Report to the Committee on Health, Education, Labor, and Pensions, U.S. Senate, and the Committee on Energy and Commerce, U.S. 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

/s/ 5-4-18

_____ Date _____

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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 generally recognized as safe and effective (GRASE) standards. FDA has met all of its statutory obligations and deadlines under the Sunscreen Innovation Act (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).

Introduction

The 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 and on the date that is 2 years thereafter, a report be issued to the Committee on Health, Education, Labor, and Pensions of the U.S. Senate and the Committee on Energy and Commerce of the U.S. House of Representatives describing actions taken pursuant to the SIA, 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 Federal Food, Drug, and Cosmetic Act (FDCA) section 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.

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. These expectations are consistent with current 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. Consistent with recommendations of the Nonprescription Drugs Advisory Committee, FDA recommends

a Maximal Usage Trial (MUsT) to make this determination; this type of study has been commonly performed since the mid-1990s for drug products applied to the skin. Products absorbed through the skin have the potential to cause systemic adverse effects, affecting the safety assessment.

The MUsT design is described in a draft guidance,[1] one final guidance,[2] and a publication.[3] If a MUsT shows that the active ingredient is not absorbed or is minimally absorbed, FDA waives certain safety testing that would otherwise be necessary to ensure that sunscreens containing that ingredient would be safe. FDA 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.

Section 586G Report

In accordance with section 586G of the SIA, 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 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), Germany proposed that an ingredient with a pending SIA request be identified as a Substance of Very High Concern and be removed from the

[1] Draft Guidance for Industry: *Acne Vulgaris: Developing Drugs for Treatment*

[2] Final Guidance for Industry: *Over-the-Counter Sunscreens: Safety and Effectiveness Data*

[3] 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.

market due to its endocrine-disrupting properties.[4] Although the proposal was later withdrawn because some member states requested additional information, it raised similar concerns to those noted in the FDA Proposed Order for this ingredient. In addition, the EU Commission on Regulation removed a structurally similar ingredient from the EU market due to safety concerns,[5] based on the advice of the Scientific Committee on Consumer Safety.[6] 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 the 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 since the last report to Congress, from February 13, 2016, through February 12, 2018, are $8.4 million. FDA estimates that approximately 56 FDA employees 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 others have spent part of their time on SIA and part on other FDA work. FDA estimates that, from February 13, 2016, until February 12, 2018, FDA has dedicated a total

[4] Annex XV report. Proposal for identification of a substance of very high concern on the basis of the criteria set out in reach article 57, submitted by Germany, 25 February 2016. Downloaded at: https://echa.europa.eu/documents/10162/a9e12f40-872c-4096-8141-f379b57f2037

[5] 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

[6] SCCS (Scientific Committee on Consumer Safety), Opinion on 3-Benzylidene camphor. Colipa No S61, 18 June 2013. Downloaded at: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_134.pdf

of 12.76 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 full-time equivalent (FTE) cost to be $6,884,613 for the 2-year reporting period. 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. During this time period, FDA used these resources to develop guidances; provide technical assistance for the Government Accountability Office report issued November 15, 2017; continue work on finalizing the sunscreen monograph (including SPF and dosage forms); and respond to various sponsor requests, including meetings.

In addition to FTEs, FDA has paid $1.2 million to the National Center for Toxicological Research for contract toxicological review work during FY 2017. Also, FDA has funded four Oak Ridge Institute for Science and Education fellows. The portion of their effort dedicated to SIA activities during the above period cost approximately $360,000.

At the time of enactment of the SIA, appropriations funded only 18 FTEs for all review work devoted to all therapeutic areas of the over-the-counter (OTC) drug monograph.[7] In FY 2016, Congress appropriated $716,000 to go toward sunscreen review activities. However, there are approximately 88 OTC drug monograph rulemakings, with the sunscreen monograph being only one of them. Of the total OTC monograph scientific review resources available to FDA, 31 percent are currently being utilized to work on the sunscreen monograph and other sunscreen-related matters required under SIA. 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 proposed sunscreen orders issued under the SIA, FDA outlined the data the

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

Agency needs to determine that a sunscreen active ingredient is GRASE. FDA also issued draft guidance on this topic as well as other topics specified in the SIA within a year of the SIA's enactment, and finalized these guidances within 2 years of enactment, as required by SIA (FDCA 586D(a)). None of the additional data requested have been received by FDA to date; 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 586(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.[8]

- 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 1 year of enactment. All four of these guidances were finalized within 2 years of enactment. See FDCA 586D(a)(1)(B). FDA has also been responsive to comments and stakeholder questions about these guidances.

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 in this area. Although Congress updated the regulatory process for new sunscreen ingredients under the SIA, the regulatory process for the OTC monograph system, which regulates most OTC drugs in the United States, is burdensome and outdated. FDA, the OTC drug industry, and numerous stakeholders have held extensive discussions regarding proposed reforms. Congress is considering legislation for these reforms and an accompanying user fee program, which would substantially increase resources for review of all OTC drugs, including sunscreens. FDA is supportive of this legislative effort, and the Agency continues to provide technical assistance to the Committee on Health, Education, Labor, and Pensions, U.S. Senate, and the Committee on Energy

[8] https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm439022.htm

and Commerce, U.S. House of Representatives, upon request.

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 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 GRASE, but none of the additional data requested have been received by FDA to date; there are no timelines imposed by SIA for industry to submit these data.

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	12/5/05	2/28/06 11/29/06	11/13/14	1/10/15	1/7/15	Pending[9]	Pending data submission
Bisoctrizole [FDA-2005-N-0453]	4/11/05	12/5/05	2/27/06	9/3/14	1/10/15	1/7/15	Pending[9]	Pending data submission
Drometrizole Trisiloxane [FDA-2003-N-0196]	1/16/09	6/2/10	1/16/09 7/14/10	8/29/14	1/10/15	1/7/15	Pending[10]	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	6/23/14	1/10/15	1/7/15	Pending[9]	Pending data submission
Amiloxate [2003N-0233 SUP3 and RPT1]	8/14/02	7/11/03	10/1/03 8/15/03	2/25/14	1/10/15	1/7/15	Pending; No contact from sponsor since 2003	Pending data submission

[9] 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. An additional meeting with BASF took place on October 12, 2017. BASF was seeking feedback for the planning and execution of the requested MUsT studies. FDA provided written responses to all sponsor questions on October 11, 2017 and additional feedback on November 15, 2017 as part of the memorandum of meeting minutes.

[10] 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	1/10/15	1/7/15	Pending; No contact from sponsor since 2010	Pending data submission
Ecamsule[11] 9FDA-2008-N-0474]	9/19/07	9/12/08	11/14/08	Not applicable	2/24/15	2/24/15	Pending[10]	Pending data submission
Enzacamene[12] [2003N-0233]	8/21/02	7/11/03	10/9/03	Not applicable	2/24/15	2/24/15	Pending; No contact from sponsor since 2003	Pending data submission

[11] 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.

[12] In 2013 (SCCS/151/13), the Scientific Committee on Consumer Safety (SCCS) opined that the use of 3-benzylidene camphor, a chemical structurally similar to enzacamene, as a UV-filter in cosmetic products in a concentration up to 2.0% is not safe. [Note: The European Commission relies on the SCCS for scientific advice on health and safety risks of consumer products, including cosmetics.] In February 2016, Germany proposed both 3-benzylidine camphor and enzacamene (4-methylbenzlidine camphor) be identified as substances of very high concern (SVHC) due to endocrine disruptive effects by the European Chemicals Agency (ECHA). Germany's conclusion on both ingredients was based on endocrine disruptor properties, which were also noted in FDA's proposed order for enzacamene. Although Germany's proposal on enzacamene was later withdrawn, in July 2015, 3-benzlidene camphor was banned as a UV filter by the EU (Commission Regulation (EU) 2015/1298). As of January 2018, the European Commission submitted notification to the World Trade Organization that a draft Commission Decision was aimed at identifying 3-benzylidene camphor as a substance of very high concern. To date, no similar action has been taken on enzacamene itself.