U.S. Food and Drug Administration

Proposed Administrative Order (OTC000039)

Amending Over-the-Counter Monograph M020:

Sunscreen Drug Products for Over-the-Counter Human Use

(Issued December 12, 2025)

Pursuant to section 505G(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h(b)), the U.S. Food and Drug Administration (FDA or Agency) is issuing a proposed administrative order (proposed order) as described herein and set forth in section VIII below.

I. Introduction

FDA is issuing this proposed order to amend the requirements for sunscreen drug products for over-the-counter (OTC) human use, in Over-the-Counter Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use (OTC Monograph M020).[1] On September 23, 2024, DSM Nutritional Products LLC (DSM or Requestor) submitted a Tier 1 OTC monograph order request (OMOR)[2] to add a new active ingredient, bemotrizinol, at concentrations up to 6 percent,[3] to OTC Monograph M020 for use as a sunscreen.

Based on our scientific review of the data submitted in the OMOR, FDA proposes to amend OTC Monograph M020 to add bemotrizinol as a sunscreen active ingredient.[4] If finalized, the proposed order would establish that for a drug product containing bemotrizinol as a sunscreen

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[1] OTC Monograph M020 is currently set forth in Final Administrative Order OTC000006 Over-the-Counter Monograph 020: Sunscreen Drug Products for Over-the-Counter Human Use, available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/. On Sep 24, 2021, FDA issued Proposed Administrative Order OTC000008 Amending Over-the-Counter Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use, available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/. Proposed Administrative Order OTC000008, if finalized, would amend and revise OTC Monograph M020 to establish certain new conditions under which nonprescription sunscreen drug products would be determined to be generally recognized as safe and effective (GRASE). Therefore, sunscreen drug products marketed under OTC Monograph M020, including products containing bemotrizinol, if added to the OTC monograph as a sunscreen active ingredient, would be required to meet the conditions described in OTC Monograph M020, as amended by OTC000008, if finalized.

[2] An OMOR means a request for an order submitted under section 505G(b)(5) of the FD&C Act (see section 744L(7) of the FD&C Act (21 U.S.C 379j-71(7)). A Tier 1 OMOR means any OMOR not determined to be a Tier 2 OMOR (see section 744L(8) of the FD&C Act (21 U.S.C. 379j-71(8)). An OMOR requesting the addition of an active ingredient to an OTC monograph is not categorized as a Tier 2 OMOR and is, therefore, a Tier 1 OMOR.

[3] For the purposes of OTC Monograph M020, FDA interprets a concentration up to 6 percent to mean up to and including 6 percent.

[4] That is, in accordance with section 505G(b)(1) of the FD&C Act, FDA proposes to determine that there are conditions under which a sunscreen drug product containing bemotrizinol as a sunscreen active ingredient is GRASE under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)) and not subject to section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)), and FDA proposes that among these conditions are certain conditions specific to the use of bemotrizinol as an active ingredient.

active ingredient to be legally marketed without an approved application under section 505 of the FD&C Act (21 U.S.C. 355), among other requirements, it must conform to certain conditions that address the concentration of bemotrizinol in the drug product, permitted combinations of bemotrizinol with other sunscreen active ingredients and with skin protectant active ingredients, and permitted dosage forms.[5]

As further described in this proposed order, proposed specific bemotrizinol-related conditions include that:

- Bemotrizinol is present in the drug product in a concentration up to 6 percent, and the finished drug product provides a minimum sun protection factor (SPF) value of not less than 2.
- A single drug product may combine bemotrizinol with any single sunscreen active ingredient identified in § M020.10 of OTC Monograph M020 except for aminobenzoic acid (PABA) or trolamine salicylate or may combine bemotrizinol with any combination of sunscreen active ingredients identified in § M020.20(a) of OTC Monograph M020 that does not include PABA or trolamine salicylate, provided that certain other conditions are met.
- A single drug product may combine certain skin protectant active ingredients identified in OTC Monograph M016: Skin Protectant Drug Products for Over-the-Counter Human Use (OTC Monograph M016)[6] with bemotrizinol in any combination with other sunscreen active ingredients identified in § M020.20 of OTC Monograph M020 that does not include PABA or trolamine salicylate, provided that certain other conditions are met.
- A drug product containing bemotrizinol is in one of the following dosage forms: oil, lotion, cream, gel, butter, paste, ointment, stick, or spray (provided that certain spray-specific conditions are met).

II. Public Comments

A. Dates

Submit electronic comments on the proposed order by 11:59 p.m. Eastern Time at the end of January 26, 2026. Comments submitted after this time will not be considered.

B. Instructions

Comments must be submitted electronically. The Federal eRulemaking Portal https://www.regulations.gov will accept comments at any time until 11:59 p.m. Eastern Time at the end of January 26, 2026.

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[5] See section 505G(b)(1)(B) of the FD&C Act.

[6] OTC Monograph M016 is set forth in Final Administrative Order OTC000005 Over-the-Counter Monograph M016: Skin Protectant Drug Products for Over-the-Counter Human Use, available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/.

Submit electronic comments to Proposed Order ID OTC000039 as follows:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. All comments received must include the Proposed Order ID OTC000039 and the Docket No. FDA-2025-N-6494 for "Amending Over-the-Counter Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use."

- Comments submitted electronically, including attachments, to https://www.regulations.gov will generally be posted to the docket unchanged, subject to any FDA redactions of confidential information as discussed below and subject to FDA's review of content that may have copyright protections.

- Under section 505G(d) of the FD&C Act (21 U.S.C. 355h(d)), FDA must make any information submitted by any person with respect to this proposed order available to the public upon submission, with limited exceptions. FDA will not make public any information pertaining to pharmaceutical quality information unless such information is necessary to establish standards under which a drug is generally recognized as safe and effective (GRASE) under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)) (see section 505G(d)(2)(B)(i) of the FD&C Act). FDA will also not make public information that is of the type contained in raw datasets (see section 505G(d)(2)(B)(iv) of the FD&C Act).

- Confidential information will be identified and redacted by FDA: Submissions should not contain any redactions for claimed confidential information. FDA will review submissions to determine whether they contain information that, pursuant to section 505G(d) of the FD&C Act and any other applicable disclosure law, will not be made public. FDA will redact any such information prior to the comment being publicly viewable.

- Additionally, for information not subject to any FDA redactions of confidential information and not subject to FDA's review of content that may have copyright protections, your comment should not include any information that you or a third party may not wish to be publicly posted, such as medical information or your or anyone else's Social Security number. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- Comments that are submitted in a timely manner (see Dates and Instructions) will be placed in the docket and will be publicly viewable on https://www.regulations.gov after FDA's review and redaction for confidential information.

C. Contact Information

For further information, contact: Shannon Liu, Center for Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 240-402-2484.

III. Background

A. Legal

OTC Monograph M020, as set forth in Final Administrative Order OTC000006, is a final administrative order (final order) as deemed by sections 505G(b)(8) and 505G(k)(2)(B) of the FD&C Act (21 U.S.C. 355h(b)(8) and 355h(k)(2)(B)), effective upon enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Public Law 116-136, on March 27, 2020. In order to be deemed to be GRASE under section 201(p)(1) of the FD&C Act (21 U.S.C. 321(p)(1)), not a new drug under section 201(p) of the FD&C Act, and not subject to section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)), a sunscreen drug product marketed without an application approved under section 505 of the FD&C Act must be in conformity with OTC Monograph M020, as currently set forth, among other requirements.[7]

The conditions described in OTC Monograph M020 may be amended, revoked, or otherwise modified in accordance with the procedures of section 505G(b) of the FD&C Act.[8]

Either FDA or a requestor[9] can initiate the administrative order process in section 505G(b). A requestor can initiate the order process by submitting an OMOR with respect to certain drugs, classes of drugs, or combinations of drugs.[10] The OMOR may request that the Agency issue an order determining: (1) whether a drug is GRASE or (2) whether a change to a condition of use of a drug is GRASE.[11]

The OMOR must be submitted to FDA in the form and manner specified by the Agency.[12] FDA will file the OMOR if FDA determines that the OMOR is sufficiently complete and formatted to permit FDA to conduct a substantive review.[13] Additionally, in order for FDA to file an OMOR requesting a GRASE determination for a nonprescription drug that contains an active ingredient not previously incorporated in a drug that is: (1) specified in subsection (a)(1), (a)(2), or (a)(3) of section 505G of the FD&C Act; (2) subject to a final order under section 505G; or (3) subject to

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[7] See section 505G(a)(1) and (2) of the FD&C Act (21 U.S.C 355(h)(a)(1) and (2)). Among other things, a sunscreen drug product marketed without an application approved under section 505 of the FD&C Act must also conform to the general requirements for nonprescription drugs. See section 505G(a)(1); see also footnote 14. Furthermore, "notwithstanding subsection [505G](a)," by operation of section 505G(m)(2) of the FD&C Act, sunscreens in all dosage forms other than oil, lotion, cream, gel, butter, paste, ointment, stick, spray, and powder currently require an application approved under section 505 of the FD&C Act in order to be marketed. See Final Administrative Order OTC000006 at 2, footnote 7.

[8] See section 505G(b)(8)(A) of the FD&C Act.

[9] Under section 505G(q)(3) of the FD&C Act (21 U.S.C. 355h(q)), the term *requestor* refers to any person or group of persons marketing, manufacturing, processing, or developing an OTC monograph drug.

[10] See section 505G(b)(5) of the FD&C Act.

[11] See section 505G(b)(5)(B) of the FD&C Act.

[12] See section 505G(b)(5)(B)(i) of the FD&C Act.

[13] See section 505G(b)(5)(A) of the FD&C Act.

a final sunscreen order (as defined in section 586(2)(A) of the FD&C Act (21 U.S.C. 360fff)), the OMOR must include information regarding safe nonprescription marketing and use.[14]

If an OMOR is filed, then under section 505G(b)(1)(A) of the FD&C Act, FDA is tasked with determining whether there are conditions under which a specific drug, a class of drugs, or a combination of drugs is GRASE under section 201(p)(1) of the FD&C Act and not subject to section 503(b)(1) of the FD&C Act. FDA must find that a drug is not GRASE under section 201(p)(1) if the evidence shows that the drug is not GRASE or is inadequate to show that the drug is GRASE.[15] However, if evidence is adequate to show that a drug is GRASE, and FDA issues a final order under section 505G(b) determining that there are conditions under which a drug is GRASE and nonprescription, a drug product will not require approval under section 505 of the FD&C Act if it conforms to applicable final order conditions under section 505G(b) (referred to in this document as "*OTC monograph conditions*"), meets the general requirements for nonprescription drugs, and meets the requirements under section 505G(c) and (k) of the FD&C Act.[16]

The CARES Act also added section 744M to the FD&C Act (21 U.S.C. 379j-72), authorizing FDA to assess and collect user fees dedicated to OTC monograph drug activities, referred to as the OTC Monograph Drug User Fee Program. The Over-the-Counter Monograph User Fee Program Performance Goals and Procedures document, commonly referred to as the OMUFA commitment letter,[17] specifies FDA and industry's mutually agreed-upon timelines for various OTC monograph drug activities, including the timeline to issue certain proposed and final orders.

B. Bemotrizinol

Bemotrizinol, or bis-ethylhexyloxyphenol methoxyphenyl triazine, is an organic ultraviolet (UV) filter. Bemotrizinol exhibits high photostability and broad-spectrum coverage across the UVB (280 to 320 nanometers (nm)) and UVA (320 to 400 nm) ranges. Currently, drug products containing bemotrizinol cannot be legally marketed in the United States. FDA has not approved an application for a drug product containing bemotrizinol as an active ingredient and bemotrizinol is not an active ingredient currently permitted under any OTC monograph.[18]

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[14] See section 505G(b)(6) of the FD&C Act.

[15] See section 505G(b)(1)(C) of the FD&C Act.

[16] See section 505G(b)(1)(B) of the FD&C Act.

[17] The document can be accessed at https://www.fda.gov/media/106407/download. Based on passage of the CARES Act, FDA updated goal dates for fiscal years 2021 through 2025. That document can be accessed at https://www.fda.gov/media/146283/download.

[18] FDA determined that a nonprescription sunscreen containing bemotrizinol as an active ingredient is a drug described under section 505G(b)(6)(B) of the FD&C Act. Bemotrizinol is an active ingredient not previously incorporated in a drug that is (1) specified in subsection (a)(1), (a)(2), or (a)(3) of section 505G of the FD&C Act; (2) subject to a final order under section 505G; or (3) subject to a final sunscreen order (as defined in section 586(2)(A) of the FD&C Act).

C. OMOR

On September 23, 2024, DSM submitted a Tier 1 OMOR pursuant to section 505G(b)(5) of the FD&C Act requesting FDA issue an administrative order finding that a sunscreen drug product containing bemotrizinol as an active ingredient is GRASE under the conditions described in OTC Monograph M020.[19] Prior to submission of the OMOR, the Requestor had formal meetings with FDA regarding the OTC monograph drug development program for bemotrizinol.[20]

On December 4, 2024, FDA filed the OMOR after having determined that the OMOR was (1) sufficiently complete and formatted to conduct a substantive review;[21] and (2) contained information sufficient to demonstrate safe nonprescription marketing and use of bemotrizinol.[22,23] On May 19, 2025, DSM submitted a major amendment consisting of two new human clinical efficacy studies.[24] Therefore, consistent with the timelines set forth in the

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[19] Data and information submitted in the OMOR is available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/. In general, the OTC monograph order process is a public process. Under this order process, section 505G(d) of the FD&C Act limits the information that can remain confidential after submission to FDA in connection with proceedings on an order, including an OMOR. In general, until disclosure is triggered under section 505G(d)(2) of the FD&C Act, any information, including reports of testing conducted on the drug or drugs involved, that is submitted by a requestor in connection with proceedings on an order under section 505G of the FD&C Act and is a trade secret or confidential information subject to 5 U.S.C. 552(b)(4) or 18 U.S.C. 1905 will not be disclosed to the public unless the requestor consents to that disclosure (see section 505G(d)(1) of the FD&C Act). However, FDA generally must make any information submitted by a requestor in support of an OMOR (e.g., the contents of the OMOR) available to the public not later than the date on which the proposed order is issued (see section 505G(d)(2)(A)(i) of the FD&C Act). Nonetheless, the information will remain confidential if (1) the information pertains to pharmaceutical quality information, unless such information is necessary to establish standards under which a drug is GRASE; (2) the information is of the type contained in raw datasets; (3) the information is submitted in a requestor-initiated request, but the requestor withdraws the request in accordance with withdrawal procedures established by FDA before FDA issues the proposed order; or (4) FDA requests and obtains the information under section 505G(c) of the FD&C Act and the information is not submitted in relation to an order under section 505G(b) of the FD&C Act (see section 505G(d)(2)(B) of the FD&C Act). Prior to publicly posting the OMOR and related submissions, FDA reviewed the documents to determine whether they contained information that, pursuant to section 505G(d) of the FD&C Act and any other applicable disclosure law, must not be made public and made any appropriate redactions.

[20] Because the type and quantity of data and information necessary to support a GRASE determination is OMOR-specific, FDA encourages requestors to request a formal meeting with the FDA to discuss specific data, studies, and related information to be submitted in an OMOR. See the draft guidance for industry *Formal Meetings Between FDA and Sponsors or Requestors of Over-the-Counter Monograph Drugs* (February 2022). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[21] See section 505G(b)(5)(A) of the FD&C Act.

[22] See section 505G(b)(6) of the FD&C Act.

[23] FDA's Scientific Review Supporting Proposed Administrative Order is available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/, under the supporting documents for this Proposed Administrative Order OTC000039. For information about FDA's filing determination, see the Scientific Review Supporting Proposed Administrative Order, section II. OTC Monograph Order Request.

[24] See section II.F.4 of the OMUFA commitment letter. The document can be accessed at https://www.fda.gov/media/106407/download. See also the Scientific Review Supporting Proposed Administrative Order, section III. A. Human Clinical Efficacy Studies.

OMUFA commitment letter,[25] FDA's goal date for issuing this proposed order is December 23, 2025.[26]

IV. Statement of Reasons for Issuance of Proposed Order

FDA is issuing this proposed order pursuant to section 505G(b) of the FD&C Act in response to DSM's submission of an OMOR.

FDA conducted a scientific review of the data and information submitted by the Requestor in the OMOR.[27] FDA evaluated the safety and efficacy of bemotrizinol at concentrations up to 6 percent as a sunscreen active ingredient under the conditions described in OTC Monograph M020.

Discussion of the data and information and FDA's proposed conclusions are set forth below.

A. Efficacy

FDA conducted a review of the human efficacy data for bemotrizinol submitted by the Requestor in the OMOR.[28] To demonstrate efficacy, FDA generally expects two independent, adequate, and well-controlled studies[29] that follow the testing method described in § M020.80 of OTC Monograph M020 and demonstrate that the active ingredient has an SPF of not less than 2.[30] The Requestor submitted a total of four human clinical efficacy studies, which focus on the SPF determination. The Requestor initially submitted two human clinical efficacy studies in the OMOR. However, upon review, FDA determined these studies were not conducted consistent with the testing method outlined in § M020.80 of OTC Monograph M020. In addition, the two originally submitted studies each utilized a different protocol and as such, the results were not comparable. Therefore, FDA recommended the Requestor conduct two additional human clinical efficacy studies that both followed the testing method outlined in § M020.80 of OTC Monograph

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[25] Major amendments (whether solicited or unsolicited) submitted by the original requestor prior to issuance of the proposed order may extend the time to issuance of the proposed order by 3 months and, consequently, may extend the final goal date by 3 months. See section II.F.4 of the OMUFA commitment letter. The document can be accessed at https://www.fda.gov/media/106407/download.

[26] Due to the submission of a major amendment to the OMOR, the goal date to issue the proposed order was extended by 3 months.

[27] See FDA's Scientific Review Supporting Proposed Administrative Order.

[28] For FDA's review of data regarding the effectiveness of bemotrizinol as a sunscreen active ingredient, see the Scientific Review Supporting Proposed Administrative Order, section III. A. Human Clinical Efficacy Studies.

[29] See 21 CFR 330.10(a)(4)(ii) describing proof of effectiveness as generally consisting of "controlled clinical investigations as defined in 21 CFR 314.126(b)." FDA has interpreted this as generally requiring at least two adequate and well-controlled studies to demonstrate effectiveness of a sunscreen drug product. See the guidance for industry *Nonprescription Sunscreen Drug Products—Safety and Effectiveness Data* (November 2016).

[30] See § M020.10 of OTC Monograph M020. For more information on conducting studies, see also the guidance for industry *Nonprescription Sunscreen Drug Products—Safety and Effectiveness Data* (November 2016).

M020. Subsequently, the Requestor submitted two new human clinical efficacy studies, constituting a major amendment to the OMOR.[31]

FDA reviewed the two additional human clinical efficacy studies submitted by the Requestor in the major amendment. FDA determined that the studies were conducted consistent with the testing method in § M020.80 of OTC Monograph M020 and demonstrated that all bemotrizinol-containing test product formulations evaluated in the new human clinical efficacy studies exhibited a mean SPF value greater than 2. Both series of test product formulations exhibited a concentration-related increase in SPF, and positive and negative controls showed expected results.

Based on FDA's review of the data on the efficacy of bemotrizinol, FDA tentatively concludes that there is adequate evidence of the efficacy of bemotrizinol for use as an active ingredient in nonprescription sunscreen drug products intended for use in adults and children 6 months of age and older.

B. Safety

FDA conducted a review of the safety data for bemotrizinol submitted by the Requestor in the OMOR, including nonclinical and human clinical safety studies and information.[32]

1. Nonclinical Safety

FDA conducted a review of the nonclinical information and studies on the safety of bemotrizinol submitted by the Requestor in the OMOR.[33] The Requestor submitted nonclinical information, including a dermal carcinogenicity study, and developmental and reproductive toxicity studies.

The Requestor submitted a dermal carcinogenicity study in rats, which found that bemotrizinol was not carcinogenic at doses up to 1,000 milligrams/kg/day. FDA determined that based on the results of a human maximal usage trial (MUsT)[34] (see section IV.B.2. Clinical Pharmacology of this proposed order), the data submitted by the Requestor was sufficient to assess the carcinogenicity of bemotrizinol, and FDA concludes that there were no neoplastic findings of concern.

The Requestor submitted developmental and reproductive toxicity information for bemotrizinol, including a fertility and early embryonic development study in rats, embryofetal developmental

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[31] See the Scientific Review Supporting Proposed Administrative Order, section II. OTC Monograph Order Request.

[32] For FDA's review of data and information regarding the safety of bemotrizinol, see the Scientific Review Supporting Proposed Administrative Order, section III. B. Nonclinical Safety Studies and Information and section III. C. Human Clinical Safety Studies and Information.

[33] For FDA's review of nonclinical data and information on the safety of bemotrizinol as an active ingredient in sunscreen, see the Scientific Review Supporting Proposed Administrative Order, section III. B. Nonclinical Safety Studies and Information.

[34] A MUsT is a standard approach to assess the in vivo bioavailability of topical drug products intended for local therapeutic effects. See the 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* (May 2019).

studies in rats and rabbits, and a pre- and post-natal development study in rats. Based on the data, there were no dose-limiting reproductive or developmental findings of concern.

The Requestor submitted limited toxicokinetic/pharmacokinetic data. Based on sufficient high doses tested, and lack of adverse effects identified in the nonclinical dermal carcinogenicity, and developmental and reproductive toxicity studies, FDA determined that no additional nonclinical toxicokinetic/pharmacokinetic data are recommended for bemotrizinol.

Based on FDA's review of the nonclinical information and studies submitted by the Requestor on the safety of bemotrizinol, FDA tentatively concludes that the nonclinical data do not demonstrate safety concerns with bemotrizinol with respect to carcinogenicity, or developmental and reproductive toxicity.

2. Clinical Pharmacology

The Requestor conducted a human dermal pharmacokinetic study, a MUsT, to understand the extent to which bemotrizinol is absorbed through human skin. The MUsT for bemotrizinol was a two-part, open-label, multidose study in healthy adult subjects.

The results of the pivotal study showed that bemotrizinol is not readily absorbed through human skin, even with repeat application. Most data points were below the limit of quantitation (0.1 nanogram (ng)/milliliter (mL)), and the overall mean absorption remained consistently below 0.5 ng/mL.[35] Although some sporadic absorption occurred, most quantifiable measurements were in the range of 0.1 to 0.5 ng/mL, and findings were not formulation specific.

3. Clinical Safety

FDA conducted a review of the human clinical safety data of bemotrizinol submitted by the Requestor in the OMOR.[36] In addition to the MUsT discussed above, the Requestor submitted three human dermal safety studies including: (1) a repeated insult patch test and cumulative irritation patch test; (2) a photo-allergenicity test; and (3) a phototoxicity test. Together, the MUsT and three human dermal safety studies enrolled a total of 484 healthy adult subjects who were exposed to bemotrizinol in a range from minimal (patch exposure) application over a 3-week time period to an exposure of over 70 percent of the body surface area for 4 days in the MUsT. An additional 47 healthy adult subjects were exposed to bemotrizinol on a single day in

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[35] FDA expects that a systemic carcinogenicity study would not be needed to support a GRASE determination for a sunscreen active ingredient if an adequately conducted human pharmacokinetic MUsT program resulted in a steady state blood level less than 0.5 ng/mL, and an adequately conducted toxicology program did not reveal any other safety signals for the ingredient or any known structurally similar compounds, including metabolites, indicating the potential for adverse effects. The threshold value of 0.5 ng/mL is based on the assessment that the level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose. This threshold value is consistent with the threshold of toxicological concern concept. For sunscreen active ingredients, FDA expects that the 0.5 ng/mL concentration will be sufficiently above the assay's limit of quantitation—limit of detection to allow a signal-to-noise ratio that ensures confidence in either the detected concentrations or lack of concentrations (see Proposed Administrative Order OTC000008 at 22).

[36] For FDA's review of the human clinical safety data of bemotrizinol as an active ingredient in sunscreen, see the Scientific Review Supporting Proposed Administrative Order, section III. C. Human Clinical Safety Studies and Information.

the 4 SPF efficacy trials. FDA determined that the studies were sufficient to demonstrate that repeat exposure to bemotrizinol did not cause irritation or elicit a sensitization, photo-allergenic, or phototoxicity response. Only one serious adverse event (appendicitis) was reported across the clinical studies, which was not attributed to the study formulations. Based on the extensive postmarket history of bemotrizinol in other countries coupled with the clinical trial data, FDA determined that the clinical safety data were adequate, despite the fact that the number of subjects and duration of premarket exposure in clinical trials is much lower than typically expected.[37]

Pediatric data for bemotrizinol is limited. The studies submitted by the Requestor were conducted in patient populations ages 18 and older. Infants and younger children have a greater skin surface to body volume than adults which can increase systemic exposure to topically applied products, and younger infants may have differences in skin maturity.[38] However, given that the mean overall absorption is well below 0.5 ng/mL,[39] FDA does not consider additional MUsT in pediatric subjects to be necessary. Additionally, because the dermal studies had no instances of irritation, sensitization, phototoxicity, or photo-allergenicity, FDA does not consider similar studies in the pediatric population to be necessary.

4. Postmarket Safety

Sunscreen products containing bemotrizinol are marketed on every continent except for Antarctica. Most jurisdictions regulate sunscreens as a cosmetic; whereas in the United States, sunscreens are regulated as drugs. However, Australia and Canada also regulate sunscreens as drugs. The Requestor submitted limited postmarketing safety reports, provided primarily from the Australian Therapeutic Goods Administration (TGA)[40] Database of Adverse Event Notifications. This difference between countries in regulatory oversight may explain the lack of reports from other jurisdictions because generally cosmetic reporting requirements differ from drug reporting requirements and are less robust. FDA reviewed a total of 225 safety reports submitted by the Requestor. The most frequent events were sunburn, blistering, erythema (redness), rashes, and drug inefficacy. In all of these safety reports, bemotrizinol was combined with other sunscreen active ingredients, limiting the ability to attribute causality of the adverse events to a single ingredient. A total of 78 adverse events were identified as having occurred in the pediatric population (ages 17 to younger than 1). The majority of adverse events in children were similar to those found in adults and included sunburn, blistering, and drug ineffectiveness.

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[37] See the International Council for Harmonisation guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995).

[38] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products* (September 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[39] See footnote 32.

[40] The TGA is Australia's government authority responsible for evaluating, assessing, and monitoring products that are defined as therapeutic goods. The TGA regulates medicines, medical devices, and biological products. For more information, see https://www.tga.gov.au.

A review of the literature submitted by the Requestor showed only two published case reports, both of which were adults with contact dermatitis of the face. FDA also conducted an independent literature search and found only one additional case report of contact dermatitis. While these reports document the most frequently occurring adverse events for sunscreen products containing bemotrizinol, they did not directly raise safety concerns regarding the use of bemotrizinol.

5. Proposed Safety Conclusions

Based on FDA's review of the nonclinical, clinical pharmacology, and clinical safety studies and information, FDA tentatively concludes that there is adequate evidence of the safety of bemotrizinol at concentrations up to 6 percent for use as an active ingredient in nonprescription sunscreen drug products intended for use in adults and children 6 months of age and older.

C. Other Considerations Relevant to OTC Monograph Conditions for Sunscreen Drug Products Containing Bemotrizinol

To inform consideration of potential OTC monograph conditions needed specifically to help assure that sunscreen drug products that contain bemotrizinol are GRASE, FDA conducted a review of the data submitted by the Requestor in the OMOR and conducted literature searches to determine whether: (1) bemotrizinol can be manufactured as a drug substance and the identified impurity levels are supported by sufficient data; (2) bemotrizinol can be manufactured into a drug product, including the different types of dosage forms; (3) a single drug product may combine bemotrizinol with other permitted sunscreen active ingredients in § M020.10 of OTC Monograph M020; (4) a single drug product may combine bemotrizinol alone or in an allowed combination with other sunscreen active ingredients, with one or more skin protectant active ingredients identified in § M016.10 of OTC Monograph M016; and (5) a drug product containing bemotrizinol as a sunscreen active ingredient would need different labeling from other sunscreen OTC monograph drugs.[41]

1. Drug Substance Manufacturing and Impurities

FDA conducted a review of the data and information submitted by the Requestor on the manufacturing of bemotrizinol as a drug substance, including the impurities resulting from the manufacturing process. Bemotrizinol has 10 identified impurities that are mostly structurally similar to the parent compound and are a result of the manufacturing process. Based on the totality of the data, FDA agrees with the impurity specifications proposed by the Requestor, which are consistent with those in the proposed United States Pharmacopeia monograph for bemotrizinol. Establishing the specific characteristics of bemotrizinol is necessary so that if this proposed order is finalized, it can help assure that the composition of a future sunscreen drug product formulated using bemotrizinol as an active ingredient is GRASE under section 201(p)(1) of the FD&C Act.

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[41] For FDA's review of data regarding evaluation of bemotrizinol under the conditions described in OTC Monograph M020, see the Scientific Review Supporting Proposed Administrative Order, section III. D. Other Considerations Relevant to OTC Monograph Conditions for Sunscreen Drug Products Containing Bemotrizinol.

2. Drug Product Manufacturing, Including Dosage Forms

In its OMOR, the Requestor sought to have FDA determine that sunscreen drug products containing bemotrizinol at concentrations up to 6 percent as an active ingredient are GRASE if they are in any of the topical dosage forms permitted for products marketed under the OTC sunscreen monograph;[42] at present, these are oil, lotion, cream, gel, butter, paste, ointment, stick, spray, and powder.[43] The Requestor created and submitted data regarding four *market image* drug product formulations containing bemotrizinol: (1) oil-in-water emulsion; (2) water-in-oil emulsion; (3) sunscreen oil; and (4) petrolatum. Based on FDA's review, FDA tentatively concludes that the data regarding these four drug product formulations provide sufficient support that bemotrizinol as a sunscreen active ingredient can be used to formulate drug products in the following dosage forms: oil, lotion, cream, gel, butter, paste, ointment, and stick. In addition, these four drug product formulations support that bemotrizinol as a sunscreen active ingredient can be used to formulate a drug product in a spray dosage form that is manufactured and packaged with no propellant (e.g., a pump spray) or that is manufactured and packaged so that all propellant is isolated from the drug product formulation within the container closure system and there is no contact between propellant and the drug product formulation (e.g., a bag-on-valve spray). However, the data from these four drug product formulations, which were the only support provided for the dosage forms for any bemotrizinol-containing sunscreens, do not support a drug product formulation combined with a propellant to create an aerosol spray dosage form (e.g., a propellant-based aerosol spray). Additionally, the Requestor did not submit data or information to demonstrate that a drug product containing bemotrizinol as a sunscreen active ingredient can be manufactured in a powder dosage form.

In Proposed Administrative Order OTC000008, FDA proposed that, regardless of their active ingredients, all sunscreen drug products in spray dosage form would be subject to additional conditions to address potential risks associated with inhalation and flammability.[44] Because sprays containing bemotrizinol as a sunscreen active ingredient would also have the potential risks associated with inhalation and flammability, FDA expects that, if finalized, the proposed conditions in Proposed Administrative Order OTC000008 for any sunscreen drug product in a spray dosage form would apply to all spray drug products containing bemotrizinol as a sunscreen active ingredient.

With regard to the powder dosage form, in Proposed Administrative Order OTC000008, FDA proposed that, regardless of their active ingredients, there is insufficient data to classify sunscreen drug products in the powder dosage form as GRASE. The Requestor did not submit data to address these general concerns regarding powder dosage forms for bemotrizinol-containing drug products.

In sum, FDA proposes that OTC monograph conditions for drug products containing bemotrizinol as a sunscreen active ingredient include conditions that limit such products to the

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[42] While the OMOR referred to 21 CFR part 352, the current iteration of the OTC monograph for sunscreen drug products can be found at OTC Monograph M020 as set forth in Final Administrative Order OTC000006.

[43] These are the only dosage forms permitted now for other sunscreen drug products marketed pursuant to section 505G of the FD&C Act. See Final Administrative Order OTC000006, at 2, footnote 7.

[44] See Proposed Administrative Order OTC000008 at 7, 55–64.

following dosage forms: oil, lotion, cream, gel, butter, paste, ointment, stick, and spray, provided that the product in spray dosage form is manufactured and packaged with no propellant (e.g., a pump spray) or is manufactured and packaged in a spray delivery system where all propellant is isolated from the drug product formulation within the container closure system and there is no contact between the propellant and the drug product formulation (e.g., a bag-on-valve spray).[45]

3. Combination With Other Permitted Sunscreen Active Ingredients

Consistent with § M020.20 of OTC Monograph M020 which allows for permissible combinations of sunscreen active ingredients, the Requestor proposed that bemotrizinol at concentrations up to 6 percent be allowed to be combined with all permissible sunscreen active ingredients identified in § M020.10 of OTC Monograph M020. Generally, unless data suggest that there may be a safety or efficacy concern with a particular combination of active ingredients, FDA anticipates that a sunscreen drug product containing a sunscreen active ingredient identified in § M020.10 of OTC Monograph M020 could be combined with other sunscreen active ingredients also identified in § M020.10 of OTC Monograph M020.[46]

FDA reviewed postmarketing data submitted by the Requestor and conducted a review of publicly available scientific literature to determine the safety and efficacy of bemotrizinol combined with other sunscreen active ingredients. FDA did not identify any data to suggest that a drug product that combines bemotrizinol with other sunscreen active ingredients creates any new or previously unidentified safety concerns. Rather, FDA identified studies demonstrating that the use of bemotrizinol in combination with certain other sunscreen active ingredients may be beneficial due to bemotrizinol's ability to act as a photostabilizer.

However, in Proposed Administrative Order OTC000008, FDA proposed to find that sunscreen drug products containing PABA and trolamine salicylate, two sunscreen active ingredients currently identified in § M020.10 of OTC Monograph M020, are not GRASE due to data demonstrating significant safety issues. FDA has not received data that mitigate FDA's identified safety concerns with PABA or trolamine salicylate, or that demonstrate that bemotrizinol in combination with either PABA or trolamine salicylate alleviates those concerns. Therefore, because of the noted safety concerns with PABA and trolamine salicylate, FDA is proposing to find that sunscreen drug products containing bemotrizinol in combination with PABA and/or trolamine salicylate are not GRASE.[47]

Because FDA has not identified any data to suggest that a drug product that contains bemotrizinol as an active ingredient in combination with permissible sunscreen active ingredients other than PABA and trolamine salicylate poses any safety or efficacy concerns, FDA proposes to find that such combinations are GRASE.

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[45] This is in addition to the outstanding proposed conditions in Proposed Administrative Order OTC000008 for all sprays, to address risks of inhalation and flammability that potentially exist, irrespective of the sunscreen drug product's active ingredient(s).

[46] See Proposed Administrative Order OTC000008 at 16.

[47] See section 505G(b)(1)(C)(i) of the FD&C Act.

4. Combination With Skin Protectant Active Ingredients

In addition to combinations of sunscreen active ingredients addressed in § M020.20 of OTC Monograph M020, § M016.20(e) of OTC Monograph M016 lists permitted combinations of certain skin protectant active ingredients[48] with any single sunscreen active ingredient under § M020.10 of OTC Monograph M020 and with any permitted combination of sunscreen active ingredients in § M020.20 of OTC Monograph M020. FDA conducted a review of publicly available scientific literature to identify any existing safety or efficacy concerns related to using bemotrizinol in combination with those skin protectants identified in § M016.20(e) of OTC Monograph M016. A single case report was found where bemotrizinol combined with dimethicone (a skin protectant active ingredient permitted for combination with sunscreen active ingredients in § M016.20(e) of OTC Monograph M016) resulted in a positive reaction; however, when exposed to the individual ingredients, the subject had a positive reaction to multiple ingredients, including bemotrizinol and dimethicone, suggesting that the combination itself did not create the reaction.

In addition, FDA reviewed data from the three human dermal safety studies submitted by the Requestor in the OMOR (section IV.B.3. Clinical Safety of this proposed order). All three studies included a test article which was a dispersion of 6 percent bemotrizinol in petrolatum, which is a skin protectant active ingredient permitted for combination with sunscreen active ingredients in § M016.20(e) of OTC Monograph M016.[49] Overall, a total of 308 adult subjects received bemotrizinol in petrolatum. The data did not indicate any evidence of sensitization, phototoxicity, or photo-allergy with bemotrizinol in petrolatum. The cumulative irritation score of the combination of bemotrizinol in petrolatum demonstrated no evidence of cumulative irritation.

FDA did not identify any efficacy concerns associated with use of bemotrizinol in combination with any of the skin protectant active ingredients identified in § M016.20(e) of OTC Monograph M016.

Based on FDA's review of the data, FDA has determined that there are no safety or efficacy concerns if bemotrizinol is combined with skin protectant active ingredients identified in § M016.20(e) of OTC Monograph M016.

5. Labeling Requirements

The Requestor proposed that the labeling requirements for sunscreen drug products in § M020.50 of OTC Monograph M020 apply to sunscreen drug products containing bemotrizinol without

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[48] Section M016.20(e) of OTC Monograph M016: "Combinations of skin protectant and sunscreen active ingredients. Any one (two when required to be in combination) or more of the skin protectant active ingredients identified in § M016.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r) may be combined with any generally recognized as safe and effective single sunscreen active ingredient, provided the product meets the conditions in § M020.10; or any permitted combination of these ingredients, provided the product meets the conditions in § M020.20 of OTC Monograph M020; and is labeled according to § M016.60(b)(3) and § M020.50(c) of OTC Monograph M020."

[49] The Requestor submitted a market image drug product formulation that consisted of 6 percent bemotrizinol with 94 percent petrolatum, which is consistent with the requirements for petrolatum in § M016.10(m) of OTC Monograph M016 (30 to 100 percent petrolatum).

revision. The totality of the data and information submitted by the Requestor in the OMOR did not raise any safety or efficacy concerns that would necessitate amending the labeling requirements in § M020.50 of OTC Monograph M020 specifically for sunscreen drug products containing bemotrizinol.

Consistent with FDA's review of the safety and efficacy data for bemotrizinol, in this proposed order, FDA does not propose any distinct labeling as an OTC monograph condition for sunscreen drug products that contain bemotrizinol as an active ingredient.[50]

D. Proposed Conclusions

Based on our scientific review of the data submitted in the OMOR, FDA proposes to find that there are conditions under which a drug product containing bemotrizinol as a sunscreen active ingredient is GRASE under section 201(p)(1) of the FD&C Act and not subject to section 503(b)(1) of the FD&C Act. Among these conditions are conditions specific to the use of bemotrizinol as an active ingredient, including a concentration up to 6 percent,[51] permitted combinations of bemotrizinol with other sunscreen active ingredients and with skin protectant active ingredients, and permitted dosage forms. This proposed order also includes minor stylistic, formatting, and technical changes to improve the readability, clarity, and presentation of OTC Monograph M020.

V. Exclusivity

If this proposed order is finalized, exclusivity will be addressed in the final order (see section 505G(b)(5)(C) of the FD&C Act (21 U.S.C. 355h(b)(5)(C)).

VI. Effective Date

This proposed order, if finalized, shall take effect—

(a) 60 calendar days after the date on which notice of the final order is published in the *Federal Register*; or

(b) if the final order is disputed under section 505G(b) of the FD&C Act, in accordance with section 505G(b)(2)(A)(iv)(I) of such Act.

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[50] See footnote 4. FDA proposed several labeling changes to § M020.50 of OTC Monograph M020 in Proposed Administrative Order OTC000008. If Proposed Administrative Order OTC000008 is finalized to establish new or revised labeling requirements in OTC Monograph M020, sunscreen drug products marketed under OTC Monograph M020, including sunscreens containing bemotrizinol as an active ingredient, would be required to meet those new or revised conditions.

[51] In addition, a finished drug product containing bemotrizinol as a sunscreen active ingredient must also provide a minimum SPF of not less than 2 as measured by the testing procedures established in § M020.80 of OTC Monograph M020.

VII. Analysis of Environmental Impact

FDA has determined that an environmental assessment, which must contain sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment, is necessary. See 21 CFR 25.15(a) and 25.20. Environmental consideration of the proposed action is ongoing to determine whether an environmental impact statement is required or whether a finding of no significant impact is appropriate. See 21 CFR 25.15(b).

VIII. Proposed Administrative Order (OTC000039)

A. Proposed OTC Monograph Determinations

FDA is proposing that the following conditions are necessary, but not alone sufficient,[52] for a sunscreen drug product containing bemotrizinol as an active ingredient to be GRASE under section 201(p)(1) of the FD&C Act and not subject to FD&C Act section 503(b)(1):

- Bemotrizinol is present in the drug product in a concentration up to 6 percent, and the finished drug product provides a minimum SPF value of not less than 2 as measured by the testing procedures established in § M020.80 of OTC Monograph M020;
- The composition of a single drug product may combine bemotrizinol with any single active ingredient identified in § M020.10 of OTC Monograph M020, except for PABA or trolamine salicylate, or may combine bemotrizinol with any combination of sunscreen active ingredients identified in § M020.20(a) of OTC Monograph M020 that does not include PABA or trolamine salicylate, provided that the following additional conditions are met: (1) each active ingredient is used in the concentration established for it in § M020.10 of OTC Monograph M020; (2) the concentration of each active ingredient is sufficient to contribute a minimum SPF of not less than 2 to the finished product; (3) the finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination, multiplied by 2; and (4) the SPF of the product is measured by the testing procedures established in § M020.80 of OTC Monograph M020;
- The composition of a single drug product may combine any one (two when required to be in combination) or more of the skin protectant active ingredients identified in § M016.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r) of OTC monograph M016 with bemotrizinol as a single sunscreen active ingredient provided that the drug product meets the conditions for a drug product that contains bemotrizinol in OTC Monograph M020; and is labeled according to § M016.60(b)(3) of OTC Monograph M016;

[52] If this proposed order is finalized, to be GRASE under section 201(p)(1) of the FD&C Act, a sunscreen drug product containing bemotrizinol must also conform to other applicable conditions in final orders under 505G(b) of the FD&C Act. In addition, to be legally marketed without an approved application under section 505 of the FD&C Act, such a drug product must meet other requirements including the general requirements for nonprescription drugs. See 505G(b)(1)(B) of the FD&C Act and section III.A of this proposed order.

- The composition of a single drug product may combine any one (two when required to be in combination) or more of the skin protectant active ingredients identified in § M016.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r) of OTC monograph M016 with bemotrizinol in any combination with other sunscreen active ingredients identified in § M020.20 of OTC Monograph M020 that does not include PABA or trolamine salicylate; provided the drug product meets the conditions for a drug product that contains bemotrizinol in OTC Monograph M020; and is labeled according to § M016.60(b)(3) of OTC Monograph M016;

- The drug product containing bemotrizinol as a sunscreen active ingredient is in one of the following dosage forms and meets additional conditions specified: oil, lotion, cream, gel, butter, paste, ointment, stick, or spray, provided that the spray product is manufactured and packaged with no propellant or is manufactured and packaged in a spray delivery system where all propellant is isolated from the drug product formulation within the container closure system and there is no contact between the propellant and the drug product formulation.

FDA is also proposing to find that a drug product containing bemotrizinol as a sunscreen active ingredient is not GRASE if it includes bemotrizinol in combination with PABA and/or trolamine salicylate.

Thus, FDA is issuing Proposed Administrative Order (OTC000039), which, if finalized, would amend OTC Monograph M020 including technical amendments as follows:

1. Amend the heading of Part B of OTC Monograph M020 to read as follows:

   Part B—Active Ingredients, Route of Administration, and Dosage Forms

2. Amend § M020.10 to redesignate paragraphs (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), and (p) as (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p), and (q), respectively.

3. Amend § M020.10(c) to add new paragraph (c) to read as follows:

   (c) Bemotrizinol up to 6 percent.

4. Amend § M020.20(a)(1) to read as follows:

   (1) Two or more sunscreen active ingredients identified in §§ M020.10(a), (d), (e), (f), and (g) through (q) may be combined with each other in a single product when used in the concentrations established for each ingredient in § M020.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

5. Amend § M020.20(a)(2) to read as follows:

   (2) Two or more sunscreen active ingredients identified in §§ M020.10(b), (d), (e), (g), (i) through (l), (n), and (p) may be combined with each other in a single product when used in the concentrations established for each ingredient in § M020.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

6. Amend § M020.20 to include subparagraph (a)(3) to read as follows:

   (3) The sunscreen active ingredient identified in § M020.10(c) may be combined with any one active ingredient identified in §§ M020.10(b), (d) through (o), and (q) in a single product when used in the concentrations established for each ingredient in § M020.10. The sunscreen active ingredient identified in § M020.10(c) may be combined with one or more active ingredients identified in §§ M020.10(b), (d), (e), (g), (i) through (l), and (n) in a single product when used in the concentrations established for each ingredient in § M020.10. The sunscreen active ingredient identified in § M020.10(c) may be combined with one or more active ingredients identified in §§ M020.10(d), (e), (f), (g) through (o), and (q) when used in the concentrations established for each ingredient in § M020.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

7. Add § M020.40 under Part B with the heading “Dosage forms” to read as follows:

   The product is in one of the following dosage forms and meets any additional conditions specified, as applicable:

   (a) If it contains skin protectant active ingredient(s) identified in § M016.20(e) of OTC Monograph M016 it complies with applicable dosage form conditions in § M020.40.

   (b) If it contains the sunscreen active ingredient identified in § M020.10(c),

      (1) oil

      (2) lotion

      (3) cream

      (4) gel

      (5) butter

      (6) paste

      (7) ointment

(8) stick

(9) spray, provided that the product is manufactured and packaged

(i) with no propellant; or

(ii) in a spray delivery system where all propellant is isolated from the drug product formulation within the container closure system and there is no contact between propellant and the drug product formulation.

8. Amend § M020.50(h) to read as follows:

(h) Labeling of products containing a combination of sunscreen and skin protectant active ingredients identified in § M016.20(e) of OTC Monograph M016. Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. Labeling provisions in § M016.50(e) of OTC Monograph M016 shall not apply to these products.

B. Proposed Revision: OTC Monograph M020 Sunscreen Drug Products for Over-the-Counter Human Use

Upon the effective date of this order, if finalized, as a reflection of the cumulative product of Final Administrative Order OTC000006 and this order, OTC Monograph M020 would read, in its entirety, as follows:

U.S. Food and Drug Administration

Over-the-Counter (OTC) Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use

Part A—General Provisions

Sec.

Part B—Active Ingredients, Route of Administration, and Dosage Forms

Part C—Labeling

Part D—Testing Procedures

Part A—General Provisions

§ M020.1 Scope

An over-the-counter (OTC) sunscreen drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this OTC monograph and each general condition established in 21 CFR 330.1.

Part B—Active Ingredients, Route of Administration, and Dosage Forms

§ M020.10 Sunscreen active ingredients

The active ingredient of the product consists of any of the following, within the concentration specified for each ingredient, and the finished product provides a minimum sun protection factor (SPF) value of not less than 2 as measured by the testing procedures established in § M020.80:

(a) Aminobenzoic acid (PABA) up to 15 percent.

(b) Avobenzone up to 3 percent.

(c) Bemotrizinol up to 6 percent.

(d) Cinoxate up to 3 percent.

(e) Dioxybenzone up to 3 percent.

(f) Ensulizole up to 4 percent.

(g) Homosalate up to 15 percent.

(h) Meradimate up to 5 percent.

(i) Octinoxate up to 7.5 percent.

(j) Octisalate up to 5 percent.

(k) Octocrylene up to 10 percent.

(l) Oxybenzone up to 6 percent.

(m) Padimate O up to 8 percent.

(n) Sulisobenzone up to 10 percent.

(o) Titanium dioxide up to 25 percent.

(p) Trolamine salicylate up to 12 percent.

(q) Zinc oxide up to 25 percent.

§ M020.20 Permitted combinations of active ingredients

The SPF of any combination product is measured by the testing procedures established in § M020.80.

(a) Combinations of sunscreen active ingredients.

(1) Two or more sunscreen active ingredients identified in §§ M020.10(a), (d), (e), (f), and (g) through (q) may be combined with each other in a single product when used in the concentrations established for each ingredient in § M020.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

(2) Two or more sunscreen active ingredients identified in §§ M020.10(b), (d), (e), (g), (i) through (l), (n), and (p) may be combined with each other in a single product when used in the concentrations established for each ingredient in § M020.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

(3) The sunscreen active ingredient identified in § M020.10(c) may be combined with any one active ingredient identified in §§ M020.10(b), (d) through (o), and (q) in a single product when used in the concentrations established for each ingredient in § M020.10. The sunscreen active ingredient identified in § M020.10(c) may be combined with one or more active ingredients identified in §§ M020.10(b), (d), (e), (g), (i) through (l), and (n) in a single product when used in the concentrations established for each ingredient in § M020.10. The sunscreen active ingredient identified in § M020.10(c) may be combined with one or more active ingredients identified in §§ M020.10(d), (e), (f), (g) through (o), and (q) when used in the concentrations established for each ingredient in § M020.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

§ M020.40 Dosage forms

The product is in one of the following dosage forms and meets any additional conditions specified, as applicable:

(a) If it contains skin protectant active ingredient(s) identified in § M016.20(e) of OTC Monograph M016, it complies with applicable dosage form conditions in § M020.40.

(b) If it contains the sunscreen active ingredient identified in § M020.10(c),

(1) oil

(2) lotion

(3) cream

(4) gel

(5) butter

(6) paste

(7) ointment

(8) stick

(9) spray, provided that the product is manufactured and packaged

(i) with no propellant; or

(ii) in a spray delivery system where all propellant is isolated from the drug product formulation within the container closure system and there is no contact between propellant and the drug product formulation.

Part C—Labeling

§ M020.50 Labeling of sunscreen drug products

(a) Principal display panel. In addition to the statement of identity in § M020.50(b), the following labeling shall be prominently placed on the principal display panel:

(1) Effectiveness claim

(i) For products that pass the broad spectrum test in § M020.90.

(A) The labeling states “Broad Spectrum SPF [insert numerical SPF value resulting from testing under § M020.80]”.

(B) Prominence. The Broad Spectrum SPF statement shall appear as continuous text with no intervening text or graphic. The entire text shall appear in the same font style, size, and color with the same background color.

(ii) For sunscreen products that do not pass the broad spectrum test in § M020.90. The labeling states “SPF [insert numerical SPF value resulting from testing under § M020.80]”. The entire text shall appear in the same font style, size, and color with the same background color.

(2) Water resistance statements

(i) For products that provide 40 minutes of water resistance according to the test in § M020.80(g)(1). The labeling states “Water Resistant (40 minutes)”.

(ii) For products that provide 80 minutes of water resistance according to the test in § M020.80(g)(2). The labeling states “Water Resistant (80 minutes)”.

(b) Statement of identity. The labeling of the product contains the established name of the drug, if any, and identifies the drug as a "sunscreen."

(c) Indications. The labeling of the product states, under the heading "Uses," the phrases listed in § M020.50(c), as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in § M020.50(c), may also be used, as provided in 21 CFR 330.1(c)(2), subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 352) relating to misbranding and the prohibition in section 301(d) of the FD&C Act (21 U.S.C. 331(d)) against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the FD&C Act (21 U.S.C. 355(a)).

(1) For all sunscreen products, the following indication statement must be included under the heading "Uses": "[Bullet][53] helps prevent sunburn".

(2) For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in §§ M020.80 and M020.90, the labeling may include the following statement in addition to the indication in § M020.50(c)(1): "[Bullet] if used as directed with other sun protection measures (see Directions [in bold italic font]), decreases the risk of skin cancer and early skin aging caused by the sun".

(3) Any labeling or promotional materials that suggest or imply that the use, alone, of any sunscreen reduces the risk of or prevents skin cancer or early skin aging will cause the product to be misbranded under section 502 of the FD&C Act.

(d) Warnings. The labeling of the product contains the following warnings under the heading "Warnings".

(1) For all sunscreen products.

(i) The labeling states "Do not use [bullet] on damaged or broken skin".

(ii) The labeling states "When using this product [bullet] keep out of eyes. Rinse with water to remove."

(iii) The labeling states "Stop use and ask a doctor if [bullet] rash occurs".

(2) For sunscreen products that are broad spectrum with SPF values of at least 2 but less than 15 according to the SPF test in § M020.80 or that do not pass the broad spectrum test in § M020.90. The first statement under the heading "Warnings" states "Skin Cancer/Skin Aging Alert [in bold font]: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging."

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[53] See 21 CFR 201.66(b)(4).

(e) Directions. The labeling of the product contains the following statements, as appropriate, under the heading "Directions." More detailed directions applicable to a particular product formulation may also be included.

(1) For all sunscreen products.

(i) As an option, the labeling may state "For sunscreen use:".

(ii) The labeling states "[bullet] apply [select one of the following: 'Liberally' or 'generously'] [and, as an option: 'And evenly'] 15 minutes before sun exposure".

(iii) As an option, the labeling may state "[bullet] apply to all skin exposed to the sun".

(iv) The labeling states "[bullet] children under 6 months of age: Ask a doctor".

(2) For sunscreen products with a Broad Spectrum SPF value of 15 or higher according to the tests in §§ M020.80 and M020.90. The labeling states "[bullet] Sun Protection Measures. [in bold font] Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF value of 15 or higher and other sun protection measures including: [Bullet] limit time in the sun, especially from 10 a.m.-2 p.m. [bullet] wear long-sleeved shirts, pants, hats, and sunglasses".

(3) For products that satisfy the water resistance test in § M020.80(g). The labeling states "[bullet] reapply: [Bullet] after [select one of the following determined by water resistance test: '40 minutes of' or '80 minutes of'] swimming or sweating [bullet] immediately after towel drying [bullet] at least every 2 hours".

(4) For products that do not satisfy the water resistance test in § M020.80(g). The labeling states "[bullet] reapply at least every 2 hours [bullet] use a water resistant sunscreen if swimming or sweating".

(f) Other information. The labeling of the product contains the following statement under the heading "Other information:" "[bullet] protect the product in this container from excessive heat and direct sun".

(g) False and misleading claims. There are claims that would be false and/or misleading on sunscreen products. These claims include but are not limited to the following: "Sunblock," "sweatproof," and "waterproof." These or similar claims will cause the product to be misbranded under section 502 of the FD&C Act.

(h) Labeling of products containing a combination of sunscreen and skin protectant active ingredients identified in § M016.20(e) of OTC Monograph M016. Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. Labeling provisions in § M016.50(e) of OTC Monograph M016 shall not apply to these products.

Part D—Testing Procedures

§ M020.80 Sun protection factor (SPF) test procedure

(a) UV source (solar simulator).

(1) Emission spectrum. A single port or multiport solar simulator should be filtered so that it provides a continuous emission spectrum from 290 to 400 nanometers (nm) with a limit of 1,500 Watts per square meter (W/m2) on total irradiance for all wavelengths between 250 and 1,400 nm.

(i) The solar simulator should have the following percentage of erythema-effective radiation in each specified range of wavelengths:

Solar Simulator Emission Spectrum

Wavelength range (nm)	Percent erythemal contribution [1]
<290	<0.1
290-300	1.0-8.0
290-310	49.0-65.0
290-320	85.0-90.0
290-330	91.5-95.5
290-340	94.0-97.0
290-400	99.9-100.0

[1]Calculation of erythema action spectrum described in § M020.80(a)(2).

(ii) In addition, UVA II (320-340 nm) irradiance should equal or exceed 20 percent of the total UV (290-400 nm) irradiance. UVA I (340-400 nm) irradiance should equal or exceed 60 percent of the total UV irradiance.

(2) Erythema action spectrum.

(i) Calculate the erythema action spectrum weighting factor (Vi) at each wavelength λ:

(A) $Vi\ (\lambda) = 1.0\ (250 < \lambda \leq 298\ nm)$

(B) $Vi\ (\lambda) = 10^{0.094*(298-\lambda)}\ (298 < \lambda \leq 328\ nm)$

(C) $Vi\ (\lambda) = 10^{0.015*(140-\lambda)}\ (328 < \lambda \leq 400\ nm)$

(ii) Calculate the erythema-effective UV dose (E) delivered by a solar simulator as follows:

$$E = \sum_{250}^{400} V_i(\lambda) * I(\lambda) * t$$

Where Vi(λ) = erythema action spectrum weighting factor at each wavelength λ

I (λ) = irradiance (Watts per square meter) at each wavelength λ

t = exposure time (seconds)

Erythema-effective dose (E) is expressed as effective Joules per square meter (J/m^2-eff).

(iii) The emission spectrum must be determined using a handheld radiometer with a response weighted to match the spectrum in ISO 17166 CIE S 007/E entitled "Erythemal reference action spectrum and standard erythema dose," dated 1999 (First edition, 1999-12-15; corrected and reprinted 2000-11-15), which is incorporated by reference and is available for inspection at FDA. For further information about inspecting incorporated materials, see https://www.fda.gov. Copies may also be available from the publisher/ISO Copyright Office. The solar simulator output should be measured before and after each phototest or, at a minimum, at the beginning and end of each test day. This radiometer should be calibrated using side-by-side comparison with the spectroradiometer (using the weighting factors determined according to § M020.80(a)(2)(i)) at the time of the annual spectroradiometric measurement of the solar simulator as described in § M020.80(a)(4).

(3) Operation. A solar simulator should have no significant time-related fluctuations (within 20 percent) in radiation emissions after an appropriate warm-up time and demonstrate good beam uniformity (within 20 percent) in the exposure plane. The delivered dose to the UV exposure site must be within 10 percent of the expected dose.

(4) Periodic measurement. To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, the emission spectrum of the solar simulator should be measured at least annually with an appropriate and accurately calibrated spectroradiometer system (results should be traceable to the National Institute for Standards and Technology). In addition, the solar simulator must be recalibrated if there is any change in the lamp bulb or the optical filtering components (i.e., filters, mirrors, lenses, collimating devices, or focusing devices). Daily solar simulator radiation intensity should be monitored with a broadband radiometer with a response weighted to match the erythema action spectrum in ISO 17166 CIE S 007/E entitled "Erythemal reference action spectrum and standard erythema dose," which is incorporated by reference in § M020.80(a)(2)(iii). If a lamp must be replaced due to failure or aging during a phototest, broadband device readings consistent with those obtained for the original calibrated lamp will suffice until measurements can be performed with the spectroradiometer at the earliest possible opportunity.

(b) SPF standard

(1) Preparation. The SPF standard should be a formulation containing 7-percent padimate O and 3-percent oxybenzone.

Composition of the Padimate O/ oxybenzone SPF Standard

Ingredients	Percent by weight
Part A:	
Lanolin	4.50
Cocoa butter	2.00
Glyceryl monostearate	3.00
Stearic acid	2.00
Padimate O	7.00
Oxybenzone	3.00
Part B:	
Purified water USP	71.60
Sorbitol solution	5.00
Triethanolamine, 99 percent	1.00
Methylparaben	0.30
Propylparaben	0.10
Part C:	
Benzyl alcohol	0.50
Part D:	
Purified water USP	QS [1]

[1] Quantity sufficient to make 100 grams.

Step 1. Add the ingredients of Part A into a suitable stainless-steel kettle equipped with a propeller agitator. Mix at 77 to 82 °C until uniform.

Step 2. Add the water of Part B into a suitable stainless-steel kettle equipped with a propeller agitator and begin mixing at 77 to 82 °C. Add the remaining ingredients of Part B and mix until uniform.

Step 3. Add the batch of Step 1 to the batch of Step 2 and mix at 77 to 82 °C until smooth and uniform. Slowly cool the batch to 49 to 54 °C.

Step 4. Add the benzyl alcohol of Part C to the batch of Step 3 at 49 to 54 °C. Mix until uniform. Continue to cool batch to 35 to 41 °C.

Step 5. Add sufficient water of Part D to the batch of Step 4 at 35 to 41 °C to obtain 100 grams of SPF standard. Mix until uniform. Cool batch to 27 to 32 °C.

(2) High-performance liquid chromatography (HPLC) assay. Use the HPLC procedure to verify the concentrations of padimate O and oxybenzone in the SPF standard:

(i) Instrumentation.

(A) Equilibrate a suitable liquid chromatograph to the following or equivalent conditions:

(1) Column	C-18, 250 millimeters (mm) length, 4.6 mm inner diameter (5 microns)
(2) Mobile Phase	85:15:0.5 methanol: water: acetic acid
(3) Flow Rate	1.5 milliliters (mL) per minute
(4) Temperature	Ambient
(5) Detector	UV spectrophotometer at 308 nanometers
(6) Attenuation	As needed

(B) Use HPLC grade reagents for mobile phase.

(ii) Preparation of the HPLC reference standard.

(A) Weigh 0.50 gram (g) of oxybenzone USP reference standard into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(B) Weigh 0.50 g of padimate O USP reference standard into a 250-mL volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(C) Pipet 3.0 mL of the oxybenzone solution and 7.0 mL of the padimate O solution into a 100-mL volumetric flask. Dilute to volume with isopropanol and mix well.

(iii) HPLC system suitability.

(A) Make three replicate 10-microliter injections of the HPLC reference standard (described in § M020.80(b)(2)(ii)). The relative standard deviation in peak areas should not be more than 2.0 percent for either oxybenzone or padimate O.

(B) Calculate the resolution (R) between the oxybenzone and padimate O peaks from one chromatogram as follows:

$$R = \frac{2 * (t_o - t_p)}{W_o + W_p}$$

Where t_o = retention time for oxybenzone

t_p = retention time for padimate O

W_o = oxybenzone peak width at baseline

W_p = padimate O peak width at baseline

If the resolution (R) is less than 3.0, adjust the mobile phase or replace the column.

(iv) SPF standard assay

(A) The SPF standard is diluted to the same concentration as the HPLC reference standard according to the following steps:

(1) Step 1. Weigh 1.0 g of the SPF standard (described in § M020.80(b)(1)) into a 50-mL volumetric flask.

(2) Step 2. Add approximately 30 mL of isopropanol and heat with swirling until contents are evenly dispersed.

(3) Step 3. Cool to room temperature (15 to 30 °C) and dilute to volume with isopropanol. Mix well.

(4) Step 4. Pipet 5.0 mL of the preparation into a 50-mL volumetric flask and dilute to volume with isopropanol. Mix well.

(B) Inject 10-microliter of diluted SPF standard from paragraph § M020.80(b)(2)(iv)(A) and calculate the amount of oxybenzone and padimate O as follows:

$$\text{Percent Oxybenzone} = \frac{\text{Peak area of oxybenzone in sunscreen standard}}{\text{Peak area of oxybenzone in HPLC reference standard}} * 100$$

$$\text{Percent Padimate O} = \frac{\text{Peak area of padimate O in sunscreen standard}}{\text{Peak area of padimate O in HPLC reference standard}} * 100$$

The percent of oxybenzone and padimate O in the SPF standard should be between 95 and 105.

(c) Test subjects

(1) Number of subjects. A test panel should include enough subjects to produce a minimum of 10 valid test results. A maximum of three subjects may be rejected from this panel based on § M020.80(e)(5).

(2) Medical history.

(i) Obtain a medical history from each subject with emphasis on the effects of sunlight on the subject's skin. Determine that each subject is in good general health with skin type 1, 2, or 3 as follows:

(1) Always burns easily; never tans (sensitive).

(2) Always burns easily; tans minimally (sensitive).

(3) Burns moderately; tans gradually (light brown) (normal).

(4) Burns minimally; always tans well (moderate brown) (normal).

(5) Rarely burns; tans profusely (dark brown) (insensitive).

(6) Never burns; deeply pigmented (insensitive).

(ii) Skin type is based on first 30 to 45 minutes of sun exposure after a winter season of no sun exposure. Determine that each subject is not taking topical or systemic medication that is known to alter responses to UV radiation. Determine that each subject has no history of sensitivities to topical products and/or abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(3) Physical examination. Conduct a physical examination to determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. A suitable source of low power UVA, such as a Woods lamp, is helpful in this process. If any of these conditions are present, the subject is not qualified to participate in the study. The presence of nevi, blemishes, or moles will be acceptable if, in the physician's judgment, they will neither compromise the study nor jeopardize a subject's safety. Subjects with dysplastic nevi should not be enrolled. Excess hair on the back is acceptable if the hair is clipped. Shaving is unacceptable because it may remove a significant portion of the stratum corneum and temporarily alter the skin's response to UV radiation.

(4) Informed consent. Obtain legally effective written informed consent from all test subjects.

(d) Sunscreen application.

(1) Test site. Test sites are locations on each subject's back, between the beltline and the shoulder blades (scapulae) and lateral to the midline, where skin responses to UV radiation are determined. Responses on unprotected skin (no test material applied) and protected skin (sunscreen test product(s) or SPF standard applied) are determined at separate unprotected and protected test sites, respectively. Test sites should be randomly located in a blinded manner. Each test site should be a minimum of 30 square centimeters and outlined with indelible ink.

(2) Test subsite. Test subsites are the locations to which UV radiation is administered within a test site. At least five test subsites should receive UV doses within each test site. Test subsites should be at least 0.5 square centimeters (cm^2) in area and should be separated from each other by at least 0.8 cm. Each test subsite should be outlined with indelible ink.

(3) Applying test materials. Apply the sunscreen test product and the SPF standard at 2 milligrams per square centimeter (mg/cm^2) to their respective test sites. Use a finger cot compatible with the sunscreen to spread the product as evenly as possible.

(4) Waiting period. Wait at least 15 minutes after applying a sunscreen product before exposing the test sites to UV radiation as described in § M020.80(e). For water resistant sunscreen products, proceed with the water resistance testing procedure described in § M020.80(g) after waiting at least 15 minutes.

(e) UV exposure

(1) Definition of minimal erythema dose. The minimal erythema dose (MED is the smallest UV dose that produces perceptible redness of the skin (erythema) with clearly defined borders at 16 to 24 hours after UV exposure. The MED for unprotected skin (MEDu) is determined on a test site that does not have sunscreen applied. The MED for protected skin (MEDp) is determined on a test site that has sunscreen applied. An MEDp is determined for the SPF standard (ssMEDp). An MEDp is determined for the sunscreen test product (tpMEDp).

(2) UV exposure for initial MEDu. For each test subject, administer a series of UV radiation doses expressed as J/m ^{2}-eff (as determined according to § M020.80(a)(2)(ii)) to the test subsites within an unprotected test site using an accurately calibrated solar simulator. Select doses that are a geometric series represented by 1.25^{n} (i.e., each dose is 25 percent greater than the previous dose).

(3) UV exposure for final MEDu, ssMEDp, and tpMEDp. For each subject, determine the final MEDu, ssMEDp, and tpMEDp by administering a series of five UV doses to the appropriate test sites. The middle dose (X) in each of these dose series (i.e., the third dose) should equal the initial MEDu times the expected SPF. Note that the expected SPF equals 1 and 16.3 for the final MEDu and ssMEDp, respectively. The remaining UV doses in the series depend upon the expected SPF value of the sunscreen test product(s).

For products with an expected SPF less than 8, administer UV doses that increase by 25 percent with each successive dose (i.e., 0.64X, 0.80X, 1.00X, 1.25X, and 1.56X). For products with an expected SPF from 8 to 15, administer UV doses that increase by 20 percent with each successive dose (i.e., 0.69X, 0.83X, 1.00X, 1.20X, and 1.44X). For products with an expected SPF higher than 15, administer UV doses that increase by 15 percent with each successive dose (i.e., 0.76X, 0.87X, 1.00X, 1.15X, and 1.32X).

(4) Evaluation of test subsites. In order that the person who evaluates the test subsites is not biased, he/she should not be the same person who applied the sunscreen drug product to the test site or administered the UV doses. After UV doses are administered, all immediate responses should be recorded. These may include an immediate darkening or tanning, typically grayish or purplish in color, which fades in 30 to 60 minutes; an immediate reddening at the subsite, due to heating of the skin, which fades rapidly; and an immediate generalized heat response, spreading beyond the subsite, which fades in 30 to 60 minutes. After the immediate responses are noted, each subject should shield the exposed area from further UV radiation until the MED is determined. Determine the MED 16 to 24 hours after UV exposure. Because erythema is evaluated 16 to 24 hours after UV exposure, the final MEDu, ssMEDp, and tpMEDp are typically determined the day following determination of the initial MEDu. Evaluate the erythema responses of each test subsite using either tungsten or warm white fluorescent lighting that provides at least 450 lux of illumination at the test site. For the evaluation, the test subject should be in the same position as when the test site was irradiated.

(5) Invalid test data. Reject test data for a test subject if erythema is not present on either the unprotected or protected test sites; or erythema is present at all subsites; or the responses are inconsistent with the series of UV doses administered; or the subject was noncompliant (e.g., the subject withdraws from the test due to illness or work conflicts or does not shield the exposed testing sites from further UV radiation until the MED is determined).

(f) Determination of SPF.

(1) Calculate an SPF value for each test subject (SPFi) as follows:

$$\text{SPFi} = \frac{\text{MEDp}}{\text{MEDu}}$$

(2) Calculate the mean:

$$\text{SPF} = \left(\overline{SPF}\right)$$

and the standard deviation (s) from the SPFi values. Calculate the standard error (SE), which equals s/√n (where n equals the number of subjects who provided valid test results). Obtain the t value from Student's t distribution table corresponding to the upper 5-percent point with n-1 degrees of freedom. Determine the labeled SPF value, which equals the largest whole number less than:

$$\overline{\text{SPF}} - (\text{t} * \text{SE})$$

In order for the SPF determination of a test product to be considered valid, the SPF value of the SPF standard should fall within the standard deviation range of the expected SPF (i.e., 16.3 ± 3.43).

(g) Determination of water resistance.

The following procedure should be performed in an indoor fresh water pool, whirlpool, and/or hot tub maintained at 23 to 32 °C. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity should be recorded.

(1) Water resistance (40 minutes). The labeled SPF should be determined after 40 minutes of water immersion using the following procedure:

(i) Step 1: Apply the sunscreen as described in § M020.80(d).

(ii) Step 2: Perform moderate activity in water for 20 minutes.

(iii) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(iv) Step 4: Perform moderate activity in water for 20 minutes.

(v) Step 5: Allow test sites to dry completely without toweling.

(vi) Step 6: Apply the SPF standard as described in § M020.80(d).

(vii) Step 7. Expose test sites to UV doses as described in § M020.80(e).

(2) Water resistance (80 minutes). The labeled SPF should be determined after 80 minutes of water immersion using the following procedure:

(i) Step 1: Apply the sunscreen as described in § M020.80(d).

(ii) Step 2: Perform moderate activity in water for 20 minutes.

(iii) Step 3: Rest out of water for 15 minutes. Do not towel test site(s).

(iv) Step 4: Perform moderate activity in water for 20 minutes.

(v) Step 5: Rest out of water for 15 minutes. Do not towel test site(s).

(vi) Step 6: Perform moderate activity in water for 20 minutes.

(vii) Step 7: Rest out of water for 15 minutes. Do not towel test site(s).

(viii) Step 8: Perform moderate activity in water for 20 minutes.

(ix) Step 9: Allow test sites to dry completely without toweling.

(x) Step 10: Apply the SPF standard as described in § M020.80(d).

(xi) Step 11: Expose test sites to UV doses as described in § M020.80(e).

§ M020.90 Broad spectrum test procedure

(a) UV Spectrometry.

(1) Plate. Use optical-grade polymethylmethacrylate (PMMA) plates suitable for UV transmittance measurements. The plate should be roughened on one side to a three dimensional surface topography measure (Sa) between 2 and 7 micrometers and must have a rectangular application area of at least 16 square centimeters (with no side shorter than 4 cm).

(2) Sample holder. The sample holder should hold the PMMA plate in a horizontal position to avoid flowing of the sunscreen drug product from one edge of the PMMA plate to the other. It should be mounted as close as possible to the input optics of the spectrometer to maximize capture of forward scattered radiation. The sample holder should be a thin, flat plate with a suitable aperture through which UV radiation can pass. The PMMA plate should be placed on the upper surface of the sample holder with the roughened side facing up.

(3) Light source. The light source should produce a continuous spectral distribution of UV radiation from 290 to 400 nanometers.

(4) Input optics. Unless the spectrometer is equipped with an integrating sphere, an ultraviolet radiation diffuser should be placed between the sample and the input optics of the spectrometer. The diffuser will be constructed from any UV radiation transparent material (e.g., Teflon ® or quartz). The diffuser ensures that the radiation received by the spectrometer is not collimated. The spectrometer input slits should be set to provide a bandwidth that is less than or equal to 1 nanometer.

(5) Dynamic range of the spectrometer. The dynamic range of the spectrometer should be sufficient to measure transmittance accurately through a highly absorbing sunscreen product at all terrestrial solar UV wavelengths (290 to 400 nm).

(b) Sunscreen product application to PMMA plate. The accuracy of the test depends upon the application of a precisely controlled amount of sunscreen product with a uniform distribution over the PMMA plate. The product is applied at 0.75 mg per square centimeter to the roughened side of the PMMA plate. The sunscreen product should be applied in a series of small dots over the entire PMMA plate and then spread evenly using a gloved finger. Spreading should be done with a very light spreading action for approximately 30 seconds followed by spreading with greater pressure for approximately 30 seconds. The plate should then be allowed to equilibrate for 15 minutes in the dark before the pre-irradiation described in § M020.90(c).

(c) Sunscreen product pre-irradiation. To account for lack of photostability, apply the sunscreen product to the PMMA plate as described in § M020.90(b) and then irradiate with a solar simulator described in § M020.80(a). The irradiation dose should be 4 MEDs which is equivalent to an erythemal effective dose of 800 J/m^2 (i.e., 800 J/m^2-eff).

(d) Calculation of mean transmittance values. After pre-irradiation described in § M020.90(c), mean transmittance values should be determined for each wavelength λ over the full UV spectrum (290 to 400 nanometers). The transmittance values should be measured at 1 nanometer intervals. Measurements of spectral irradiance transmitted for each wavelength λ through control PMMA plates coated with 15 microliters of glycerin (no sunscreen product) should be obtained from at least 5 different locations on the PMMA plate [C1(λ), C2(λ), C3(λ), C4(λ), and C5(λ)]. In addition, a minimum of 5 measurements of spectral irradiance transmitted for each wavelength λ through the PMMA plate covered with the sunscreen product will be similarly obtained after pre-irradiation of the sunscreen product [P1(λ), P2(λ), P3(λ), P4(λ), and P5(λ)].

The mean transmittance for each wavelength,

$$\overline{T(\lambda)}$$

is the ratio of the mean of the C(λ) values to the mean of the P(λ) values, as follows:

$$\overline{T(\lambda)} = \frac{\sum_1^n P(\lambda)/n}{\sum_1^n C(\lambda)/n}$$

Where n ≥5

(e) Calculation of mean absorbance values.

(1) Mean transmittance values,

$$\overline{T(\lambda)}$$

are converted into mean absorbance values,

$$\overline{A(\lambda)}$$

at each wavelength by taking the negative logarithm of the mean transmittance value as follows:

$$\overline{A(\lambda)} = -\log\overline{T(\lambda)}$$

(2) The calculation yields 111 monochromatic absorbance values in 1 nanometer increments from 290 to 400 nanometers.

(f) Number of plates. For each sunscreen product, mean absorbance values should be determined from at least three individual PMMA plates. Because § M020.90(d) requires at least 5 measurements per plate, there should be a total of at least 15 measurements.

(g) Calculation of the critical wavelength. The critical wavelength is identified as the wavelength at which the integral of the spectral absorbance curve reaches 90 percent of the integral over the UV spectrum from 290 to 400 nm. The following equation defines the critical wavelength:

$$\int_{290}^{\lambda c} A(\lambda)d\lambda = 0.9 \int_{290}^{400} A(\lambda)d\lambda$$

Where λc = critical wavelength

$A(\lambda)$ = mean absorbance at each wavelength

$d\lambda$ = wavelength interval between measurements

A mean critical wavelength of 370 nm or greater is classified as broad spectrum protection.

KAREN M. MURRY -S

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Center for Drug Evaluation and Research
December 9, 2025