U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Office of New Drugs

Office of Nonprescription Drugs

Scientific Review Supporting Proposed Administrative Order

December 9, 2025

Order ID:	OTC000039
Order Title:	Amending Over-the-Counter Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use
OTC Monograph:	M020
Active Ingredients:	Bemotrizinol, at concentrations up to 6 percent[1]
Route of Administration:	Topical
Purpose of Review:	Review of Safety and Efficacy

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

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I. Introduction

This scientific review describes the findings and proposals supporting Proposed Administrative Order OTC000039 Amending Over-the-Counter Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use (OTC Monograph M020). OTC Monograph M020 describes the conditions under which OTC sunscreen drug products are generally recognized as safe and effective (GRASE).[2]

In this scientific review, FDA evaluated the safety and efficacy of bemotrizinol as a sunscreen active ingredient to determine whether there are conditions under which a drug product containing bemotrizinol as a sunscreen active ingredient is GRASE.

II. OTC Monograph Order Request

On September 23, 2024, DSM Nutritional Products LLC (DSM) (hereinafter referred to as DSM or Requestor) submitted a Tier 1 OTC monograph order request (OMOR)[3] to add a new active ingredient, bemotrizinol, at concentrations up to 6%, for use as a sunscreen active ingredient in adults and children aged 6 months and older under the conditions described in OTC Monograph M020. DSM requested that a drug product containing bemotrizinol be allowed to be combined with: 1) other sunscreen active ingredients as described in § M020.20 of OTC Monograph M020, and 2) other skin protectant active ingredients as described in § M016.20(e) of OTC Monograph M016: Skin Protectant Drug Products for Over-the-Counter Human Use.[4] DSM also requested that a drug product containing bemotrizinol be allowed to be marketed in the following dosage forms: oil, lotion, cream, gel, butter, paste, ointment, stick, spray, and powder.[5]

Prior to the enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Public Law 116-136, which added section 505G of the FD&C Act, bemotrizinol was one of the eight sunscreen active ingredients that were originally submitted under the "time and extent application" (TEA) procedures established in 21 CFR 330.14 and that was the subject of

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[2] OTC Monograph M020 is set forth in Final Administrative Order OTC000006 available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/.

[3] 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). A Tier 1 OTC monograph order requests means any OTC monograph order request not determined to be a Tier 2 OTC Monograph order request (see section 744L(8) of the FD&C Act). An OTC monograph order request requesting the addition of an active ingredient to an OTC monograph is not categorized as a Tier 2 OTC monograph order request and is therefore a Tier 1 OMOR.

[4] OTC Monograph M016 is set forth in Final Administrative Order OTC000005, available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/.

[5] By operation of section 505G(m)(2) of the FD&C Act, sunscreen drug products under OTC Monograph M020 may be legally marketed in the following dosage forms: oil, lotion, cream, gel, butter, paste, ointment, stick, spray, and powder, without the need for an approved new drug application. See also Proposed Administrative Order OTC000008 Amending Over-the-Counter Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use, at pages 55-56, available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/) (proposing, with the exception of powders, that sunscreens in the following dosage forms -- oil, lotion, cream, gel, butter, paste, ointment, stick, and sprays -- are subject to certain conditions).

proposed orders issued under section 586C of the FD&C Act established by the Sunscreen Innovation Act.[6] On November 13, 2014, FDA issued a proposed order (2014 feedback letter)[7] for bemotrizinol outlining the data needed to support a finding that a drug product containing bemotrizinol as a sunscreen active ingredient is GRASE based on FDA's review of the available safety and efficacy data for bemotrizinol at that time.

DSM had formal meetings with FDA regarding its OTC monograph drug development program for bemotrizinol.[8] FDA's formal meetings with the Requestor and the 2014 feedback letter helped inform the content the Requestor submitted in the OMOR.

In order for FDA to file this OMOR, FDA had to determine if the OMOR: 1) was sufficiently complete and formatted to permit FDA to conduct a substantive review;[9] and 2) included the information set forth in section 505G(b)(6)(C) of the FD&C Act with respect to safe nonprescription marketing and use of bemotrizinol because it is an active ingredient that has not been previously incorporated in a drug marketed in the United States as described under section 505G(b)(6)(B).[10]

For filing purposes, FDA determined that the OMOR was sufficiently complete and formatted to permit FDA to conduct a substantive review. In addition, with respect to safe nonprescription marketing and use of bemotrizinol, FDA conducted a review pursuant to section 505G(b)(6)(C)(ii) of the FD&C Act to determine whether the OMOR contained information sufficient for a prima facie demonstration that bemotrizinol was: 1) marketed and safely used under comparable conditions of marketing and use in a country listed in section 802(b)(1)(A) of the FD&C Act; 2) marketed in that country for a period sufficient to provide reasonable assurances concerning the safe nonprescription use of the drug; and 3) during such time was subject to sufficient monitoring by a regulatory body considered acceptable for such monitoring purposes, including for adverse events associated with nonprescription use of the drug.[11] The Requestor submitted marketing information for sunscreen products containing bemotrizinol from

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[6] See the Regulation Policy Information for the Sunscreen Innovation Act available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/regulatory-policy-information-sunscreen-innovation-act.

[7] See Determination and Feedback Letter from FDA/Center for Drug Evaluation and Research (CDER) to Ciba Specialty Chemicals Corporation (Ciba) (Morgan, Lewis & Bockius LLP) re Time and Extent Application (TEA) Bemotrizinol for Use in Over-the-Counter (OTC) Sunscreen available at https://www.regulations.gov/docket/FDA-2005-N-0453/document. This letter was later deemed to be a proposed sunscreen order after the enactment of the Sunscreen Innovation Act.

[8] 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.

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

[10] See section 505G(b)(6) of the FD&C Act. Information regarding safe nonprescription marketing and use as a condition for filing a generally recognized as safe and effective request applies to a drug described in section 505G(b)(6)(B). Section 505G(b)(6)(B) describes such a drug as a nonprescription drug which contains an active ingredient not previously incorporated in a drug—''(i) specified in subsection (a)(1), (a)(2), or (a)(3); ''(ii) subject to a final order under this section; or "(iii) subject to a final sunscreen order (as defined in section 586(2)(A))."

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

Europe, Asia Pacific, Latin America, Middle East & Africa, Australia, and Canada. However, most jurisdictions regulate sunscreens as a cosmetic, whereas in the United States sunscreens are regulated as drugs. The Requestor also submitted data to establish the length and breadth of sales of bemotrizinol around the world. Sunscreen products containing bemotrizinol are marketed on all continents except for Antarctica and have been marketed in some jurisdictions for at least 20 years. Aggregate sales data indicate sales in millions of units sold.

FDA considered the information provided for Australia and Canada, as those two nations were the only two that met the conditions of 505G(b)(6)(C)(ii) of the FD&C Act. Australia and Canada are countries listed in section 802(b)(1)(A) of the FD&C Act and regulate sunscreens, including those containing bemotrizinol, as nonprescription drug products, demonstrating comparable conditions of marketing including safety monitoring. The data submitted by the Requestor demonstrates that sunscreen products containing bemotrizinol have been marketed for a sufficient period of time to provide reasonable assurance of safe nonprescription use and sufficient monitoring by a regulatory body.

FDA determined that the OMOR provided information to meet the conditions set forth in section 505G(b)(6)(C) of the FD&C Act. For these reasons, on December 4, 2024, FDA filed the OMOR.

On May 19, 2025, the Requestor submitted a major amendment to provide two new clinical efficacy studies (see Section III.A Human Clinical Efficacy Studies).[12]

III. Scientific Review

Bemotrizinol, or bis-ethylhexyloxyphenol methoxyphenyl triazine, is an organic ultraviolet (UV) filter. Bemotrizinol exhibits high photostability and broad-spectrum coverage across UVB (280-320 nm) and UVA (320-400 nm) ranges. Bemotrizinol is stable when exposed to UV light, unlike many UV filters which degrade under continuous exposure. Bemotrizinol is known to stabilize avobenzone [13] enhancing its photostability and ensuring more reliable and prolonged UVA protection in sunscreen formulations.[14]

Bemotrizinol has a molecular weight of 627.81 g/mol and a chemical formula of $C_{38}H_{49}N_3O_5$. Bemotrizinol is insoluble in polar solvents and is marketed by at least one manufacturer as a mixture with inactive ingredients to enhance solubility in final formulations.

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[12] The CARES Act also added section 744M to the FD&C Act 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 OMUFA commitment letter, specifies FDA and industry mutually agreed-upon timelines for various OTC monograph drug activities. 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 2021–2025. That document can be accessed at https://www.fda.gov/media/146283/download. For information on major amendments to an OMOR, see Section II.F.4 of the OMUFA commitment letter.

[13] Avobenzone is a sunscreen active ingredient in § M020.10 of OTC Monograph M020.

[14] Chatelain, E., & Gabard, B. (2001). Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a new UV broadband filter. *Photochem Photobiol*, *74*(3), 401-406.

To date, 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 for marketing in the United States and bemotrizinol is not an active ingredient currently permitted under any OTC monograph.[15]

FDA conducted a scientific review of the data on the safety and efficacy of bemotrizinol submitted in the OMOR which included human clinical and nonclinical studies and related information. In addition, FDA conducted a scientific review of data pertaining to various conditions of use of bemotrizinol with respect to its inclusion in OTC Monograph M020.

A. Human Clinical Efficacy Studies

To demonstrate efficacy of a sunscreen active ingredient, FDA generally expects two independent, adequate, well-controlled studies that follow the testing method described in § M020.80 of OTC Monograph M020 and demonstrate that the active ingredient has a sun protection factor (SPF) of not less than 2. The Requestor submitted a total of four human clinical efficacy studies evaluating SPF (Table 2). The Requestor initially submitted two human clinical efficacy studies in the OMOR. However, upon review, FDA determined that neither of the two studies were conducted consistent with the testing method in § M020.80 of OTC monograph M020. In addition, the two originally submitted studies utilized two different protocols and as such, the results were not comparable. Therefore, FDA recommended the Requestor conduct two studies utilizing the same protocol and the testing method outlined in § M020.80 of OTC Monograph M020. Subsequently, the Requestor submitted two new human clinical efficacy studies, constituting a major amendment to the OMOR.[16]

[15] 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(b); or 3) subject to a final sunscreen order (as defined in section 586(2)(A) of the FD&C Act).

[16] See section II.F.4 of the OMUFA commitment letter. The document can be accessed at https://www.fda.gov/media/106407/download.

Section M020.80 of OTC Monograph M020 includes testing to support SPF claims. Sunscreen efficacy is evaluated by the measurement of SPF at concentrations of the active ingredient, in a suitable formulation, below the maximum requested concentration which, for bemotrizinol is 6 percent. SPF is a measurement of absorption in the UVB (280-320 nm) range. The formulations studied must provide a SPF of at least 2 as defined in § M020.10 of OTC Monograph M020.

The broad spectrum test is not used to determine efficacy of active ingredients for two reasons; first, not all sunscreen active ingredients absorb in the UVA portion (320-400 nm) of the UV spectrum which is the portion of the spectrum evaluated in the broad spectrum test. Second, broad spectrum is currently a pass/fail test related to the final formulated drug product (often containing more than one active ingredient) where any absorption by an active ingredient at 370 nm is considered a pass of the test. It does not indicate that the ingredient provides protection in the UVB range (SPF).

1. SPF Study

FDA reviewed the two new efficacy studies submitted by the Requestor in the major amendment: BE_HP-25-0307a and BE_HP-25-0307b and determined that the protocols were consistent with § M020.80 of OTC Monograph M020.

In brief, 45 cm^2 test sites for the unprotected control, SPF reference standard, and 6 test products (two market image formulations of bemotrizinol each at concentrations of 0, 1.5% and 3%) were located on the study participant's back. Each test site was outlined in indelible ink and contained 5 exposure subsites of 0.64 cm^2. Test sites and subsites were separated from one another by a minimum distance of 1 cm and 0.8 cm, respectively. A product amount of 2.00±0.05 mg/cm^2 was applied as measured by weigh-back procedures. An initial (i.e., preliminary) unprotected minimal erythema dose was determined one day before the test exposures to define the UV exposure doses for each test site.

The UV exposure series consisted of 5 UV doses. The middle dose of each series corresponded to the initial unprotected minimal erythema dose of the study subject multiplied by the expected SPF of the test or reference product. The remaining doses in each UV series were calculated using a geometric dose progression based on the expected SPF value of the sunscreen test product. The protocol states that all test products in the present studies had an expected SPF of less than eight. Thus, the geometric dosing increment for all series administered to evaluate the test products was 25%. Because the SPF reference standard has an expected SPF of 16.3, the protocol states that the dosing increment for the standard was 15%. Lastly, the protocol states that all unprotected minimal erythema dose exposures for the test day were conducted using a 25% geometric dose progression. Following UV exposure, immediate skin responses (i.e., immediate darkening or reddening or any heat response extending beyond the subsite) were observed and recorded for each study subject.

A total of 12 healthy adult subjects were enrolled in each of two replicative SPF studies. The studies demonstrated that all test product formulations with bemotrizinol (concentrations of 1.5 and 3.0%) had a mean SPF value of greater than 2, and results were comparable between the two independent studies. Summary results for BE_HP-25-0307a and BE_HP-25-0307b are presented in Table 1. Both series of formulations showed a concentration-related increase in SPF. In addition, the mean SPF of the SPF reference standard was reported to be within the standard deviation range of the expected SPF (i.e., 16.3 ± 3.43).

Table 1. Mean SPF Values and SD for Each BEMT Test Product and the SPF Standard Evaluated in the BE_HP-25-0307a and BE_HP-25-0307b Clinical Efficacy Studies

Formulation Type	Sample Code	BEMT wt %	Expected In Silico SPF	In Vivo SPF Test Results (Mean SPF ±SD)
Oil-in-Water	476	0.0	1.0	1.0 ± 0.2
	347	1.5	4.1	4.3 ± 1.0
	104	3.0	7.1	7.2 ± 1.5
Oil	176	0.0	1.0	1.1 ± 0.1
	041	1.5	4.1	3.9 ± 0.8
	237	3.0	7.1	5.0 ± 1.3
SPF Standard*		0.0	16.3	15.0 ± 2.41 (Oil-in-Water SPF Tests) 15.6 ± 1.95 (Oil SPF Tests)

*SPF testing was conducted in batches according to the formulation type. As such, the SPF standard was measured and reported separately for each testing batch.
Abbreviations: BEMT = bemotrizinol; SPF = sun protection factor; wt = weight

2. Proposal Based on Clinical Efficacy Studies

The two SPF efficacy studies demonstrated that all test product formulations with bemotrizinol (concentrations of 1.5 and 3.0%) had a mean SPF value of greater than 2, with an expected increase with increased dosage of bemotrizinol. Therefore, FDA tentatively proposes that bemotrizinol meets the efficacy requirement for a sunscreen active ingredient as defined in § M020.10 of OTC Monograph M020.

B. Nonclinical Safety Studies and Information

FDA conducted a review of the nonclinical studies and information submitted by the Requestor on the safety of bemotrizinol for use as a sunscreen active ingredient in a drug product.

FDA has provided the public with a general outline of nonclinical data that may be necessary to support a determination that a sunscreen drug product is GRASE: [17]

Nonclinical (toxicology) data:

- Dermal carcinogenicity
- Systemic carcinogenicity
- Developmental and reproductive toxicity (DART)

[17] See the proposed rule entitled "Sunscreen Drug Products for Over-the-Counter Human Use, 84 FR 6204 (February 26, 2019). See also Proposed Administrative Order OTC000008. FDA issued this proposed order to amend and revise the final administrative order, Over-the-Counter Monograph M020: Sunscreen Drug Products for Over-the-Counter Human Use, as deemed by sections 505G(b)(8) and 505G(k)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h(b)(8) and 355h(k)(2)(B)) (Deemed Final Order). This proposed order, if finalized, would replace the Deemed Final Order in its entirety with new conditions under which nonprescription sunscreen drug products would be determined to be GRASE under the FD&C Act. Among other things, it also sets forth certain characteristics that would establish that a sunscreen drug product is not GRASE. See also FDA guidance for industry *Nonprescription Sunscreen Drug Products—Safety and Effectiveness Data* (November 2016).

- Toxicokinetics
- Additional testing when data suggest a concern about other long-term effects, such as endocrine effects

The Requestor submitted the following pivotal nonclinical assessments in the OMOR. See additional information related to drug substances impurities under Section III. D. 2.

1. Carcinogenicity Assessment

In a 2-year dermal carcinogenicity study, rats received topical doses up to 1000 mg/kg/day bemotrizinol in polyethylene glycol (PEG) 400. High dose selection was based on maximum feasible dose (MFD). No statistically significant dose-dependent neoplastic findings were observed.

A carcinogenicity study in a second rodent species was not submitted and not recommended. See Section III.B.4. Conclusions for more information.

2. Developmental and Reproductive Toxicity Assessments

A sufficient battery of DART studies using a limit dose[18] were submitted to support the safety of bemotrizinol. In a fertility and early embryonic development (fertility) study, male and female rats received doses up to 1000 mg/kg/day bemotrizinol by oral gavage. No test article-related effects were observed.

In an embryofetal development (EFD) study in rats, female animals received doses up to 1000 mg/kg/day bemotrizinol by oral gavage. No test article-related effects were observed.

In an EFD study in rabbits, female animals received doses up to 1000 mg/kg/day bemotrizinol by oral stomach tube. No test article-related effects were observed.

In a pre- and postnatal development (PPND) study, female rats received doses up to 1000 mg/kg/day bemotrizinol by oral gavage. There were no test article-related effects on the reproductive parameters of F0 dams, or the viability and development of F1 and F2 offspring.

In summary, the No Observed Adverse Effect Level (NOAEL) in all pivotal nonclinical assessments was the high dose.

[18] Recommended in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021).

3. Considerations To Minimize Nonclinical Animal Testing

FDA aims to minimize the burden of nonclinical data on Requestors for eligible ingredients reviewed in OMORs and strives to implement the ICH-recommended 3Rs principles (Replace, Reduce, Refine) in pharmaceutical development to minimize animal testing and improve animal welfare. These principles were utilized in FDA's review of this OMOR.

The following data, which are typically recommended for new molecular entities intended for chronic use, were not submitted by the Requestor and are not recommended considering the overall submission, including the pivotal carcinogenicity and DART studies previously described, the maximal usage trial (MUsT) data, and previous human experience:

- A 2-year oral (systemic) carcinogenicity study in a second rodent species is not recommended because the clinical pharmacology review indicated that an adequately conducted human pharmacokinetic MUsT program resulted in a steady state blood level of less than 0.5 ng/mL bemotrizinol,[19] and the sufficient nonclinical toxicology data did not reveal any other safety signals for the ingredient or any relevant structurally similar compound indicating the potential for adverse effects.
- Limited toxicokinetic data in rats or rabbits was submitted, and it was insufficient to enable an exposure margin calculation. Based on the nonclinical data submitted, however, an exposure margin is not recommended to support a safety determination for bemotrizinol because there were no notable adverse test article related findings in pivotal tests, and doses in the pivotal studies were sufficient. Specifically, high dose selections in DART studies were based on limit doses recognized internationally by ICH, as described above. Further, the dermal carcinogenicity study utilized the MFD, meaning that studies with higher doses are not feasible. Considering that higher doses are not recommended or feasible for the pivotal studies in the nonclinical program, and no adverse findings were identified, exposure margins are not essential to support safety for bemotrizinol, from the nonclinical perspective.

[19] 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 page 22)

- FDA has long recognized the extensive previous human experience with bemotrizinol that was considered as part of the eligibility criteria for this OMOR[20]. In contrast to nonclinical data recommended for a chronic-use cutaneous drug product reviewed under a new drug application (NDA), which include comprehensive nonclinical pharmacology and toxicology safety testing, the approach to nonclinical safety testing for sunscreen drug products under OTC Monograph M020 "largely focuses on potential long-term adverse effects or effects not otherwise readily detected from human use (i.e., carcinogenicity and reproductive toxicity)"[21].
- A comprehensive chronic general toxicity assessment was considered by FDA during the review of the TEA for bemotrizinol[22], and FDA made the determination not to recommend a comprehensive chronic general toxicity assessment for certain sunscreen active ingredients with extensive human use.[23]
- Fertility and PPND studies were submitted and reviewed but were not recommended because the clinical pharmacology review indicated that an adequately conducted human pharmacokinetic MUsT program resulted in a steady state blood level of less than 0.5 ng/mL BEMT, and the sufficient nonclinical toxicology data did not reveal any other safety signals for the ingredient or any relevant structurally similar compound indicating the potential for adverse effects. See Section III.B.4. for more information.
- Regarding nonclinical data to support use in the pediatric population, no additional nonclinical studies were submitted or recommended based on the totality of the clinical and nonclinical data reviewed as part of this application.[24] See Section II.

[20] 70 FR 232 at 72449.

[21] This principle is outlined in the guidance for industry *Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data* (November 2016).

[22] In 2006, a TEA, as defined in 21 CFR 330.14, was submitted to FDA to evaluate bemotrizinol for inclusion in the OTC sunscreen monograph. The data submitted by the Requestor was for lots of bemotrizinol that were generated for nonclinical studies used to support the TEA. FDA's response to the TEA can be found at: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/regulatory-policy-information-sunscreen-innovation-act.

[23] See footnote 17.

[24] Considerations for additional pediatric studies are described in the guidance for industry *Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data* (November 2016).

4. Proposal Based on Nonclinical Safety Data

Based on sufficient nonclinical carcinogenicity, and DART assessments, the nonclinical data do not demonstrate concerns about the safety of bemotrizinol when used as an active ingredient in a topically applied sunscreen drug product.

A second rodent study evaluating systemic carcinogenicity, and fertility and PPND studies are not recommended for bemotrizinol for several reasons, including the fact that 1) no nonclinical findings of concern were identified in the dermal carcinogenicity assessment or the embryofetal development studies, and 2) the clinical pharmacology review determined that there are no human metabolites of concern and that the systemic absorption of bemotrizinol is limited. The Requestor, however, submitted fertility and PPND studies which were reviewed and determined to be negative. These results provide additional reassurance of safety.

C. Human Clinical Safety Studies and Information

FDA conducted a review of the safety data from human clinical studies evaluating bemotrizinol submitted by the Requestor (Table 2). The Requestor submitted a MUsT study to establish the degree to which bemotrizinol is absorbed through the skin, which could potentially lead to systemic effects. Additionally, the Requestor submitted three dermal safety studies including: 1) a repeated insult patch test (HRIPT) and cumulative irritation patch test; 2) a photo-allergenicity test; and 3) a phototoxicity test. FDA also evaluated postmarketing safety reports.

All the clinical trials were conducted in healthy adult subjects. As sunscreen drug products are intended for use in healthy people and contain the warning “Do not use on damaged or broken skin”, no studies were requested or conducted in persons with skin disease. The four clinical 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 three-week time period to an exposure of over 70% of the body for four days in the MUsT (BEMT-001).

Table 2. Human Clinical Safety Studies

Study Identity	Study Identifier Number	Study Design	Regimen/Schedule/Route	Treatment Duration and Follow Up	Number of Participants Enrolled and Participant Age	Number of Centers and Location
Studies to Support Safety						
Pharmacokinetic Study						
Maximal Usage Trial (MUsT) Part I Pilot Study	BEMT-001 Part I	Pilot PK phase 1 open-label study of plasma BEMT from one BEMT 6% formulation	2.0 mg (0.12 mg BEMT) weighed amounts at 2.0 mg/cm2 skin 75% body surface area dosed	4 days; 4 times/day (0, 2, 4, 6h)	14 healthy adult subjects 18-75 years	Single center West Bend, Wisconsin USA
Maximal Usage Trial (MUsT) Part II Pivotal Study	BEMT-001 Part II	3-arm study of plasma BEMT from three different BEMT 6% formulations	2.0 mg (0.12 mg BEMT) weighed amounts at 2.0 mg/cm2 skin 75% body surface area dosed	4 days; 4 times/day (0, 2, 4, 6h)	162 healthy adult subjects; 54 per arm 21-82 years	Single center West Bend, Wisconsin USA
Dermal Safety Studies						
Repeated Insult Patch Test (HRIPT)	CRLNJ 2020-0493	Skin contact allergy after repeated dosing	0.2 g each patch at BEMT 6% in oil, vehicle oil formulation, BEMT 6% in petrolatum, vehicle petrolatum, & 0.9% saline control	Induction: 9 applications at 24-48h intervals over 3 weeks. 14 days' rest. Challenge: one 24-hr application, site graded at 24, 48, 72, 96h	190 healthy adult subjects (185 completed) 18-74 years	Single center Piscataway, New Jersey USA
Cumulative Irritation Patch Test	CRLNJ 2020-0493	Cumulative skin irritation study	0.2 g each patch at BEMT 6% in oil, vehicle oil formulation, BEMT 6% in petrolatum, vehicle petrolatum, 0.9% saline control, 0.1% SLS control, & empty patch	21 daily applications; sites graded at patch removal	34 healthy adult subjects (30 completed) 22-74 years	Single center Piscataway, New Jersey USA

Study Identity	Study Identifier Number	Study Design	Regimen/Schedule/Route	Treatment Duration and Follow Up	Number of Participants Enrolled and Participant Age	Number of Centers and Location
Phototoxicity Test	CRLNJ 2020-0494	UV irradiation induced skin toxicity, irritation*	0.15 g each patch at BEMT 6% in oil, vehicle oil formulation, BEMT 6% in petrolatum, and vehicle petrolatum	1 application each to left & right of spine for 24h. Patches removed then UVB at 0.5 MED then 5 J/cm2 UVA	34 healthy adult subjects (34 completed) 21-71 years	Single center Piscataway, New Jersey USA
Photo Allergenicity Test	CRLNJ 2020-0495	UV irradiation induced skin contact allergy after repeated dosing*	0.15 g each patch at BEMT 6% in oil, vehicle oil formulation, and BEMT 6% in petrolatum	Induction: 6 2x-weekly exposures; 10-21 days' rest Challenge: 24-hr application to untreated skin then UVA 10 J/cm2	50 healthy adult subjects (48 completed) 21-72 years	Single center Piscataway, New Jersey USA
Studies to Support Efficacy						
Sun Protection Factor/ Sunburn Prevention**	BE-H-22-0683P	UV exposure study based on each subject's minimal erythema dose	Oil at 0.0, 1.0, or 3.0 wt% BEMT and Oil-in water at 0.0, 1.5, 3.0, or 4.5 wt% BEMT; Reference control mixture. 2.0 mg product/cm^2 spread by fingercot on 40 cm^2	Minimal erythema dose determined 16-24 hours after UV irradiation	13 healthy adult subjects 18-70 years	Single center Holzminden, Germany
Sun Protection Factor/ Sunburn Prevention**	DSM PC 2022-0231	UV exposure study based on each subject's minimal erythema dose	Oil at 0.0, 1.0, or 3.0 wt% BEMT and Oil-in water at 0.0, 1.5, 3.0, or 4.5 wt% BEMT; Reference control mixture. 2.0 mg product/cm^2 spread by fingercot on 40 cm^2	Minimal erythema dose determined 16-24 hours after UV irradiation	10 healthy adult subjects 18-70 years	Single center Rockdale, NSW, Australia

Study Identity	Study Identifier Number	Study Design	Regimen/Schedule/Route	Treatment Duration and Follow Up	Number of Participants Enrolled and Participant Age	Number of Centers and Location
Sun Protection Factor/ Sunburn Prevention	BE_HP-25-0307a	UV exposure study based on each subject's minimal erythema dose	Oil and Oil-in water each at 0.0, 1.5, or 3.0, wt% BEMT; Reference control mixture. 2.0 mg product/cm^2 spread by fingercot on 40 cm^2	Minimal erythema dose determined 16-24 hours after UV irradiation	12 healthy adult subjects 18-70 years	Single center Holzminden, Germany
Sun Protection Factor/ Sunburn Prevention	BE_HP-25-0307b	UV exposure study based on each subject's minimal erythema dose	Oil and Oil-in water each at 0.0, 1.5, or 3.0, wt% BEMT; Reference control mixture. 2.0 mg product/cm^2 spread by fingercot on 40 cm^2	Minimal erythema dose determined 16-24 hours after UV irradiation	12 healthy adult subjects; 18-70 years	Single center Holzminden, Germany

*UV source: Xenon Arc Solar Simulator filtered for exposure spectrum.
**These studies were submitted in the original OMOR but were determined to be insufficient to support the efficacy of bemotrizinol. These studies are not discussed in this review.
Abbreviations: BEMT = bemotrizinol; MED = minimal erythema dose; HRIPT = human repeated insult patch test; MUsT = maximal usage trial; No. = number; PK = pharmacokinetic; SLS = sodium lauryl sulfate; USA = United States of America; UV = ultraviolet; UVA = ultraviolet A; UVB = ultraviolet B.

1. Human Dermal Pharmacokinetics (Bioavailability) Study

BEMT-001 was a two-part, open-label, multiple-dose study in healthy adult subjects. BEMT-001 is a MUsT, which FDA views as a standard approach to assess the in vivo bioavailability of topical drug products intended for local therapeutic effects.[25] Part 1 was a single-arm pilot study to explore and evaluate the pharmacokinetics of bemotrizinol following four applications per day for 4 days of one selected topical sunscreen formulation containing 6% of bemotrizinol. Part 2 was a randomized, 3-arm pivotal study to evaluate the pharmacokinetics of bemotrizinol following four applications per day for 4 days of three selected topical sunscreen formulations containing 6% of bemotrizinol.

The objectives of Part 1 (Pilot) were to explore whether bemotrizinol is systemically absorbed under maximal use conditions and to obtain preliminary information to optimize the study design of Part 2 of the study (Pivotal). The objectives of Part 2 were to assess the

[25] 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).

systemic absorption and pharmacokinetics of bemotrizinol from one or more market-image drug product formulations[26] under maximal usage conditions.

The key study design features of BEMT-001 are summarized in Table 3. The dose application timepoints and pharmacokinetic (PK) sampling timepoints are summarized in Table 4.

Table 3. Key Study Design Features of BEMT-001

Study Characteristic	Part 1 Pilot	Part 2 Pivotal
Sample Size	14	162
Treatment arm (s)	1	3
Formulation(s)	BEMT 6% in oil with 10% ethanol (with butyloctyl salicylate)	BEMT 6% Oil BEMT 6% O/W BEMT 6% W/O
Dosing Regimen	4 applications per day (every 2 hours for 6 hours) for 4 days to 75% BSA. The application rate was approximately 2 mg of formulation (0.12 mg of BEMT) per 1 cm^2 of skin surface area Application areas: face except eye area, ears, neck, torso, arms, and legs	
LLOQ of bioanalytical assay	0.5 ng/mL	0.1 ng/mL

Abbreviations: BEMT = bemotrizinol; BSA = body surface area; LLOQ = lower limit of quantification; O/W = oil-in-water; W/O = water-in-oil.

Table 4. Dose Application Timepoints and PK Sampling Timepoints in Study BEMT-001

		PK Sampling Timepoints[a] (h)	
Study Day	Dose Application Timepoints[a] (h)	Part 1 Pilot	Part 2 Pivotal
1	0, 2, 4, 6	Predose, 2, 4, 8, 12	
2	24, 26, 28, 30	23.5, 28, 32	
3	48, 50, 52, 54	47.5, 52, 56	
4	72, 74, 76, 78	71.5, 74, 76, 78, 80, 82, 84, 86	71.5, 74, 75[b], 76, 77[b] 78, 79[b], 80, 82, 84, 86
5	-	-	96
8	-	168	-
12	-	264	-

[a] Hour relative to first dose.
[b] additional sampling timepoints compared to Part 1.
Note: Predose samples were collected within ±30 minutes before the first dose. Samples at 168 h and 264 h were collected within ±4 hours of the nominal time. All other samples were collected within ±5 minutes of the nominal time.
Abbreviations: BEMT = bemotrizinol; PK = pharmacokinetic.

[26] For information on the market-image drug product formulations, see also Section III.D.1 Manufacturing and Dosage Form.

Key inclusion criteria included healthy adults ≥18 years of age and a body mass index of 18.0 to 34.9 kg/m^2, inclusive. Key exclusion criteria included subjects with an active sunburn, broken, irritated, or unhealed skin, known skin or autoimmune disease(s), use of a tanning bed in the previous 4 weeks, use of any product(s) containing bemotrizinol within 14 days before Check-in (Day -1) and at any time before the end of study procedures.

BEMT-001 Part 1 (Pilot Maximal Usage Trial)

A total of 14 healthy adult subjects were enrolled and 13 subjects (92.9%) completed Part 1. One subject discontinued on Day 4 after receiving 12 of the 16 planned doses due to treatment-emergent adverse events of erythema and urticaria. The PK population comprised all 14 subjects.

Of the 299 PK samples analyzed, 13 samples (4.3%) were quantifiable, 9 samples (3.0%) were not reportable due to lack of internal standard reproducibility, and the remainder of samples (92.6%) were below the limit of quantification, <0.5 ng/mL. Of 14 subjects, 7 subjects (50%) had no quantifiable PK samples (Table 5).

The quantifiable samples had concentrations ranging from 0.56 to 2.29 ng/mL, which are 1.12 to 4.58 times higher than 0.5 ng/mL, a safety threshold of steady-state blood concentration for sunscreen active ingredients to help determine the need for additional nonclinical toxicity assessments (Table 5 and Table 6).[27]

After 82 hours of the first dose application, all samples were below the limit of quantification. Based on this finding, the Requestor proposed to shorten the PK sampling duration in Part 2 of the Study to 96 hours, and FDA agreed.

Table 5. Individual Subject Plasma Bemotrizinol Concentrations—Part 1 (Pilot)

	Day 1							Day 3													
						Day 2						Day 4								Day 8	Day 12
	Nominal Time (h)																				
	0	2	4	8	12	23.5	28	32	47.5	52	56	71.5	74	76	78	80	82	84	86	96	168	264
SUBJID	Reported Concentration (ng/mL)																				
1001														2.29	0.74						
1002																					
1003																					
1004				0.74				1.63			0.91			1.08	0.82						
1005			0.67																		
1006																					
1007													0.56				0.58				
1008																					
1009																					
1010							0.61														
1011								1.23													
1012																					
1013															0.74						
1014																					

Note: Blank cell = below the limit of quantification (<0.5 ng/mL); orange shading = no reportable concentration; grey shading = no sample; red font = observed concentration at 2 hours after the fourth (last) daily dose application.

There were only two instances where two consecutive samples had concentrations above the lower limit of quantification (i.e., on Day 4 in Subjects 1001 and 1004), and no subject had more than two consecutive samples above the lower limit of quantification. Due to the sporadic

[27] See the guidance for industry *Nonprescription Sunscreen Drug Products–Safety and Effectiveness Data* (November 2016).

occurrence of concentrations above the lower limit of quantification, a reliable estimation of the PK parameters such as area under the concentration-time curve (AUC) and terminal elimination half-life ($t_{1/2}$) was not possible and/or are deemed not meaningful for this pilot part of the study. While it is challenging to draw a definitive conclusion due to the scarcity of quantifiable samples and the low systemic absorption, the relatively consistent C_{2h} data suggest that there is no significant accumulation of bemotrizinol in plasma with multiple dosing over 4 days.

Table 6. Summary of Bemotrizinol PK Parameters—Part 1 (Pilot)

	C_{2h} (ng/mL)[1]				C_{trough} (ng/mL)[2,3]				C_{max} (ng/mL)			
Statistic	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 1**	**Day 2**	**Day 3**	**Day 4**
n	14	14	14	11	14	13	14	12	14	14	14	13
Mean	0.28	0.42	0.30	0.25	0.25	0.25	0.30	0.25	0.31	0.44	0.30	0.42
SD	0.13	0.44	0.18	0.0	0.0	0.0	0.0	0.0	0.16	0.44	0.18	0.28
Min	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Median	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Max	0.74	1.6	0.91	0.25	0.25	0.25	0.25	0.25	0.74	1.6	0.91	1.1

[1] Concentration at 2 hours after the fourth daily study drug application (i.e., 8, 32, 56 and 80 hours on Days 1 through 4).
[2] Concentration at the end of the daily dosage interval (i.e., 23.5, 47.5, 71.5, and 96 hours on Days 1 through 4).
[3] Concentrations were below the limit of quantification in all subjects.
Note: All postdose concentrations below the limit of quantification (<0.5 ng/mL) were set to one-half of the lower limit of quantification (i.e., 0.25 ng/mL).
Abbreviations: C_{2h} = concentration at 2 hours after the fourth daily study drug application (i.e., 8, 32, 56 and 80 hours on Days 1 through 4); C_{max} = maximum concentration; C_{trough} = concentration at the end of the daily dosage interval (i.e., 23.5, 47.5, 71.5, and 96 hours on Days 1 through 4); PK = pharmacokinetic.

BEMT-001 Part 2 (Pivotal Maximal Usage Trial)

Similar to Part 1, in Part 2, systemic absorption of bemotrizinol was sporadic and low in general. A total of 162 healthy adult subjects were enrolled and all subjects (100%) completed Part 2. Five (3.1%) of the 162 subjects in Part 2 did not have any quantifiable bemotrizinol concentrations in any of their 22 plasma samples. Of the 3722 PK samples analyzed from 162 subjects, 1169 (31.4%) of samples were quantifiable and the remaining 2553 (68.6%) samples had concentrations below the limit of quantification, i.e., <0.1 ng/mL. A greater proportion of the PK samples were quantifiable in Part 2 compared to Part 1, which could be, at least in part, due to the use of a more sensitive bioanalytical assay in Part 2 (i.e., the lower limit of quantification was 0.1 ng/mL in Part 2 compared to 0.5 ng/mL in Part 1).

Most (28.4%) of the quantifiable samples had concentrations between 0.1 and 0.5 ng/mL, and only 3% of the total samples were above 0.5 ng/mL (Table 7). The distribution of PK samples across concentration ranges appeared to be comparable among the three formulations (Table 7).

The number of subjects who had PK samples with bemotrizinol concentrations ≥0.5 ng/mL, the frequency of samples with concentrations ≥0.5 ng/mL, and the number of consecutive samples with concentrations ≥0.5 ng/mL are summarized in Table 8. Of 162 subjects, 68 subjects (42%) had at least one sample with a concentration ≥0.5 ng/mL, with the majority of those subjects with only one sample ≥0.5 ng/mL. Additionally, there were only 3 to 4 occurrences of two consecutive samples having concentrations ≥0.5 ng/mL per treatment group, and only one occurrence of three consecutive samples having concentrations ≥0.5 ng/mL in the bemotrizinol 6% water-in-oil group, suggesting the sporadic nature of systemic absorption of bemotrizinol. The PK profiles of individual subjects, as shown in Figure 1, further corroborate the intermittent nature of bemotrizinol systemic absorption.

Table 7. Summary of PK Sample Distribution Across Concentration Ranges—Part 2 (Pivotal)

	BEMT 6% Oil (Without BOS)		BEMT 6% O/W		BEMT 6% W/O		Total	
	Count	%	Count	%	Count	%	Count	%
Subjects (N)	54	100.0	54	100.0	54	100.0	162	100.0
Samples Analyzed (n)	1240	100.0	1241	100.0	1241	100.0	3722	100.0
Cp <0.1 ng/mL	888	71.6	808	65.1	857	69.1	2553	68.6
Cp ≥0.1 ng/mL	352	28.4	433	34.9	384	30.9	1169	31.4
0.1≤ Cp <0.5 ng/mL	320	25.8	394	31.7	342	27.6	1056	28.4
Cp ≥0.5 ng/mL	32	2.6	39	3.1	42	3.4	113	3.0

Abbreviations: BEMT = bemotrizinol; BOS = butyloctyl salicylate; Cp = plasma concentration; O/W = oil-in-water; PK = pharmacokinetic; W/O = water-in-oil

Table 8. Summary of Frequency of PK Samples With Bemotrizinol Concentrations ≥0.5 ng/mL—Part 2, BEMT-001(Pivotal)

		BEMT 6% Oil (Without BOS) N=54	BEMT 6% O/W N=54	BEMT 6% W/O N=54	Total N=162
Number of samples analyzed		1240	1241	1241	3722
No. of Samples ≥0.5 ng/mL		32	39	42	113
No. of Subjects with concentration ≥0.5 ng/mL (% of the treatment group)		22 (41%)	22 (41%)	24 (44%)	68 (42%)
Frequency of Samples ≥0.5 ng/mL in one subject[1]	1	16	10	12	
	2	3	9	9	
	3	2	2	1	
	4	1	0	1	
	5	0	1	1	
Two Consecutive Concentrations ≥0.5 ng/mL[2]		3 pairs	4 pairs	3 pairs	-
Three Consecutive Concentrations ≥0.5 ng/mL[3]		None	None	1 pair	-

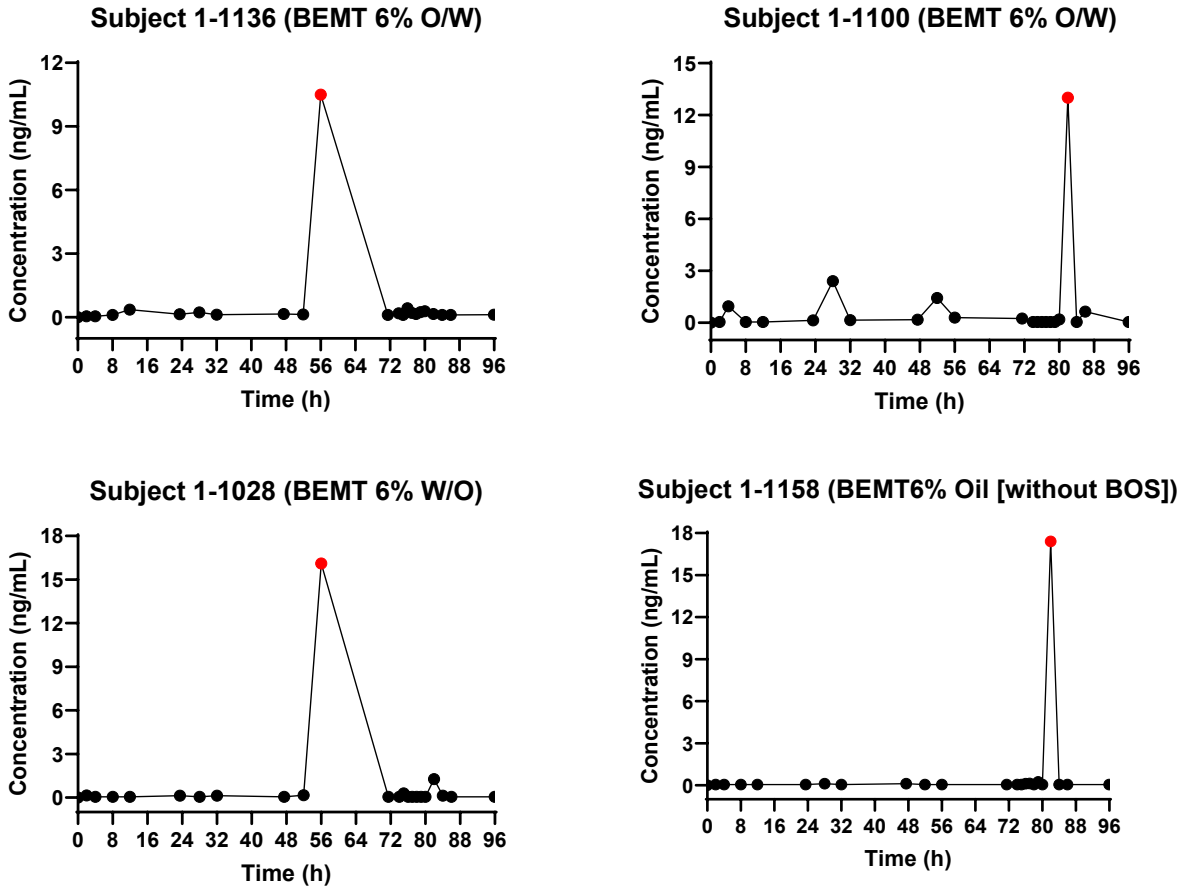
[1] No subject had more than 5 samples ≥0.5 ng/mL.
[2] Each pair was in separate individuals.
[3] There was no occurrence of more than three consecutive samples ≥0.5 ng/mL.
Abbreviations: BEMT = bemotrizinol; BOS = butyloctyl salicylate; O/W = oil-in-water; PK = pharmacokinetic; W/O = water-in-oil.

Among the samples whose concentrations were ≥0.5 ng/mL, there were four samples that were abnormally high (i.e., >5 ng/mL). Those four samples were:

- 10.5 ng/mL at 56 hours for Subject 1-1136 (bemotrizinol 6% oil-in-water)
- 13.0 ng/mL at 82 hours for Subject 1-1100 (bemotrizinol 6% oil-in-water)
- 16.1 ng/mL at 56 hours for Subject 1-1028 (bemotrizinol 6% water-in-oil)
- 17.4 ng/mL at 82 hours for Subject 1-1158 (bemotrizinol 6% oil [without butyloctyl salicylate])

Based on the review of the PK profiles from these four subjects, these abnormally high concentrations appeared to be outliers. There was no clear pattern of such high concentrations in the samples preceding or following these points in the individual PK profiles (Figure 1).

Figure 1. Individual PK Profiles of Potential Outliers—Part 2, BEMT-001



Note 1: Red circle represents a random spike in concentration without a clear pattern in the samples preceding or following the spike.
Note 2: All postdose concentrations below the limit of quantification (0.1 ng/mL) were set to one-half of the lower limit of quantification (i.e., 0.05 ng/mL).
Abbreviations: BEMT = bemotrizinol; BOS = butyloctyl salicylate; O/W = oil-in-water; PK = pharmacokinetic; W/O = water-in-oil.

The mean plasma bemotrizinol concentration over time profiles, with samples whose concentrations were above lower limit of quantification only and with all samples including samples whose concentrations were below the limit of quantification set to one-half of the lower

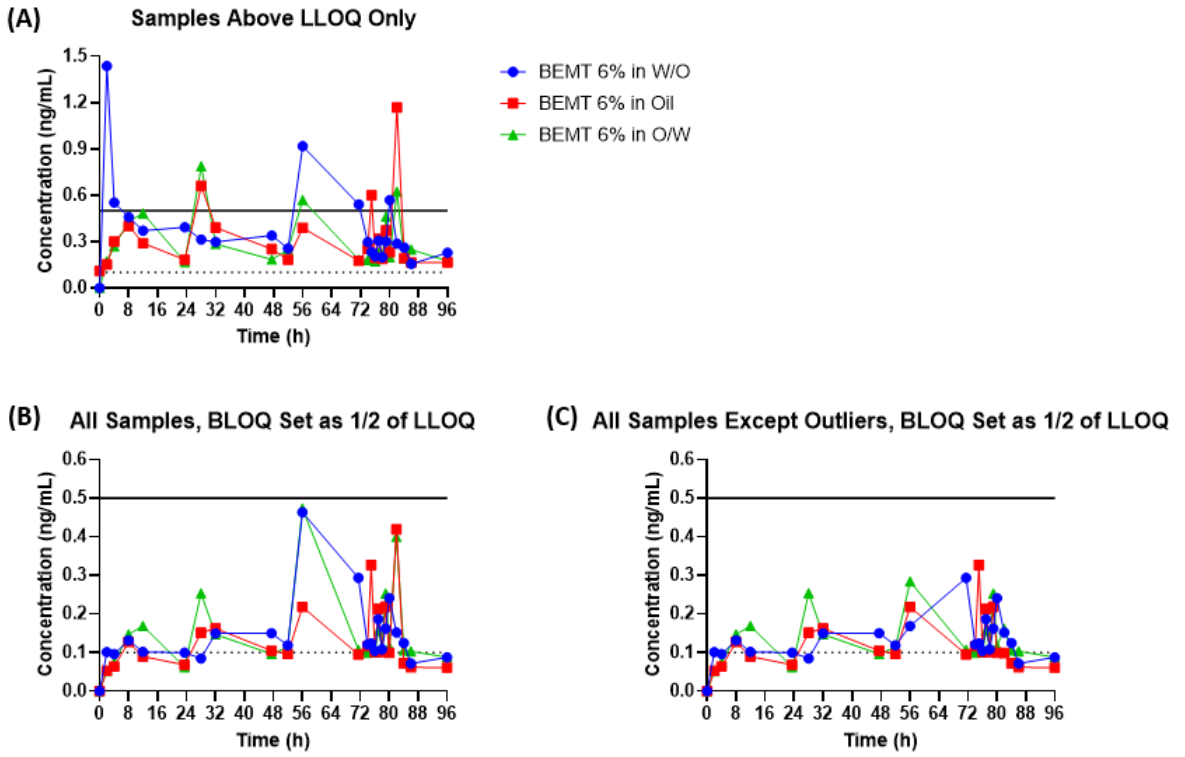
limit of quantification (i.e., 0.05 ng/mL) are shown in Figure 2 (A) and (B), respectively. Figure2 (C) is the same as Figure 2 (B), but without the four concentrations that were abnormally high which appear to be outliers as described above (Figure 1). The number of samples used at each time point to calculate the mean for Figure 2 (A) is shown in Figure 2 (D).

While the mean concentrations calculated from only the quantifiable samples were above the 0.5 ng/mL threshold on a few occasions, the mean concentrations from all subjects (Figure 2 (B) and (C)) remained below 0.5 ng/mL at all times, even with the potential outliers included. There appeared to be no differences in terms of systemic absorption among the three formulations evaluated. In addition, subgroup analyses by sex, age group, race and by treatment group did not show any meaningful differences in terms of systemic exposures (C_{max} and $AUC_{day4,0\text{-}last}$).

The plasma PK parameters of bemotrizinol calculated using all available samples (i.e. samples with concentrations below the limit of quantification were treated as 1/2 of the lower limit of quantification) were highly variable, but suggest that C_{max} and $AUC_{day4,0\text{-}last}$ are very low and that bemotrizinol is at or near steady-state by Day 4.

While one subject in Part 1 of the study withdrew on Day 4 after receiving 12 of the 16 planned doses due to adverse events of erythema and urticaria, there were no discontinuations in Part 2. Adverse events in the study were generally mild, with the most common adverse events being rash, itching, erythema, eye irritation, and conjunctival hyperemia. There were no serious adverse events.

Figure 2. Mean Plasma Bemotrizinol Concentration-Time Profile—Part 2, BEMT-001



(D) Number of Samples with Concentrations Above LLOQ at Each Sampling Timepoint

Time (h)		0	2	4	8	12	23.5	28	32	47.5	52	56	71.5	74	75	76	77	78	79	80	82	84	86	96
n	BEMT 6% in W/O	0	2	5	11	9	10	7	22	19	20	26	27	16	23	19	30	23	26	21	24	20	12	12
	BEMT 6% in Oil	1	2	3	12	9	8	9	18	15	20	27	21	18	27	21	33	21	30	16	18	9	7	7
	BEMT 6% in O/W	0	1	6	14	15	6	15	23	19	18	27	24	22	25	23	32	24	27	25	33	22	15	17

Figure (A): Mean BEMT concentrations of samples with concentrations above the lower limit of quantification (i.e., 0.1 ng/mL).
Figure (B): Mean BEMT concentrations of all samples (54 subjects per treatment arm). Samples with concentrations below the lower limit of quantification were set to one-half of the lower limit of quantification (i.e., 0.05 ng/mL). One pre-dose sample from the BEMT 6% in Oil treatment group whose concentration was 0.11 ng/mL was set to 0 for this mean calculation.
Figure (C): Figure (B) but without the four concentrations that appear to be outliers.
Figure (D): Number of samples with concentrations above the lower limit of quantification at each PK sampling timepoint which was used to calculate the mean in Figure (A).
Note: The solid black line set at 0.5 ng/mL represents the safety threshold value by the FDA which is used to determine the need for additional nonclinical toxicity assessments. The dotted line set at 0.1 ng/mL represents the lower limit of quantification of the bioanalytical assay used to analyze the PK samples.
Abbreviations: BEMT = bemotrizinol; BLOQ = below the limit of quantification; LLOQ = lower limit of the quantification; O/W = oil-in-water; PK = pharmacokinetic; W/O = water-in-oil.

2. Dermal Safety Studies

a. Human Repeat Insult Patch Test and Cumulative Irritation Patch Test

Study CRLNJ 2020-0493 was conducted to determine the potential of 6% bemotrizinol either in a market-image sunscreen oil formulation or as a dispersion in petrolatum to elicit dermal irritation or induce sensitization following repeated patch application.

In the human repeat insult patch test (HRIPT) portion of the study, subjects received 7 different test articles applied under occlusion on their backs during the 3-week induction phase. Test articles were administered three times per week for a total of 9 applications. This was followed 14 days later by a challenge phase in which 6 test articles (no positive control) were applied under occlusion to a naïve site of the back and evaluated for irritation at removal 24 hours later. Additional assessments were performed at 48, 72, and 96 hours. Test materials are shown in Table 9 below. The HRIPT study enrolled a total of 190 healthy subjects (51 male and 139 female), ranging in age from 18 to 74 years; 185 subjects completed the study while 5 were lost to follow up. None of the test materials caused irritancy or induction of sensitization in any of the subjects.

In the cumulative irritation patch test portion of the study, subjects received 21 daily applications of each test formulation, with irritation graded daily on an 8-point scale (score 0 to 7) giving a maximum potential irritation score of 4410 for each ingredient (maximum score of 7 x 21 days x 30 subjects). A total of 34 (15 male and 19 female) subjects, ranging in age from 22 to 74 years, were enrolled; 30 subjects completed the study. Two subjects withdrew from the study for personal reasons and two subjects were lost to follow up. The cumulative irritation study contained two controls, a 0.9% saline low irritant control and a 0.1% sodium lauryl sulfate high irritant control. Test materials are shown in Table 10 below. Of the three bemotrizinol formulations tested, 6% bemotrizinol in petrolatum had the highest cumulative irritation score of 15. The irritation score for the 0.9% saline control was 53 while the irritation score for 0.1% sodium lauryl sulfate was 189, 3.5 times greater and 12.6 times greater than the score for 6% bemotrizinol in petrolatum, respectively. All test formulations and controls were graded by the Requestor as “no evidence of cumulative irritation”, suggesting a failed study, due to failure of the positive controls. However, because both the low and high irritancy controls are shown to cause irritation that exceeds that of the three test formulations, FDA considers the study to be adequate. Therefore, FDA considers the cumulative irritation study sufficient to support that bemotrizinol does not cause dermal irritation with repeat exposure.

No adverse events were reported in either the HRIPT or the cumulative irritation portion of the study.

Table 9. Test Materials, BEMT and Vehicle Formulations, Study DSM RIPT 2020 (CRLNJ2020-0493)

Requestor Identification
Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer
Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT (BEMT replaced by Isopropylmyristate)
Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum
Petrolatum vehicle
Empty Control
0.9% Saline Control
0.1% Sodium Laurel Sulfate

Abbreviations: BEMT = bemotrizinol; DSM = the "Requestor"; RIPT = repeated insult patch test.

Table 10. Test Materials Potential to Elicit Cumulative Irritation, Study DSM RIPT 2020 (CRLNJ2020-0493)

Test Materials	**Cumulative Irritation Score**	**Potential Max Score**	**Percent of Potential Max Score**
Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer	0	4410	0.00
Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT (BEMT replaced by Isopropyl myristate)	7	4410	0.16
Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum	15	4410	0.34
Petrolatum vehicle	0	4410	0.00
Empty Control	0	4410	0.00
0.9% Saline control	53	4410	1.20
0.1% SLS control	189	4410	4.29

Abbreviations: BEMT = bemotrizinol; DSM = the "Requestor"; RIPT = repeated insult patch test.

b. Human Allergenicity Test

Study RLNJ 2020-0495 was conducted to assess the photo-allergenicity potential of bemotrizinol compared to vehicle control and a negative control.

On the first visit, the minimal erythema dose of each subject was assessed by applying a progressive geometric sequence of UV radiation exposures to five sub-sites, each of which graduated incrementally by 25% over the previous site. The minimal erythema dose was evaluated 16 to 24 hours after ultraviolet radiation.

During the induction phase, two doses (one irradiated and one nonirradiated) of the investigational products and two doses (one irradiated and one nonirradiated) of the vehicle controls were applied to the back of each subject once on Day 1 under occlusive patches. In addition, two undosed negative control occlusive patches were applied once on Day 1. See Table 11 for a list of test materials. Patches remained in place for approximately 24 hours and were removed on Day 2. Subjects returned to the laboratory 24 hours and 48 hours postirradiation for dermal evaluations. This procedure was carried out 2x/week for a total of 6 applications and postirradiation readings during the induction phase.

The challenge phase of the study occurred approximately 10 to 21 days following the last induction application. During the challenge phase, duplicate patches were applied to sites previously unexposed to the test material. In addition, 2 sets of patches without test material were applied on 2 sides of the back. Approximately 24 hours later, the patches were removed, and the test sites were evaluated. The test sites on one side of the back were irradiated with a nonerythrogenic dose of UVA radiation (wavelengths 320-400 nm) equivalent to approximately 10 J/cm^2. The sites on the other side of the back served as a test material treated, non-irradiated control site and non-treated non-irradiated control. The challenge sites were graded at 24, 48, and 72 hours following irradiation according to the dermal grading scale. Subjects could be rechallenged with the test material if reactions indicative of sensitization or photo sensitization were observed during the challenge phase.

Table 11. Test Materials, Study DSM PA 2020 (CRLNJ2020-0495)

Requestor Identification
Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer
Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT (BEMT replaced by Isopropyl myristate)
Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum

Abbreviations: BEMT = bemotrizinol; DSM = the "Requestor"; PA = photoallergenicity.

A total of 50 (13 male and 37 female) subjects ranging in age from 21 to 72 years were enrolled. The number of subjects with Fitzpatrick skin types were: Type I = 12, Type 2 = 23, and Type III = 15.[28] A total of 48 subjects completed the study; one subject discontinued for personal reasons and one subject discontinued for a serious adverse event. Under the conditions of this study and in this test population, none of the test formulations elicited a photo-allergic response.

[28] https://www.arpansa.gov.au/sites/default/files/legacy/pubs/RadiationProtection/FitzpatrickSkinType.pdf.

There was one serious adverse event of appendicitis, which was determined to be unrelated to the study drugs.

c. Human Phototoxicity Test

Study CRLNJ 2020-0494 was conducted to assess the phototoxic potential of a test material, compared to vehicle control and a negative control. On the first visit, the minimal erythema dose of each subject was assessed by applying a progressive geometric sequence of UV radiation exposures to five sub-sites, each of which graduated incrementally by 25% over the previous site. The minimal erythema dose was evaluated 16 to 24 hours after ultraviolet radiation.

Two doses (one irradiated and one nonirradiated) of the investigational products and two doses (one irradiated and one nonirradiated) of the vehicle controls were applied to the back of each subject once on Day 1 under occlusive patches. Two undosed negative control occlusive patches were applied once on Day 1. See Table 12 for the investigational products. All patches remained in place for approximately 24 hours and removed on Day 2. Subjects returned to the laboratory 24 hours and 48 hours postirradiation for dermal evaluations.

Table 12. Test Materials, Study DSM PT 2020 (CRLNJ2020-0494)

Requestor Identification
Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer
Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT (BEMT replaced by Isopropylmyristate)
Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum
Petrolatum vehicle

Abbreviations; BEMT = bemotrizinol; DSM = the "Requestor"; PT = phototoxicity.

A total of 34 (10 male and 24 female) subjects, ranging in age from 21 to 72 years, were enrolled in the study and all subjects completed the study. The number of subjects with Fitzpatrick skin types were: Type I = 5, Type 2 = 14, and Type III = 15. Under the conditions of this study and in this test population, neither of the test formulations containing 6% bemotrizinol elicited a phototoxic response, and there were no adverse events reported.

3. Postmarketing Safety Reports

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. Australia and Canada also regulate sunscreens as drugs. The Requestor submitted postmarketing safety reports, which were limited and were provided primarily from the Australian Therapeutics Goods Administration (TGA)[29] Database of Adverse Event Notifications (DAEN). This difference between countries in regulatory oversight may

[29] The Therapeutic Goods Administration is Australia's government authority responsible for evaluating, assessing, and monitoring products that are defined as therapeutic goods. They regulate medicines, medical devices, and biologicals. For more information, see https://www.tga.gov.au.

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. The most frequent events were sunburn, blistering, erythema (redness), rashes, and drug inefficacy. A total of 78 adverse events were identified as having occurred in the pediatric population (ages 17 to below 1). The majority of the events were similar to those found in adults and included sunburn, blistering, and drug ineffectiveness.

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 to the two case reports provided by the Requestor.

4. Proposal Based on Clinical Safety Data

The four clinical 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 three-week time period to an exposure of over 70% of the body for four days in the maximal use studies (BEMT-001). An additional 47 adult subjects were exposed to bemotrizinol in various patch tests on a single day in the 4 SPF efficacy trials.

Repeat exposure did not result in irritation, sensitization, photo-allergenicity, or phototoxicity. Application of bemotrizinol over the majority of body surface area in the pivotal pharmacokinetic study (MUsT) resulted in few adverse events, no serious adverse events, and no recorded dropouts. Overall dropout rates for the eight (4 clinical and 4 SPF) studies were acceptable with rates ranging from 12% (4 of 34 dropped in the cumulative irritation study) to zero dropouts (MUsT pivotal and phototoxicity test). No adverse events occurred in the SPF studies.

The most frequent adverse events in postmarketing reports were sunburn, blistering, erythema (redness), rashes, and drug inefficacy, and there were only three case reports of safety events with bemotrizinol in the literature, all three related to topical reactions. Based on the extensive post-market 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 pre-market exposure in clinical trials is much lower than typically expected[30].

Pediatric data for bemotrizinol is limited. The studies submitted by the Requestor were conducted in patient populations ages 18 and above. 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.[31] However, given

[30] See 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, 1995. Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life.

[31] See Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biologic Products, 2022. Accessed at https://www.fda.gov/media/90358/download.

that the mean overall absorption is well below 0.5 ng/mL,[32] FDA does not consider additional MUsT in pediatric subjects to be necessary. Additionally, because the dermal studies had no instances of irritation, phototoxicity, or photoallergenicity, FDA does not consider similar studies in the pediatric population to be necessary. While the post marketing safety reports in children were very few, the types of adverse events reported were similar to those in adults.

Therefore, FDA proposes that the clinical human safety data submitted by the Requestor demonstrate that bemotrizinol at concentrations up to 6% is safe for use as an active ingredient in nonprescription sunscreen products intended for use in adults and children ages 6 months and older.

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

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 identified in § M020.10 of OTC Monograph M020; 4) a single drug product may combine bemotrizinol alone or in an allowed combination with other sunscreen ingredients, with one or more skin protectant active ingredients identified in § M016.10 of OTC Monograph M016: Skin Protectant Drug Products for OTC Human Use (OTC Monograph M016)[33]; and 5) a drug product containing bemotrizinol as a sunscreen active ingredient would need different labeling from other OTC monograph products.

1. Drug Substance and Drug Substance Impurities

FDA conducted a review of the data and information submitted by the Requestor on manufacturing of bemotrizinol as a drug substance and drug product to identify and evaluate the impurities resulting from the manufacturing process.

Bemotrizinol is a UV filter that has two stereocenters and is manufactured as a racemic mixture. It is a light yellow to yellow coarse to fine powder that is practically insoluble in water but is highly soluble in oil and nonpolar solvents.

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[32] See Footnote 19.

[33] OTC Monograph M016 is set forth in Final Administrative Order OTC000005, available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/.

Table 13. Bemotrizinol Drug Substance Impurity Specifications

Names	Specified Limit
Impurity 1 (Impurity a)	NMT 0.10%
Impurity 2 (Impurity b)	NMT 0.10%
Impurity 3 (Impurity c)	NMT 0.10%
Impurity 4 (Impurity d)	NMT 0.50%
Impurity 5 (Impurity g)	NMT 0.50%
Impurity 6 (Impurity h)	NMT 0.10%
Impurity 7 (Impurity i)	NMT 0.10%
Impurity 8 (Impurity j)	NMT 0.70%
Impurity 9 (Impurity e)	NMT 0.02%
Impurity 10 (Impurity f)	NMT 0.10%

Abbreviations: NMT = Not More Than.

FDA conducted a review of the data and information submitted by the Requestor on manufacturing of bemotrizinol as a drug substance, including the impurities resulting from the manufacturing process (Table 13).[34] The 10 identified impurities (a, b, c, d, e, f, g, h, i, j) are mostly structurally similar to bemotrizinol.[35] The Requestor submitted proposed impurity specifications, consistent with those in the proposed USP monograph for bemotrizinol, in the OMOR. However, the proposed impurity specifications are not consistent with the approaches recommended in the ICH guidance for industry *Q3A(R2) Impurities in New Drug Substances* partly because the proposed qualification threshold (QT) of no more than (NMT) 0.15% is based on a maximum daily dose (MDD) of less than 2 grams.[36] Using an application of 2 mg/cm^2, which is the amount applied to determine product sun protection factor (SPF) under OTC Monograph M020, with application over 70% of the body, and with a reapplication rate of every 2 hours over an 8 hour period, the MDD would be over 7 grams, which is associated with a QT of 0.05%.

FDA considered if the 10 impurities could be qualified relying on nonclinical data, noting that one of the impurities (Impurity e) was proposed at a specification below the qualification threshold (QT), but exceeded the threshold of toxicological concern (TTC) in the ICH guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.[37] FDA conducted a quantitative structure-activity relationship ((Q)SAR) analysis of the ten impurities to predict bacterial mutagenicity only. Nine of the 10 impurities (a, c, d, e, f, g, h, i, and j) were negative for bacterial mutagenic potential, but one impurity, impurity b was predicted to be equivocal for bacterial mutagenicity based on a read-across assessment to a structurally similar molecule. To further derisk the potential for mutagenicity, FDA considered if ICH Q3A - recommended "genotoxicity studies

[34] In 2006, a time and extent application (TEA) as defined in 21 CFR 330.14, was submitted to FDA to evaluate bemotrizinol for inclusion in the OTC sunscreen monograph. The data submitted by the Requestor was for lots of bemotrizinol that were generated for nonclinical studies used to support the TEA. FDA's response to the TEA can be found at: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/regulatory-policy-information-sunscreen-innovation-act.

[35] Impurity 2 (Impurity b) is a synthetic precursor to bemotrizinol and therefore, is not structurally similar.

[36] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3ar-impurities-new-drug-substances.

[37] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-m7r2-assessment-and-control-dna-reactive-mutagenic-impurities-pharmaceuticals.

(point mutation, chromosomal aberration)" and "general toxicity studies"[38] (one species, 90-day duration study to support a chronic use drug) were available and conducted with sufficient levels of the impurities. General toxicity was addressed for impurities in the OMOR submission.

FDA also considered the extent of absorption of the proposed impurities. While the absorption level of the impurities cannot be assumed to be equivalent to that of bemotrizinol, given the structural similarities to bemotrizinol and high molecular weight[39], FDA believes that the actual absorption of the structurally similar impurities would also be less than 100%. Considering this information, the nonclinical data are supportive of the proposed impurity specifications overall and the (Q)SAR assessment suggest impurity b is equivocal, but not positive for mutagenicity.

Thus, FDA determined that the totality of information on the impurities, including nonclinical information, human clinical safety studies, high molecular weight, and structural similarity to bemotrizino, is sufficient to justify the proposed impurity specifications as proposed in the draft USP monograph for bemotrizinol submitted in the OMOR.

2. Drug Product and Allowed Dosage Forms

FDA reviewed the data and information to determine the dosage forms in which the drug product can be manufactured.

In its OMOR, the Requestor sought to have FDA determine that sunscreen drug products containing bemotrizinol as an active ingredient are GRASE if they are in any of the topical dosage forms permitted for other sunscreens marketed under the OTC sunscreen monograph.[40] These dosage forms are: oil, lotion, cream, gel, butter, paste, ointment, stick, spray, and powder.[41] To support these dosage forms, FDA requested that the Requestor provide market image examples to demonstrate that bemotrizinol can be manufactured into a drug product in all of the requested dosage forms. Therefore, the Requestor created and submitted information on four "market image" drug product formulations:

- Oil-in-water emulsion
- Water-in-oil emulsion
- Sunscreen oil
- Petrolatum

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[38] The ICH guidance for industry Q3A(R2) Impurities in New Drug Substances recommends the following on page 13 of the guidance: "Consider patient population and duration of use and consider conducting: • Genotoxicity studies (point mutation, chromosomal aberration) • General toxicity studies (one species, usually 14 to 90 days) • Other specific toxicity endpoints, as appropriate."

[39] Impurity b is not structurally similar to bemotrizinol

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

[41] These are the only dosage forms permitted now for other sunscreen products marketed pursuant to section 505G of the FD&C Act. See Final Administrative Order OTC000006, at page 2-3. We note that in Proposed Administrative Order OTC000008, FDA made additional proposals regarding spray and powder dosage forms. These dosage form proposals from Proposed Administrative Order OTC000008 remain under consideration and FDA is not aware of any evidence that the inclusion of bemotrizinol as an active ingredient in a sunscreen drug

These four drug product formulations were used as the test materials in the clinical safety studies discussed earlier in this review. The four drug product formulations provide sufficient support that bemotrizinol as an active ingredient can be formulated as a sunscreen drug product in the following dosage forms: oil, lotion, cream, gel, butter, paste, ointment, stick, and certain sprays.

The four drug product formulations do not support that bemotrizinol as an active ingredient can be formulated as a sunscreen drug product in an aerosol spray dosage form where the drug product formulation is combined with a propellent.[42] While the Requestor did not create a drug product formulation combined with a propellant to support an aerosol spray dosage form,[43] the provided drug product formulations do support that bemotrizinol can be formulated in sprays in which the drug product formulation is either separated from the propellant (e.g., bag-on-valve) [44] or the dosage form does not utilize a propellant (e.g., pump spray)[45].

In addition, the drug product formulations provided do not support that a sunscreen drug product containing bemotrizinol can be manufactured in a powder dosage form, as the formulation provided to support a powder dosage form, oil in water, does not appear to exist as a powder. In Proposed Administrative Order OTC000008, FDA addressed powder dosage forms and explained the need for additional data to support powders as an allowed dosage form under OTC monograph M020.[46] The data submitted by the Requestor did not address FDA's concerns related to the use of a powder dosage form in sunscreens described in Proposed Administrative Order OTC000008. Therefore, the Requestor did not submit sufficient information to permit bemotrizinol in a powder dosage form.

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product would change the considerations that gave rise to them. Thus, FDA expects that, if finalized, the proposed conditions in OTC000008 would apply to all sunscreen drug products, irrespective of their active ingredients, and thus would apply to sunscreens containing bemotrizinol as an active ingredient if this current proposed order is finalized.

[42] Aerosols are dosage forms packaged under pressure and contain therapeutic agent(s) and propellant(s) that are released upon actuation of an appropriate valve system. Upon actuation of the valve system, the drug substance is released as a plume of fine particles or droplets. Only 1 dose is released from the preparation upon actuation of a metered valve. In the case of topical products and depending on the nature of the drug substance and the conditions being treated, actuation of the valve may result in a metered release of a controlled amount of the formulation or the continuous release of the formulation as long as the valve is depressed. Topical aerosols produce fine particles or droplets for application to the skin. See United States Pharmacopeia (USP) General Chapter <1151> Pharmaceutical Dosage Forms.

[43] Based on information submitted by the Requestor on marketed drug products from multiple regulatory jurisdictions and FDA's search of marketed products with bemotrizinol in other countries, bemotrizinol is not often marketed in an aerosol dosage form.

[44] Bag-on-valve sprays contain the drug product(s) in the liquid state as a solution or suspension and is intended for administration as a mist. Bag-on-valve sprays are in canisters where the drug product is packaged in a flexible bag separated from the propellant in the canister. Upon activation of the canister-head, the propellant squeezes the flexible bag containing the drug product(s), dispensing the drug product but not the propellant.

[45] Sprays are dosages forms that may deliver either accurately metered or nonmetered amounts of formulation. A spray drug product is a dosage form that contains a drug substance in the liquid state as a solution or suspension and is intended for administration as a mist. Sprays are distinguished from aerosols in that spray containers are not pressurized. Most of the sprays are generated by manually squeezing a flexible container or actuation of a pump that generates the mist by discharging the contents through a nozzle. See United States Pharmacopeia (USP) General Chapter <1151> Pharmaceutical Dosage Forms.

[46] See Proposed Administrative Order OTC000008 at pages 64-65

3. Sunscreen Combinations

The Requestor proposed that bemotrizinol at concentrations up to 6% be allowed to be combined with all sunscreen active ingredients identified in § M020.10 of OTC Monograph M020. The Requestor submitted postmarketing safety reports collected by the Therapeutic Goods Administration[47] between 2015 to 2024 on sunscreen drug products containing bemotrizinol. Most of the postmarket safety reports were for products in which bemotrizinol was combined with other sunscreen active ingredients. While these reports document the most frequently occurring adverse events for sunscreen drug products containing bemotrizinol, they did not directly raise safety or efficacy concerns regarding the use of bemotrizinol in combination with other sunscreen active ingredients.

In addition to the postmarketing data submitted by the Requestor, FDA conducted a review of publicly available scientific literature to identify any existing safety or efficacy concerns related to using bemotrizinol in combination with other sunscreen active ingredients. This literature search did not identify any data to suggest that a sunscreen drug product that combines bemotrizinol with other sunscreen active ingredients creates any new or previously unidentified safety or efficacy concerns when combined with other sunscreen active ingredients.

The use of bemotrizinol in combination with other sunscreen active ingredients is reportedly beneficial due to its ability to act as a photostabilizer.[48,49,50,51,52] One publication demonstrated that bemotrizinol improves the photostability of avobenzone and octinoxate, resulting in sustained SPF and UVA ratio following UV irradiation.[53] Furthermore, one study found that the presence of bemotrizinol in a sunscreen formulation decreased the phototoxic potential of avobenzone according to the in vitro 3T3 neutral red uptake phototoxicity assay.[54] The authors of the study note that bemotrizinol may reduce phototoxicity due to its capacity to quench the triplet excited state of avobenzone, which can generate reactive oxygen species. Another recent study also showed that bemotrizinol reduces photodegradation of avobenzone and octinoxate through both spectral overlap and quenching mechanisms.[55]

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[47] The Therapeutic Goods Administration is Australia's government authority responsible for evaluating, assessing, and monitoring products that are defined as therapeutic goods. They regulate medicines, medical devices, and biologicals. For more information, see https://www.tga.gov.au.

[48] Benevenuto, CG, LO Guerra, and LR Gaspar, 2015, Combination of retinyl palmitate and UV-filters: phototoxic risk assessment based on photostability and in vitro and in vivo phototoxicity assays, Eur J Pharm Sci, 68:127-136.

[49] Chatelain, E and B Gabard, 2001, Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a new UV broadband filter, Photochem Photobiol, 74(3):401-406.

[50] Freitas, JV, NP Lopes, and LR Gaspar, 2015, Photostability evaluation of five UV-filters, trans-resveratrol and beta-carotene in sunscreens, Eur J Pharm Sci, 78:79-89.

[51] Herzog, B, J Giesinger, and V Settels, 2020, Insights into the stabilization of photolabile UV-absorbers in sunscreens, Photochemical & Photobiological Sciences, 19(12):1636-1649.

[52] Lhiaubet-Vallet, V, M Marin, O Jimenez, O Gorchs, C Trullas, and MA Miranda, 2010, Filter-filter interactions. Photostabilization, triplet quenching and reactivity with singlet oxygen, Photochem Photobiol Sci, 9(4):552-558.

[53] See footnote 22.

[54] See footnote 21.

[55] See footnote 24.

A survey of 2183 sunscreen products marketed in South Korea as of May 2019 indicated that, in addition to avobenzone and octinoxate, bemotrizinol is also commonly used in combination with octisalate, homosalate, octocrylene, and titanium dioxide.[56] The survey of South Korean sunscreen products also identified bemotrizinol combinations with zinc oxide and ensulizole. A survey of sunscreen products in the Thai market also analyzed the co-occurrence of sunscreen active ingredients and found that bemotrizinol is most commonly used in combination with titanium dioxide, followed closely by octinoxate, avobenzone, and octocrylene.[57] In addition, the examples of marketed products containing bemotrizinol show that bemotrizinol is currently marketed in other regions in combination with the majority of sunscreen active ingredients identified in OTC Monograph M020.

Based on FDA's review of the postmarketing data and published literature, FDA did not identify any data to suggest that there are any new or previously unidentified safety or efficacy concerns with using bemotrizinol in combination with other permissible sunscreen active ingredients identified in OTC monograph M020.[58] Note that in Proposed Administrative Order OTC000008, FDA proposed to find that sunscreens containing aminobenzoic acid (PABA) and trolamine salicylate, two sunscreen active ingredients currently permissible 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.

4. Sunscreen—Skin Protectant Combinations

Section M016.20(e) of OTC Monograph M016 lists permitted combinations of certain skin protectant active ingredients with any single sunscreen active ingredient identified in § M020.10 of OTC Monograph M020 and with any permitted combination of sunscreen active ingredients under § M020.20. Because OTC Monograph M016 states that only specific skin protectant active ingredients may be combined with sunscreen active ingredients, FDA evaluated whether there are any existing safety or efficacy concerns related to combining bemotrizinol with those skin protectant active ingredients.

Of the four market image drug product formulations submitted by the Requestor (see Section III.D.3 Drug Product/Dosage Form), the combination of bemotrizinol in petrolatum represents an example of a sunscreen-skin protectant combination, as petrolatum is a skin protectant active ingredient permitted for combination with sunscreen active ingredients in M016.20(e) of OTC Monograph M016. The drug product formulation consisted of 6%

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[56] Jo, A. R., Kwon, B. R., Lee, I., Min, J., Choi, S., Park, N. Y., Kho, Y., Park, J., Kim, H., & Choi, K. (2025). A novel approach for unveiling co-occurrence patterns of UV filter mixtures in sunscreens: Prioritization for hazard and risk assessment. *Ecotoxicol Environ Saf*, *290*, 117527. https://doi.org/10.1016/j.ecoenv.2024.117527.

[57] Chaiyabutr, C., Sukakul, T., Kumpangsin, T., Bunyavaree, M., Charoenpipatsin, N., Wongdama, S., & Boonchai, W. (2021). Ultraviolet filters in sunscreens and cosmetic products-A market survey. *Contact Dermatitis*, *85*(1), 58-68. https://doi.org/10.1111/cod.13777.

[58] Generally, unless data suggest that there may be a safety or efficacy concern with a particular combination of active ingredients, FDA anticipates that an active ingredient that is found to be GRASE for use in sunscreens could be combined with other active ingredients that are also GRASE for use in sunscreens. See Proposed Administrative Order OTC000008 at pages 16, 32-37.

bemotrizinol with 94% petrolatum, which is consistent with the requirements for petrolatum in § M016.10(m) (30 to 100% petrolatum). The drug product formulation demonstrates that bemotrizinol can be formulated with a skin protectant. This formulation was evaluated in the repeat insult, allergenicity, and phototoxicity dermal studies discussed above, none of which indicated a safety concern with this formulation. These results provide clinical support for the sunscreen-skin protectant combination.

FDA also conducted a literature search to identify any existing safety or efficacy concerns related to using bemotrizinol in combination with the skin protectant active ingredients. Only the search for bemotrizinol in combination with dimethicone, a skin protectant active ingredient permitted for combination with sunscreen active ingredients in § M016.20(e) of OTC Monograph M020, returned search results. This search identified a single case report of a 39-year-old female patient suffering from allergic contact dermatitis, which patch testing showed was due to sunscreen and cosmetic foundation products.[59] Patch testing showed that the patient had a positive reaction to multiple ingredients in the sunscreen and cosmetic foundation products including bemotrizinol and dimethicone/methicone copolymer. Because the patient had positive patch test results to bemotrizinol and dimethicone individually, it is unlikely that the patient's skin reaction was specifically related to the combination of bemotrizinol and dimethicone. No other searches for bemotrizinol in combination with any of the skin protectant active ingredients permitted for use in combinations with sunscreen active ingredients returned results.

Based on FDA's review of the clinical studies submitted in the OMOR and the published literature, 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

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 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.

6. Proposal Based on Conditions Under OTC Monograph Relevant Information and Studies

The Requestor did not submit data or information to demonstrate that a sunscreen containing bemotrizinol can be manufactured in an aerosol spray dosage form or a powder dosage form. In addition, the Requestor did not address concerns raised by FDA in Proposed Administrative Order OTC000008 regarding sunscreen drug products in powder dosage form. Therefore, FDA proposes that the OTC monograph conditions for sunscreen drug products containing

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[59] Luna-Bastante, L., Gatica-Ortega, M. E., Pastor-Nieto, M. A., Vergara-de-la-Campa, L., Gomez-Dorado, B. A., Alonso-Naranjo, L., & PerezHortet, C. (2020). Allergic contact dermatitis to Tinosorb S, Scutellaria baicalensis, and other emerging allergens in cosmetics. *Contact Dermatitis*, *82*(5), 307-309. https://doi.org/10.1111/cod.13460.

bemotrizinol as an active ingredient is in one of the 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., bag-on-valve spray).

Based on FDA's review of the totality of data and information for this OMOR, FDA has tentatively concluded that other specific conditions of use for bemotrizinol include permitted combinations of bemotrizinol with other sunscreen active ingredients identified in OTC Monograph M020, as well as permitted combinations of bemotrizinol with skin protectants identified in OTC Monograph M016.

IV. Proposal Based on Scientific Review

Based on our comprehensive 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 concentrations up to 6 percent, permitted combinations of bemotrizinol with other sunscreen active ingredients and with skin protectant active ingredients, and permitted dosage forms.

Specifically, proposed specific bemotrizinol-related conditions include that:

- Bemotrizinol is present in the drug product in concentrations up to 6 percent, and the finished drug product provides a minimum SPF value of not less than 2.
- A single drug product may combine bemotrizinol with any single sunscreen active ingredient identified in § M020.10 except for PABA or trolamine salicylate or may combine bemotrizinol with any combination of sunscreen active ingredients identified in § M020.20(a) 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 with bemotrizinol in any combination with other sunscreen active ingredients identified in M020.20 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).

KAREN M. MURRY -S

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December 9, 2025