Report to the Committee on Health, Education, Labor and Pensions of the Senate

Report to the Committee on Energy and Commerce of the House of Representatives

Report in Response to the Sunscreen Innovation Act (P.L. 113-195)

Section 586G.

U.S. Department of Health and Human Services

Food and Drug Administration

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Commissioner of Food and Drugs

Table of Contents

Introduction

The Sunscreen Innovation Act (SIA) enacted on November 26, 2014 (P.L. 113-195) requires that no later than 18 months after the date of enactment of the SIA, a report be issued to the Committee on Health, Education, Labor and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives describing actions taken pursuant to the SIA, and including the following:

(A) a review of the progress made in issuing determinations that an active ingredient in a pending request is generally recognized as safe and effective (GRASE), including:

1. the number of pending requests reviewed and the decision times for each request, measured from the date of the original request for an eligibility determination submitted by the sponsor;
2. the number of pending requests resulting in a determination that the nonprescription sunscreen active ingredient or combination is GRASE and not misbranded;
3. the number of pending requests resulting in a determination that the nonprescription sunscreen active ingredient or combination is not GRASE and is misbranded, along with the reasons for such determinations; and
4. the number of pending requests for which a determination has not been made, an explanation for the delay, a description of the current status, and the length of time each such request has been pending, measured from the date of the original request for an eligibility determination.

(B) a review of the progress made in issuing GRASE determinations for requests not included in the reporting under subparagraph (A) (i.e., new requests submitted pursuant to FDCA 586A), including:

1. the number of such requests reviewed and the decision times for each request;
2. the number of such requests resulting in a determination that the nonprescription sunscreen active ingredient or combination is GRASE and not misbranded;
3. the number of such requests resulting in a determination that the nonprescription sunscreen active ingredient or combination is not GRASE and is misbranded, along with the reasons for such determinations; and
4. the number of such requests for which a determination has not been made, an explanation for the delay, a description of the current status, and the length of time each such request has

been pending, measured from the date of the original request for an eligibility determination.

(C) an annual accounting (including information from years prior to the date of enactment of the SIA where such information is available) of the total number of requests submitted, pending, or completed under the SIA, including whether such requests were the subject of an advisory committee convened by the Secretary.

(D) a description of the staffing and resources relating to the costs associated with the review and decision-making pertaining to requests under the SIA.

(E) a review of the progress made in meeting the deadlines with respect to processing requests under the SIA.

(F) recommendations for process improvement in the handling of requests, including the advisory committee meeting review process.

Executive Summary

FDA is committed to doing its part to provide American consumers with additional options for safe and effective sunscreen formulations containing active ingredients that meet GRASE standards. FDA has met all of its statutory obligations and deadlines under the SIA to date. FDA relies on industry to submit the data needed to support a determination that a given active ingredient is GRASE for use in nonprescription sunscreen products. We are pleased to provide additional information in this report as required by the SIA (P.L. 113-195, Sec. 586G).

Discussion

The SIA was enacted to provide a new process for FDA review of safety and effectiveness of nonprescription sunscreen active ingredients and for other purposes. The SIA provides strict deadlines for FDA to take certain actions on sunscreen active ingredients, but does not relax FDA's scientific standards for evaluating the ingredients' safety and effectiveness or our need for adequate data on which to base such determinations. A large increase in the amount and frequency of sunscreen usage, together with advances in scientific understanding and safety evaluation methods, have given rise to new questions about what information is necessary and available to support general recognition of safety and effectiveness of sunscreen active ingredients for use in nonprescription sunscreen products. In particular, certain potential risks from long-term, regular exposure to sunscreen active ingredients cannot be detected or evaluated on the basis of commercial marketing experience.

FDA's expectations for safety and effectiveness data for sunscreen ingredients that are being considered through the SIA process are set to ensure consumers have access to sunscreens that are safe and effective, and are consistent with modern scientific thinking concerning the safety and effectiveness of sunscreens.

In the United States, sunscreens are regulated as drug products. A key element of the safety evaluation of a drug applied to the skin is determining to what extent the active ingredient is absorbed through the skin into the body. To determine the extent of absorption through the skin, FDA recommends a Maximal Usage Trial (MUsT), a version of which has been commonly performed for dermal products since the mid 1990s. This study is described in two draft guidances[1] and a publication.[2] If the MUsT shows that the active ingredient is not absorbed or is minimally absorbed into the body, FDA can waive certain safety testing that would otherwise be necessary to ensure that sunscreens containing that ingredient would be safe. FDA notes that industry has long been aware that dermally applied drugs may be absorbed through the skin; in fact, certain ingredients are used by industry to increase skin penetration of drugs that need to enter the body to be effective. FDA further notes that some marketed sunscreens contain inactive ingredients such as alcohol that, though added for other purposes, are known to be potential penetration enhancers. Therefore, FDA recommends that representative sunscreen formulations containing sunscreen active ingredients being evaluated pursuant to the SIA process be assessed under MUsT conditions as a key element of the safety evaluation before the sunscreen ingredients enter the U.S. market.

Sec. 586G Report

In accordance with section Sec. 586G, FDA is pleased to provide the following report.

A. Review of Progress In GRASE Determinations – Pending Requests

In late 2014 and early 2015, FDA issued eight proposed sunscreen orders, covering all requests that were pending when the SIA was enacted. FDA tentatively determined that the data are insufficient to classify each ingredient or combination of ingredients as GRASE and

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[1]Draft guidance for industry *Acne Vulgaris: Developing Drugs for Treatment* and Draft guidance for industry: *Over-the-Counter Sunscreens: Safety and Effectiveness Data.*

[2]Bashaw ED, Tran DC, Shukla CG, et al., 2014, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, Therapeutic Innovation & Regulatory Science, published online 27 June 2014, DOI:10.1177/2168479014539157.

not misbranded for use in nonprescription sunscreens. FDA will make final GRASE determinations when it receives the necessary data from industry.

See Appendix A: Status of Pending SIA Requests. FDA has provided significant feedback and advice to sponsors regarding how to complete data gaps noted in the proposed sunscreen orders, all of which is publicly available. In the case of three ingredients, FDA has not heard from the sponsor since the time of the initial data submission (2003 for two ingredients and 2010 for one). In addition, we note that despite long-term marketing in the European Union (EU), the EU Commission on Regulation recently removed one ingredient with a pending SIA request from the EU market due to safety concerns,[3] based on the advice of the Scientific Committee on Consumer Safety.[4] Similar concerns were raised in the FDA Proposed Order for this ingredient. Another ingredient with a pending SIA request is already included in sunscreens marketed under new drug applications in the United States.

B. Review of Progress In GRASE Determinations – New Requests

FDA has not received any requests not included in the reporting above pursuant to FDCA 586G(a)(2)(A) (or, in other words, new requests for GRASE determinations) since the enactment of SIA.

C. Annual Accounting of Progress

There are eight pending requests being evaluated pursuant to the SIA, all of which were submitted before the SIA was enacted. FDA has not received any new (post-enactment) requests. FDA has issued proposed sunscreen orders for all eight pending requests as required by SIA. None of the pending requests were the subject of an advisory committee meeting, although the framework for safety data requested was discussed at a meeting of the Nonprescription Drugs Advisory Committee in September 2014.

D. Description of Staffing and Resources

FDA estimates that costs for required SIA activities from the time of enactment (November 26, 2014) through February 12, 2016, are $5.5 million. FDA estimates that, since enactment of the SIA, approximately 56 FDA employees

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[3] Commission Regulation (EU) 2015/1298 of 28 July 2015 amending Annexes II and VI to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products. Downloaded at: http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32015R1298&from=EN

[4] SCCS (Scientific Committee on Consumer Safety), Opinion on 3-Benzylidene camphor. Colipa No S61, 18 June 2013.

have been working on the activities required under the statute. Disciplines include dermatology; multiple other physician specialties; photobiology; nanotechnology; biology; clinical pharmacology; nonclinical pharmacology; toxicology; maternal health; pediatrics; interdisciplinary science; chemistry, manufacturing and controls; law; economics; communications; project management; information technology; and others. Some employees have been working full-time on SIA implementation, and many have spent part of their time on SIA and part on other FDA work. FDA estimates that, from enactment on November 26, 2014, until February 12, 2016, FDA has dedicated a total of 14.55 person-years to SIA activities. This number includes both scientific review resources and non-review resources such as legal counsel. Using a "fully loaded full-time equivalent" rate, FDA estimates the FTE cost to be $4,710,711. A "fully loaded full-time equivalent" represents the cost of supporting one full-time staff person for a full year. This support includes salary, benefits, office space, technological support, equipment, and a share of overhead expenses such as campus security.

In addition to full-time equivalents (FTEs), FDA has paid $355,030 to the National Center for Toxicological Research for contract toxicological review work. Also, FDA has funded four Oak Ridge Institute for Science and Education fellows dedicated to SIA implementation at a cost of $100,000 each (total $400,000).

Current appropriations fund only 18 FTEs for all review work devoted to the over-the-counter (OTC) drug monograph.[5] There are approximately 88 OTC drug monographs. Fifty three percent (53 percent) of the total OTC monograph scientific review resources available to FDA have been utilized to work on the sunscreen monograph and other sunscreen-related matters required under SIA since enactment. This number could easily increase to 100 percent when data are provided by industry for FDA review.

Even before the SIA was enacted, OTC monograph review was critically under-resourced. FDA's ability to fulfill its regulatory responsibility to ensure that products containing monograph ingredients are safe and effective is at serious risk without a substantial increase in resources.

E. Progress in meeting Deadlines for Processing Requests

The SIA requires FDA to meet multiple timelines for completing specified actions on pending and new sunscreen requests. In accordance with the timelines in the SIA, FDA has completed reviews for all pending requests for sunscreen active ingredients and has tentatively determined that the sunscreen active ingredients are not GRASE for use in nonprescription sunscreens because the data are insufficient to classify the ingredients as GRASE and not misbranded, and additional information is necessary for FDA to determine otherwise. In the

[5] FDA is not permitted to use funds from user fee programs for monograph work.

proposed sunscreen orders it issued under the SIA, FDA outlined the data the Agency needs in order to determine that a sunscreen active ingredient is GRASE. FDA also issued draft guidance on this topic within a year of the SIA's enactment, as required by SIA (FDCA 486D(a)(1)(ii)). None of the additional data requested have been received by FDA to date and there are no timelines imposed by SIA for industry to submit these data. FDA has therefore met its statutory obligations under the SIA with respect to processing requests. Actions with respect to processing requests included:

- Issuance of a notice of availability announcing that the six feedback letters sent pursuant to 21 CFR 330.14(g) prior to enactment of the SIA had been deemed under the SIA to be proposed sunscreen orders within 45 days of enactment. See FDCA 586C(b)(3).

- Completion of reviews for two pending requests and issuance of proposed sunscreen orders within 90 days of enactment. See FDCA 586C(b)(4).

- Public meetings requested by sponsors of four pending requests to discuss sunscreen data requirements were held within 45 days of the meeting requests. See FDCA 586C(b)(7). (The sponsor of a fifth ingredient withdrew its meeting request before the scheduled meeting.) FDA provided written feedback to each sponsor's questions before the meetings as well as meeting minutes, all of which are available to the public.[6]

- Issuance of four draft guidances, including one that discusses the data required to meet the safety and effectiveness standard for determining whether a nonprescription sunscreen active ingredient or combination is GRASE, within one year of enactment. See FDCA 586D(a)(1)(A). FDA has also been responsive to stakeholder questions.

F. Recommendations for Process Improvements

FDA receives very few resources that it can allocate to monograph review work and as described in section D, is critically under-resourced. The Agency is exploring options to increase resources dedicated to OTC monograph review, including resources for review of sunscreen active ingredients in line with the SIA implementation costs.

[6] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm439022.htm

Conclusion

FDA has met all of its statutory obligations under the SIA to date. FDA is committed to doing its part to provide American consumers with additional options for safe and effective sunscreen active ingredients. FDA met promptly with sponsors to discuss sunscreen data requirements and provided relevant draft guidance to assist sponsors. FDA relies on industry to submit the additional data needed to support a determination that a sunscreen containing a given active ingredient would be generally recognized as safe and effective.

Appendix A: Status of Pending SIA Requests

Ingredient [Docket No.]	Date of Time and Extent Application	Eligibility Determination Date	Date(s) of Industry Data Submission	Feedback Letter Issued (Deemed by SIA's enactment to be Proposed Sunscreen Order)	Statutory Deadline for Proposed Sunscreen Order or Notice Thereof (in case of prior Feedback Letter)	Date Proposed Sunscreen Order or Notice Issued	Date of Industry Submission of Missing Data	Date Final Sunscreen Order Issued
Bemotrizinol [FDA-2005-N-0453]	4/11/05	12/5/2005	2/28/2006 11/29/2006	11/13/2014	1/10/2015	1/7/2015	Pending[1]	Pending data submission
Bisoctrizole [FDA-2005-N-0453]	4/11/05	12/5/05	2/27/06	9/3/2014	1/10/2015	1/7/2015	Pending[1]	Pending data submission
Drometrizole Trisiloxane [FDA-2003-N-0196]	1/16/2009	6/2/10	1/16/09 7/14/10	8/29/2014	1/10/2015	1/7/2015	Pending[2]	Pending data submission
Octyl Triazone [2003N-0233]	8/21/02	7/11/03	10/3/03 1/9/04 7/2/04 12/21/06	6/23/2014	1/10/2015	1/7/2015	Pending[1]	Pending data submission
Amiloxate [2003N-0233 SUP3 and RPT1]	8/14/02	7/11/03	10/1/03 8/15/03	2/25/2014	1/10/2015	1/7/2015	Pending; No contact from sponsor since 2003	Pending data submission

[1] Meetings held with BASF, the sponsor of bemotrizinol, bisoctrizole, and octyl triazone on March 19, 2015, and March 20, 2015. Detailed written responses to all sponsor questions and minutes of these meetings were provided. FDA provided additional written feedback on October 8, 2015. Then-FDA Acting Commissioner Dr. Ostroff and then-Deputy Commissioner Dr. Califf held a call with BASF senior management on June 2, 2015. The sponsor has submitted no data or protocols for review.

[2] Meeting held with L'Oreal, the sponsor of drometrizole, trisiloxane, and ecamsule on May 11, 2015. Detailed written responses to all sponsor questions and minutes of this meeting were provided. FDA provided additional written feedback on August 31, 2015, December 14, 2015, and March 25, 2016. Then-FDA Acting Commissioner Dr. Ostroff and then-Deputy Commissioner Dr. Califf held a call with L'Oreal senior management on May 19, 2015. The sponsor has submitted no data or protocols for review.

Ingredient [Docket No.]	Date of Time and Extent Application	Eligibility Determination Date	Date(s) of Industry Data Submission	Feedback Letter Issued (Deemed at SIA's enactment to be Proposed Sunscreen Order)	Statutory Deadline for Proposed Sunscreen Order or Notice Thereof (in case of prior Feedback Letter)	Date Proposed Sunscreen Order or Notice Issued	Date of Industry Submission of Missing Data	Date Final Sunscreen Order Issued
Diethylhexyl Butamido Triazone [FDA-2006-0-0314]	9/16/05	7/26/06	10/24/06 7/6/07 5/6/10	2/21/2014	1/10/2015	1/7/2015	Pending; No contact from sponsor since 2010	Pending data submission
Ecamsule[3] 9FDA-2008-N-0474]	9/19/07	9/12/08	11/14/08	Not applicable	2/24/2015	2/24/2015	Pending[2]	Pending data submission
Enzacamene[4] [2003N-0233]	8/21/02	7/11/03	10/9/03	Not applicable	2/24/2015	2/24/2015	Pending; No contact from sponsor since 2003	Pending data submission

[3] Ecamsule is already available in four different sunscreen products in the United States, marketed under NDAs 021502, 021501, 021471, and 022009. Currently there are no exclusivities remaining or unexpired patents listed for these applications in FDA's Orange Book, which means that patents and exclusivities would not impact FDA's ability to approve generic versions, thereby potentially increasing availability in the United States if generic approval is sought.

[4] In 2013 (SCCS/151/13), the Scientific Committee on Consumer Safety (SCCS) opined that the use of enzacamene as a UV-filter in cosmetic products in a concentration up to 2.0% is not safe. Their conclusion was based on endocrine disruptor properties, which were also noted in FDA's proposed order. [Note: The European Commission relies on the SCCS for scientific advice on health and safety risks of consumer products, including cosmetics.] In 2011, the French regulatory authorities adopted a decision to prohibit manufacture, import, export, wholesale distribution or marketing of enzacamene-containing products in France. See: SCCS (Scientific Committee on Consumer Safety), Opinion on 3-Benzylidene camphor. Colipa No S61, 18 June 2013.