concerns about the potential conflict in labeling for the insect repellent and the sunscreen portions of combination products, EPA postponed a decision on whether to reregister the combination DEET/sunscreen products until it could obtain additional information.

Regulatory Status of the Insect Repellent Ingredients

Information regarding the use of insect repellent products is available on EPA's website at <http://www.epa.gov/pesticides/factsheets/chemicals/deet.htm>. In addition to the three insect repellent active ingredients used in combination with sunscreen (DEET, oil of citronella, and IR3535), two other active ingredients are approved for use in insect repellent products (p-methane-3,8-diol and KBR 3023 (picaridin)). Neither p-methane-3,8-diol nor picaridin is currently available in a combination sunscreen formulation. Both DEET and oil of citronella have been reregistered, during which EPA evaluated and analyzed the complete database for both chemicals. IR3535, picaridin, and p-methane-3,8-diol are newly registered active ingredients, which EPA evaluated during the registration process to ensure they met the statutory standard under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

In December 1998, EPA issued the RED for DEET. EPA indicated in the DEET RED: "The Agency is concerned about consumer use of products that combine sunscreen and DEET, since the directions to reapply sunscreens generously and frequently may promote greater use of DEET than needed for pesticidal efficacy, and thus pose unnecessary exposure to DEET." Current DEET labels recommend that products be used sparingly and not be reapplied too often. Sunscreen products, however, recommend frequent reapplication. When EPA issued the DEET RED, it did not make a regulatory decision about whether to reregister combination products because, EPA states, it believed that adequate information was not available. In February 1997, EPA completed the RED for oil of citronella, which includes a comprehensive reassessment of the required target data and the use patterns of currently registered products. IR3535 is the third currently registered insect repellent used in combination with sunscreen. In 1997, EPA classified IR3535 as a biochemical.

Regulatory Status of the Sunscreen Ingredients

On May 21, 1999, FDA promulgated the final monograph for OTC sunscreen drug products in 21 C.F.R. Part 352, establishing conditions under which these products are generally recognized as safe and effective and not misbranded. The monograph includes 16 sunscreen active ingredients in Section 352.10; provides for combinations of sunscreen active ingredients in Section 352.20; specifies required labeling in Sections 352.50, 352.52, and 352.60; and sets forth required testing procedures in Sections 352.70 through 352.77. The initial



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effective date for the final monograph was May 21, 2001, but on December 31, 2001, FDA stayed the effective date until further notice. FDA delayed the effective date to prepare an amendment addressing formulation, labeling, and testing requirements for ultraviolet A (UVA) radiation protection and to revise some of the requirements for ultraviolet B (UVB) radiation protection in a more comprehensive final monograph.

Insect repellent-sunscreen combination products were marketed before FDA began the OTC drug review in 1972, and FDA has not explicitly addressed them at any time in the rulemaking for OTC sunscreen drug products. Because the combination products have always contained a pesticide, they have also historically been registered with and regulated by EPA. FDA has not objected to the marketing of the combination products pending the issuance of the final sunscreen monograph, so long as the products contained sunscreen ingredients included in the FDA rulemaking and were registered with EPA. According to the February 22, 2007, *Federal Register* notices, FDA is interested in determining whether it should amend the monograph to address combination products before the monograph becomes effective. Any combination product containing an active drug ingredient that is not included in the final monograph after the effective date will be considered a new drug and require an approved new drug application (NDA) to be marketed legally, even if the product is also registered with EPA.

Issues Related to Insect Repellent-Sunscreen Drug Products

Below are some of the issues identified by EPA and FDA for comment in connection with the regulation of these combination products:

- **Possible Manufacturing Conflicts:** Any insect repellent/sunscreen combination product would have to comply with EPA's data requirements in 40 C.F.R. Part 158 and with FDA's current good manufacturing practice for finished pharmaceuticals requirements in 21 C.F.R. Part 211. According to the notices, EPA and FDA are not aware of any specific manufacturing requirements that conflict and invite specific comment and information on this subject. FDA also asks for comment on how current combination products should be addressed in the final monograph, and whether any current product manufacturers have conducted any of the testing procedures described in 21 C.F.R. Part 352, Subpart D.

- **Possible Formulation Conflicts:** EPA requested information from registrants of combination insect repellent/sunscreen products regarding the possibility of formulation conflicts. EPA states that it "is aware of some limited, conflicting information, which raises the question of



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whether combining a sunscreen and an insect repellent component in a single product diminishes the efficacy of either the sunscreen or the insect repellent.” EPA and FDA invite specific comments and information on this subject.

■ **Possible Labeling Conflicts:**

- According to the notices, insect repellent/sunscreen products can have labeling requirements for their individual components that could theoretically conflict. Insect repellents must be labeled in accordance with 40 C.F.R. Part 156 and should comply with directions set out in the registration notice or RED for the appropriate active ingredient. Once FDA issues a final sunscreen rule, sunscreens would be labeled in accordance with 21 C.F.R. Sections 201.66, 352.50, 352.52, and 352.60.
- FIFRA does not require that pesticide product labels list the identities of the inert ingredients. Under the Federal Food, Drug, and Cosmetic Act (FFDCA), all OTC drug products must list the inactive ingredients, however. Failure to list all of the inactive ingredients in the product’s labeling, including all such ingredients in the insect repellent, would cause a combination insect repellent-sunscreen drug product to be misbranded under FFDCA Section 502(e)(1)(A)(iii). FDA asks where there is a way to label combination products that satisfies FFDCA’s requirements does not violate FIFRA. FDA also asks whether those ingredients that are “inert” under FIFRA are also necessarily “inactive” under FFDCA.
- Should there be a single integrated label, or would an insect repellent (EPA) and a sunscreen (FDA) section in the product’s labeling be preferable. EPA and FDA are exploring whether it is possible for products to comply with both sets of requirements and recommendations without confusing or misleading users.



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- **Effectiveness Issues:** For some products, there are effectiveness concerns because of the interval of time required between applications of the product. EPA identifies reapplication times on product labels so consumers maintain protection against insect bites, while avoiding over-exposure. The reapplication time identified by EPA relates to the effectiveness of the insect repellent portion of the product, not to the sunscreen protection. The sunscreen reapplication time is under the purview of the FDA. For some of the insect repellent products currently registered, the recommended reapplication time to maintain the effectiveness of the insect repellent could potentially be longer than that recommended to ensure the protectiveness of the sunscreen portion of the product. EPA and FDA request comment on specific product formulation issues and information on any chemical or physical incompatibilities between insect repellents and sunscreen active ingredients when used separately or in combination products.

EPA identifies the following safety issues:

- **Application Frequency:** Combination products could contain conflicting use instructions on product labels, which compromise safe use of these products. For example, some DEET products require a six-hour interval between applications, and their directions state “use just enough repellent to cover exposed skin and/or clothing” and “avoid over-application of this product.” The directions for sunscreen drug products in 21 C.F.R. Section 352.52(d)(1) and (d)(2) state to “apply (select ‘liberally,’ ‘generously,’ ‘smoothly,’ or ‘evenly’), before sun exposure and as needed,” and “reapply as needed or after towel drying, swimming, or (select ‘sweating’ or ‘perspiring’).” EPA invites suggestions on how to alleviate this potential concern.
- **Application Location:** EPA directs that insect repellents not be used for certain areas of the body (*e.g.*, over cuts, applied by spray directly to the face, etc.), and be applied sparingly around ears. Sunscreen use directions, however, encourage consumers to apply the products, on the face and ears, “liberally, generously, smoothly, or evenly” “before sun exposure and as needed,” and “reapply as needed or after towel drying, swimming, or (select ‘sweating’ or ‘perspiring’).” EPA is soliciting comment on how to reconcile the safety concern of a potential misapplication of the insect



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repellent with the need to provide complete coverage of exposed skin for the sunscreen component.

- **FIFRA Registration:** Given its safety concerns and potential conflicts, EPA would like to solicit comments on whether these insect repellent-sunscreen combination products should be registered at all.

FDA states that it is aware of only two studies examining percutaneous absorption when combining an insect repellent with a sunscreen. One study involved hairless mice, and the other study involved piglets. According to FDA, both studies demonstrate increased absorption of the insect repellent DEET and different sunscreens when the components were combined. Thus, FDA would like more information concerning the safety of insect repellent-sunscreen drug products:

- Are there data available to show whether increased absorption of the sunscreen ingredients(s) occurs as a result of being combined with an insect repellent ingredient? For example, is there any evidence that absorption increases as the particle size of titanium dioxide and zinc oxide decreases (down to a few nanometers) in insect repellent-sunscreen products? If so, is there evidence regarding the health or safety effects associated with the increased absorption?
- Are there reports or other information relating to skin irritation resulting from use of a combination insect repellent-sunscreen drug product are manufacturers of these products or others aware of? FDA requests a summary of the types of events reported and, if possible, an estimate of the incidence of occurrence.

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We hope this information is helpful. As always, please call if you have any questions.