



November 2017

SUNSCREEN

FDA Reviewed Applications for Additional Active Ingredients and Determined More Data Needed

Accessible Version

Why GAO Did This Study

Using sunscreen as directed with other sun protective measures may help reduce the risk of skin cancer—the most common form of cancer in the United States. In the United States, sunscreen is considered an over-the-counter drug, which is a drug available to consumers without a prescription. Some sunscreen active ingredients not currently marketed in the United States have been available in products in other countries for more than a decade. Companies that manufacture some of these ingredients have sought to market them in the United States by applying to add the ingredients to the sunscreen monograph, which lists ingredients that can be used in sunscreens without FDA's premarket approval. FDA reviews the applications and corresponding safety and effectiveness data for the ingredients.

The Sunscreen Innovation Act includes a provision for GAO to examine FDA's implementation of the act. This report examines (1) the extent to which FDA implemented requirements for reviewing applications for sunscreen active ingredients within mandated time frames, and (2) the status of the sunscreen applications. GAO reviewed FDA regulations and guidance documents, Federal Register notices, and FDA and sponsor documents for all eight sunscreen applications. GAO also interviewed FDA officials; sponsors of sunscreen applications; and stakeholders with interests in sunscreen, including health care providers, researchers, and industry groups. Stakeholders were selected based on knowledge of the monograph process and sunscreen active ingredients. The perspectives of these stakeholders are not generalizable.

View [GAO-18-61](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

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What GAO Found

The Food and Drug Administration (FDA), within the Department of Health and Human Services, implemented requirements for reviewing applications for sunscreen active ingredients within time frames set by the Sunscreen Innovation Act, which was enacted in November 2014. For example, the agency issued a guidance document on safety and effectiveness testing in November 2016.

As of August 2017, all applications for sunscreen active ingredients remain pending after the agency determined more safety and effectiveness data are needed. By February 2015, FDA completed its initial review of the safety and effectiveness data for each of the eight pending applications, as required by the act. FDA concluded that additional data are needed to determine that the ingredients are generally recognized as safe and effective (GRASE), which is needed so that products using the ingredients can subsequently be marketed in the United States without FDA's premarket approval. To make a GRASE determination, FDA requested that the application sponsors provide additional data, including human clinical studies, animal studies, and efficacy studies.

Sponsors of some of the sunscreen applications and some stakeholders GAO interviewed questioned FDA's requests, stating, for example, that the agency's recommended absorption test has never been conducted on sunscreen ingredients and there is a lack of knowledge on how to conduct it. At the same time, other stakeholders support the additional testing FDA requested. FDA reports that the increase in the amount and frequency of sunscreen usage, coupled with advances in scientific understanding and safety evaluation methods, has informed the agency's perspective that it needs additional data to determine that sunscreen active ingredients are GRASE. However, none of the sponsors reported current plans to provide the requested information—that is, they are either still considering whether to conduct the additional tests or they do not plan to do so. They cited the following reasons:

- **Return on investment.** The testing FDA requested is extensive, would cost millions of dollars, or take several years to conduct, according to sponsor representatives. Some stakeholders and sponsor representatives said that sponsors are currently working to develop newer sunscreen ingredients and are therefore reluctant to invest in the testing FDA requested for the older ingredients covered by the pending applications.
- **Alternatives not accepted.** Some sponsor representatives and stakeholders said that when they proposed alternative testing methods for absorption, for example, the agency rejected the alternatives.
- **Animal testing.** One stakeholder and some sponsor representatives reported concerns about the effect that the animal testing requested by FDA may have on companies' marketing of sunscreen products worldwide. Additionally, one stakeholder and representatives from one sponsor expressed concern that sunscreen manufacturers may face backlash from animal rights groups and shareholders if animal testing is conducted.

The Department of Health and Human Services provided technical comments on a draft of this report, which GAO incorporated as appropriate.

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Abbreviations

FDA	Food and Drug Administration
GRASE	generally recognized as safe and effective
MUsT	Maximal Usage Trial
NDA	new drug application
OTC	over-the-counter
SIA	Sunscreen Innovation Act
SPF	sun protection factor
TEA	time and extent application
UV	ultraviolet

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November 15, 2017

The Honorable Lamar Alexander
Chairman
The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Greg Walden
Chairman
The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

With nearly 5 million people treated each year, skin cancer is the most common form of cancer in the United States and rates are rising. To help reduce the risk of skin cancer, the U.S. Surgeon General and other authorities recommend using sunscreen in conjunction with other preventive measures.¹ Given this recommendation, there is interest in ensuring Americans have access to the most effective sunscreen products. Furthermore, authorities encourage people to apply sunscreen liberally and frequently when out in the sun; and Americans are using sunscreen more often and in larger quantities than in the past. However, heightened concerns about possible adverse effects from absorbing sunscreen ingredients through the skin have accompanied this increase in sunscreen use.

Some sunscreen active ingredients not currently marketed in the United States have been available in products in other countries for more than a decade, and companies that manufacture some of these sunscreen ingredients have sought to bring these ingredients to the U.S. market. In the United States, sunscreen is considered an over-the-counter (OTC) drug, which is a drug available to consumers without a prescription. The Federal Food, Drug, and Cosmetic Act authorizes the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services, to ensure that OTC drugs, such as sunscreens, are

¹Department of Health and Human Services. *The Surgeon General's Call to Action to Prevent Skin Cancer*. (Washington, D.C.: 2014).

safe and effective in order to be marketed in the United States. There are two routes that can be used to market an OTC drug:

- One route is through FDA's OTC monograph process, which focuses on the conditions, such as active ingredients, dosage forms, and labeling for OTC drug products. Under the OTC monograph process, FDA reviews active ingredients and other conditions to determine whether they are generally recognized as safe and effective (GRASE) for use in an OTC drug, such as sunscreen. If FDA finds an active ingredient to be GRASE for use in a particular category of OTC drugs, OTC drug products that contain such ingredients do not need individual preapproval from FDA to be marketed, assuming compliance with applicable regulations.
- The other route is through the new drug application (NDA) process, under which FDA determines the safety and effectiveness of an individual drug product. FDA must review and approve an NDA before a product can be marketed.

For active ingredients that have previously been marketed only in other countries or in drug products individually approved for the U.S. market through an NDA, FDA's time and extent application (TEA) process provides a pathway for FDA to determine whether an ingredient is GRASE and can be marketed under the OTC monograph process.² To be eligible for review under the TEA process, an active ingredient must be shown to have been marketed for a material time and material extent in an OTC product, as described in FDA regulations. Once the agency determines that a TEA is eligible for review, sponsors—such as the manufacturers of these ingredients—and other interested parties may submit safety and effectiveness data for FDA to review and make a GRASE determination.

Sponsors submitted TEAs for eight sunscreen active ingredients between 2002 and 2009. Amid concerns that these TEAs had been pending with FDA for several years, Congress enacted the Sunscreen Innovation Act (SIA) in November 2014.³ SIA altered the process FDA uses to determine whether a sunscreen active ingredient is GRASE and established time

²According to FDA officials, the agency has only received TEAs for additional active ingredients, and not for other conditions, such as dosage forms, dosage strengths, and routes of administration. Therefore, we refer to the TEA process in the context of determining whether active ingredients are GRASE in this report.

³Pub. L. No. 113-195, 128 Stat. 2035 (2014).

frames for the agency's review. The act also included requirements for the agency related to this new process, such as developing guidance. Additionally, the act included a provision for GAO to report on FDA's implementation of the act. This report examines

1. the extent to which FDA has implemented requirements for reviewing applications for sunscreen active ingredients within mandated time frames, and
2. the status of FDA's review of applications for sunscreen active ingredients.

This report also describes information about the steps FDA has taken to review TEAs for non-sunscreen active ingredients. (See app. I.)

To examine the extent to which FDA has implemented requirements for reviewing applications for sunscreen active ingredients (sunscreen applications) within mandated time frames, we reviewed the Federal Food, Drug, and Cosmetic Act (as amended by SIA), applicable FDA regulations, and agency guidance related to the TEA process and sunscreen active ingredients.⁴ We also reviewed agency documentation regarding SIA implementation, such as a May 2016 report to Congress required by SIA, and interviewed agency officials.

To examine the status of FDA's review of applications for sunscreen active ingredients, we reviewed documentation associated with each sunscreen application from regulations.gov and FDA. This documentation included the TEA submitted by each sponsor of a sunscreen active ingredient, Federal Register notices of eligibility, feedback letters, and minutes from meetings between FDA and sponsors, when applicable. We also reviewed applicable FDA regulations and guidance, and interviewed FDA officials. Additionally, we interviewed representatives from five sponsors, which represent all eight sunscreen applications submitted to FDA (all of which were submitted prior to the enactment of SIA).⁵ We also

⁴Our review examined sunscreen active ingredient applications for GRASE determinations under the OTC monograph process. We did not include applications for sunscreen products submitted through the NDA process in our review.

⁵We interviewed representatives from the following sponsors of sunscreen applications (and the corresponding active ingredients): 3V SIGMA USA INC. (diethylhexyl butamido triazone); BASF Corporation (octyl triazone, bemotrizinol, and bisoctrizole); L'Oréal USA (drometrizole trisiloxane and ecamsule); EMD Performance Materials, an affiliate of Merck KGaA (enzacamene); and Symrise (amiloxate).

interviewed nine stakeholders with interest in sunscreens, including industry groups, researchers, and health care providers.⁶ We identified stakeholders through our interviews with and review of key documents from FDA, sponsors, and other stakeholders. We selected stakeholders knowledgeable with the OTC monograph process for sunscreen active ingredients, including stakeholders who commented on FDA draft guidance and participated in FDA advisory committee and SIA implementation meetings. These selected stakeholder organizations provided their own insights on these issues, and their perspectives are not generalizable.

To examine the steps FDA has taken to review TEAs for non-sunscreen active ingredients, we reviewed SIA, applicable FDA regulations and guidance, and other relevant documentation associated with the non-sunscreen TEAs. We also interviewed FDA officials and representatives of the sponsors associated with the six non-sunscreen TEAs submitted prior to the enactment of SIA in 2014.⁷

We conducted this performance audit from December 2016 to November 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

⁶We interviewed the following stakeholders: American Academy of Dermatology; American Academy of Pediatrics; Consumer Healthcare Products Association; Environmental Working Group; National Center for Health Research; Public Access to SunScreens Coalition; Personal Care Products Council; Pew Charitable Trusts; and Skin Cancer Foundation.

⁷We interviewed representatives from the following sponsors of non-sunscreen active ingredient TEAs [active ingredients (type of drug)]: Boehringer Ingelheim Pharmaceuticals, Inc. [sodium picosulfate (laxative)]; BASF Corporation [triclosan (acne and anti-gingivitis)]; Clariant [piroctone olamine (anti-dandruff)]; Cordes, Hermann & Co. [sodium shale oil sulfonate (anti-dandruff)]; and Symrise [climbazole (anti-dandruff)].

Background

Skin Cancer and Sunscreen

The most common kinds of skin cancer, including the deadliest kind of skin cancer (melanoma), are associated with exposure to ultraviolet (UV) light.⁸ Sunscreen is one of the most common methods of protection against UV exposure used by Americans. To lower the risk of skin cancer, the Centers for Disease Control and Prevention and FDA recommend that consumers use broad spectrum sunscreens with a sun protection factor (SPF) of 15 or more as directed and in conjunction with other sun-protective measures, such as seeking shade and wearing protective clothing, hats, and sunglasses. Current recommendations also state that sunscreen should be reapplied every 2 hours and after swimming, sweating, and toweling off. When used incorrectly, sunscreen may provide a false sense of protection, which can ultimately lead to increased UV exposure.⁹

How Sunscreen Works

Most sunscreen products work by absorbing, reflecting, or scattering sunlight. Sunscreen contains chemicals that interact with the skin to protect it from ultraviolet (UV) rays. UV rays are an invisible form of radiation from the sun, tanning beds, and sunlamps that can penetrate the skin and change skin cells.

Source: Centers for Disease Control and Prevention.
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Broad Spectrum Sunscreen and Sun Protection Factor (SPF)

There are two types of ultraviolet (UV) radiation from which one needs protection—UVA and UVB. UVA radiation penetrates the skin more deeply and can cause skin cancer and other skin damage. UVB radiation can cause sunburn and result in skin damage. Broad spectrum sunscreens provide protection against both UVA and UVB rays. Products labeled as “broad spectrum” have been tested for both UVA and UVB protection.

Sunscreens are made in a wide range of SPFs. The SPF value indicates the level of sunburn protection provided by the sunscreen product. Higher SPF values (up to 50) provide greater sunburn protection. Because SPF values are determined from a test that measures protection against sunburn, SPF values primarily indicate a sunscreen’s UVB protection.

Sources: Food and Drug Administration and the Surgeon General’s Call to Action to Prevent Skin Cancer.
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FDA Regulation of Sunscreens and Other OTC Drugs

Because sunscreens are intended to help prevent sunburn and, in some cases, decrease the risks of skin cancer and early skin aging caused by the sun, these products are considered drugs under the Federal Food, Drug, and Cosmetic Act.¹⁰ Sunscreens are regulated as OTC (i.e., nonprescription) drugs, which are drugs considered to be safe for use by consumers without the intervention of a health care professional, such as a physician.

Most OTC drugs, including nearly all sunscreen products, are marketed in the United States by following the OTC monograph process. An OTC monograph is a regulation that specifies the active ingredients that may be used to treat certain diseases or conditions without a prescription, and the appropriate dose and labeling for use, among other things. OTC

⁸Department of Health and Human Services. *Call to Action*.

⁹Department of Health and Human Services. *Call to Action*.

¹⁰The Federal Food, Drug, and Cosmetic Act defines a drug to include, among other things, articles intended for use in the diagnosis, cure, mitigation, or prevention of disease in man or other animals. 21 U.S.C. 321(g)(1).

Examples of Over-the-Counter Drug Categories

- Antacids
- Antidiarrheal products
- Antiperspirants
- Cough and cold products
- Dandruff products
- Hemorrhoidal products
- Ophthalmic products
- Sleep aids
- Sunscreens

Source: Food and Drug Administration. | GAO-18-61

drugs that meet a monograph's requirements may be marketed without FDA's prior approval, assuming compliance with all other applicable regulations.

FDA regulations designate categories of OTC drugs, including antacids, cough and cold products, and sunscreens, to be covered by OTC monographs.¹¹ OTC drug products that do not fit under an existing monograph must be approved under an NDA to be marketed, which is an application also used for new prescription drugs.¹² See table 1 for a summary of the differences between marketing an OTC drug product, such as a sunscreen product, under the OTC monograph process compared to under an NDA. According to FDA officials, more than 100,000 OTC drugs are marketed under the OTC monograph process, and about 400 are approved to be marketed under NDAs.¹³

¹¹21 C.F.R. § 330.5 (2017). Those OTC monographs that are finalized in regulations can be found at 21 C.F.R. parts 330 et seq (2017).

¹²For some OTC drugs, FDA has ongoing OTC monograph proceedings (i.e., FDA has not yet finalized an OTC monograph for that drug category or a final monograph has not yet gone into effect). Until a monograph is finalized and goes into effect, the agency generally does not object to marketing of these drugs, unless failure to take regulatory action against marketing of the drugs poses a potential hazard to the consumer.

¹³Some drugs were approved for the U.S. market as a prescription drug under an NDA, but were subsequently approved for OTC use (e.g., Aleve® and Claritin®).

Table 1: Comparison of Marketing an OTC Drug Product under the OTC Monograph Process and under a New Drug Application

An over-the counter (OTC) drug, such as a sunscreen product, can be marketed in the United States by complying with the conditions contained in an OTC monograph and any other applicable regulations, or under an approved new drug application (NDA).

Marketing an OTC drug under the OTC monograph process	Marketing an OTC drug under an NDA ^a
No premarket approval necessary if the product is in compliance with the conditions in the monograph	Premarket approval of a product specific application (including formulation and labeling)
No user fees	User fees associated with application review ^b
Safety and effectiveness testing of each individual product not required if product is in compliance with the monograph ^c	Safety and effectiveness testing required for each individual product to be approved
Product changes do not require approval when in compliance with monograph	Certain subsequent labeling and formulation changes require prior approval through supplemental application
Limited postmarket reporting requirements (serious adverse events only)	Adverse event and other postmarket reporting requirements
Comply with good manufacturing practices	Comply with good manufacturing practices
No market exclusivity	A period of market exclusivity (if certain conditions are met)

Source: GAO review of Food and Drug Administration documentation. | GAO-18-61

^aAn OTC drug product may also be marketed under the authority of an abbreviated new drug application, which generally contains information to show that the proposed product is bioequivalent to, and, in certain ways, the same as an already approved drug product. Abbreviated new drug applications are used to market generic drugs.

^bIn fiscal year 2017, the fee for an application requiring review of clinical data was \$2,038,100.

^cFinal formulation testing (e.g., sun protection factor testing for sunscreens) may be required as a condition of a monograph or under another regulation to ensure that that the drug is safe and effective.

The sunscreen monograph currently includes 16 active ingredients.¹⁴ The last active ingredients (avobenzone and zinc oxide) were added to the sunscreen monograph in the late 1990s.¹⁵ FDA issued a final sunscreen OTC monograph in 1999; before it could go into effect, however, FDA stayed its effective date indefinitely, because the agency had not yet established UVA/broad spectrum testing and labeling requirements for sunscreen products.¹⁶ To date, the sunscreen monograph is not in effect.

¹⁴See 21 C.F.R. part 352 (2017).

¹⁵Since then, FDA has approved four NDAs for OTC sunscreen products that contain a new sunscreen active ingredient (ecamsule) used in combination with active ingredients currently included in the sunscreen monograph.

¹⁶See 64 Fed. Reg. 27666, 27687 (May 21, 1999) (part 352 effective May 21, 2001); 65 Fed. Reg. 36319 (June 8, 2000) (extended part 352 effective date to Dec. 31, 2002); 66 Fed. Reg. 67485 (Dec. 31, 2001) (stayed part 352 until further notice); 68 Fed. Reg. 33362, 33372, 33380, 33381 (June 4, 2003) (lifted stay of, amended, and then stayed part 352 until further notice).

While the sunscreen monograph's effective date is stayed, FDA has indicated that it will not take enforcement action against the marketing of sunscreens using the 16 active ingredients included in the stayed final monograph or some combination thereof, provided the products are marketed in compliance with other applicable regulations and consistent with FDA's 2011 draft guidance.¹⁷

TEA Process

In 2002, FDA created a two-part process, referred to as the TEA process, by which an active ingredient that was not included in OTC drugs marketed in the United States prior to the beginning of the monograph process in the 1970s can be considered for marketing under the OTC monograph process by receiving a GRASE determination.¹⁸

Part 1: Eligibility determination. To be eligible for review under the TEA process, the sponsor must submit an application showing that the active ingredient has been marketed in OTC drugs for a material time and to a material extent, as shown by, for example

- a minimum of 5 continuous years in the same country, or multiple countries outside the United States, or in an OTC product with an approved NDA in the United States; and
- a sufficient quantity as measured by the total number of dosage units or weight of active ingredient sold, and in a population reasonably extrapolated to the population of the United States.¹⁹

¹⁷Food and Drug Administration, *Draft Guidance for Industry: Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application* (Silver Spring, Md.: June 2011), accessed September 22, 2017, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM259001.pdf>. According to FDA officials, the agency plans to issue final guidance by the end of 2017.

¹⁸In addition to active ingredients, other conditions, such as dosage forms, strength, and route of administration may also be considered under the TEA process. According to FDA officials, the TEAs submitted have been to add active ingredients for marketing under the OTC monograph process.

¹⁹21 C.F.R. § 330.14 (2017). FDA's regulations do not provide a threshold for what would be a sufficient quantity of dosage units or active ingredients sold.

For ingredients found to meet the eligibility requirements, FDA publically posts this determination in the Federal Register and requests safety and effectiveness data to be submitted for the agency's review.

Part 2: GRASE determination. FDA reviews the safety and effectiveness data submitted by sponsors and other interested parties to determine whether the ingredient is generally recognized as safe and effective for OTC use. Standards for GRASE determinations are established in FDA regulations.²⁰

- **General recognition** is based upon published studies, which may be corroborated by unpublished studies and other data.
- **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 that can occur when the drug is widely available.
- **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.

Based on its review, FDA may initially determine that the active ingredient is GRASE or not GRASE for OTC use; a not GRASE determination could result from FDA's determination that the safety and effectiveness data submitted are insufficient. FDA issues its initial GRASE determination in the Federal Register and provides a period of time for public comments. The agency then reviews any comments received and issues its final GRASE determination in the Federal Register.

SIA altered the process FDA is required to use for its review of sunscreen active ingredients and established time frames for the agency's review. It also established a process for convening the agency's Nonprescription Drugs Advisory Committee to review and provide recommendations regarding sunscreen applications at certain points in the process, and created a mechanism for sponsors to request FDA's Office of the Commissioner to review sunscreen applications. At the time SIA was enacted in November 2014, FDA had received TEAs for eight sunscreen active ingredients. For all eight of these ingredients, FDA had deemed the

²⁰See 21 C.F.R. § 330.10 (2017).

applications eligible for review under the TEA process (that is, the sponsors demonstrated that the ingredients had been marketed for a material time and to a material extent), and the agency had requested data to demonstrate safety and effectiveness.

FDA Implemented SIA Requirements for Reviewing Applications for Sunscreen Active Ingredients within Mandated Time Frames

FDA implemented requirements for reviewing applications for sunscreen active ingredients within the time frames required by SIA. For example, by November 2016, FDA issued final guidance for applications for sunscreen active ingredients, such as guidance on safety and effectiveness testing standards and on convening the Nonprescription Drugs Advisory Committee to discuss sunscreen active ingredients.²¹ In May 2016, FDA also issued its first required report to Congress on specific performance metrics, such as the number of sunscreen applications with pending GRASE determinations.²² In addition to requiring FDA to issue two additional reports to Congress in 2018 and 2020, SIA requires FDA to

²¹Food and Drug Administration, *Guidance for Industry: Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data* (Silver Spring, Md.: November 2016), accessed September 22, 2017, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM473464.pdf>; and *Guidance for Industry: Sunscreen Innovation Act: Section 586C(c) Advisory Committee Process* (Silver Spring, Md.: October 2016), accessed September 22, 2017, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM473770.pdf>. While SIA included provisions for optional advisory committee meetings, as of August 2017, FDA officials stated that it had not been necessary to convene a meeting of the Nonprescription Drugs Advisory Committee to discuss a sunscreen active ingredient since SIA was enacted.

²²Food and Drug Administration, *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*, accessed September 22, 2017, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM503441.pdf>.

finalize the sunscreen monograph by November 26, 2019.²³ See table 2 for the status of FDA's implementation of SIA requirements and corresponding time frames.

²³Pub. L. No. 113-195, § 2, 128 Stat. 2035 (codified in pertinent part at 21 U.S.C. §§ 360fff-5, 360fff-7(a)). If the final sunscreen monograph does not include provisions on the effectiveness of various SPF levels and address all dosage forms used in sunscreens marketed in the United States without an NDA, FDA must report to Congress with a plan and timeline to compile the information necessary to address these items, among other things.

Table 2: Status of FDA Completion of Requirements Associated with Applications for Sunscreen Active Ingredients

Requirement	Statutory deadline	Completion date
Issue notice that feedback letters from FDA, sent to sponsors of some sunscreen applications prior to the enactment of SIA, are considered proposed orders. ^a (21 U.S.C. § 360fff-3(b)(3))	1/10/2015	1/7/2015
Issue proposed orders for pending sunscreen applications submitted prior to SIA that did not receive feedback letters prior to SIA's enactment. (21 U.S.C. § 360fff-3(b)(4))	2/24/2015	2/24/2015 ^b
Issue draft guidance for sunscreen applications on <ul style="list-style-type: none"> • format and content of data submissions, • safety and efficacy data, • withdrawal of applications, and • use of advisory committee. (21 U.S.C. § 360fff-4(a)(1)(A)) 	11/26/2015	11/20/2015
Issue first report to Congress on various performance metrics. (21 U.S.C. § 360fff-7(a))	5/26/2016	5/25/2016
Issue final guidance for sunscreen applications on <ul style="list-style-type: none"> • format and content of data submissions, • safety and efficacy data, • withdrawal of applications, and • use of advisory committee. (21 U.S.C. § 360fff-4(a)(1)(B)) 	11/26/2016	10/7/2016 – 11/22/2016
Issue second report to Congress on various performance metrics. (21 U.S.C. § 360fff-7(a))	5/26/2018	Pending
Finalize sunscreen monograph. (21 U.S.C. § 360fff-5)	11/26/2019	Pending
Issue third report to Congress on various performance metrics. (21 U.S.C. § 360fff-7(a))	5/26/2020	Pending

Source: Food and Drug Administration (FDA) and Sunscreen Innovation Act (SIA). | GAO-18-61

Note: References are to provisions of law added to the Federal Food, Drug, and Cosmetic Act by SIA, as codified to the U.S. Code.

^aSIA changed the process FDA uses to issue its initial and final determinations of whether sunscreen applications are generally recognized as safe and effective to administrative orders rather than through rulemaking.

^bThe proposed orders for the active ingredients that did not receive feedback letters prior to SIA were filed for publication in the Federal Register on February 24, 2015 and published on February 25, 2015.

FDA also implemented changes to the process for reviewing sunscreen applications as required by SIA.

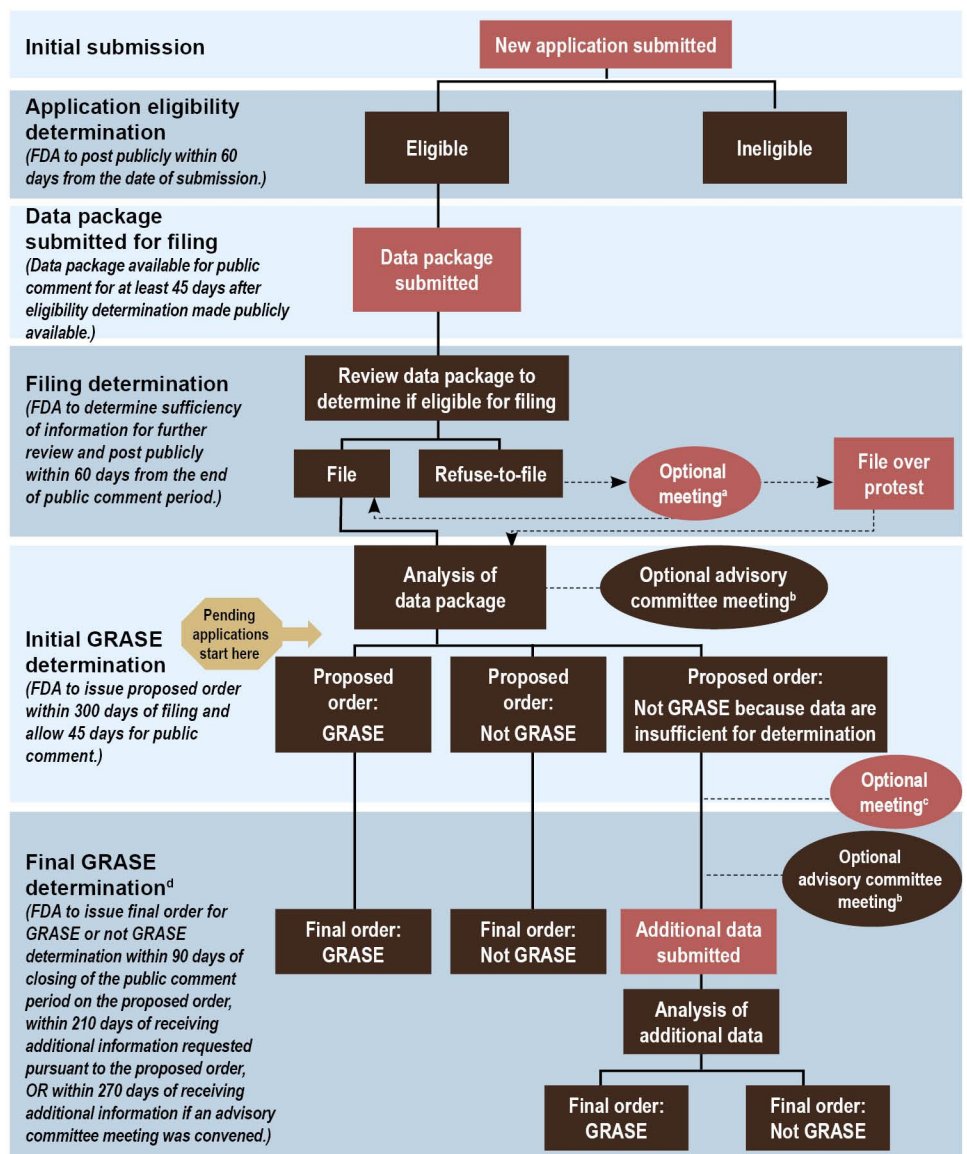
- **Administrative orders.** SIA changed the process for issuing initial and final GRASE determinations for sunscreen applications to administrative orders. FDA officials stated that this approach is more efficient than rulemaking. Agency officials noted that administrative orders are not subject to multiple-stage rulemaking procedures, and generally undergo fewer levels of review outside of FDA.

- **Time frames.** SIA established time frames for each step in the review process for sunscreen applications. For example, the agency is required to determine whether a new application for a sunscreen active ingredient is eligible for review and notify the sponsor within 60 days of receipt by the agency. These time frames only include FDA's review, and do not include the time for the sponsor or other interested parties to prepare and submit safety and effectiveness data, or respond to additional FDA requests.
- **Filing determination.** SIA added a step, known as a filing determination, in which FDA reviews the safety and effectiveness data to determine whether it is sufficiently complete for the agency to begin its more substantive review to determine whether an active ingredient is GRASE. If FDA determines that the data are sufficiently complete to determine whether the active ingredient is GRASE, the agency will file the application and further analyze the data. If FDA determines that the data are not sufficiently complete, the agency can refuse-to-file the application, which involves notifying the sponsor and providing reasons for the refusal. Sponsors can protest FDA's decision to refuse-to-file the application, known as "file over protest," in which case FDA will proceed with its more substantial review to determine if the active ingredient is GRASE.
- **Office of the Commissioner review.** SIA established a mechanism for sponsors to request the Office of the Commissioner to issue GRASE determinations if FDA does not meet required time frames. The mechanism has not been employed to date, because, as of August 2017, FDA had met its required time frames for reviewing and initially responding to sunscreen applications.

Figure 1 illustrates the post-SIA process for FDA's review of pending and new applications for sunscreen active ingredients, including time frames.

Figure 1: Process for Reviewing Pending and New Applications for Sunscreen Active Ingredients and Associated Time Frames

Following the enactment of the Sunscreen Innovation Act, FDA implemented changes to the process for reviewing applications to determine if sunscreen active ingredients are GRASE, and can therefore be used in sunscreens marketed in the United States.



Legend: GRASE = generally recognized as safe and effective.

- FDA action
- Optional FDA initiated meeting
- Sponsor action
- Optional sponsor initiated meeting

Source: GAO analysis of Sunscreen Innovation Act (SIA) and Food and Drug Administration (FDA) documentation. | GAO-18-61

Notes: Pending applications are those for sunscreen active ingredients for which sponsors and other interested parties submitted safety and effectiveness data before SIA was enacted in November 2014. New sunscreen active ingredient applications are those submitted to FDA after SIA's enactment.

If FDA does not complete its initial review for a GRASE determination and issue a proposed order within 300 days of the request being filed, the sponsor may request a review by the Office of the

Commissioner. Additionally, a sponsor may request a review by the Office of the Commissioner if FDA does not issue a final order within the applicable time frame. The Office of the Commissioner has 60 days to issue the proposed or final order.

A sponsor or other interested party may submit additional safety and effectiveness data for FDA's consideration after the application is determined eligible for review.

A sponsor may request that the application or safety and effectiveness data be withdrawn from review at any point. Alternatively, FDA may consider an application to be withdrawn if a sponsor fails to provide the agency with an update or other information within 90 days of such a request from FDA.

^aSponsors may request to meet with FDA within 30 days of receiving notification of the agency's refusal to file. FDA is to convene a meeting within 30 days of receiving such a meeting request. FDA officials said that they strongly encourage sponsors to meet with FDA if the agency refuses to file the application.

^bFDA may initiate a meeting of the Nonprescription Drugs Advisory Committee to review and provide recommendations for any applications for sunscreen active ingredients pending agency review prior to the enactment of SIA.

^cSponsors may request to meet with FDA within 30 days of the agency issuing a proposed order. FDA is to convene a meeting within 45 days of receiving such a request.

^dAn initial GRASE determination may be different from the final GRASE determination if additional information is submitted in response to the proposed order that changes FDA's determination. For example, a sunscreen active ingredient may have an initial determination of GRASE, but in response to the proposed order, sponsors or other interested parties may submit additional safety and effectiveness information questioning this decision. This additional safety and effectiveness information may then change FDA's final determination to be not GRASE in the final order.

All Eight Sunscreen Active Ingredient Applications Pending After FDA Determined More Safety and Effectiveness Data Needed; Sponsors Questioned Need for Additional Data

FDA completed its review of the safety and effectiveness data for each of the eight sunscreen active ingredient applications that it received prior to the enactment of SIA. The agency concluded that the ingredients were not GRASE because the data were insufficient and additional safety and effectiveness data are needed to determine otherwise. Sponsors questioned FDA's request for additional data and no data have been provided.

Maximal Usage Trial (MUsT)

A MUsT is a type of human pharmacokinetic study that is designed to capture the effect of maximal use of the drug on absorption of an active ingredient into the body. According to FDA officials, this test helps to determine the potential effect of the long-term use of an active ingredient. The test measures the amount of the ingredient that is absorbed through the skin and into the bloodstream, when used in the highest concentration for which a generally recognized as safe and effective determination is sought and on the upper limit of skin surface area on which the ingredient would be applied. For a sunscreen active ingredient, FDA recommends that the MUsT be conducted with a minimum of four formulations using the active ingredient on at least 75 percent of the body surface area.

Source: Food and Drug Administration (FDA). | GAO-18-61

For all eight pending sunscreen applications, FDA requested additional safety and effectiveness data to support a GRASE determination.²⁵ The data FDA requested include

- **Human clinical safety studies** including skin irritation, sensitization, and photosafety studies, as well as human pharmacokinetic tests (which measure the amount of absorption of a drug into the body).²⁶ Among other studies, FDA specifically recommends that sponsors conduct a Maximal Usage Trial (MUsT), a type of human pharmacokinetic study, to support an adequate assessment of safety.²⁷
- **Human safety data** from adverse event reports and other safety-related information from marketed products that contain the active ingredient. This includes a summary of all available reported adverse events potentially associated with the ingredient, all available documented case reports of serious side effects, any available safety information from studies of the safety and effectiveness of sunscreen products containing the ingredient in humans, and relevant medical literature describing adverse events.
- **Nonclinical animal studies** that characterize the potential long-term dermal and systemic effects of exposure to the active ingredient. These tests include dermal and systemic carcinogenicity studies, as well as toxicokinetic tests (to help determine the relationship between exposure in toxicology studies in animals and the corresponding exposure in humans). In most cases, FDA also recommended developmental and reproductive toxicity studies to evaluate the potential effects of the active ingredient on developing offspring. FDA's guidance states that if the ingredient is not absorbed into the

²⁵For one of the pending applications for a sunscreen active ingredient (bisotrizole), FDA requested that the sponsor explain how the safety and effectiveness data submitted, which relates to one specific sunscreen product, supported a GRASE determination for the active ingredient, because it was not clear to FDA how the information provided related to the active ingredient.

²⁶FDA's guidance details the agency's recommendations for each type of study needed by the agency to determine that a sunscreen active ingredient is GRASE for use in nonprescription sunscreen products. See Food and Drug Administration, *Guidance for Industry: Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data* (November 2016).

²⁷For more information about the MUsT see, Bashaw, E.D., Tran, D.C., Shukla, C.G, and Liu X. "Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products." *Therapeutic Innovation & Regulatory Science*, vol. 49, issue 1, 108-115 (2015).

body past an identified threshold, some of these studies will not be needed.²⁸

- **Effectiveness data** from at least two SPF studies showing that the active ingredient prevents sunburn.²⁹ FDA stated these studies should demonstrate protection at an SPF of 2 or higher.

FDA's 2016 guidance on safety and effectiveness data for sunscreen states that its approach for evaluating the safety of sunscreen active ingredients is based on the agency's current scientific understanding of topical products for chronic use. According to FDA, the standard for determining GRASE has remained the same over time. However, FDA reports that the increase in the amount and frequency of sunscreen usage, coupled with advances in scientific understanding and safety evaluation methods, has changed the agency's perspective on what it needs to determine if sunscreen active ingredients are GRASE. As a result, the agency stated that these additional tests, such as the MUsT, are necessary to determine whether a sunscreen active ingredient is safe for chronic use. FDA reported that the studies it is requesting are not novel and are consistent with the requirements for chronically used topical drug products approved through the NDA process.

For the eight sunscreen applications FDA received since 2002, FDA took between approximately 6 and 13 years to issue initial GRASE determinations starting from the date that the application was submitted. For six of the eight sunscreen applications, it took FDA more than 8 years to issue an initial GRASE determination. (See table 3.) Sponsors or other parties may submit safety and effectiveness data after FDA determines the application is eligible for review. From the most recent date that safety and effectiveness data were submitted for each application, the range of time for FDA to issue an initial GRASE determination was between about 4 and 11 years.

²⁸Food and Drug Administration, *Guidance for Industry: Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data* (November 2016).

²⁹Sunburn prevention is the minimum indication for an OTC sunscreen product marketed without an NDA. The current procedures for SPF testing are described in 21 C.F.R. § 201.327(i) (2017).

Table 3: Key Dates Associated with Sunscreen Active Ingredient Applications

Sunscreen active ingredient	Date application submitted	Date FDA notified sponsor the application was eligible for review	Date(s) sponsor or other interested party submitted safety and effectiveness data	Date FDA issued initial GRASE determination
Amiloxate	8/14/2002	7/11/2003	8/15/2003 10/1/2003	2/25/2014
Octyl triazone	8/21/2002	7/11/2003	10/3/2003 1/9/2004 7/2/2004 12/21/2006	6/23/2014
Enzacamene	8/21/2002	7/11/2003	10/9/2003	2/25/2015 ^a
Bisotrizole	4/11/2005	12/5/2005	2/27/2006	9/3/2014
Bemotrizinol	4/11/2005	12/5/2005	2/28/2006 11/29/2006	11/13/2014
Diethylhexyl butamido triazone	9/16/2005	7/26/2006	10/24/2006 7/6/2007 5/6/2010	2/21/2014
Ecamsule	9/18/2007	9/12/2008	11/14/2008	2/25/2015 ^a
Drometrizole trisiloxane	1/16/2009	6/2/2010	7/14/2010	8/29/2014

Source: GAO analysis of documentation from the Food and Drug Administration (FDA) and regulations.gov. | GAO-18-61

Note: Sponsors and other interested parties may have provided information in support of or in opposition to whether an active ingredient is generally recognized as safe and effective (GRASE) as the data became available, according to FDA officials. Therefore, an application may have more than one date associated with the submission of safety and effectiveness data.

^aThe proposed orders for the active ingredients that did not receive feedback letters prior to the enactment of the Sunscreen Innovation Act were filed for publication in the Federal Register on February 24, 2015 and published on February 25, 2015.

According to FDA officials, the delays in reviewing sunscreen applications can be attributed to inadequate resources to carry out the agency's OTC drug responsibilities and a lengthy multi-step rulemaking process, which the applications were subject to prior to SIA. The officials added that the delays in FDA's review of sunscreen applications are indicative of the larger issues affecting the OTC monograph process more generally. For example, though the OTC monograph process began over 40 years ago, FDA officials said that the agency has still not been able to complete many monographs, or make timely changes based on emerging safety issues and evolving science, because of the burdensome regulatory process and inadequate resources. FDA officials estimate that as of October 2017 approximately one third of the monographs are not yet final, and several hundred active ingredients, including those used in sunscreen products, do not have a final GRASE determination.

Some stakeholders and sponsor representatives said that one effect associated with SIA was that FDA took action on the sunscreen applications that had been pending for many years. Without the act, some of them questioned whether FDA would have reviewed the sunscreen applications or provided feedback to the sponsors. Though the agency has made an initial GRASE determination, the timing of FDA's final GRASE determination for each of the eight sunscreen active ingredients will be determined, in part, by when each ingredient's sponsor provides FDA with the additional safety and effectiveness data the agency requested.

Sponsors Questioned FDA's Request for Additional Safety and Effectiveness Data; No Additional Data Have Been Provided

Sponsor representatives and some stakeholders questioned the additional safety and effectiveness data requested by FDA citing the following reasons

- **Requested test not previously conducted on sunscreen.** Some of the sponsor representatives and stakeholders we interviewed stated that they were not aware of one of the tests FDA requested, the MUsT, ever being conducted on sunscreen active ingredients. Some of these sponsor representatives and stakeholders said there is a lack of knowledge by sponsors and testing laboratories on how to conduct this test, as well as a lack of testing protocols. Further, representatives from some of the sponsors said that the thresholds set by FDA for these test results, which affects whether FDA will recommend additional testing, were unreasonably low or unrealistic.³⁰ FDA officials stated that a MUsT is a fairly recent term for a pharmacokinetic test under maximum use, which is a test that has

³⁰FDA's guidance states that if human absorption of an active ingredient measured by the MUsT is less than a blood level of 0.5 nanograms per milliliter, and toxicology studies for the ingredient do not indicate any other safety concerns, then FDA expects that certain toxicology studies in animals will not be necessary to support the safety of the ingredient. However, the guidance states that if human absorption is equal to or higher than 0.5 nanograms per milliliter, FDA will recommend that the active ingredient be subject to additional carcinogenicity and reproductive toxicity tests. In general, FDA's guidance documents do not establish legally enforceable responsibilities, but instead should be viewed as recommendations. Food and Drug Administration, *Guidance for Industry: Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data* (November 2016).

been used for dermal products since the 1990s. They added that the threshold FDA established for this test is considered by the agency to minimize risk, and that at or above this threshold, the risk for cancer may increase. According to agency officials, FDA's draft guidance on conducting a MUSt is expected to be issued in 2018.

- **Equal to or more rigorous than NDA testing requirements.** Some of the sponsor representatives and stakeholders said that the additional safety and effectiveness data FDA requested are equal to or more rigorous than what are submitted for an NDA. In particular, a stakeholder noted that FDA requested additional safety and effectiveness testing for an application to market the ingredient under the OTC monograph process from a company that already had an approved NDA for a product containing the same active ingredient (ecamsule). FDA officials indicated that active ingredients under consideration for inclusion in an OTC monograph may require some studies to demonstrate that the ingredient is GRASE for OTC use that would not be required for approval of an individual drug product through an NDA.³¹ Specifically, FDA officials said such studies may be needed because once an ingredient is found to be GRASE it can be formulated in many ways (in accordance with the monograph) and marketed in multiple sunscreen products without further agency review. Additionally, the combination of sunscreen active ingredients with other inactive ingredients in a sunscreen spray, for example, may affect the absorption of the sunscreen active ingredient, according to FDA officials. In contrast, NDAs are product-specific and once approved, further changes to the products require FDA approval.
- **Raising the bar.** Some of the sponsor representatives and stakeholders said that FDA's requests for additional safety and effectiveness data equate to FDA raising the bar or otherwise changing what is required to demonstrate GRASE for additional active ingredients in sunscreen. Some stakeholders noted that sunscreen active ingredients that are currently marketed are not subject to this level of scrutiny. According to FDA officials, given the increased usage of sunscreen, coupled with increased knowledge of how drugs are absorbed into the skin, the agency has changed its perspective on what it needs to determine if sunscreen active ingredients are GRASE. FDA officials said that when the OTC monographs first

³¹FDA officials also stated that since the marketing history of the active ingredient is taken into consideration in determining which studies are required to make a GRASE determination, some studies required for NDA products are not generally needed to support the safety or efficacy of monograph ingredients.

started in the 1970s, it was thought that topical products would remain on the skin rather than be absorbed, but science has shown that some topical drugs, including some active ingredients used in sunscreens, are absorbed through the skin. Because of this knowledge, FDA officials said that the agency now considers potential dermal absorption for every topically applied drug.

- **Lack of access to some requested data.** In some cases, the sponsor or another interested party submitted a study's summary results or summary information on adverse events associated with an active ingredient, but FDA requested more detailed data behind the study or detailed data on adverse events. However, some sponsor representatives and stakeholders said that the sponsor may not have access to this level of detail if it had not conducted the study itself or received the associated adverse event reports. For example, if the sponsor is the company that manufactures the active ingredient, it would not necessarily have access to adverse event reports for specific sunscreen products, because these reports would instead be submitted to the company that manufactures the actual sunscreen product used by consumers. One stakeholder also questioned why FDA has not attempted to obtain relevant adverse event data directly from regulatory agencies in other countries. FDA officials said that the agency does not generally have access to adverse event reports from foreign regulatory agencies, and that the agency relies on sponsors to provide adequate information to support a GRASE determination.³²

Some stakeholders supported FDA's request that sponsors provide additional safety and effectiveness data to determine if an active ingredient is GRASE for use in sunscreens. In particular, some of the stakeholders we interviewed stated that FDA is justified in requesting additional safety and effectiveness data from the sponsors given that science has evolved and the recommended use of sunscreen has changed over time.

As of October 2017, FDA officials said that the agency has not received any of the additional safety and effectiveness data requested for the eight sunscreen active ingredients seeking a GRASE determination. According to sponsor representatives we spoke with, the sponsors are either still

³²FDA officials said that in certain circumstances, FDA may request data from foreign regulatory agencies, but the agencies are under no obligation to provide it. In addition, the officials said that adverse event information obtained from a foreign regulatory agency is sometimes considered confidential and so could not be utilized to support a GRASE determination.

considering whether to conduct the additional tests FDA requested or they do not plan to do so. The reasons cited by the sponsor representatives and stakeholders included

- **Return on investment.** Sponsor representatives said the testing FDA requested is extensive, would cost millions of dollars, or take several years to conduct. Some of the stakeholders said the profit margins for these types of products can be low, and other stakeholders and sponsors said that once an active ingredient is determined to be GRASE and added to the OTC monograph, then anyone can market products using that active ingredient, as there is no period of market exclusivity granted to sponsors. Additionally, some stakeholders and sponsors added that the sponsors are reluctant to spend money on additional testing, because many of these sunscreen active ingredients have been on the market in other countries for many years. Instead, according to one sponsor representative, sponsors may choose to devote their resources into developing a newer generation of sunscreen active ingredients.
- **Alternatives not accepted.** Some sponsor representatives and stakeholders said that when alternative testing methods were proposed to FDA in place of the MUsT and other tests recommended by the agency, FDA rejected the alternatives. Further, when a sponsor asked the agency if the ingredient's experience being marketed in other countries could be used to waive some of the carcinogenicity studies requested by FDA, the agency said that marketing experience can guide the design of studies, but it is not sufficient to appropriately assess carcinogenicity. The main purpose of carcinogenicity studies, according to FDA, is to detect the potential for cancer risks associated with lifelong exposure to the active ingredient, which are difficult to detect through the adverse event data associated with marketing experience.³³
- **Animal testing.** Some sponsor representatives and one stakeholder mentioned concerns about conducting tests on animals, because of the effect it may have on a company's ability to market products worldwide. For example, European regulations prohibit cosmetics, including sunscreens, from being tested on animals, though they

³³FDA officials said that marketing experience was considered sufficient to establish aspects of safety that usually need to be shown via a number of other studies, such as short-term toxicity studies in animals and chronic safety studies in humans.

would not prohibit such testing as required by other countries.³⁴

Additionally, one sponsor and one stakeholder expressed concern that sunscreen manufacturers may face backlash from animal rights groups and shareholders if animal testing is conducted.

- **Uncertainty if more tests will be requested by FDA in the future.**

One sponsor representative said that there is uncertainty whether FDA may request additional studies in the future based on the outcomes of the FDA-recommended tests. According to one stakeholder, there is concern that sponsors may spend additional time and money on conducting the tests requested by FDA and the sunscreen active ingredient may still not be determined to be GRASE.

Sponsor representatives for the pending sunscreen applications and most stakeholders said that the sponsors and FDA are essentially at a standstill about adding more sunscreen active ingredients to the U.S. market through the OTC monograph process. Sponsor representatives acknowledged that they could have submitted an NDA to market a new sunscreen product instead of seeking a GRASE determination for a sunscreen active ingredient. However, some sponsor representatives and a stakeholder said that NDAs are impractical for sunscreen products, because the formulations are continually changing; for example, sunscreen products may have a new fragrance based on the season. Additionally, many of the sponsors that submitted sunscreen applications manufacture the active ingredient, but not the finished sunscreen products; yet, it is the finished products that receive approval through the NDA process.

Though FDA stated that it needs additional resources to complete its work related to the OTC monograph process—and most stakeholders agree—additional resources alone will not lead to additional sunscreen

³⁴Regulation (EC) No. 1223/2009 of the European Parliament and Council of the European Union (cosmetic products), arts. 11(e) (provision of animal testing data as required by other countries), 18.1 (prohibitions on animal testing for European Union marketing approval), O.J. (L 342) 59, 68, 71. In the European Union, sunscreen is regulated as a cosmetic and ingredients used in cosmetics are reviewed for safety by the Scientific Committee on Consumer Safety. Based on recommendations from the committee, ingredients are listed in the Annexes to the European Union Cosmetics Regulation, allowing the ingredients to be used in cosmetic products marketed in the European Union. In addition to compliance with the prohibitions on animal testing, cosmetics marketed in the European Union must also be manufactured in compliance with good manufacturing practices and follow labeling requirements, and companies that manufacture cosmetics may also be required to update safety reports associated with their products. Regulation (EC) No. 1223/2009, arts. 8 (GMP compliance), 10 (safety assessment), 19 (labelling), O.J. (L 342) 67, 72.

active ingredients on the U.S. market. Movement on sunscreen active ingredients will also depend on sponsors and other interested parties submitting data that FDA determines are sufficient for a GRASE determination. Some stakeholders said that they agree with FDA on the need for testing to ensure the safety and effectiveness of sunscreen ingredients, but some of them said the agency should also consider the potential benefit of preventing skin cancer if new ingredients—which could offer better protection against UVA rays—become available for the U.S. market.

Agency Comments

We provided a draft of this report to the Department of Health and Human Services for review and comment. The department provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the Secretary of the Department of Health and Human Services, appropriate congressional committees, as well as other interested parties. In addition, the report is available at no charge on the GAO website at <http://www.gao.gov>.

If your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix II.



Marcia Crosse
Director, Health Care

Appendix I: Steps the FDA Has Taken To Review Applications for Non-Sunscreen Active Ingredients

To examine the steps the Food and Drug Administration (FDA) has taken to review time and extent (TEA) applications for non-sunscreen active ingredients, we reviewed the Sunscreen Innovation Act (SIA), applicable FDA regulations and guidance, and other relevant documentation associated with the non-sunscreen TEAs. We also interviewed FDA officials and representatives of the sponsors associated with the six non-sunscreen TEAs submitted prior to the enactment of SIA in 2014.¹

SIA Requirements and FDA Implementation

SIA included requirements related to FDA's review of non-sunscreen TEAs.² Specifically, SIA required FDA to

- provide sponsors of certain non-sunscreen TEAs submitted prior to the enactment of SIA, upon request, with the opportunity to select from among different options for FDA's review (called a review framework), including corresponding time frames;
- issue regulations establishing time frames for reviewing non-sunscreen TEAs submitted after SIA was enacted, as well as metrics for tracking the extent to which the time frames are met; and
- submit a letter to Congress that includes a report on the status of FDA's review of non-sunscreen TEAs that were pending before SIA's enactment.

FDA implemented these requirements associated with non-sunscreen TEAs by November 2016. For example, FDA provided each sponsor that requested review framework options with the ability to select the process

¹We interviewed representatives from the following sponsors of non-sunscreen active ingredient TEAs [active ingredients (type of drug)]: Boehringer Ingelheim Pharmaceuticals, Inc. [sodium picosulfate (laxative)]; BASF Corporation [triclosan (acne and anti-gingivitis)]; Clariant [piroctone olamine (anti-dandruff)]; Cordes, Hermann & Co. [sodium shale oil sulfonate (anti-dandruff)]; and Symrise [climbazole (anti-dandruff)].

²Pub. L. No. 113-195, § 3, 128 Stat. 2046 (codified at 21 U.S.C. § 360fff-6).

and corresponding time frames to be applied to its pending TEA.³ The review framework options included FDA using an administrative order or rulemaking process, with or without a filing determination. The time frames FDA established to initially respond to the pending non-sunscreen TEAs ranged from 90 days (when an option with a filing determination is selected) to 3.5 years (when an option without a filing determination is selected) from the date the sponsor selected a review framework. For example, when a sponsor chooses to receive a filing determination with the administrative order process, FDA is to determine within 90 days whether the safety and effectiveness data provided by the sponsor or other interested party are sufficiently complete for the agency to begin its substantive review and issue a filing determination. If FDA determines that the application can be filed, the agency then has 2 years after the filing date to issue a proposed order determining whether the ingredient is generally recognized as safe and effective (GRASE). When a sponsor chooses to not receive a filing determination with the rulemaking process, FDA has 3.5 years to issue a proposed rule with the GRASE determination.

Additionally, FDA issued a final rule in November 2016 outlining the process and time frames by which the agency will review and take action on new non-sunscreen TEAs submitted after the enactment of SIA, including time frames for each step in the review process.⁴ (See fig. 3.) In establishing these time frames, FDA noted that it considered the agency's public health priorities and available resources, as required by SIA, and accounted for the anticipated variations in the content, complexity, and format of submissions, as permitted by SIA. The overall time frames for FDA's review are estimated to be about 6 years from the date FDA receives a TEA to the date a final GRASE determination is issued. Specifically, the approximately 6 years consists of 180 days for an eligibility determination, 90 days for a filing determination, 1,095 days for an initial GRASE determination, and 912 days for a final GRASE determination.⁵ These time frames only include FDA's review, and do not include time for the sponsor or other interested parties to submit safety and effectiveness data, respond to additional FDA requests, or request meetings with the agency before such filing.

³See 21 U.S.C. § 360fff-6(a)(2).

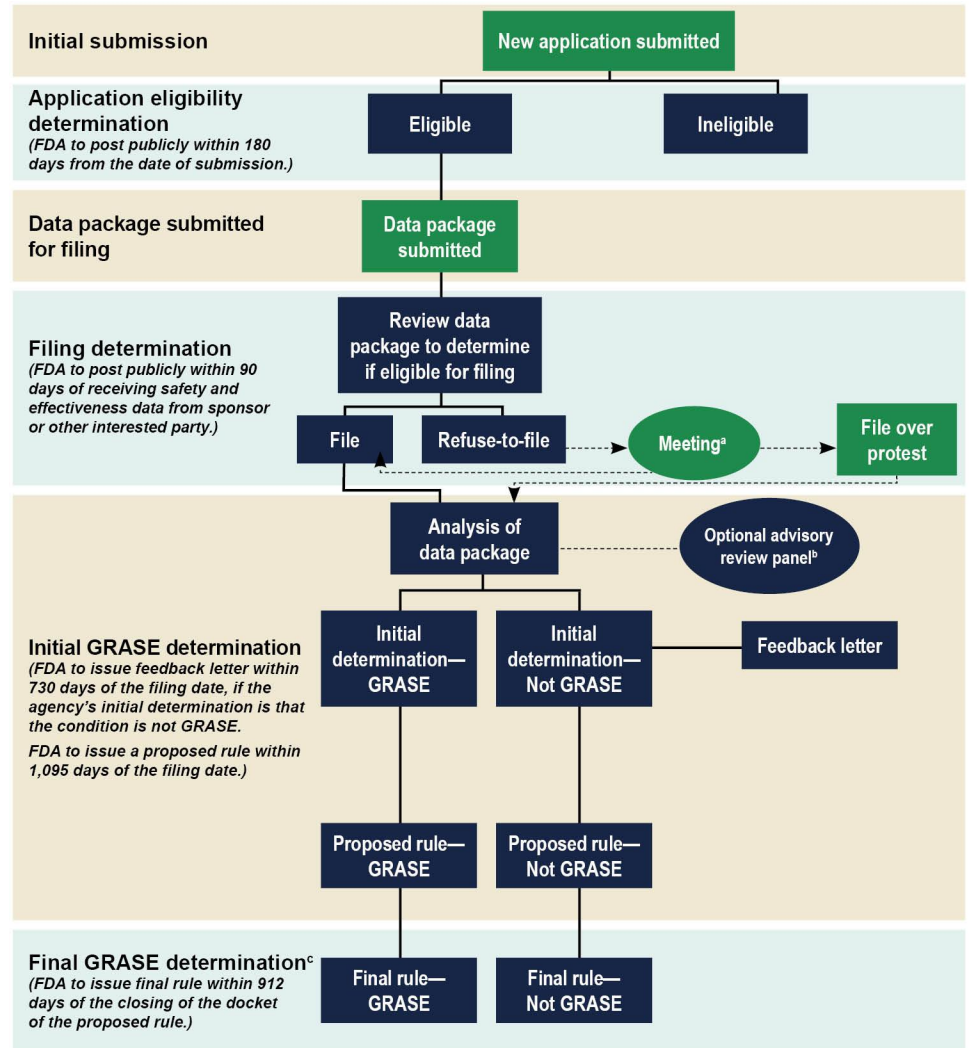
⁴81 Fed. Reg. 84465, 84475 (Nov. 22, 2016) (amending 21 C.F.R. § 330.14 and adding 21 C.F.R. § 330.15).

⁵21 C.F.R. § 330.15(c) (2017).

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Figure 3: Process for Reviewing New Applications for Non-Sunscreen Active Ingredients and Associated Time Frames

Following the enactment of the Sunscreen Innovation Act, FDA implemented changes to the process for reviewing new time and extent applications (TEAs) for non-sunscreen active ingredients, which included time frames for each step in the process.



Legend: GRASE = generally recognized as safe and effective.

■ FDA action ● Optional FDA initiated meeting ■ Sponsor action ● Sponsor initiated meeting

Source: GAO analysis of Food and Drug Administration (FDA) rules and documentation. | GAO-18-61

Notes: A sponsor or other interested party may submit additional safety and effectiveness data for FDA's consideration at any point after the application is determined eligible for review.

A sponsor may request that the TEA or safety and effectiveness data be withdrawn from review at any point.

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^aSponsors may request to meet with FDA within 30 days of receiving notification of the agency's refusal to file. FDA is to convene a meeting within 30 days of receiving such a meeting request.

^bFDA may initiate a meeting of an Advisory Review Panel after a sponsor submits a data package for filing.

^cAn initial GRASE determination may be different from the final GRASE determination if additional information is submitted in response to the proposed rule that changes FDA's determination. For example, an active ingredient may have an initial determination of GRASE, but in response to the proposed rule, sponsors or other interested parties may submit additional safety and effectiveness information questioning this decision. This additional safety and effectiveness information may then change FDA's final determination to be not GRASE in the final rule.

FDA also established metrics for tracking the extent to which the agency meets the time frames set forth in the regulations, and sent a letter to Congress reporting on the status of the non-sunscreen TEAs submitted prior to SIA. These metrics are included in FDA's regulation for non-sunscreen TEAs. The metrics include the number of non-sunscreen TEAs that have been submitted post SIA, and the number and percent of these TEAs to which FDA has responded within its required time frames. Agency officials said that FDA has not received any additional non-sunscreen TEAs as of August 2017 beyond the six that were submitted prior to the enactment of SIA, and therefore has not publicly reported metrics for non-sunscreen TEAs. Lastly, FDA submitted a letter to Congress in May 2016 describing the status of the six non-sunscreen TEAs submitted prior to SIA, including the review framework selected by each sponsor, when applicable.⁶

Non-Sunscreen Active Ingredient TEAs Submitted before SIA Was Enacted

As of August 2017, FDA had not issued a GRASE determination for any of the six TEAs for non-sunscreen active ingredients that were submitted before SIA was enacted.⁷ FDA has not made a GRASE determination because

- **FDA refused to file the applications.** Two non-sunscreen TEAs were determined by FDA to contain insufficient information to be filed for review in 2016. FDA requested that the sponsors for these

⁶Food and Drug Administration, Letter to Congress on review of non-sunscreen requests, accessed October 23, 2017, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM503935.pdf>.

⁷According to FDA officials, the agency has not determined that an active ingredient is GRASE for over-the-counter use in response to a TEA since the process originated in 2002.

applications provide a detailed chemical description of the active ingredients, assessments of carcinogenicity, and safety and efficacy data, among other things. Representatives of sponsors for both ingredients said they do not plan on conducting the additional tests that FDA requested, because of concerns about return on investment. According to FDA officials, the sponsors of these applications did not elect to “file over protest.”

- **Sponsors withdrew their applications.** Three non-sunscreen TEAs were withdrawn in 2016. Representatives of the sponsors of these three applications said the companies did so because of increased regulatory scrutiny of the active ingredient, and the additional safety and effectiveness data requested by FDA.
- **TEA is still pending FDA’s initial GRASE determination.** One non-sunscreen TEA that was submitted in 2004 to add an anti-dandruff ingredient to the over-the-counter monograph was pending FDA review as of August 2017. The sponsor for this application did not request to select a review framework from the agency and so the application is subject to the regulations that FDA issued in November 2016. In accordance with the time frames established in the regulations, FDA officials expect to issue a proposed rule with a GRASE determination for this TEA in 2019—within 1,095 days (3 years) of when the regulation was finalized. This date is nearly 15 years after the application was originally submitted.

For those two non-sunscreen TEAs for which FDA refused to file the applications, FDA’s determination came about 8 and 13 years after the TEA was originally submitted. Sponsors that withdrew the three non-sunscreen TEAs did so 11 or more years after submitting the application. (See table 4.)

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Review Applications for Non-Sunscreen Active
Ingredients**

Table 4: Key Dates Associated with Non-Sunscreen Active Ingredient Time and Extent Applications (TEAs)

Non-sunscreen active ingredient (type of drug)	Date TEA submitted	Date FDA notified sponsor the TEA was eligible for review	Sponsor selected framework? (date)	Status (date)
Piroctone olamine (anti-dandruff)	7/11/2003	2/18/2004	Yes (2/2/2015)	Refuse-to-file (3/16/2016)
Sodium shale oil sulfonate (anti-dandruff)	11/30/2007	4/7/2009	Yes (5/19/2015)	Refuse-to-file (4/20/2016)
Sodium picosulfate (laxative)	6/24/2005	6/22/2006	Yes (3/26/2015)	Withdrawn ^a (6/24/2016)
Triclosan (anti-gingivitis)	11/25/2003	7/6/2004	No	Withdrawn (8/22/2016)
Triclosan (acne treatment)	12/17/2004	12/5/2005	No	Withdrawn (8/22/2016)
Climbazole (anti-dandruff)	12/15/2004	12/5/2005	No	Pending (required by 2019)

Source: GAO analysis of documentation from the Food and Drug Administration (FDA) and regulations.gov. | GAO-18-61

^aThe sponsor for sodium picosulfate selected a review framework that did not include a filing determination by FDA. However, the agency issued initial review comments to the sponsor to provide initial feedback before making an initial determination of whether the ingredient is generally recognized as safe and effective. Based on FDA's initial review comments, the sponsor requested to withdraw the TEA for this active ingredient.

Appendix II: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov

Staff Acknowledgments

In addition to the contact named above, Kim Yamane (Assistant Director), Rebecca Hendrickson (Analyst-in-Charge), Kristin Ekelund, and Toni Harrison made key contributions to this report. Also contributing were George Bogart, Karen Howard, Drew Long, and Vikki Porter.

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