

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

**Report in Response to Section 586G of the Federal
Food, Drug, and Cosmetic Act (as Added by the
Sunscreen Innovation Act (P.L. 113-195))**

U.S. Department of Health and Human Services
U.S. Food and Drug Administration

A handwritten signature in black ink, appearing to read "S. Hahn". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

May 22, 2020

Stephen M. Hahn, M.D.
Commissioner of Food and Drugs

Date

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Executive Summary

The Food and Drug Administration (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) (P.L. 113-195) for processing requests required to be reported under section 586G of the Federal Food, Drug, and Cosmetic Act, as added by the SIA. 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. FDA is pleased to provide additional information in this report as required by section 586G.

Introduction

The Sunscreen Innovation Act (SIA) (P.L. 113-195), enacted on November 26, 2014, requires that no later than 18 months after the date of enactment of the SIA and on dates that are 2 and 4 years thereafter, a report be issued by the Secretary of Health and Human Services 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 section 586A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), 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 both to provide a new process for the Food and Drug Administration (FDA or the Agency) to use in reviewing the safety and effectiveness of nonprescription sunscreen active ingredients and to fulfill other purposes. The SIA provides strict deadlines for FDA to follow when taking certain actions on sunscreen active ingredients but relaxes neither FDA's scientific standards for evaluating these ingredients' safety and effectiveness nor FDA's need for adequate data on which to base such evaluations.

A large increase in the amount and frequency of sunscreen usage, together with new information about sunscreen absorption, has given rise to new questions about what information is necessary and available to support a 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 for regular, lifelong use. These expectations are

consistent with current scientific thinking concerning the safety and effectiveness of sunscreens.

In February 2019, FDA issued the proposed rule Sunscreen Drug Products for Over-the-Counter Human Use,¹ which was issued, in part, to meet the requirements of section 586E of the FD&C Act (as added by the SIA). Section 586E required FDA to amend and finalize regulations under part 352 of Title 21 of the Code of Federal Regulations concerning nonprescription sunscreens (and, among other things, to report to Congress if these regulations do not include provisions related to the effectiveness of both various sun protection factor (SPF) levels and dosage forms).² This proposed rule includes provisions addressing both SPF levels and dosage forms. Specifically, for SPF levels, FDA proposes new SPF and broad spectrum requirements for sunscreens marketed without approved applications that would raise the maximum labeled SPF from SPF 50+ to 60+, require any sunscreen SPF 15 or higher to now be broad spectrum, and require that for all broad spectrum products SPF 15 and above, as the SPF increases, broad spectrum protection must also increase. For sunscreen dosage forms, FDA proposes (1) that sunscreen oils, lotions, creams, gels, butters, pastes, ointments, and sticks are GRASE and (2) that sunscreen sprays are GRASE subject to FDA's proposed testing and labeling aimed at minimizing the potential risks from unintended inhalation and flammability. In addition, FDA proposes to add powders to the list of dosage forms that are eligible for the sunscreen monograph and suggests that additional data are needed to make a positive GRASE determination for sunscreen powders.

The same expectations that FDA has applied to the sunscreen active ingredients being considered under the new process established by the SIA (Appendix A), as further amended by section 3854 of the Coronavirus Aid, Relief, and Economic Security (CARES) Act, were applied to the sunscreen active ingredients evaluated in the proposed rule (i.e., those already listed in current, stayed 21 CFR 352). In the proposed rule, FDA proposes (1) that two of the active ingredients evaluated (i.e., zinc oxide and titanium dioxide) are GRASE for use in sunscreens and (2) that two of the sunscreen active ingredients (i.e., trolamine salicylate and para-amino benzoic acid (PABA)) are not GRASE for use in sunscreens because of safety concerns. For the other 12 ingredients evaluated in the proposed rule, FDA identifies data gaps that the Agency believes need to be addressed before a final positive GRASE determination

¹ This proposed rule is available at <https://www.federalregister.gov/documents/2019/02/26/2019-03019/sunscreen-drug-products-for-over-the-counter-human-use>.

² Note that section 586E of the FD&C Act, as added by the SIA, was removed by section 3854 (b)(5) of the Coronavirus Aid, Relief, and Economic Security Act.

can be issued. To help the public fill these data gaps, FDA conducted a thorough review of the publicly available literature and data and described in detail the data the Agency requests for each of these 12 ingredients.

FDA also states in the proposed rule that it would consider requests to defer further rulemaking with respect to sunscreen active ingredients to allow the submission of new safety and/or effectiveness data to the record. The comment period for the proposed rule closed on June 27, 2019 (after FDA granted an extension requested by industry). FDA received approximately 15,000 public comments on the sunscreen proposed rule.

In addition to issuing the proposed rule, FDA has, since the last report to Congress, taken a number of steps to provide guidance to industry. For instance, in May 2018, FDA issued a final guidance describing the Agency's enforcement approach with respect to over-the-counter (OTC) sunscreen products marketed without approved applications.³

Further, a number of FDA's recent efforts have been aimed at assisting with the conduct of the Maximal Usage Trial (MUsT), which is recommended to determine the extent to which an active ingredient is absorbed through the skin and into the body. At the time of the last report to Congress, the MUsT design was described in a final guidance⁴ and in a publication.⁵ In May 2019, FDA published a final guidance on the MUsT, which is for topically applied active ingredients for inclusion in an OTC drug monograph, that included recommendations for designing and conducting a MUsT relevant to active ingredients being considered for inclusion in a future final effective

³ Guidance for Industry: Enforcement Policy—OTC Sunscreen Drug Products Marketed Without an Approved Application, available at <https://www.fda.gov/media/80403/download>. Note that FDA is still evaluating how the CARES Act has affected the regulatory status of sunscreens marketed without approved new drug applications.

⁴ Guidance for Industry: Nonprescription Sunscreen Drug Products: Safety and Effectiveness Data, available at <https://www.fda.gov/media/94513/download>.

⁵ 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.

sunscreen monograph.⁶ As described in that guidance, if a MUsT shows that the active ingredient is not absorbed or is minimally absorbed, FDA believes that certain safety testing that it would otherwise expect to be necessary to ensure that sunscreens containing that ingredient would be safe will not be needed.

In addition, to aid industry in its study design for the MUsT, FDA conducted a two-part pilot study, which was published in May 2019⁷ and January 2020,⁸ evaluating multiple commercial sunscreens using the MUsT concept. These preliminary studies found that all sunscreen active ingredients tested from commercially marketed sunscreens (1) were absorbed into the bloodstream even when the sunscreen was only applied once per day and (2) persisted in the body for extended periods of time. FDA also cohosted, with the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), a two-day workshop held in June 2019 on the MUsT design.⁹ The workshop was held on the University of Maryland's Baltimore campus and brought together academia, members of industry, consultants, and federal scientists to discuss the use of the MUsT for topical pharmaceutical ingredients and the future of topical drug development.

On March 27, 2020, the President signed into law the CARES Act, a \$2 trillion emergency relief bill that will continue to aid the response efforts and ease the economic impact of COVID-19. Importantly, the CARES Act includes a significant legislative initiative that reforms and modernizes the way certain OTC drugs, including sunscreens, are regulated in the United States. The Agency's analysis of this recently

⁶ Guidance for Industry: Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations, available at <https://www.fda.gov/media/125080/download>.

⁷ Matta MK, Zusterzeel R, Pilli NR, et al. Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. *JAMA*. 2019;321(21):2082–2091. doi:10.1001/jama.2019.5586.

⁸ Matta MK, Florian J, Zusterzeel R, et al. Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. *JAMA*. 2020;323(3):256–267. doi:10.1001/jama.2019.20747.

⁹ "Topical Drug Development - Evolution of Science and Regulatory Policy," July 29-30, 2019. University of Maryland, Baltimore School of Pharmacy, available at <https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-public-workshop-topical-drug-development-evolution-science-and-regulatory-policy-day-1-07292019>.

enacted OTC monograph reform legislation is ongoing, and FDA's development and dissemination of its interpretation of this new statutory authority will be consistent with good guidance practices and other applicable statutory and regulatory requirements.

Section 586G Report

In accordance with section 586G of the FD&C Act (as added by the SIA), FDA is pleased to provide the following report.

A. Review of Progress in GRASE Determinations - Pending Requests¹⁰

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 publicly available feedback and advice to sponsors regarding how to close data gaps noted in these proposed sunscreen orders. For three ingredients, FDA has not heard from the sponsor since the time of its initial data submission (2003 for two ingredients and 2010 for one). In addition, despite long-term marketing in the European Union (EU), Germany proposed that an ingredient, enzacamene, with a pending SIA request be identified as a Substance of Very High Concern (SVHC) and be removed from the market because of its endocrine-disrupting

¹⁰ With regard to all eight proposed sunscreen orders FDA issued pursuant to section 586C of the FD&C Act (as added by the SIA), the Agency notes that section 3854(a)(1) of the CARES Act provides the following: "A sponsor of a nonprescription sunscreen active ingredient or combination ... that, as of the date of enactment of this Act, is subject to a proposed sunscreen order under section 586C of the [FD&C Act] ... may elect, ... to transition into the review of such ingredient or combination ... pursuant to the process set out in section 505G of the [FD&C Act] as added by section 3851 of this subtitle."

properties.¹¹ Although this proposal was later withdrawn because some member states requested additional information, the proposal raised similar concerns to those noted in FDA's proposed order for this ingredient. Also, the EU Commission on Regulation removed a structurally similar ingredient from the EU market, based on the advice of the Scientific Committee on Consumer Safety,¹² because of safety concerns.¹³ Another ingredient with a pending SIA request is already included in sunscreens approved and 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 section 586G(a)(2)(A) of the FD&C Act (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 the SIA. None of the pending requests was 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.

In 2019, FDA was approached by a company interested in generating data to address concerns raised in one of the eight pending requests.¹⁴ FDA engaged in discussions with this company regarding study design and development timelines. FDA remains

¹¹ 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, available at <https://echa.europa.eu/documents/10162/a9e12f40-872c-4096-8141-f379b57f2037>.

¹² Scientific Committee on Consumer Safety (SCCS), Opinion on 3-Benzylidene camphor. Colipa No S61, 18 June 2013, available at https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_134.pdf.

¹³ 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, available at <http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32015R1298&from=EN>.

¹⁴ DSM Nutritional Products June 7, 2019 Meeting Minutes, available at <https://www.regulations.gov/document?D=FDA-2005-N-0453-0055>.

committed to continued discussions with any interested sponsor for any of the eight pending requests.

D. Description of Staffing and Resources

FDA estimates that costs for SIA-related activities since the last report to Congress (i.e., from February 13, 2018, through January 29, 2020) are \$10.3 million. FDA estimates that approximately 56 FDA employees have been working on the activities required under the statute. FDA's work has included the following disciplines: 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 the SIA and part on other FDA work. FDA estimates that, from February 13, 2018 to January 29, 2020, the Agency dedicated a total of 12.24 years of staff time to SIA-related 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 \$6,962,353 for the two-year reporting period. A "fully loaded full-time equivalent" represents the cost of supporting one full-time staff person for a full year, which 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 to be issued in May 2020, 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 \$2.2 million to the National Center for Toxicological Research for contract toxicological review work during fiscal years (FYs) 2018 and 2019. Also, FDA has funded two sunscreen studies for a total of approximately \$1.1 million.

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.¹⁵ In FY 2016, Congress appropriated \$716,000 to go toward sunscreen review activities.

¹⁵ The only user fees FDA can use to support its regulation of OTC monograph drugs are those authorized under the recently passed CARES Act, once those fees are appropriated.

However, there are approximately 88 OTC drug monograph rulemakings, with the sunscreen monograph being only one of them. As of January 29, 2020, of the total OTC monograph scientific review resources available to FDA, 25 percent are currently being utilized to work on the sunscreen monograph and other sunscreen-related matters required under the SIA.

OTC monograph review remains critically under-resourced. However, the CARES Act establishes authority under the FD&C Act for a user fee program to support FDA's regulation of OTC monograph products.

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 (1) 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 (2) additional information is necessary for FDA to determine otherwise. In the proposed sunscreen orders issued under the SIA, FDA outlined the data the Agency needs to determine that a sunscreen active ingredient is GRASE. FDA also issued draft guidance on this topic and others specified in the SIA within a year of the SIA's enactment; FDA finalized these guidances within two years of enactment, as required by section 586D(a) of the FD&C Act, as added by the SIA. None of the additional data requested has been received by FDA to date; there are no timelines imposed by the 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 have 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 section 586C(b)(3) of the FD&C Act.
- Completion of reviews for two pending requests and issuance of proposed sunscreen orders within 90 days of enactment. See section 586C(b)(4) of the FD&C Act.
- Public meetings requested by sponsors of four pending requests to discuss sunscreen data requirements were held within 45 days of the meeting requests. See section 586(b)(7) of the FD&C Act. (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.¹⁶

- Issuance of four draft guidances within one year of enactment, 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. All four of these guidances were finalized within two years of enactment, as required by section 586D(a)(1)(B) of the FD&C Act. FDA has also been responsive to comments and stakeholder questions about these guidances.

F. Recommendations for Process Improvements

FDA is currently evaluating the impact of the recently enacted CARES Act legislation on the regulation of OTC monograph drugs, including sunscreens. FDA expects that the transformative new authorities granted by the law will meaningfully advance the Agency's efforts to modernize the OTC drug development and review process to help advance innovative, safe, and effective options for consumers and to secure a robust OTC marketplace.

Conclusion

FDA has met all of its statutory obligations for processing requests required to be reported under section 586G of the FD&C Act, as added by the SIA. In addition, 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 data needed to support a determination that a sunscreen containing a given active ingredient would be GRASE, but, to date, FDA has not received any of the data requested. The SIA does not impose any timelines on industry to submit these requested data.

¹⁶ FDA's Sunscreen Meetings website is available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm439022.htm>.

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 ^{17, 18}	Pending data submission

¹⁷ 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 its 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.

¹⁸ Meeting held with DSM Nutritional Products LLC on June 7, 2019, a new party interested in providing data for bemotrizinol.

Bisoctrizole [FDA-2005-N-0453]	4/11/05	12/5/05	2/27/06	9/3/14	1/10/15	1/7/15	Pending ¹⁸	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 ¹⁹	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 ¹⁸	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
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	Date Proposed Sunscreen Order or Notice Issued	Date of Industry Submission of Missing Data	Date Final Sunscreen Order Issued

¹⁹ 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.

					Feedback Letter)			
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 ²⁰ [9FDA-2008-N-0474]	9/19/07	9/12/08	11/14/08	Not applicable	2/24/15	2/24/15	Pending ¹⁴	Pending data submission
Enzacamene ²¹ [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

²⁰ Ecamsule is already available in four different sunscreen products in the United States, marketed under new drug applications 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 their availability in the United States if generic approval is sought.

²¹ In 2013 (SCCS/151/13), the 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 percent 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 that both 3-benzylidene camphor and enzacamene (4-methylbenzylidene camphor) be identified as substances of very high concern SVHCs by the European Chemicals Agency (ECHA) because of endocrine disruptive effects. 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-benzylidene camphor was banned as a UV filter by the EU (Commission Regulation (EU) 2015/1298); and in January 2019, Germany's proposal included 3-benzylidene camphor on the candidate list of SVHCs. In May 2019, the European Commission published a call for data on enzacamene as a cosmetic ingredient with potential endocrine-disrupting properties.