DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

John Tomaszewski
Director Regulatory Affairs
L'Oreal USA Products, Inc.
133 L'Oreal Way
Clark, NJ 07066

AUG 29 2014

RE: Docket No. FDA-2003-N-0196 (Legacy Docket No. 2003N-0233)

Dear Mr. Tomaszewski:

In accordance with 21 CFR 330.14(g)(4), this letter provides FDA's initial determination and feedback on safety and effectiveness data submitted by L'Oréal USA Products, Inc. to demonstrate the safety and effectiveness of the sunscreen active ingredient drometrizole trisiloxane (also known as Mexoryl XL) at concentrations up to 15 percent (the drometrizole trisiloxane submissions) for use in over-the-counter (OTC) sunscreen products. We acknowledge the submissions made by L'Oréal USA Products, Inc. on January 16, 2009 and July 14, 2010. These data were provided in response to our announcement that drometrizole trisiloxane was found eligible to be considered for inclusion in the OTC sunscreen monograph (21 CFR part 352, currently stayed) based on our review of a Time and Extent Application (TEA) submitted by L'Oréal USA Products, Inc. under 21 CFR § 330.14(c) (the TEA regulation), and our related call for submission of safety and effectiveness data.[1]

We have reviewed the available public data on drometrizole trisiloxane for use in OTC sunscreens. Based on that review, we have made an initial determination that the scientific record is not sufficient to establish that drometrizole trisiloxane is generally recognized as safe and effective (GRASE) for over-the-counter (OTC) sunscreen use. However, in accordance with the TEA regulation, we are including a copy of this letter in the public docket and providing you and any other interested parties with an opportunity to submit additional data. This letter describes our review of the drometrizole trisiloxane data submissions, identifies additional data needed to demonstrate that drometrizole trisiloxane is GRASE, and explains our rationale for specific data requirements.

Background

The TEA regulation creates a process through which a sponsor can request that an active

[1] 75 FR 30838 (June 02, 2010).

ingredient or other condition[2] be added to an OTC drug monograph. First, the sponsor must provide a TEA application package containing the information on time and extent of marketing (eligibility information) described at 21 CFR 330.14(c)(1). If the condition is found eligible, then FDA will publish a notice of eligibility in the *Federal Register* requesting that the sponsor and other interested parties provide data to demonstrate the safety and effectiveness of the condition for its intended OTC use, as was done for drometrizole trisiloxane.[3] After evaluating the safety and effectiveness data provided, FDA will make an initial determination as to the status of the condition (i.e., whether it is GRASE) for use in the United States.[4] If we make an initial determination that the condition is GRASE, we will propose to amend or establish a relevant OTC monograph regulation to include the condition, followed by publication of a final rule reflecting our consideration of public comments on the proposed rule.[5] If we initially determine that the condition is not GRASE, we will so inform the sponsor (and other interested parties that have submitted data) by way of a feedback letter that will also be placed in the public docket.[6] (As noted above, this letter provides that feedback.) Where FDA initially determines that the condition is not GRASE, FDA also will publish a proposed rule to codify this determination by adding the condition to 21 CFR 310.502, Certain Drugs Accorded New Drug Status Through Rulemaking Procedures, followed by publication of a final rule (or a new proposed rule to add the condition to the monograph) after consideration of public comments on the proposed rule.[7]

In order for FDA to propose to amend the OTC sunscreen monograph to include drometrizole trisiloxane, we must make an initial determination, based on appropriate scientific evidence, that any sunscreen product that could be formulated using the active ingredient concentrations, permitted combinations, or other applicable limitations specified in the monograph (including the proposed amendment) would be GRASE for use under the conditions prescribed, recommended, or suggested in its labeling.[8] We have reviewed the drometrizole trisiloxane data submissions and also performed a search for published scientific literature on drometrizole trisiloxane. Based on our review, we have made an initial determination that the data currently available in the public record are not sufficient to support the requisite GRASE determination; therefore, FDA cannot propose to amend the OTC sunscreen monograph (21 CFR part 352) to include drometrizole trisiloxane. However, because our thinking about the necessary safety data for OTC sunscreen active ingredients has evolved over time, we are not at this time proposing to preclude

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[2] For purposes of the TEA regulation, "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 21 CFR 330.14(a).
[3] 21 CFR 330.14(e); for the notice of eligibility for drometrizole trisiloxane, see 75 FR 30838 (June 02, 2010).
[4] 21 CFR 330.14(g). This determination is governed by the same safety, effectiveness, and labeling standards that apply to existing monograph ingredients under 21 CFR § 330.10(a)(4).
[5] 21 CFR 330.14(g)(3), 330.14(g)(5).
[6] 21 CFR 330.14(g)(4).
[7] 21 CFR 330.14(g)(4), 330.14(g)(5). OTC drugs and conditions listed in 21 CFR 310.502 may not be marketed without an approved NDA or ANDA.
[8] 21 CFR 330.14(g): *see also* Food, Drug, & Cosmetic Act § 201(p).

monograph status.[9] Rather, we are providing you and any other interested parties with an opportunity to submit additional data to address the current data gaps.[10] Nonetheless, we remind you that at present, sunscreens containing drometrizole trisiloxane require an approved new drug application in order to be legally marketed in the United States.[11]

In accordance with the TEA regulation, we are placing a copy of this feedback letter in the public docket, and we invite you and any other interested parties to submit additional data and/or comments on appropriate data requirements for drometrizole trisiloxane. We also have scheduled a meeting of the Nonprescription Drugs Advisory Committee to be held on September 4 and 5, 2014, to discuss current considerations in FDA's evaluation of OTC sunscreens. Information about this advisory committee meeting is available on the Internet at http://www.fda.gov/AdvisoryCommittees/Calendar/ucm407137.htm.

A general discussion of the type and extent of data we believe would be sufficient to support the necessary safety determination for drometrizole trisiloxane, as well as our assessment of the currently available safety data on drometrizole trisiloxane, is explained in Section I below. Section II contains the corresponding discussion on efficacy data requested for drometrizole trisiloxane, as well as our assessment of the currently available efficacy data. Data gaps for drometrizole trisiloxane based on the assessments described in Sections I and II are summarized in Section III.

Discussion

I. Safety Data Considerations for OTC Sunscreen Products Containing Drometrizole Trisiloxane

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

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[9] See 21 CFR 330.14(g)(4), indicating that the agency will propose to include any TEA-eligible condition that is not found to be GRASE in 21 CFR 310.502, Certain Drugs Accorded New Drug Status Through Rulemaking Procedures; *see also* Food, Drug, & Cosmetic Act § 201(p).

[10] See 67 FR 3067 (Jan. 23, 2002) ("Parties can respond to a feedback letter and supplement their submissions."). If we issue a proposed rule to amend 310.502, then the process of comment on that proposal would provide an additional opportunity for supporting data to be submitted. 21 CFR 330.14(g)(5); see also 67 FR 3067 (Jan. 23, 2002) ("Parties will have another opportunity to respond when the agency publishes a notice of proposed rulemaking to include the condition in § 310.502.").

[11] 21 CFR 330.14(h).

> 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.[12]

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 generally recognized as safe (GRAS).[13] 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 drometrizole trisiloxane for use in sunscreen, FDA considers the circumstances under which OTC products that could contain drometrizole trisiloxane 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.[14] 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.[15] Given these conditions of use, our safety evaluation of an OTC sunscreen active ingredient such as drometrizole trisiloxane 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 below is to establish whether an OTC sunscreen product containing drometrizole trisiloxane and otherwise meeting all requirements applicable to OTC sunscreens under 21 CFR 330.1 would be GRAS for use as labeled. To demonstrate that these requirements are met for drometrizole trisiloxane, initial safety testing should be performed using drometrizole trisiloxane as the sole active ingredient up to the highest concentration for which monograph status is sought and eligibility has been established: 15%. If initial testing suggests a particular safety concern associated with drometrizole trisiloxane (e.g., a hormonal activity), FDA may request additional studies to address that concern.

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[12] 21 CFR 330.10(a)(4)(i).
[13] 21 CFR 330.10(a)(2).
[14] 21 CFR 201.327(e).
[15] *Id.*

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 drometrizole trisiloxane-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., drometrizole trisiloxane 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 drometrizole trisiloxane, 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.[16] Photosafety studies, like sensitization and irritation studies, should be conducted using drometrizole trisiloxane 15% in an appropriate test vehicle, the vehicle alone, and a negative control. In addition, phototoxicity studies should include at least 30 evaluable subjects and photoallergenicity studies should include at least 45 evaluable subjects.

Data Available for Drometrizole Trisiloxane: Human Irritation, Sensitization and Photosafety Studies

Reports for 34 clinical safety studies conducted in adults were submitted.[17] In these studies, approximately 2000 individuals were exposed to formulations containing drometrizole trisiloxane. No serious adverse events were reported. Most of these studies assessed formulations containing more than one active ingredient, including drometrizole trisiloxane in concentrations of 0.5% and 3.0%, well below the requested 15% maximum. Only three studies tested formulations in which drometrizole trisiloxane was the sole active ingredient, thus allowing for more direct assessment of drometrizole trisiloxane's effects. One study that assessed skin irritation and sensitization suggested that the potential for drometrizole trisiloxane 15% to cause either is low.[18] However, definitive conclusions cannot be made based on this study regarding irritation, given data gaps due to missed evaluations, or regarding sensitization, due to insufficient sample size. Two submitted studies assessed phototoxicity.[19] [20] While these

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[16] FDA, Guidance for Industry: "Guidance on Photosafety testing," May 2003, available on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079252.pdf.
[17] FDA-2003-N-0196-0042-0044, Vols. 10 through 12.
[18] FDA-2003-N-0196-0044, Study TOIS95015, Vol. 12.
[19] FDA-2003-N-0196-0044, Study HPPH97001, Vol. 12.
[20] FDA-2003-N-0196-0044, Study HPPS97002, Vol. 12.

studies appear to suggest that the potential for drometrizole trisiloxane to cause phototoxicity is low, definitive conclusions cannot be reached because the studies enrolled only a small number of subjects and relevant information, such as concentration of the active ingredient and protocol exclusion criteria, was not reported.

Reports were submitted for 16 clinical studies conducted in the pediatric population.[21] In these studies, approximately 550 pediatric subjects were exposed to formulations containing drometrizole trisiloxane in concentrations of 0.5% to 3.0%. Multiple dermal adverse events were reported, including two serious dermal reactions that forced discontinuation of the subjects from the study. None of these studies tested a formulation in which drometrizole trisiloxane was the sole active ingredient, which limits our ability to draw definitive conclusions about irritation, sensitization and phototoxicity effects of the active ingredient drometrizole trisiloxane at concentrations up to 15%.

A literature search conducted by FDA did not identify references that provide information to further support the safety of drometrizole trisiloxane 15% for use as an OTC sunscreen.

FDA concludes that the data submitted are not sufficient to assess the dermal safety of drometrizole trisiloxane and specifically its potential to cause irritation, sensitization, photoirritation or photoallergenicity. Submission of data from human irritation, sensitization, and photosafety studies conducted in accordance with FDA guidance are recommended to demonstrate that an OTC sunscreen product containing up to 15% is not an irritant, sensitizer, photosensitizer, or photoirritant.

2. Human Dermal Pharmacokinetic (Bioavailability) Studies

Because sunscreens are topically applied, another important safety concern for drometrizole trisiloxane for use in sunscreens is whether dermal application may result in skin penetration and systemic exposure to the drometrizole trisiloxane, and if so, to what extent. A well-designed and -conducted human dermal pharmacokinetic study can be expected to detect and quantify the presence in blood or other bodily fluids of drometrizole trisiloxane and/or any metabolites that may have a bearing on safety, using recognized parameters such as percent bioavailability, C_{max}, T_{max}, 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 drometrizole trisiloxane exists. FDA recommends that the pharmacokinetic studies performed on drometrizole trisiloxane 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. Studies should continue until steady state is reached, to ensure that maximum penetration of drometrizole trisiloxane has taken place and chances of it being detected are optimal.

[21] FDA-2003-N-0196-0045-0046, Vols. 13 and 14.

General information and recommendations on the design and conduct of human pharmacokinetic studies can be found in FDA's guidance entitled "Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application."[22] In order to support a GRAS determination for drometrizole trisiloxane (up to 15%), such a study should be conducted under maximal use conditions using drometrizole trisiloxane 15% in various vehicles, including vehicles that would be expected to enhance absorption. We encourage study sponsors to consult with FDA before conducting pharmacokinetic studies, as the properties of drometrizole trisiloxane may bear on the optimal design.

Data Available for Drometrizole Trisiloxane: Human Dermal Pharmacokinetic (Bioavailability) Studies

No human dermal pharmacokinetic studies for drometrizole trisiloxane were submitted in response to our call for data. We reviewed two in vitro studies that evaluated the potential for dermal penetration of topically applied drometrizole trisiloxane from human skin samples.[23] [24] Because these studies were not designed to detect or quantify drometrizole trisiloxane in the blood or other body fluids, they provide no useful information about systemic exposure. Our literature search found no additional supportive information regarding human pharmacokinetics. 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 your proposed maximum concentration as discussed above.

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 drometrizole trisiloxane, as well as from other sources, is a critical aspect of FDA's safety review for drometrizole trisiloxane. The TEA regulation specifically calls for submission of information on all serious adverse drug experiences, as defined in §§ 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 OTC drug; in addition, it calls for submission of all data generally specified in 21 CFR 330.10(a)(2), which itself includes documented case reports and identification of expected or frequently reported side effects.[25] To evaluate drometrizole trisiloxane, FDA thus seeks individual adverse drug experience reports, a summary of all serious adverse drug experiences, and expected or frequently reported side effects of the condition.[26] To assist in the Agency's safety evaluation of drometrizole trisiloxane, FDA emphasizes our need for the

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[22] This guidance is available on the Internet at http://www.fda.gov/downloads/drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072112.pdf.
[23] FDA-2003-N-0196-0041, Study 94/04/26: G4375, Vol. 9.
[24] FDA-2003-N-0196-0041, Study 16004, Vol. 9.
[25] 21 CFR § 330.14(f)(2), 330.14(f)(1).
[26] *Id.*

following data:

- A summary of all available reported adverse events potentially associated with drometrizole trisiloxane;
- All available documented case reports of serious side effects;[27]
- Any available safety information from studies of the safety and effectiveness of drometrizole trisiloxane in humans; and
- Relevant medical literature describing adverse events associated with drometrizole trisiloxane.

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 drometrizole trisiloxane's TEA package.

While 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 drometrizole trisiloxane 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 drometrizole trisiloxane's adverse event profile.[28]

Data Available for Drometrizole Trisiloxane: Human Safety Data to Establish Adverse Event Profile

The TEA application describes the collection of post-marketing safety information, including adverse events.[29] L'Oréal USA Products, Inc. stated that a "Cosmetovigilance" system was in place worldwide to collect and evaluate reports. The submission also states that all sunscreen products containing drometrizole trisiloxane are sold abroad (outside the United States) as cosmetics or OTC drugs, and that L'Oréal is not aware of any withdrawals of these products due to adverse health claims in any of the countries where it is used as an active ingredient in sunscreen formulations. For adults using sunscreen products, a total of 1,634 adverse events were reported during the 2003 to 2008 reporting period and 63% of these were categorized as skin or subcutaneous tissue disorders. For children using sunscreen products, a total of 1,519 adverse events were reported during the same period and 74% of these were categorized as skin or subcutaneous tissue disorders. Eight case reports were provided for serious adverse events, all of which involved skin reactions and most were also associated with systemic symptoms

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[27] 21 CFR 330.14(f)(2).

[28] 67 FR 3060, 3070 (Jan. 23, 2002) ("The agency agrees 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.").

[29] FDA-2003-N-0196-0033, Vol. 1, Sections 5.3 and 5.4.

suggestive of hypersensitivity type reactions. In one case, a skin test conducted subsequent to the adverse event confirmed that the patient had an allergy to drometrizole trisiloxane.

The submitted information discussed above contributes to our evaluation of the safety profile of drometrizole trisiloxane and we request submission of any additional available post-marketing information, as previously specified.

B. Nonclinical (Animal) Studies

Another important element of FDA's GRAS review of drometrizole trisiloxane 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 drometrizole trisiloxane. Even if the bioavailability data discussed above at Section I.A.2 suggest that dermal application is unlikely to result in skin penetration and systemic exposure to drometrizole trisiloxane, FDA still considers data on the effects of systemic exposure to be an important aspect of our safety evaluation of drometrizole trisiloxane. The addition of drometrizole trisiloxane to the OTC sunscreen monograph 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 drometrizole trisiloxane, were systemic exposure to occur, is critical to determine whether and how regulatory parameters can be defined to assure that all conforming drometrizole trisiloxane-containing sunscreens would be GRASE as labeled.

FDA recommends animal testing of the potential long-term dermal and systemic effects of exposure to drometrizole trisiloxane 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 below at subsections I.B.1-3 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 drometrizole trisiloxane in OTC sunscreens.

Data Available for Drometrizole Trisiloxane: Nonclinical (Animal) Studies Generally

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

- Acute dose toxicity studies
  - Single oral toxicity (rat & mouse)[30]
  - Acute intraperitoneal toxicity (rat & mouse)[31]
  - Dermal toxicity (rat & mouse)[32]

[30] FDA-2003-N-0196-0036, Vol. 4, Study 93/06/261 (rat), Study 607353 (rat), and Study 753164 (mouse).
[31] FDA-2003-N-0196-0036, Vol. 4, Study 753186 (mouse) and Study 753197 (rat).

- Skin irritation (rabbit)[33]
- Eye irritation (rabbit)[34]
- Sensitizing potential[35]/contact hypersensitivity (guinea pig)[36]
- Phototoxicity and photoallergenicity potential (guinea pig)[37]
- Skin tolerance (guinea pig)[38]

- Repeat dose oral toxicity studies
  - 14 days oral (rat)[39]
  - 13 week oral (rat); 13-26 weeks followed by 4-week recovery period (rat) [40]
  - 13 week dermal (mouse)[41]

- Genotoxicity and mutagenicity assays
  - Ames test (*Salmonella typhimurium*)[42]
  - Micronucleus test (bone marrow; mice)[43]
  - Chromosome aberration assay (Chinese hamster V79 cells)[44]
  - Reverse Mutation (*Salmonella typhimurium, E Coli*)[45]
  - Gene Mutation (Chinese hamster ovary cells)[46]
  - Photomutagenicity (*E. Coli* & Chinese hamster ovary cells)[47]

- Reproductive and developmental toxicity studies
  - Androgenic activity to immature castrated rats (Hershberger Assay)[48]
  - Fertility & Embryofetal toxicity (rat)[49]
  - Embryofetal toxicity (rabbit)[50]
  - Pre & Post natal development toxicity (rat)[51]

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[32] FDA-2003-N-0196-0036, Vol. 4, Study 607364 (rat) and Study 753175 (mouse).
[33] FDA-2003-N-0196-0036, Vol. 4, Study 607375.
[34] FDA 2003-N-0196-0036, Vol. 4, Study 607386.
[35] FDA-2003-N-0196-0036, Vol. 4, Study A/K/38711.
[36] FDA-2003-N-0196-0036, Vol. 4, Study 607397 and Study 610784.
[37] FDA-2003-N-0196-0037, Vol. 5, Study 15794 and Study 607162.
[38] FDA-2003-N-0196-0037, Vol. 5, Study 607151.
[39] FDA-2003-N-0196-0037, Vol. 5, Study 365534.
[40] FDA-2003-N-0196-0038, Vol. 6, Study 607408 and Study 16539.
[41] FDA-2003-N-0196-0038, Vol. 6, Study LOL/010/1139.
[42] FDA-2003-N-0196-0039. Vol. 8, Study IPL-R931016.
[43] FDA-2003-N-0196-0041, Vol. 9, Study 607105.
[44] FDA-2003-N-0196-0041, Vol. 9, Study 607421.
[45] FDA-2003-N-0196-0039, Vol. 8, Study 607410.
[46] FDA-2003-N-0196-0041, Vol. 9, Study 607094.
[47] FDA-2003-N-0196-0041, Vol. 9, Study 607116 (E. coli) and Study 607138 (CHO cells).
[48] FDA-2003-N-0196-0040, Vol. 7, Study 22175.
[49] FDA-2003-N-0196-0040, Vol. 7, Study 19479 and Study 607184.
[50] FDA-2003-N-0196-0039, Vol. 8, Study 753153 and Study 813688.
[51] FDA-2003-N-0196-0039, Vol. 8, Study 19480.

- Carcinogenicity (2 studies)
  - 12 month photocarcinogenicity in hairless mice[52]
  - 104 week cutaneous application in mice[53]
- Toxicokinetics
  - Pharmacokinetics after single oral and dermal dosing (rat[54] & mouse[55])

These study reports were found to be adequate for review, except for the 13 week dermal study in mice[56] and the 104 week topical carcinogenicity study in mice[57] for which only summary data were provided. A comprehensive evaluation of the study findings requires that we review complete study reports, therefore we request that complete study reports be submitted. The reports should include the detailed appendices with individual animal data. If available, the tumor data from the carcinogenicity study should be provided in electronic format.

A search of the published literature did not identify additional data to support the nonclinical safety of drometrizole trisiloxane.

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 for at least 6 months or "repeatedly in an intermittent manner."[58] [59] [60] Because the proposed use of drometrizole trisiloxane in OTC sunscreens falls within this category, these studies should be conducted to help establish that drometrizole trisiloxane 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

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[52] FDA-2003-N-0196-0041, Vol. 9, Study DT029634.
[53] FDA-2003-N-0196-0041, Vol. 9, Study 19521.
[54] FDA-2003-N-0196-0041, Vol. 9, Study 11738 and Study 13294.
[55] FDA-2003-N-0196-0041, Vol. 9, Study 13295.
[56] FDA-2003-N-0196-0038, Vol. 6, Study LOL/010/1139.
[57] FDA-2003-N-0196-0041, Vol. 9, Study 19521.
[58] International Conference on Harmonization (ICH), "ICH Harmonized Tripartite Guideline. Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals S1A", 1995, available on the Internet at http://www.fda.gov/downleads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074911.pdf.
[59] ICH, "ICH Harmonized Tripartite Guideline: Testing for Carcinogenicity of Pharmaceuticals S1B," 1997, available on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM74911.pdf.
[60] ICH, "ICH Harmonized Tripartite Guideline: Dose Selection for Carcinogenicity Studies of Pharmaceuticals SIC(R2)," 2008, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance?UCM074919.pdf.

adverse effects occur (i.e., NOAEL). The NOAEL would then be used in the determination of the safety margin for human exposure to sunscreens containing drometrizole trisiloxane.

Systemic carcinogenicity studies are requested because they can help identify additional systemic toxicities for drometrizole trisiloxane may not be identified with the topical carcinogenicity study. 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 Drometrizole Trisiloxane: Genotoxicity Studies

Genotoxicity studies are reviewed as part of our assessment of potential toxic effects from long term systemic or dermal exposure. We reviewed the submitted battery of genotoxicity studies and conclude that drometriozole trisiloxane was found to be negative for genotoxic activity under the conditions of the conducted studies.

Data Available for Drometrizole Trisiloxane: Carcinogenicity Studies

We did not receive a systemic carcinogenicity study which is recommended to support the safety of drometrizole trisiloxane. We also need the full study report for the submitted dermal carcinogenicity study.[61]

2. Developmental and Reproductive Toxicity (DART) Studies[62]

FDA recommends conducting DART studies to evaluate the potential effects that exposure to drometrizole trisiloxane 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 such 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 drometrizole trisiloxane 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 Drometrizole Trisiloxane: DART Studies

We reviewed the submitted battery of developmental and reproductive toxicity assays, as well as an assay testing the potential for drometrizole trisiloxane to induce androgenic activity in castrated juvenile rats. We conclude that the findings of the DART studies do not point to a

[61] FDA-2003-N-0196-0041, Vol. 9, Study 19521.
[62] ICH, "ICH Harmonized Tripartite Guideline: Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)," 2005, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074954.pdf .

potential reproductive toxicity signal for drometrizole trisiloxane under the conditions of the conducted studies.

3. Toxicokinetics[63]

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 above.

Data Available for Drometrizole Trisiloxane: Toxicokinetics

Single dose pharmacokinetic studies conducted for drometrizole trisiloxane showed some exposure to the drug following oral exposure in a single acute toxicity study in male rats, and in the rabbit oral embryo fetal study. Exposure was dose-proportional and reached its maximum exposure within 4 hours. Detectable levels of drometrizole trisiloxane indicating systemic exposure was achieved in male and female mice after a single cutaneous exposure. Toxicokinetic data obtained following repeat dose exposure (via the oral and dermal route) would be helpful in evaluating the steady state exposure level of drometrizole trisiloxane and in comparing animal and human dose levels to establish a margin of safety for human exposure.

II. Effectiveness Data Considerations for OTC Sunscreen Products Containing Drometrizole Trisiloxane

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 § 314.126(b) of this chapter [.] . . . 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 which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon

[63] ICH, "ICH Harmonized Tripartite Guideline: The Assessment of Systemic Exposure in Toxicity Studies S3A," 1995 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074954.

published studies which may be corroborated by unpublished studies and other data.[64]

To evaluate the efficacy of drometrizole trisiloxane for use in OTC sunscreen products, FDA requests evidence from at least two adequate and well-controlled sun protection factor (SPF) studies showing that drometrizole trisiloxane effectively prevents sunburn. In order to support finding drometrizole trisiloxane to be generally recognized as effective (GRAE) for use in OTC sunscreens at concentrations in a range with the proposed maximum strength of 15% as requested, two adequate and well controlled SPF studies of drometrizole trisiloxane at a lower concentration should be conducted according to established standards.[65] These SPF studies should demonstrate that the selected concentration (below 15%) provides an SPF of 2 or more.

The current standard procedure for SPF testing is described in FDA's regulations at 21 CFR 201.327(i).[66] Further SPF tests for drometrizole trisiloxane should be performed as described in these regulations, using a test formulation containing drometrizole trisiloxane in isolation in order to identify its contribution to the overall SPF test results. (See below for further discussion of existing SPF tests of drometrizole trisiloxane, submitted to the docket.) The study should also include a vehicle control arm in order to rule out any contribution the vehicle may have on the SPF test results. Finally, as described in 21 CFR 201.327(i), an SPF standard formulation comparator arm should be another component of the study design.

While current sunscreen testing and labeling regulations also specify a "broad spectrum" testing procedure to support certain additional labeling claims for monograph products, the indications that are tied to broad spectrum testing are permitted, but not required, for monograph products.[67] To be added to the OTC sunscreen monograph, a sunscreen containing drometrizole trisiloxane need only be effective for the labeled indication of sunburn prevention, for which the SPF test can provide sufficient evidence. Broad spectrum protection is often, although not always, the result of the combined contribution of multiple active ingredients in a final sunscreen formulation. Thus, if drometrizole trisiloxane is established to be GRASE for use in sunscreens (based in part on the efficacy data requested here), the determination of whether an individual sunscreen product containing drometrizole trisiloxane may be labeled as broad spectrum and bear the related additional claims will be made on a product-specific basis, by following the requirements of existing regulations. A finished product containing drometrizole trisiloxane would be potentially eligible to make "broad spectrum"-related claims if it satisfies those regulations.

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[64] 21 CFR 330.10(a)(4)(ii).

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

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

[67] 21 CFR 201.327(c)(2), 201.327(j).

Data Available for Drometrizole Trisiloxane: Effectiveness

We reviewed data from three studies submitted by L'Oréal USA Products. [68] [69] [70] Data from these studies do not support the efficacy of drometrizole trisiloxane as only formulations with multiple active ingredients were studied. Our literature search did not identify any additional supportive information.

To support the finding that drometrizole trisiloxane is generally recognized as an effective sunscreen when used at concentrations up to 15%, we request 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. Since no study has been identified that establishes that drometrizole trisiloxane is effective at a concentration of 15%, it is recommended that such a study be conducted and submitted.

III. Summary of Current Data Gaps for Drometrizole Trisiloxane

Based on our review of the available safety and efficacy data as discussed above, we request the types of data listed below, at minimum, in order for the Agency to reverse our initial determination that drometrizole trisiloxane has not been shown to be GRASE. For additional information about the purpose and design of studies recommended to address these data gaps, please refer to the earlier sections of this letter referenced in parentheses. Note that, in some cases, the submissions provided the results of studies of the type requested below, but only in summary form. Were complete study data provided to the docket, allowing the agency to verify the validity and accuracy of the summaries, these studies might be sufficient. If data from these previously conducted studies are not made publically available, further studies would be needed in the public record, to support a finding that drometrizole trisiloxane is GRASE for use in sunscreens. We welcome discussions on design of any of the studies you intend to perform prior to commencement.

Safety Data (see Section I)

A. Human Clinical Studies
   1. Skin irritation/sensitization, and photosafety (see Section I.A.1)
   2. Human dermal pharmacokinetic (bioavailability) studies (see Section I.A.2)

B. Human Safety Data to Establish Adverse Event Profile (I.A.3)
   1. A summary of all available reported adverse events potentially associated with drometrizole trisiloxane
   2. All available documented case reports of serious side effects
   3. Any available safety information from studies of the safety and effectiveness

[68] FDA-2003-N-0196-0033, Study 09E0957-2, Vol. 1.
[69] FDA-2003-N-0196-0033, Study 09E0958-2, Vol. 1.
[70] FDA-2003-N-0196-0033, Study RRT INT.2003,Vol. 1.

of sunscreen products containing drometrizole trisiloxane in humans
4. Relevant medical literature describing adverse events associated with drometrizole trisiloxane.

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
1. Dermal carcinogenicity, full study report (see Section I.B.1)
2. Systemic carcinogenicity (see Section I.B.1)
3. Toxicokinetics (see Section I.B.3)

Effectiveness Data (see Section II)

If concentrations of drometrizole trisiloxane up to 15% are to be included in the monograph as requested, at least two SPF studies showing effectiveness of a selected concentration lower than 15%. An efficacy study of drometrizole trisiloxane at 15% is also recommended.

IV. Administrative Procedures

A copy of this letter will be filed in the Division of Dockets Management in Docket No. FDA-2003-N-0196. We encourage you and other interested parties to submit additional data regarding the safety and effectiveness of drometrizole trisiloxane for use as an OTC sunscreen product, to inform FDA's evaluation of whether this ingredient can be included in the sunscreen monograph. We also encourage interested parties to notify us in writing of their intent to submit additional data, and to request meetings with FDA to discuss protocol and data development. However, as noted previously, because the data submitted to date are not sufficient to support a determination that drometrizole trisiloxane is GRASE for use as an active ingredient in OTC sunscreen drug products, at this time OTC sunscreen products containing drometrizole trisiloxane may not be marketed without approval of a new drug application.[71]

Data submissions and other communications relating to this letter should be submitted to Docket No. FDA-2003-N-0196 at the Division of Dockets Management, 5360 Fishers Lane, rm 1601, Rockville, MD, 20852. In addition, you can submit the data through the Federal eRulemaking Portal at: http://www.regulations.gov. Follow the instructions for submitting comments.

[71] *See* 21 CFR 330.14(h); *see also* 21 CFR 314.105.

Sincerely,

Sandra L. Kweder, M.D., F.A.C.P.
RADM (Ret.) U.S. Public Health Service
Director (Acting)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research