9. Ma, R., et al., ''UV Filters With Antagonistic Action at Androgen Receptors in the MDA–kb2 Cell Transcriptional-Activation Assay.'' *Toxicological Sciences,* vol. 74(1), pp. 43–50, 2003.
10. Mueller, S.O., et al., ''Activation of Estrogen Receptor Alpha and ERbeta by 4-Methylbenzylidene-Camphor in Human and Rat Cells: Comparison With Phyto- and Xenoestrogens.'' *Toxicology Letters,* vol. 142(1–2), pp. 89–101, 2003.
11. Schlumpf, M., et al., ''Estrogenic Activity and Estrogen Receptor Beta Binding of the UV Filter 3-Benzylidene Camphor. Comparison With 4-Methylbenzylidene Camphor.'' *Toxicology,* vol. 199(2–3), pp. 109–120, 2004.
12. Schmutzler, C., et al., ''Endocrine Disruptors and the Thyroid Gland—A Combined In Vitro and In Vivo Analysis of Potential New Biomarkers.'' *Environmental Health Perspectives,* vol. 115 (Supplement 1), pp. 77–83, 2007.
13. Schreurs, R., et al., ''Estrogenic Activity of UV Filters Determined by an In Vitro Reporter Gene Assay and an In Vivo Transgenic Zebrafish Assay.'' *Archives of Toxicology,* vol. 76, pp. 257–261, 2002.
14. Seidlová-Wuttke, D., et al., ''Comparison of Effects of Estradiol With Those of Octylmethoxycinnamate and 4-Methylbenzylidene Camphor on Fat Tissue, Lipids and Pituitary Hormones.'' *Toxicology and Applied Pharmacology,* vol. 214(1), pp. 1–7, 2006.
15. Søeborg, T., et al., ''Risk Assessment of Topically Applied Products.'' *Toxicology,* vol. 236(1–2), pp. 140–148, 2007.
16. Tinwell, H., et al., ''Confirmation of Uterotrophic Activity of 3-(4-Methylbenzylidine) Camphor in the Immature Rat.'' *Environmental Health Perspectives,* vol. 110(5), pp. 533–536, 2002.
17. Durrer, S., et al., ''Estrogen Sensitivity of Target Genes and Expression of Nuclear Receptor Co-Regulators in Rat Prostate After Pre- and Postnatal Exposure to the Ultraviolet Filter 4-Methylbenzylidene Camphor.'' *Environmental Health Perspectives,* vol. 115 (Supplement 1), pp. 42–50, 2007.
18. Durrer, S., et al., ''Estrogen Target Gene Regulation and Coactivator Expression in Rat Uterus After Developmental Exposure to the Ultraviolet Filter 4-Methylbenzylidene Camphor.'' *Endocrinology,* vol. 146(5), pp. 2130–2139, 2005.
19. Faass, O., et al., ''Female Sexual Behavior, Estrous Cycle and Gene Expression in Sexually Dimorphic Brain Regions After Pre- and Postnatal Exposure to Endocrine Active UV Filters.'' *Neurotoxicology,* vol. 30(2), pp. 249–260, 2009.
20. Hofkamp, L., et al., ''Region-Specific Growth Effects in the Developing Rat Prostate Following Fetal Exposure to Estrogenic Ultraviolet Filters.'' *Environmental Health Perspectives,* vol. 116(7), pp. 867–872, 2008.
21. Maerkel, K., et al., ''Sexually Dimorphic Gene Regulation in Brain as a Target for Endocrine Disrupters: Developmental Exposure of Rats to 4-Methylbenzylidene Camphor.'' *Toxicology and Applied Pharmacology,* vol. 218(2), pp. 152–165, 2007.
22. Maerkel, K., et al., ''Sex- and Region-Specific Alterations of Progesterone Receptor mRNA Levels and Estrogen Sensitivity in Rat Brain Following Developmental Exposure to the Estrogenic UV Filter 4-Methylbenzylidene Camphor.'' *Environmental Toxicology and Pharmacology,* vol. 19(3), pp. 761–765, 2005.
23. Schlumpf, M., et al., ''In Vitro and In Vivo Estrogenicity of UV Screens.'' *Environmental Health Perspectives,* vol. 109(3), pp. 239–244, 2001. Erratum in: *Environmental Health Perspectives,* vol. 109(11), p. A517, 2001.
24. Schlumpf, M., et al., ''Estrogenic Activity and Estrogen Receptor Beta Binding of the UV Filter 3-Benzylidene Camphor. Comparison With 4-Methylbenzylidene Camphor.'' *Toxicology,* vol. 199(2–3), pp. 109–120, 2004.
25. Schlumpf, M., et al. ''Endocrine Activity and Developmental Toxicity of Cosmetic UV Filters—An Update.'' *Toxicology,* vol. 205(1–2), pp. 113–122, 2004.
26. International Conference on Harmonization (ICH), Guidance for Industry, ''The Need for Long Term Rodent Carcinogenicity Studies of Pharmaceuticals S1A,'' March 1996 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM074911.pdf*).
27. ICH, Guidance for Industry, ''S1B Testing for Carcinogenicity of Pharmaceuticals,'' July 1997 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074916.pdf*).
28. ICH, ''S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals SIC(R2)'' (Revision 1), September 2008 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074919.pdf*).
29. ICH Harmonized Tripartite Guideline for Industry, ''Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2),'' 2005 (available at *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5_R2/Step4/S5_R2__Guideline.pdf*).
30. ICH, Guideline for Industry, ''Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies S3A,'' March 1995 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074937.pdf*).

Dated: February 20, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015–03884 Filed 2–24–15; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. FDA–2008–N–0474]

Over-the-Counter Sunscreen Drug Products—Regulatory Status of Ecamsule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a proposed sunscreen order (proposed order) under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Sunscreen Innovation Act (SIA). The proposed order announces FDA's tentative determination that ecamsule (also known as terephthalylidene dicamphor sulfonic acid) at concentrations up to 10 percent is not generally recognized as safe and effective (GRASE) and is misbranded when used in over-the-counter (OTC) sunscreen products because the currently available data are insufficient to classify it as GRASE and not misbranded, and additional information is needed to allow us to determine otherwise.

DATES: Submit either electronic or written comments on this proposed order by April 13, 2015. Sponsors may submit written requests for a meeting with FDA to discuss this proposed order by March 27, 2015. See section VI for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: *http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *Mail/Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must clearly identify the specific active ingredient (ecamsule) and the Docket No. FDA–2008–N–1474 for this

rulemaking. All comments received may be posted without change to *http://www.regulations.gov,* including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket numbers, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Submit requests for a meeting with FDA to discuss this proposed order to Kristen Hardin (see **FOR FURTHER INFORMATION CONTACT**).

FOR FURTHER INFORMATION CONTACT: Kristen Hardin, Division of Nonprescription Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5491, Silver Spring, MD 20993–0002, 240–402–4246.

SUPPLEMENTARY INFORMATION:

I. Regulatory Background

A. Regulatory and Statutory Framework

The data and information addressed in this proposed order were originally submitted for review under FDA's Time and Extent Application (TEA) regulation, § 330.14 (21 CFR 330.14), a process that has since been supplemented with new statutory procedures established in the SIA (Pub. L. 113–195), enacted November 26, 2014. The discussion that follows briefly describes and compares the TEA and SIA processes as they apply to the regulatory status of ecamsule.

The TEA regulation established a process through which a sponsor could request that an active ingredient or other OTC condition,[1] particularly one not previously marketed in the United States, be added to an OTC drug monograph to enable compliant OTC drug products containing the condition to be marketed in the United States without an approved new drug application (NDA) or abbreviated new drug application (ANDA). Because this proposed order specifically addresses an OTC sunscreen active ingredient (ecamsule), the remainder of this discussion will refer only to ''active ingredients.''

Critical steps in a proceeding under the TEA regulation include the following: (1) FDA's determination that an active ingredient had been marketed for the proposed OTC use for a material time and to a material extent (eligibility determination), and public call for submission of safety and efficacy data, followed by; (2) review of safety and efficacy data submitted by the sponsor or other interested parties; and (3) FDA's initial determination that the data show the active ingredient to be either GRASE or not GRASE for OTC use under the applicable monograph conditions (including any new conditions rising from FDA's review) (GRASE determination). Under the TEA regulation, FDA's GRASE determinations are effectuated through notice and comment rulemaking to amend or establish the appropriate monograph.

The TEA process in FDA regulations was supplemented by Congress's enactment of the SIA. Among other amendments it makes to the FD&C Act, the SIA creates new procedures specifically for reviewing the safety and effectiveness of nonprescription sunscreen active ingredients, including those, such as ecamsule, that were the subject of pending TEA proceedings at the time the SIA was enacted. Like the TEA regulation, the SIA calls for an initial eligibility determination phase for nonprescription sunscreen active ingredients, followed by submissions of safety and efficacy data and a GRASE determination phase. However, the SIA requires FDA to make proposed and final GRASE determinations for nonprescription sunscreen active ingredients in the form of administrative orders rather than the multistep public rulemaking required by the TEA regulation, and establishes strict timelines for the necessary administrative actions.

Among other requirements, no later than 90 days after the SIA was enacted (*i.e.,* no later than February 24, 2015), FDA must publish a proposed sunscreen order in the **Federal Register** for any nonprescription sunscreen active ingredient, including ecamsule, for which, on the date of enactment, an eligibility determination had been issued under the TEA regulation and submissions of safety and efficacy data received, and for which a TEA feedback letter had not yet been issued (section 586C(b)(4) of the FD&C Act (21 U.S.C. 360fff-3(b)(4)), as amended by the SIA). Other provisions of the SIA that are not discussed in this proposed order address procedures applicable to other pending and future sunscreen active ingredient GRASE determinations, pending and future GRASE determinations for OTC products other than sunscreens, issuance of specified guidances and reports, and completion of pending sunscreen rulemakings, among others.

A proposed sunscreen order under the SIA is an order containing FDA's tentative determination proposing that a nonprescription sunscreen active ingredient or combination of ingredients: (1) Is GRASE and is not misbranded when marketed in accordance with the proposed order; (2) is not GRASE and is misbranded; or (3) is not GRASE and is misbranded because the data are insufficient to classify the active ingredient or combination of ingredients as GRASE and not misbranded, and additional information is necessary to allow FDA to determine otherwise (section 586(7) of the FD&C Act, as amended by the SIA). Publication of a proposed sunscreen order triggers several timelines under the SIA, including a 45-day public comment period, and a 30-day period in which a sponsor may request a meeting with FDA to discuss the proposed order.

B. FDA's Review of Ecamsule

L'Oreal asked FDA to include ecamsule in concentrations up to 10 percent as an active ingredient in the OTC sunscreen monograph in a TEA submitted September 19, 2007. FDA announced on September 12, 2008, that ecamsule had been found eligible in concentrations up to 10 percent to be considered for inclusion in the OTC sunscreen monograph (21 CFR part 352, currently stayed), and requested submissions of safety and effectiveness data to support a GRASE determination for the requested OTC use (73 FR 53029). L'Oreal submitted safety and efficacy data on ecamsule to the designated docket (FDA–2008–N–0474) on November 14, 2008 (ecamsule data submission). At the time the SIA was enacted, FDA had not issued a TEA feedback letter or otherwise responded to that submission.

In accordance with new section 586C(b)(4) of the FD&C Act as amended by the SIA, we are issuing this notice as a proposed order for ecamsule. Based on our review of the ecamsule data submission, we have made a tentative determination that ecamsule is not GRASE for OTC sunscreen use and is misbranded because the data are insufficient to classify it as GRASE and not misbranded, and additional

[1] For purposes of OTC drug regulation, a ''condition'' is defined as an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration marketed for a specific OTC use, with specific exclusions (see § 330.14(a)(2)). This document will refer simply to new ''active ingredients,'' since that is the condition under consideration.

information is necessary to allow us to determine otherwise. The remainder of this proposed sunscreen order describes our review of safety and efficacy data, identifies additional data needed to demonstrate that ecamsule is GRASE for the requested use, and explains our rationale for specific conclusions and data requirements.

This proposed order will be open for public comment (see **DATES**). The sponsor may request a meeting with FDA to discuss this proposed order (see **DATES**). We also invite the sponsor to submit additional safety and/or efficacy data to inform our further consideration, as publication of a final sunscreen order for ecamsule under the SIA will be contingent on receipt of such information. (See section 586C(b)(9)(ii) of the FD&C Act.) We specifically encourage the sponsor to discuss any proposed study protocols with us before performing the studies.

II. Safety Data Considerations for OTC Sunscreen Products Containing Ecamsule

In evaluating the safety of a proposed monograph active ingredient, FDA applies the following regulatory standard: Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (§ 330.10(a)(4)(i) (21 CFR 330.10(a)(4)(i))).

FDA's OTC drug regulations generally identify the types of information that may be submitted as evidence that an active ingredient or other OTC drug condition is safe, as part of the consideration of whether an active ingredient or other condition is GRASE (§ 330.10(a)(2)). For convenience, this order uses the term ''generally recognized as safe (GRAS)'' to refer to that aspect of the GRASE determination. To apply the general OTC safety standard to each potential new condition, FDA uses its scientific expertise to determine what constitutes ''adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use.'' In assessing what specific testing or other data are needed to adequately demonstrate the safety of ecamsule for use in sunscreen, FDA considers the circumstances under which OTC sunscreen products that could contain ecamsule would be used by consumers.

When used as directed with other sun protection measures, broad spectrum OTC sunscreen products with a sun protection factor (SPF) value of 15 or higher strongly benefit the public health by decreasing the risk of skin cancer and premature skin aging associated with solar ultraviolet (UV) radiation, as well as by helping to prevent sunburn. (Sunscreens with lower SPF values, or without broad spectrum protection, also help prevent sunburn.) When used as directed by the required labeling, all OTC sunscreen products are applied liberally to the skin and reapplied frequently throughout the day (§ 201.327(e) (21 CFR 201.327(e))). Because the effects of UV exposure are cumulative, to obtain the maximum benefit, users of broad spectrum sunscreens with an SPF value of 15 or higher are directed to use such products regularly—on a routine basis (*id.*). Given these conditions of use, our safety evaluation of an OTC sunscreen active ingredient such as ecamsule must consider both short-term safety concerns (such as skin sensitization/irritation and photosafety) and potential concerns related to long-term sunscreen use, including potential systemic exposure via dermal absorption.

The purpose of the safety testing described in this section II is to establish whether an OTC sunscreen product containing ecamsule and otherwise marketed under the conditions described in a final sunscreen order and in accordance with all requirements applicable to nonprescription drugs would be GRAS for use as labeled. To demonstrate that these requirements are met for ecamsule, initial safety testing should be performed using ecamsule as the sole active ingredient up to the highest concentration for which marketing status is sought and eligibility has been established: 10 percent. If initial testing suggests a particular safety concern associated with ecamsule (*e.g.,* a hormonal activity), FDA may request additional studies to address that concern.

A. Human Safety Data

1. Human Irritation, Sensitization, and Photosafety Studies

Studies of skin irritation, sensitization, and photosafety are standard elements in the safety evaluation of topical drug products that, like ecamsule-containing sunscreens, are applied to the skin repeatedly over long periods of time. FDA recommends separate studies for skin irritation and sensitization. Skin irritation studies should generally include at least 30 evaluable subjects and should evaluate the test formulation (*i.e.,* ecamsule in an appropriate test vehicle), the vehicle alone, and both negative and positive controls. Skin sensitization studies generally should include at least 200 subjects and should evaluate the test formulation containing ecamsule, the vehicle, and a negative control. For both irritation and sensitization studies, test site applications should be randomized and the test observer blinded to the identities of the test formulations.

FDA recommends that photosafety evaluation generally involve studies of skin photoirritation (phototoxicity) and skin photosensitization (photoallergenicity). General principles for designing and conducting photosafety studies are described in FDA guidance (Ref. 1). Photosafety studies, like sensitization and irritation studies, should be conducted using ecamsule 10 percent in an appropriate test vehicle, the vehicle alone, and a negative control. In addition, phototoxicity studies should include at least 30 evaluable subjects and photoallerginicity studies should include at least 45 evaluable subjects.

Data Available for Ecamsule: Human Irritation, Sensitization, and Photosafety Studies

We received information regarding 26 non-U.S. human dermal safety studies evaluating formulations containing up to approximately 4 percent ecamsule with one or more other additional active ingredients (Note 1). These studies exposed a total of approximately 1,500 adults to formulations containing ecamsule. Reports of 21 of these studies were complete: 2 of these studies assessed primary cutaneous irritation, 7 assessed cumulative irritation and sensitization potential, 9 assessed phototoxicity potential, and 3 assessed photosensitizing potential. However, the information provided in the 21 complete study reports does not meet FDA's current standards to support the human dermal safety of ecamsule at any concentration. All of these studies assessed formulations containing more than one active ingredient and therefore provide only limited insight into the safety of ecamsule. Furthermore, the formulations used in these studies included ecamsule only in concentrations of between 0.33 percent and 3.96 percent, and therefore would

not support a determination that ecamsule is GRAS at concentrations between 3.96 percent and 10.0 percent as found eligible for review and requested for GRASE evaluation by L'Oreal. Other deficiencies noted included:

- Failure to provide individual skin reaction scores to negative controls in all studies.
- Failure to enroll a sufficient number of subjects in the sensitization, phototoxicity, and photoallergenicity studies.
- Although the cumulative irritation studies enrolled an adequate number of evaluable subjects, there was a failure to indicate whether positive controls were used, and only three study reports indicated a negative control was used.
- Failure to indicate whether or not investigators in the primary cutaneous irritation, phototoxicity, and photoallergenicity studies were blinded to patch applications.
- Failure to indicate whether the phototoxicity and photoallergenicity studies included vehicle controls.

The ecamsule data submission also included reports for 14 studies exposing a total of over 500 children primarily between 3 and 12 years of age to sunscreen formulations containing ecamsule in concentrations of 1.5 percent to 9 percent, with 1 or more other additional active ingredients (Note 2). Numerous dermatologic reactions were reported; however, none were considered serious.

Three human safety-related literature citations listed in the submission were limited to studies describing photoallergic reactions to combination sunscreen products formulated both with and without ecamsule (Note 3). One publication described a single case of photoallergy to an ecamsule-containing sunscreen product (Ref. 2). A second publication was a review that summarized published and unpublished data from a single center's experience with patch and photopatch testing in a consecutive series of 402 patients who presented to a photobiology unit from 1981 to 1996 with suspected clinical photosensitivity (Ref. 3). The authors did not observe allergy or photoallergy to 1 percent ecamsule, but experience with ecamsule was limited in this study because it was included in the sunscreen series beginning in 1995, towards the end of the 15-year study period. The third publication was a case report describing no photoallergy to an ecamsule-containing combination sunscreen drug product in a 71-year-old male patient with persistent photocontact allergy to other UV filters (Ref. 4). A literature search conducted by FDA did not identify additional publications regarding the human dermal safety of ecamsule in concentrations up to 10 percent for use as an OTC sunscreen.

FDA concludes that the data submitted are not sufficient to assess the dermal safety of ecamsule in concentrations up to 10 percent and specifically its potential to cause irritation, sensitization, photoirritation, or photoallergenicity. Submission of data from human irritation, sensitization, and photosafety studies that meet FDA standards (see section II.A.1) is recommended to demonstrate that an OTC sunscreen product containing up to 10 percent ecamsule is not an irritant, sensitizer, photosensitizer, or photoirritant.

2. Human Dermal Pharmacokinetic (Bioavailability) Studies

Because sunscreens are topically applied, another important safety consideration for ecamsule for use in sunscreens is whether dermal application may result in skin penetration and systemic exposure to ecamsule, and if so, to what extent. A well-designed and -conducted human dermal pharmacokinetic study can be expected to detect and quantify the presence of ecamsule and/or any metabolites in blood or other bodily fluids that may have a bearing on safety, using recognized parameters such as bioavailability percentage, maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), total area under the plasma concentration versus time curve (AUC), half-life, clearance, and volume of distribution. This information can help identify potential safety concerns and help determine whether an adequate safety margin for sunscreens containing ecamsule exists. FDA recommends that the pharmacokinetic studies performed on ecamsule also collect additional safety-related data from regularly scheduled physical examinations, collection of vital signs, and other measures, which may help capture adverse skin events or other potential safety signals. To ensure that maximum penetration of ecamsule has taken place and chances of it being detected are optimal, studies should continue until steady state is reached.

General information and recommendations on the design and conduct of human pharmacokinetic studies can be found in FDA guidance (Ref. 5). To support a GRAS determination for ecamsule (up to 10 percent), such a study should be conducted under maximal use conditions using ecamsule up to 10 percent in various vehicles, including vehicles that would be expected to enhance absorption. We encourage study sponsors to consult with us before conducting pharmacokinetic studies, because the properties of ecamsule bear on the optimal design.

Data Available for Ecamsule: Human Dermal Pharmacokinetic (Bioavailability) Studies

Human dermal pharmacokinetic studies for ecamsule were submitted in response to our call for data. We reviewed one in vitro study that evaluated the potential for dermal penetration of topically applied ecamsule from human skin samples (Note 4). Because this study was not designed to detect or quantify ecamsule in the blood or other body fluids, it provides no useful information about systemic exposure. One urinary excretion study conducted with a 4.95 percent ecamsule test formulation suggested minimal systemic absorption in seven male volunteers dosed over an extensive body surface area for a total of 5 days (Note 5). A study in which radiolabeled 2 percent ecamsule was topically applied to the forearms of five male volunteers and retained for 4 hours detected a minimal level of radiation above background in urine after dosing but radiation levels above background were not detected in blood (Note 6). Although this study suggests that ecamsule is minimally absorbed following dermal application, the study formulation contained ecamsule at a concentration much lower than the requested 10 percent maximum and only a small number of subjects were dosed over a limited surface area. The last human dermal pharmacokinetic study assessed the absorption of 3 percent ecamsule from a formulation containing a total of four active ingredients (Note 7). The formulation was applied to an extensive body surface area of six male subjects twice daily for 8 days. Results showed that there were quantifiable plasma concentrations of ecamsule at several time points, suggesting that ecamsule is absorbed via dermal application. None of the submitted human dermal pharmacokinetic studies assessed an adequate number of subjects, or tested ecamsule at the maximum requested concentration of 10 percent.

Our literature search found no additional publications regarding human pharmacokinetics of ecamsule. Accordingly, we request data from human pharmacokinetic studies to assess the potential for and the extent of systemic absorption. These studies should be performed under expected

maximal use conditions with the proposed maximum concentration, as discussed previously in this section, in a sufficiently large study population to control for both gender and age.

3. Human Safety Data To Establish Adverse Event Profile

An evaluation of safety information from adverse event reports and other safety-related information derived from commercial marketing experience of sunscreen products containing ecamsule, as well as from other sources, is a critical aspect of FDA's safety review for ecamsule. The TEA regulation under which the original request for ecamsule was submitted specifically calls for submission of information on all serious adverse drug experiences, as defined in 21 CFR 310.305(a) and 314.80(a), from each country where the active ingredient or other condition has been or is currently marketed as either a prescription or an OTC drug; in addition, it calls for submission of all data generally specified in § 330.10(a)(2), which includes documented case reports and identification of expected or frequently reported side effects (§ 330.14(f)(1) and (f)(2)). To evaluate ecamsule, FDA continues to seek individual adverse drug experience reports, a summary of all serious adverse drug experiences, and expected or frequently reported side effects of the condition (*id.*). To assist in the Agency's safety evaluation of ecamsule, FDA emphasizes its need for the following data:

- A summary of all available reported adverse events potentially associated with ecamsule;
- All available documented case reports of serious side effects;
- Any available safety information from studies of the safety and effectiveness of ecamsule in humans; and
- Relevant medical literature describing adverse events associated with ecamsule. Submissions of adverse event data should also include a description of how each country's system identifies and collects adverse events, unless this information has been previously submitted as part of ecamsule's TEA package.

Although we recognize that adverse event data from foreign marketing experience may reflect patterns of use and regulatory reporting requirements that differ from those in the United States, we nonetheless consider such information to be strongly relevant both to our overall GRASE assessment of ecamsule for use in sunscreens and to our consideration of potential product labeling. FDA recognizes that such information may not be available from all countries; where that is the case, please provide a written explanation for the lack of data. Overall, we seek sufficient data to characterize ecamsule's adverse event profile.[2]

Ecamsule: Human Safety Data To Establish Adverse Event Profile

The submission describes the marketing history of ecamsule and provides eight case report forms (Form FDA 3500A) that have been submitted to FDA's MedWatch program in association with marketed sunscreen products containing ecamsule in combination with other active ingredients (Note 8). Our review of the FDA Adverse Event Reporting System (FAERS) identified one additional case report associated with such a sunscreen product. These case reports describe serious allergic reactions such as redness, swelling and urticaria, breathing difficulties, and anaphylaxis. The role, if any, of ecamsule in these cases cannot be fully assessed due in part to the presence of multiple active ingredients in the associated sunscreen products. To support the evaluation of the safety of ecamsule for use in OTC sunscreens, we request that the sponsor either supplement the information already submitted with adverse event or other safety-related data derived from commercial marketing experience, or explain why such information cannot be provided.

B. Nonclinical (Animal) Studies

Another important element of FDA's GRAS review of ecamsule for use in sunscreens is an assessment of data from nonclinical (animal) studies that characterize the potential long-term dermal and systemic effects of exposure to ecamsule. Even if the bioavailability data discussed in section II.A.2 suggest that dermal application is unlikely to result in skin penetration and systemic exposure to ecamsule, FDA still considers data on the effects of systemic exposure to be an important aspect of our safety evaluation of ecamsule. A determination that ecamsule up to 10 percent is GRASE for use in sunscreens would permit its use in as-yet-unknown product formulations, which might in turn alter the skin penetration of the active ingredient. Therefore, an understanding of the effects of ecamsule, were systemic exposure to occur, is critical to determine whether and how regulatory parameters can be defined to assure that all conforming ecamsule-containing sunscreens would be GRASE as labeled.

FDA recommends animal testing of the potential long-term dermal and systemic effects of exposure to ecamsule because these effects cannot be easily assessed from previous human use. Taken together, the carcinogenicity studies, developmental and reproductive toxicity studies, and toxicokinetic studies described in sections II.B.1 through II.B.3 should provide the information needed to characterize both the potential dermal and systemic toxic effects and the levels of exposure at which they occur. These data, when viewed in the context of human exposure data, can be used to determine a margin of safety for use of ecamsule in OTC sunscreens.

Data Available for Ecamsule: Nonclinical (Animal) Studies Generally

The ecamsule submission included reports of the following types of nonclinical safety studies:

- Single-dose toxicity studies
  - Oral toxicity (rat, mouse) (Note 9)
  - Dermal toxicity (rat, mouse) (Note 10)
  - Intravenous toxicity (rat, mouse) (Note 11)
  - Mucosal and skin irritation (rabbit) (Note 12)
  - Skin irritation and sensitization (guinea pig) (Note 13)
  - Photoirritation and photosensitization (guinea pig) (Note 14)
- Repeat-dose toxicity studies
  - 4-week bridging dermal (mouse) (Note 15)
  - 13-week dermal (mouse) (Note 16)
  - 9-month dermal (minipig) (Note 17)
- Genotoxicity and mutagenicity assays
  - Ames test (*Salmonella typhimurium, Escherichia coli*) (Note 18)
  - Chromosomal aberration assay (Chinese hamster ovary (CHO cells)) (Note 19)
  - Micronucleus test (rat) (Note 20)
  - Photomutagenicity (*E. coli*) (Note 21)
  - HPRT test (CHO cells) (Note 22)
  - Photochromosomal aberration assay (CHO cells) (Note 23)
- Reproductive and developmental toxicity studies
  - Fertility and early embryonic development, oral (rat) (Note 24)
  - Pre/postnatal development, oral (rat) (Note 25)
  - Embryotoxicity/teratogenicity, dermal (rabbit) (Note 26)

[2] See 67 FR 3060 at 3069 (January 23, 2002) (agreeing that the absence of an adverse experience reporting system in a foreign country for drugs or cosmetics does not necessarily mean that a condition cannot be GRAS/E. The GRAS/E determination will be based on the overall quality of the data and information presented to substantiate safety and effectiveness).

- Embryofetal development/teratogenicity, oral (rat) (Note 27)
- Embryofetal development/teratogenicity, oral (rabbit) (Note 28)

- Carcinogenicity and photocarcinogenicity
  - 104 weeks dermal carcinogenicity (mouse) (Note 29)
  - 12 months photocarcinogenicity (mouse) (Note 30)
- Pharmacokinetics
  - Pharmacokinetic study, oral (rat) (Note 31)
  - Pharmacokinetic study, dermal (mouse, rat) (Note 32)
  - Microsome metabolism (interspecies, in vitro) (Note 33)
  - Excretion, oral and dermal (rat) (Note 34)

The submission includes summary reports of nonclinical studies that are of the types FDA requests as a basis for evaluating whether ecamsule is GRAS for use in sunscreen (chronic toxicity, carcinogenicity, reproductive and developmental toxicity, and toxicokinetics). However, the submission did not provide the full reports and full comprehensive data sets that would be needed for an adequate review of the data for these studies. Because the summary data provided can support only tentative conclusions about these studies, full final study reports and data sets need to be made available to support a final GRASE determination.

Additional discussion of study findings and data gaps are provided in the following subsections.

1. Carcinogenicity Studies: Dermal and Systemic

FDA guidance recommends that carcinogenicity studies be performed for any pharmaceutical that is expected to be clinically used continuously or ''repeatedly in an intermittent manner'' for a total of 6 months of exposure (Refs. 6, 7, and 8). Because the proposed use of ecamsule in OTC sunscreens falls within this category, these studies should be conducted to help establish that ecamsule is GRAS for its proposed use. Carcinogenicity studies assist in characterizing potential dermal and systemic risks by identifying the type of toxicity observed, the level of exposure at which toxicity occurs, and the highest level of exposure at which no adverse effects occur (*i.e.,* NOAEL). The NOAEL would then be used in determining the safety margin for human exposure to sunscreens containing ecamsule.

Systemic carcinogenicity studies can also help to identify other systemic or organ toxicities that may be associated with ecamsule, such as hormonal effects. For example, the effect of persistent disruption of particular endocrine gland systems (*e.g.,* hypothalamic-pituitary-adrenal axis), if any, can be captured by these assays.

Data Available for Ecamsule: Genotoxicity Studies

The ecamsule submission included some information regarding genotoxicity studies. Based on the reviewable genotoxicity data included in the ecamsule data submission, ecamsule appears to be negative for causing genotoxic activity under the conditions studied (Notes 35 through 43). As we believe that data from the recommended systemic carcinogenicity and developmental and reproductive toxicology (DART) studies will provide an adequate and appropriate measure of potential long-term effects of systemic or dermal exposure to ecamsule, we do not request further genotoxicity studies.

Data Available for Ecamsule: Carcinogenicity Studies

We have reviewed study summaries for four dermal carcinogenicity and photocarcinogenicity studies, which appear to be negative (Notes 44 through 47). However, full final study reports need to be made available to support a final GRASE determination. In addition, we did not receive any systemic carcinogenicity data, which are recommended to support the safety of long-term use of ecamsule. We request that the sponsor provide a systemic carcinogenicity study, as well as make available full final study reports for the previously conducted carcinogenicity studies that were submitted in a summarized form.

2. DART Studies (Ref. 9)

FDA recommends conducting DART studies to evaluate the potential effects that exposure to ecamsule may have on developing offspring throughout gestation and postnatally until sexual maturation, as well as on the reproductive competence of sexually mature male and female animals. Gestational and neonatal stages of development may also be particularly sensitive to active ingredients with hormonal activity. For this reason, we recommend that these studies include assessments of endpoints such as vaginal patency, preputial separation, anogenital distance, and nipple retention, which can be incorporated into traditional DART study designs to assess potential hormonal effects of ecamsule on the developing offspring. We also recommend conducting behavioral assessments (*e.g.,* mating behavior) of offspring, which may also detect neuroendocrine effects.

Data Available for Ecamsule: DART Studies

We received study summaries for five developmental and reproductive toxicity assays (Notes 48 through 52), which appear to be negative for the potential to cause adverse developmental or reproductive effects. However, comprehensive data sets were not provided.

We request that the sponsor make available full final study reports, including full comprehensive datasets, to support a final GRASE determination.

3. Toxicokinetics (Ref. 10)

We recommend conducting animal toxicokinetic studies because they provide an important bridge between toxic levels seen in animal studies and potential human exposure. Data from these studies can be correlated to potential human exposure via clinical dermal pharmacokinetic study findings. Toxicokinetic data could be collected as part of animal studies being conducted to assess one or more of the safety parameters described previously.

Data Available for Ecamsule: Toxicokinetics

We reviewed single-dose pharmacokinetic studies conducted in animal models which showed that systemic exposure was achieved under the conditions of the conducted studies (Notes 53 and 54). However, we did not receive any pharmacokinetic data reflecting drug levels following long-term exposure, which are usually collected from repeat toxicity studies such as chronic (systemic or dermal) studies. We recommend that a time course toxicokinetic study be conducted following repeat-dose exposure (via the oral and dermal routes) to evaluate the steady-state exposure level of ecamsule. Data obtained from this study could be used to compare drug levels in animals to those in humans under maximal exposure conditions to establish a margin of safety for human exposure.

III. Effectiveness Data Considerations for OTC Sunscreen Products Containing Ecamsule

FDA's evaluation of the effectiveness of active ingredients under consideration for inclusion in an OTC drug monograph is governed by the following regulatory standard: Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions

for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of efficacy shall consist of controlled clinical investigations as defined in 21 CFR 314.126(b). Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details that permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (§ 330.10(a)(4)(ii)). For convenience, this order uses the term ''generally recognized as effective'' (GRAE) when referring to this aspect of the GRASE determination.

To evaluate the efficacy of ecamsule for use in OTC sunscreen products, FDA requests evidence from at least two adequate and well-controlled SPF studies showing that ecamsule effectively prevents sunburn. To determine that ecamsule is GRAE for use in OTC sunscreens at concentrations in a range with the proposed maximum strength of 10 percent as requested, two adequate and well-controlled SPF studies of ecamsule at a lower concentration should be conducted according to established standards.[3] These SPF studies should demonstrate that the selected concentration (below 10 percent) provides an SPF of 2 or more.

The current standard procedure for SPF testing is described in FDA's regulations in § 201.327(i).[4] Further SPF tests for ecamsule should be performed as described in these regulations, using a test formulation containing ecamsule as the only active ingredient to identify its contribution to the overall SPF test results. (See the following subsection *Data Available for Ecamsule: Effectiveness* for further discussion of submitted SPF tests.) The study should also include a vehicle control arm to rule out any contribution the vehicle may have on the SPF test results. Finally, as described in § 201.327(i), an SPF standard formulation comparator arm should be another component of the study design.

Although current sunscreen testing and labeling regulations also specify a ''broad spectrum'' testing procedure to support related labeling claims for certain OTC sunscreen products marketed without approved new drug applications that contain specific ingredients included in the OTC sunscreen monograph, those additional claims are permitted, but not required, for these products (§ 201.327(c)(2) and (j)). Under current regulations, sunscreen active ingredients need only be effective for the labeled indication of sunburn prevention, for which the SPF test can provide sufficient evidence. Consistent with this approach, we here do not request broad spectrum testing for ecamsule. Broad spectrum protection is often, although not always, the result of the combined contribution of multiple active ingredients in a final sunscreen formulation. Thus, under the current regulations applicable to other sunscreens, the determination of whether an individual sunscreen product may be labeled as broad spectrum and bear the related additional claims is made on a product-specific basis, applying standard testing methods set forth in those regulations. If ecamsule is established to be GRASE for use in nonprescription sunscreens (based in part on the efficacy data requested here), the final sunscreen order can likewise address broad-spectrum testing and related labeling conditions for final sunscreen formulations containing ecamsule.

Data Available for Ecamsule: Effectiveness

Study reports were submitted for two studies that assessed SPF of formulations containing ecamsule, at a concentration of either 2 percent or 3 percent (Notes 55 and 56, respectively), in combination with other active ingredients. Neither of these studies provides a direct evaluation of the efficacy of ecamsule alone. These studies were not adequately designed to provide evidence of efficacy on which to base a GRAE determination for ecamsule. No adequately designed studies of ecamsule efficacy were identified in our search of the published literature. To support the finding that ecamsule is GRAE when used at concentrations up to 10 percent, we request submission of data from two adequate and well-controlled SPF studies conducted according to established standards to demonstrate that the lowest selected concentration provides an SPF of 2 or more. Because no study has been identified that assesses the effectiveness of ecamsule at a concentration of 10 percent, it is recommended that such a study be conducted and submitted.

IV. Summary of Current Data Gaps for Ecamsule

Based on our review of the available safety and efficacy data as discussed previously, we request the types of data listed in this section of the proposed order, at minimum, for us to reverse our tentative determination that ecamsule is not GRASE and is misbranded because the data are insufficient to classify ecamsule as GRASE and not misbranded, and additional data are necessary to allow us to determine otherwise. Note that, in some cases, as discussed in section II of this proposed order, the ecamsule data submission provided some information from nonclinical studies of the type FDA requests as part of the basis for a GRAS determination, but only in summary form. Were complete study data generally available from these previously conducted studies, they might address several aspects of our GRASE consideration. If data from these previously conducted studies are not made available, further studies of those types would be needed to support a finding that ecamsule is GRASE for use in sunscreens. Further, as summarized in the following subsections, some additional studies of other types are needed. For additional information about the purpose and design of studies recommended to address present data gaps, please refer to the earlier sections of this proposed order referenced in parentheses. We welcome discussions on the design of any of the studies prior to their commencement. We request the following types of data:

- *Safety Data (see section II)*

A. Human Clinical Studies

1. Skin irritation/sensitization, and photosafety (see section II.A.1)
2. Human dermal pharmacokinetic (bioavailability) studies (see section II.A.2)

B. Human Safety Data To Establish Adverse Event Profile (see Section II.A.3)

1. A summary and analysis of all available reported adverse events potentially associated with ecamsule
2. A summary and analysis of all available documented case reports of serious side effects
3. A summary and analysis of any available safety information from studies of the safety and effectiveness of sunscreen products containing ecamsule in humans

[3] The upper bound of any concentration of ecamsule ultimately established in the OTC sunscreen monograph will be governed by the safety data, as well as by efficacy.

[4] Although the SPF testing procedure is used primarily for final formulation testing of finished products marketed without approved NDAs, under the sunscreen monograph, it is equally applicable for determining whether or not a sunscreen active ingredient is GRAE.

4. A summary and analysis of relevant medical literature describing adverse events associated with ecamsule

Alternatively, the results of a literature search that found no reports of adverse events may be provided. In that case, detailed information on how the search was conducted should be provided.

C. Nonclinical (Animal) Studies

Full study reports will be needed for the following studies:

1. Systemic and dermal carcinogenicity (see section II.B.1)
2. Reproductive and developmental toxicity studies (see section II.B.2)
3. Toxicokinetics (see section II.B.3)

- *Effectiveness Data (see section III)*

For concentrations of ecamsule up to 10 percent to be found to be GRASE for use in nonprescription sunscreen products as requested, at least two SPF studies showing effectiveness of a selected concentration lower than 10 percent should be conducted. An efficacy study of ecamsule at 10 percent is also recommended.

V. Administrative Procedures

A copy of this proposed order will be filed in the Division of Dockets Management in Docket No. FDA–2008–N–0474. To inform FDA's evaluation of whether this ingredient is GRASE and not misbranded for use in sunscreen products, we encourage the sponsor and other interested parties to submit additional data regarding the safety and effectiveness of this ingredient for use as an OTC sunscreen product. We also encourage the sponsor and other interested parties to notify us in writing of their intent to submit additional data. However, as noted previously, because the data submitted to date are not sufficient to support a determination that ecamsule is GRASE for use as an active ingredient in OTC sunscreen drug products, at present, OTC sunscreen products containing ecamsule may not be marketed without approval of an NDA or ANDA (see section 586C(e)(1)(A) of the FD&C Act, as amended by the SIA). Data submissions relating to this proposed order should be submitted to Docket No. FDA–2008–N–0474 at the Division of Dockets Management (see **ADDRESSES**). In addition, you can submit the data through the Federal eRulemaking Portal at *http://www.regulations.gov.* Follow the instructions for submitting comments.

Section 586C(b)(7) of the FD&C Act, as amended by the SIA, provides that the sponsor may, within 30 days of publication of a proposed order (see **DATES**), submit a request to FDA for a meeting to discuss the proposed order. Submit meeting requests electronically to *http://www.regulations.gov* or in writing to the Division of Dockets Management (see **ADDRESSES**), identified with the active ingredient name ecamsule, Docket No. FDA–2008–N–0474, and the heading ''Sponsor Meeting Request.'' To facilitate your request, please also send a copy to Kristen Hardin (see **FOR FURTHER INFORMATION CONTACT**).

VI. Proposed Effective Date

FDA proposes that any final administrative order based on this proposal become effective on the date of publication of the final order in the **Federal Register**.

VII. Comments

Similarly, section 586C(b)(6) of the FD&C Act, as amended by the SIA, establishes that a proposed sunscreen order shall provide 45 days for public comment. Interested persons wishing to comment on this proposed order may submit either electronic comments to *http://www.regulations.gov* or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the active ingredient name (ecamsule) and the docket number found in brackets in the heading of this proposed order. Received comments on this proposed order may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

VIII. Notes

1. FDA–2008–N–0474–0012 and FDA–2008–N–0474–0013, Volumes 6 and 7, dated November 14, 2008.
2. FDA–2008–N–0474–0015 and FDA–2008–N–0474–0016, Volumes 9 and 10, dated November 14, 2008.
3. FDA–2008–N–0474–0007, Volume 1, dated November 14, 2008, FDA–2008–N–0474–0006, TEA submission.
4. FDA–2008–N–0474–0008, Volume 2, Study no. 16039/G2347.
5. FDA–2008–N–0474–0014, Volume 8, Study no. V3156.
6. FDA–2008–N–0474–0014, Volume 8, Study no. V99.1203.
7. FDA–2008–N–0474–0014, Volume 8, Study no. CG.03.SRE.2607.
8. FDA–2008–N–0474–0007, Volume 1, dated November 14, 2008.
9. FDA–2008–N–0474–0009, Volume 3, Study no. 3667–109/309, Study no. 1.CG.03.SRE.12160.
10. FDA–2008–N–0474–0009, Volume 3, Study no. 4222–109/310, Study no. 1.CG.03.SRE.12156.
11. FDA–2008–N–0474–0009, Volume 3, Study no. 1.CG.03.SRE.12158, Study no. 1.CG.03.SRE.12157.
12. FDA–2008–N–0474–0009, Volume 3, Study no. 712332, Volume 4, Study no. 712320.
13. FDA–2008–N–0474–0010, Volume 4, Study no. 802410, Study no. 3697–109/313.
14. FDA–2008–N–0474–0010, Volume 4, Study no. 1.CG.03.SRE.12163, Study no. 1.CG.03.SRE.12164.
15. FDA–2008–N–0474–0010, Volume 4, Study no. RDA.03.SRE.12268.
16. FDA–2008–N–0474–0009, Volume 3, Study no. 93/LOL/007/0971.
17. FDA–2008–N–0474–0009, Volume 3, Study no. 1.CG.03.SRE.12183.
18. FDA–2008–N–0474–0011, Volume 5, Study no. G185–109/314.
19. FDA–2008–N–0474–0011, Volume 5, Study no. G220–109/381, Study no. G220–109/381A, Study no. 12174MIC, Study no. 413/52–D6172.
20. FDA–2008–N–0474–0011, Volume 5, Study no. 12639MAR.
21. FDA–2008–N–0474–0011, Volume 5, Study no. EU1REBRP.031.
22. FDA–2008–N–0474–0011, Volume 5, Study no. LRL 170/921503.
23. FDA–2008–N–0474–0011, Volume 5, Study no. ICHUREBRP.031.
24. FDA–2008–N–0474–0010, Volume 4, Study no. 1.CG.03.SRE.12181.
25. FDA–2008–N–0474–0011, Volume 5, Study no. 1.CG.03.SRE.12182.
26. FDA–2008–N–0474–0011, Volume 5, Study no. 10297 RSL.
27. FDA–2008–N–0474–0010, Volume 4, Study no. 1412 RMR/064.89.
28. FDA–2008–N–0474–0011, Volume 5, RCC Project 682874.
29. FDA–2008–N–0474–0010, Volume 4, Study no. 95/LOL/008/1217, Study no. LOL/011/980150.
30. FDA–2008–N–0474–0010, Volume 4, Study no. C–1012–001, Study no. RDS.03.SRE.12215.
31. FDA–2008–N–0474–0009, Volume 3, Study no. 10225PAR, Study no. 1.CG.03.SRE.12269/RDS.03.SRE.12269.
32. FDA–2008–N–0474–0009, Volume 3, Study no. 10507 PAS, Study no. RDS.03.SRE 12268, Study no. RDS.03.SRE.12269/1.CG.03.SRE.12269.
33. FDA–2008–N–0474–0009, Volume 3, Study no. 2.CG.03.SRE.11029.
34. FDA–2008–N–0474–0009, Volume 3, Study no. 1.CG.03.SRE.12270.
35. FDA–2008–N–0474–0011, Volume 5, Study no. G185–109/314.
36. FDA–2008–N–0474–0011, Volume 5, Study no. G220–109/381.
37. FDA–2008–N–0474–0011, Volume 5, Study no. G220–109/381A.
38. FDA–2008–N–0474–0011, Volume 5, Study no. 12174MIC.
39. FDA–2008–N–0474–0011, Volume 5, Study no. 413/52–D6172.
40. FDA–2008–N–0474–0011, Volume 5, Study no. 12639MAR.
41. FDA–2008–N–0474–0011, Volume 5, Study no. EU1REBRP.031.
42. FDA–2008–N–0474–0011, Volume 5, Study no. LRL 170/921503.
43. FDA–2008–N–0474–0011, Volume 5, Study no. ICHUREBRP.031.

44. FDA–2008–N–0474–0010, Volume 4, Study no. 95/LOL/008/1217.
45. FDA–2008–N–0474–0010, Volume 4, Study no. LOL/011/980150.
46. FDA–2008–N–0474–0010, Volume 4, Study no. C–1012–001.
47. FDA–2008–N–0474–0010, Volume 4, Study no. RDS.03.SRE.12215.
48. FDA–2008–N–0474–1000, Volume 4, Study no. 1.CG.03.SRE.12181.
49. FDA–2008–N–0474–0011, Volume 5, Study no. 1.CG.03.SRE.12182, Study no. 1412 RMR/064.89.
50. FDA–2008–N–0474–0011, Volume 5, RCC Project 682874.
51. FDA–2008–N–0474–0011, Volume 5, RCC Project 682874.
52. FDA–2008–N–0474–0011, Volume 5, Study no. 1.CG.03.SRE.12182.
53. FDA–2008–N–0474–0009, Volume 3, Study no. 10225PAR.
54. FDA–2008–N–0474–0009, Volume 3, Study no. 1.CG.03.SRE.12269/RDS.03.SRE.12269.
55. FDA–2008–N–0474–0017, Volume 11, Study no. PEN.810.02.
56. FDA–2008–N–0474–0017, Volume 11, Study no. PEN.810.06.

IX. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov.* (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. FDA, Guidance for Industry, ''Photosafety Testing,'' May 2003 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079252.pdf*).
2. Leonard, F., B. Kalis, H. Adamski, et al., ''The New Standard Battery of Photopatch Test in France.'' *Nouvelles Dermatologiques,* vol. 15, pp. 343–348, 1996.
3. Schauder, S., and H. Ippen, ''Contact and Photocontact Sensitivity to Sunscreens. Review of a 15-Year Experience and of the Literature.'' *Contact Dermatitis,* vol. 37(5), pp. 221–232, 1997.
4. Schmidt, T., J. Ring, and D. Abeck, ''Photoallergic Contact Dermatitis Due to Combined UVB (4-Methylbenzylidene Camphor/Octyl Methoxycinnamate) and UVA (Benzophenone-3/Butyl Methoxydibenzoylmethane) Absorber Sensitization.'' *Dermatology,* vol. 196(3), pp. 354–357, 1998.
5. FDA, Guidance for Industry, ''Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application,'' February 1987 (available at *http://www.fda.gov/downloads/drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072112.pdf*).
6. International Conference on Harmonization (ICH), Guidance for Industry, ''The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals S1A,'' March 1996 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM074911.pdf*).
7. ICH, Guidance for Industry, ''S1B Testing for Carcinogenicity of Pharmaceuticals,'' July 1997 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074916.pdf*).
8. ICH, ''S1C(R2) Dose Selection for Carcinogenicity Studies'' (Revision 1), September 2008 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074919.pdf*).
9. ICH Harmonized Tripartite Guideline for Industry, ''Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2),'' 2005 (available at *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5_R2/Step4/S5_R2__Guideline.pdf*).
10. ICH, Guideline for Industry, ''Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies S3A,'' March 1995 (available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074937.pdf*).

Dated: February 20, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015–03883 Filed 2–24–15; 8:45 am]

BILLING CODE 4164–01–P