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Office of Regulatory Operations
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Subject: MGF 400105 – Response to IR #20 [3870]

Dear Trang and Shannon,

Reference is also made to our submissions received on September 23, 27, and 30, 2024, supporting a Tier 1 Over-the-Counter (OTC) Monograph Order Request (OMOR) for a Generally Recognized as Safe and Effective (GRASE) determination for bemotrizinol (BEMT) 6% as a new sunscreen active ingredient under FDA's OTC Monograph M020: Sunscreen Drug Products for OTC Human Use.

Further reference is made to FDA's Information Request (IR) letter dated August 14, 2025 regarding FDA's comments and information requests regarding our support of the use of bemotrizinol, at concentrations up to 6%, in combination with skin protectant active ingredients (AIs) and additional information regarding your proposed impurity limits for bemotrizinol. We understand the importance of ensuring that sunscreen active ingredients are appropriately supported when used in combination with permitted skin protectant actives under OTC Monograph M016. In this letter, we address the FDA's inquiries concerning the compatibility of bemotrizinol with the listed skin protectant active ingredients, as well as provide additional data and analysis related to the proposed impurity limits and retained sample evaluations.

Bemotrizinol (BEMT)

In response to IR20, below please find the requested information attached, submitted by the due date of August 21, 2025.

FDA IR 1:

We note that the OTC monograph M016 for skin protectant drug products allows sunscreen active ingredients (AIs) to be used in combination with certain skin protectant AIs as described in § M016.20(e) (see Table 1 below).

- a. Does DSM support the use of bemotrizinol, at concentrations up to 6%, in combination with the skin protectant AIs listed in Table 1?*
- b. If so, provide an analysis to support the combination of sunscreens with skin protectant products.*

Table 1. Skin Protectant Active Ingredients Permitted for Use in Combination with Sunscreen Active Ingredients Listed Under § M020.10 Skin Protectant Active Ingredient M016 Reference

Allantoin (0.5-2%)	§ M016.10(a)
Cocoa butter (50-100%)	§ M016.10(d)
Cod liver oil (5-13.56%)	§ M016.10(e)
Dimethicone (1-30%)	§ M016.10(g)
Glycerin (20-45%)	§ M016.10(h)
Hard fat (50-100%)	§ M016.10(i)
Lanolin (12.5-50%)	§ M016.10(k)
Mineral oil (50-100%)	§ M016.10(l)
Petrolatum (30-100%)	§ M016.10(m)
White petrolatum (30-100%)	§ M016.10(r)

DSM Response:

Support for the Use of Bemotrizinol (BEMT) up to 6% in Combination with Skin-Protectant Active Ingredients under 21 CFR § M016.20(e)

DSM affirms its support for the inclusion of Bemotrizinol (BEMT)—a photostable, broad-spectrum UV filter—at concentrations up to 6% in over-the-counter (OTC) drug products that also contain skin-protectant active ingredients listed in 21 CFR § M016.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r). This support is contingent upon BEMT's formal inclusion as a GRASE (Generally Recognized as Safe and Effective) sunscreen active under § M020.10, as required by § M016.20(e).

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Regulatory Framework

Under § M016.20(e), the FDA permits combinations of specified skin-protectant actives, including allantoin, cocoa butter, cod liver oil, dimethicone, glycerin, hard fat, lanolin, mineral oil, petrolatum, and white petrolatum—with any GRASE sunscreen active or permitted combination under § M020.20, provided the finished product meets all applicable sunscreen requirements, including:

- SPF testing (§ M020.80)
- Broad Spectrum testing (§ M020.90)
- Labeling requirements (§ M016.60(b)(3), § M020.50(c–e))

As discussed further below, DSM supports the combination of Bemotrizinol (6%) together with allantoin, cocoa butter, dimethicone, glycerin, lanolin, mineral oil, petrolatum, and white petrolatum once FDA issues a Final Order listing BEMT as GRASE in § M020.10.

Scientific and Safety Rationale

Pharmacokinetics and Systemic Exposure

A maximal-use (MU_T) pharmacokinetic (PK) study of 6% BEMT demonstrated that plasma concentrations rarely exceeded 0.5 ng/mL, the FDA's threshold for systemic exposure. This indicates minimal systemic absorption, even under high-use conditions.

Physicochemical Properties

BEMT's high molecular weight (~628 Da) and extreme lipophilicity (logP ~7–11) are associated with low dermal permeation, further supporting its favorable safety profile.

Clinical Safety & Formulation Suitability:

Clinical data and post-market surveillance show a low risk of skin irritation or sensitization. It is non-phototoxic and non-photoallergenic, making it suitable for long-term topical use in a variety of formulations. Bemotrizinol has consistently demonstrated excellent dermal safety across clinical trials and global post-market surveillance. In controlled studies using petrolatum as the vehicle, 6% BEMT showed no signs of irritation, sensitization, phototoxicity, or photoallergenicity, with no adverse events reported. Surveillance data from EMA, TGA, and Health Canada confirm its well-tolerated profile, including in pediatric populations. A review of TGA's Adverse Event Notifications (2020–2023) found no confirmed causal links between BEMT and reported events across 36 products. Importantly, BEMT is well tolerated across a wide range of SPF-rated sunscreens and skin protectant formulations, supporting its inclusion in both OTC and long-term topical products.

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Occlusive Vehicle Considerations

While occlusive agents like petrolatum, mineral oil, and dimethicone can increase stratum corneum hydration and potentially enhance percutaneous absorption, the PK study already reflects maximal topical exposure, providing a conservative safety margin.

Efficacy and Formulation Compatibility

Finished products must meet SPF and Broad-Spectrum standards regardless of vehicle composition. BEMT's photostability and ability to stabilize other filters (e.g., avobenzone) support its use in protectant-rich matrices such as ointments, balms, and sticks.

Formulation and labeling considerations for skin protectant actives:

- Solubilization and photostability of BEMT
- Avoidance of crystallization, which can impair SPF/UVA performance
- Labeling harmonization per § M016.60 and § M020.50

Global Regulatory Context

BEMT is already approved at concentrations up to 10% and widely used in the EU, Australia, China, Korea, and Taiwan, often in multifunctional formulations that combine UV protection with skin barrier support. These products include moisturizers, anti-aging creams, and tinted sunscreens, indicating strong precedent for combining BEMT with skin protectants and reinforcing its safety and compatibility across diverse dosage forms. Furthermore, as previously mentioned, MGF 400105 includes BEMT dermal safety and efficacy studies, which are foundational for its use in combination products.

Market Survey BEMT Combinations with Skin Protectant Active Ingredients

A global market survey of BEMT-containing formulations was performed using a commercially available database (MINTEL SOLUTIONS, GNPD - Global New Products Database: <https://www.gnpd.com/sinatra/gnpd/search/>, data retrieved August 18, 2025). The purpose of this survey was to provide FDA with a summary of various types of sunscreen products and typical compositions existing for BEMT outside the US in combination with the listed skin protectant active ingredients as described in § M016.20(e). As part of our survey methodology, we searched the full GNPD database but limited the product search criteria by defining a cluster of personal care products that contain both BEMT and one of listed skin protectant AIs, in the product INCI lists.

These criteria returned numerous products for each BEMT combination listed globally and published on any date in the full database, except for "Cod liver oil" and "Hard Fat" (Table 1). Most

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prominent product enumerations included the combination BEMT with Glycerin (n = 12406) and Dimethicone (n = 6676).

Combination		GNDP hits	Comments
BEMT (INCI Name: bis-ethylhexyloxyphenol methoxyphenyl triazine)	Allantoin	964	
	Cocoa butter (Theobroma Cacao Seed Butter)	195	
	Cod liver oil	0	
	Dimethicone	6676	File: downloaded for < 1 year: 805 hits
	Glycerin	12406	File: downloaded for < 1 year: 1971 hits
	Hard fat	0 hits for "hard fat" 1 hit for tallow ("Adeps Bovis")	"Hard fat" is missing in the INCI nomenclature, therefore not found in Mintel or PCPC
	Lanolin	38	
	Mineral oil (paraffinum liquidum)	374	
	Petrolatum	199	
	White petrolatum	199	refined and purified form of petrolatum: same results as for petrolatum

Table 1. GNPDP hits (MINTEL SOLUTIONS) from products containing BEMT combinations with the listed skin protectant active ingredients.

“Cod liver oil” is not commonly used as an ingredient in commercial sunscreens. The limited use might be explained by the properties of Cod Liver Oil as an animal-derived product that might evolve undesirable olfactory sensibility in formulations and applied on skin such as the appearance of a “fishy” odor. The other skin protectant active ingredient “Hard fat” is not considered in the INCI nomenclature *per se*. A more specific INCI name exists as “Adeps Bovis”, with which one sunscreen product was found in the GNPDP search. Again, the AIs suffers from the fact that it is an animal-derived fat, and therefore undesirable for the cosmetic market. More commonly it is found in products used for vaginal or rectal applications. The full set of products from the GNPDP search is listed in the supplementary files - GNPDP-download Allantoin.xls, GNPDP-download Glycerin.xls*, GNPDP-download Lanolin.xls, GNPDP-download Dimethicone.xls*, GNPDP-download Cocoa butter.xls, GNPDP-download Mineral oil_paraffinum liquidum.xls, GNPDP-download, GNPDP-download Petrolatum.xls (*only entries for <1 year were downloaded, due limited download size). Global regulation of marketed cosmetic products—especially regarding stability—varies significantly across regions, but there are common principles that most regulatory bodies require to ensure product safety and efficacy.

Please note that the combination of BEMT and petrolatum is also present in the DSM test formulations used for the clinical Dermal Safety Studies provided in MFG-400105. BEMT 6% was

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added to the petrolatum vehicle resulting in the corresponding investigation products SU E 101413-82, batch #002, SU E 101413-82, batch #003 that was utilized for the Human Repeated Insult Patch Test (HRIPT) - Dermal Irritation, Sensitization, and Cumulative Irritation; Phototoxicity; and Photoallergenicity study. Details of the CMC, stability and uses of the BEMT investigative product have been provided in the OMOR submission filed on September 23, 2024 in the respective files such as in module 3.2.P Drug Product (SU-E-101413-82, Petrolatum), 2.7.4 Summary of Clinical Safety, 5.3.5 Reports of Efficacy and Safety Studies.

Conclusion

At 6%, BEMT shows minimal systemic exposure under maximal use, and its physicochemical profile supports low permeation; protectant vehicles are technically compatible, provided formulations are optimized and products pass required SPF/UVA tests.

DSM supports the inclusion of BEMT up to 6% in combination with the enumerated skin-protectant actives under § M016.20(e), contingent upon:

- FDA's final GRASE determination for BEMT under § M020.10
- Compliance with all testing and labeling requirements under § M020.50, § M020.80, § M020.90, and § M016.60

This position is grounded in robust regulatory provisions, clinical pharmacokinetic data, physicochemical evidence (as provided in MGF 400105), and global precedent.

FDA IR 2:

2. We seek additional information regarding your proposed impurity limits for Bemotrizinol.

a. Comment on whether retained samples are available from the pilot and/or pivotal maximal use studies.

b. If retained samples are available, evaluate the levels of identified impurities 1-10 in a representative number of the retained samples. Representative samples would be a subset of all samples with levels near (above or below) the 0.5 ng/mL threshold.

DSM Response:

2(a): As outlined below, we find that the currently proposed impurity limits for BEMT at 6% remain appropriate and representative of a safe and effective UV filter for inclusion in the OTC Monograph. This conclusion is supported by the design and scope of the pivotal studies, which did not include pre-specified analytes for BEMT-related impurities, and by the broader regulatory framework guiding impurity qualification.

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Consistent with FDA's MUsT guidance and ICH quality standards, the control and qualification of process- and degradation-related impurities are appropriately addressed through CMC specifications, validated stability-indicating methods, and toxicological risk assessments—rather than through retrospective plasma quantitation. The analytical method employed in the MUsT study was highly specific to BEMT and demonstrated low systemic exposure, with impurity levels projected to fall well below the validated detection threshold under maximum use conditions. Given the structural similarity of BEMT impurities to the parent compound, their low expected systemic availability, and the technical impracticality of developing ultra-trace multi-analyte assays, additional plasma testing would not be expected to yield meaningful or decision-enabling data.

Accordingly, we believe that further analytical evaluation of impurities in plasma is neither warranted nor technically feasible within the context of the current safety assessment.

2(b): We find the proposed current impurity limits for BEMT 6% remain representative of a safe and effective UV filter for addition to the OTC Monograph in the absence of further analytical evaluation of any representative samples. Consistent with FDA's MUsT guidance and ICH quality guidances, qualification and control of process- and degradation-related impurities are appropriately achieved via CMC specifications, stability-indicating methods, and risk-based toxicological qualification (e.g., ICH M7 where applicable), rather than by post hoc measurement of trace impurities in human plasma [1–4].

In the pivotal MUsT study, 113 out of 3722 plasma samples (3%) contained BEMT at or near the 0.5 ng/mL threshold, with similar detection rates observed in 42% of participants across the study arms. FDA's MUsT framework is intended to quantify the active ingredient (and clinically relevant metabolites, if any) to inform systemic exposure; it does not require plasma quantitation of process-related impurities [1]. Given that BEMT impurities 1-10 are close structural analogs of the API, they are not expected to exhibit greater systemic availability or presence in topically applied drug products - particularly considering BEMT's demonstrated formulation stability and metabolic stability in humans.

Our rationale for low systemic exposure to impurities is based on the consistently low bioavailability of BEMT via topical application, resulting in correspondingly low systemic exposure. The validated analytical method used in the study is highly specific for BEMT, with a Lower Limit of Quantitation (LLOQ) of 0.100 ng/mL plasma, and does not detect impurities. A conservative bounding calculation shows why impurity-in-plasma testing would be analytically non-informative: assuming an impurity at its highest specification (b) (4) % of API distributes identically to the parent, the expected plasma level when the parent is at 0.5 ng/mL is $0.5 \times (b) (4)$, which is (b) (4) -fold below the validated LLOQ (0.1 ng/mL). Impurities at

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(b) (4) % would be even lower. Accordingly, redevelopment and validation of ultra-trace multi-analyte assays would not be expected to generate decision-enabling data.

In our February 3, 2025 response to FDA Information Request 10 (Table 2), we provided qualification for BEMT impurity specifications and included worst case topical and systemic exposure estimates for the three impurities with the highest specification limits: (b) (4)

. A theoretical TTC assessment confirmed that none of these impurities exceeded safety thresholds or raised toxicological concern. This approach aligns with ICH Q3A(R2)/Q3B(R2) for impurity identification/qualification and with ICH M7(R2) for DNA-reactive impurities, where applicable [2–4].

Across the various data and results submitted with our OMOR, BEMT has been demonstrated to be chemically, physically, biologically and metabolically stable, with very low bioavailability and no evidence of accumulation. Pivotal nonclinical studies revealed no genotoxicity, carcinogenicity, or adverse effects that would support a point of departure for risk characterization. Long term and accelerated storage and stability results for the bemotrizinol API confirmed its stability, with no formation of new impurities or meaningful changes. Additionally, metabolic stability assessments using representative human enzyme systems did not identify any human-specific or disproportionate metabolites of concern. Because no human-specific or disproportionate metabolites have been identified, FDA's MIST paradigm is not triggered for BEMT [7].

Clinical testing has demonstrated that BEMT at 6% is safe for topical use and effective for protecting against sunburn. Excessive daily application of BEMT 6% in market representative formulations, under a MUsT protocol involving volunteers reflective of the US population, was well tolerated and did not establish a consistent plasma steady state at or above the 0.5 ng/mL threshold of relevance. Further, impurities 1–10 are close structural analogs of BEMT and equal or higher in molecular weight; based on established skin-permeation structure–property principles (e.g., the 500-Dalton rule), their cutaneous penetration would be expected to be no greater than the parent [8,9].

An analytical method with a lower limit of quantitation (LLOQ) of 0.100 ng/mL plasma for BEMT was successfully developed and validated to support plasma sample analysis. Comparable validated methodologies for the detection and evaluation of BEMT-related impurities in MUsT plasma samples are not currently available or technically feasible. Under ICH M10, each impurity would require analyte-specific method development and full validation (specificity, calibration, accuracy/precision, matrix-matched stability over storage time, ISR, documentation), as well as authentic reference standards, which renders a retrospective multi-analyte exercise infeasible and unlikely to be informative given the predicted pg/mL concentrations [5,6,11]. Further, based on the structural similarity of these impurities to BEMT, their low specification limits, and the demonstrated low systemic exposure of the parent compound, the potential presence of such impurities in plasma is not expected to pose a safety concern or alter the overall conclusions regarding BEMT's safety profile.

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The specification thresholds established for BEMT-related impurities are not expected to raise safety concerns for human topical use in commercial sunscreen formulations. Based on available data and scientific rationale, these thresholds are considered justified in the absence of further analytical evaluation. Accordingly, and consistent with FDA's MUsT guidance and ICH Q3A/Q3B/M7 frameworks, control and qualification of impurities should remain within the CMC domain; additional plasma analysis of impurities is not scientifically warranted and is unlikely to alter the safety conclusions for BEMT 6% [1–4].

References

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This response is being submitted electronically under Module 1 via FDA's NextGen portal.
Please contact me if there are any further questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Carl D'Ruiz", is positioned above the printed name and title.

Carl D'Ruiz, MPH.

Senior NA Science, Advocacy and Business Development Manager, Beauty & Care