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31 January 2025

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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 Information Request Letter #12 [3297]

Dear Trang and Shannon,

Reference is made to the FDA's Information Request (IR) letter dated January 22, 2025, concerning MGF 400105 and the review of submissions provided on January 10, 2025, and January 15, 2025. These submissions address our responses to IR#9 and the Filing Letter IR in support of a Tier 1 Over-the-Counter (OTC) Monograph Order Request (OMOR). This request seeks 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.

In its January 22, 2025, correspondence, the FDA provided clinical comments and Information Requests related to its review of our submissions dated January 10, 2025, and January 15, 2025. The FDA requested a written response to be submitted via the CDER NextGen Portal by January 27, 2025. Additional time was required to prepare our responses, which are presented below.

CLINICAL:

Review of Review of January 10, 2025, Submission

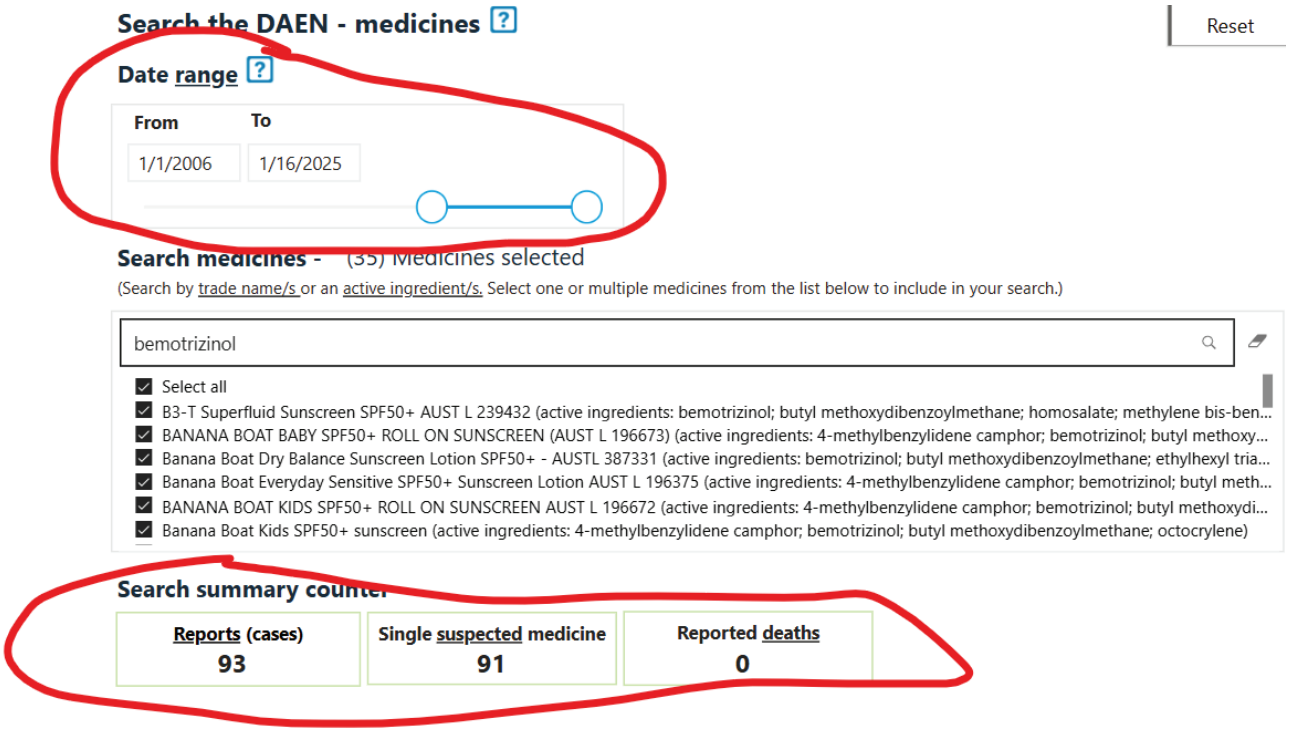
1. DAEN Data Discrepancy

a. You note that both excel files submitted under supporting document number 19 align with the DAEN search methodology detailed in your response. You state that your data query included dates from 1971 to 2024. However your data reflects entries only from 2015 to 2024. Provide justification for the absence of DAEN results between 1971 and 2014.

DSM RESPONSE:

Adverse event data reported to the Therapeutic Goods Administration (TGA) since 1971 are publicly available through the online Database of Adverse Event Notifications (DAEN), which was established in October 2012 (Attachment 1). Although the DAEN website states that the database was established in 1971 and allows date range searches from 1971 to the present—which was the default criterion employed in our search—adverse event results for Bemotrizinol (BEMT) only appear after its approval as a permitted UV filter by the TGA in 2006. This aligns with its introduction into the Australian market as a sunscreen active ingredient, further confirming that earlier records would not have included data related to BEMT. As shown in Figure 1 below, we conducted a follow-up search of DAEN "Bemotrizinol" adverse events by MedDRA system organ class and MedDRA reaction terms starting in 2006 to more accurately reflect its TGA approval date. In reviewing the search results, it appears that the system is dynamic and may have a lag in updating the numbers, as the search output indicates 96 cases rather than the 93 cases shown in Figure 1. Further updated information related to specific product cases with MedDRA reaction are presented in Attachment 2 A summary of MedDRA Organ Class and Reaction Term results for each case are presented in Attachment 3.

Figure 1. Diagram of DAEN Search Criteria Employed for BEMT

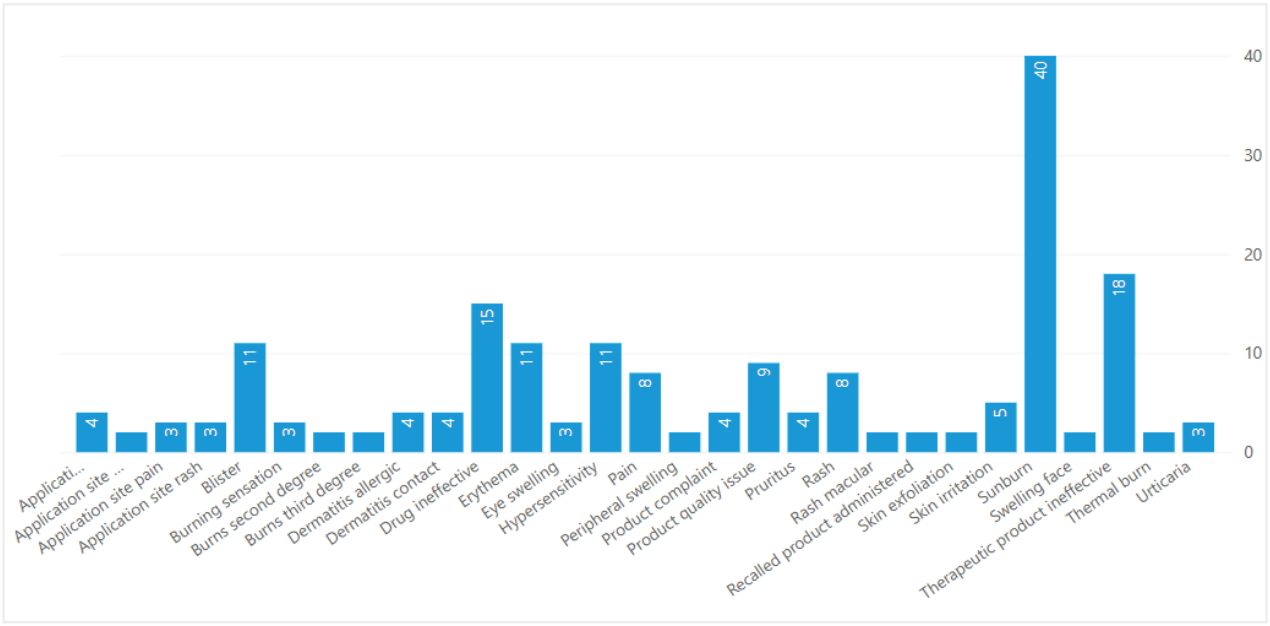


Bemotrizinol (BEMT)

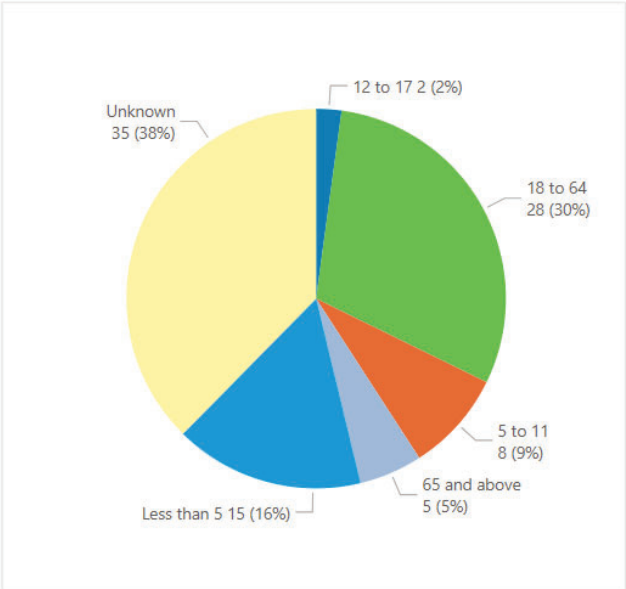
A visual representation of all reported cases by all ages, gender, and MedDRA Reaction terms is presented below. It is important to note that while BEMT was approved by TGA in 2006. DAEN data is only available beginning in the year 2015.

Data visual representation

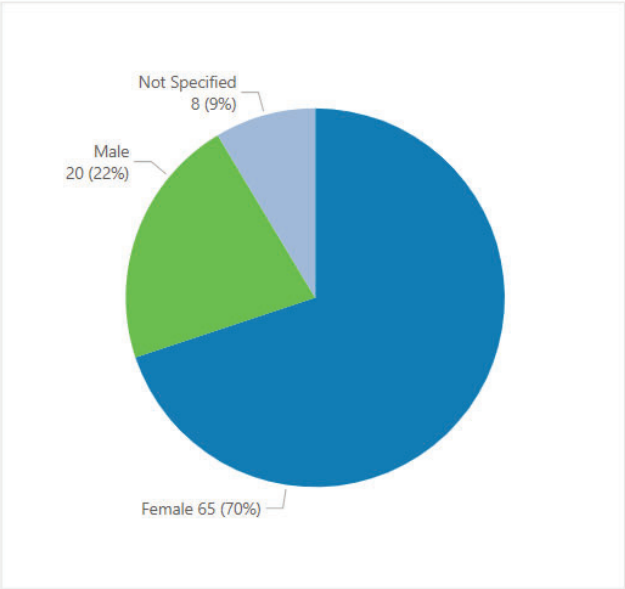
MedDRA Reaction Terms (top 25 view only)

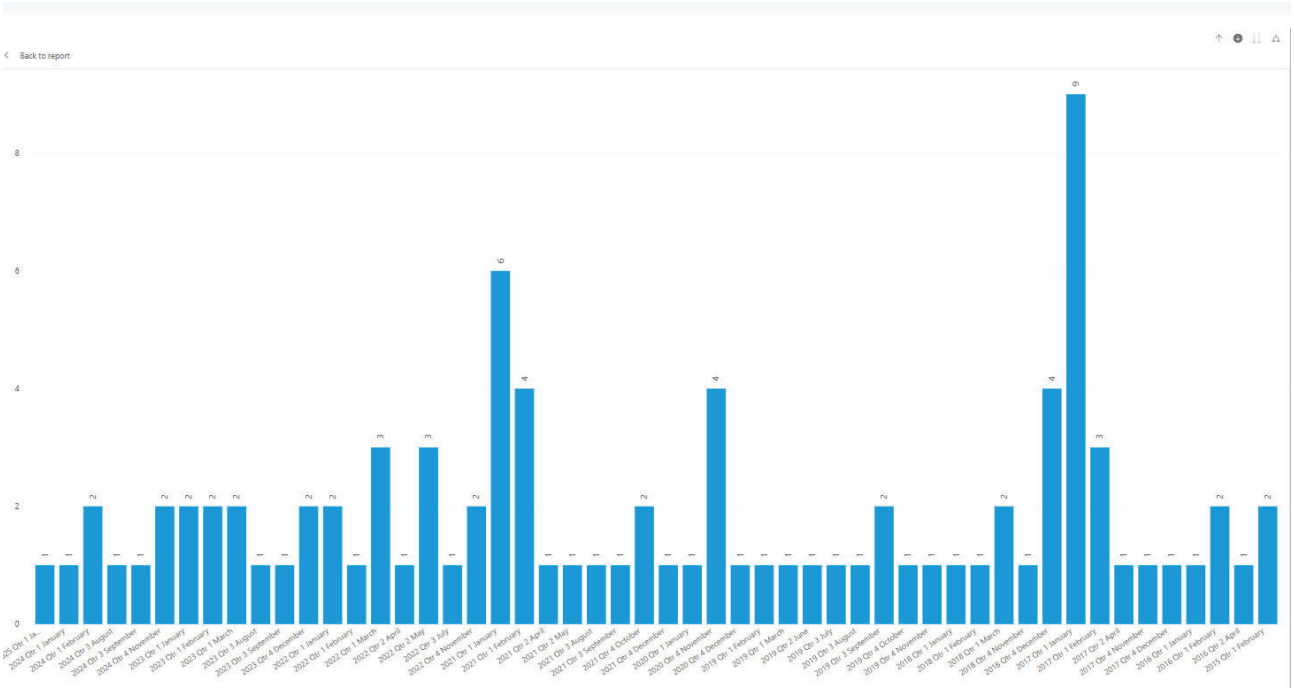


Age

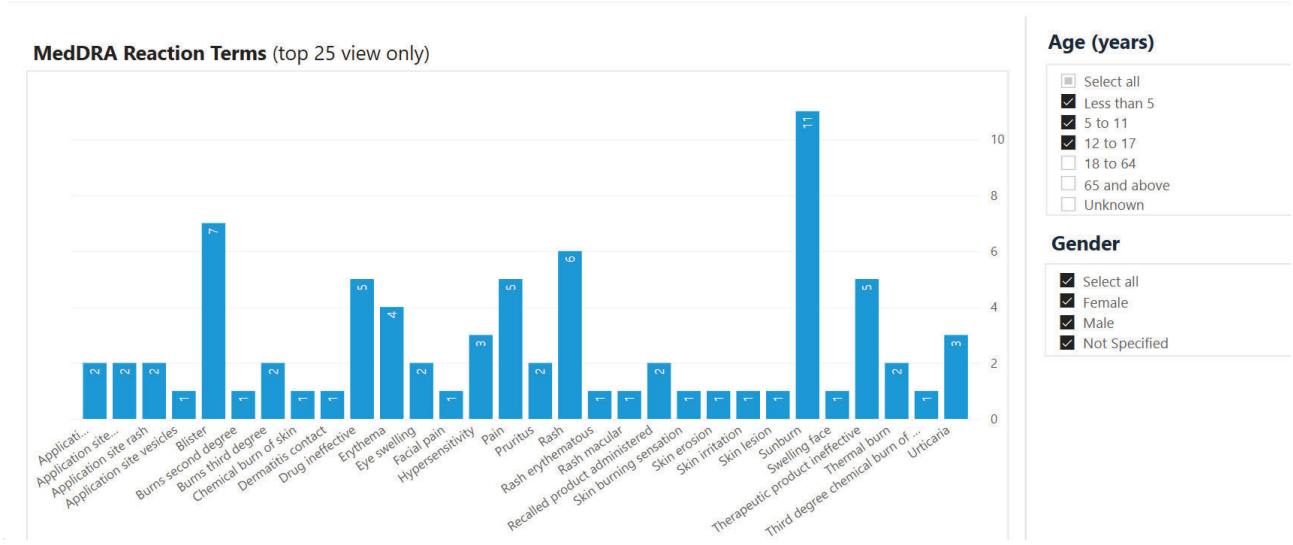


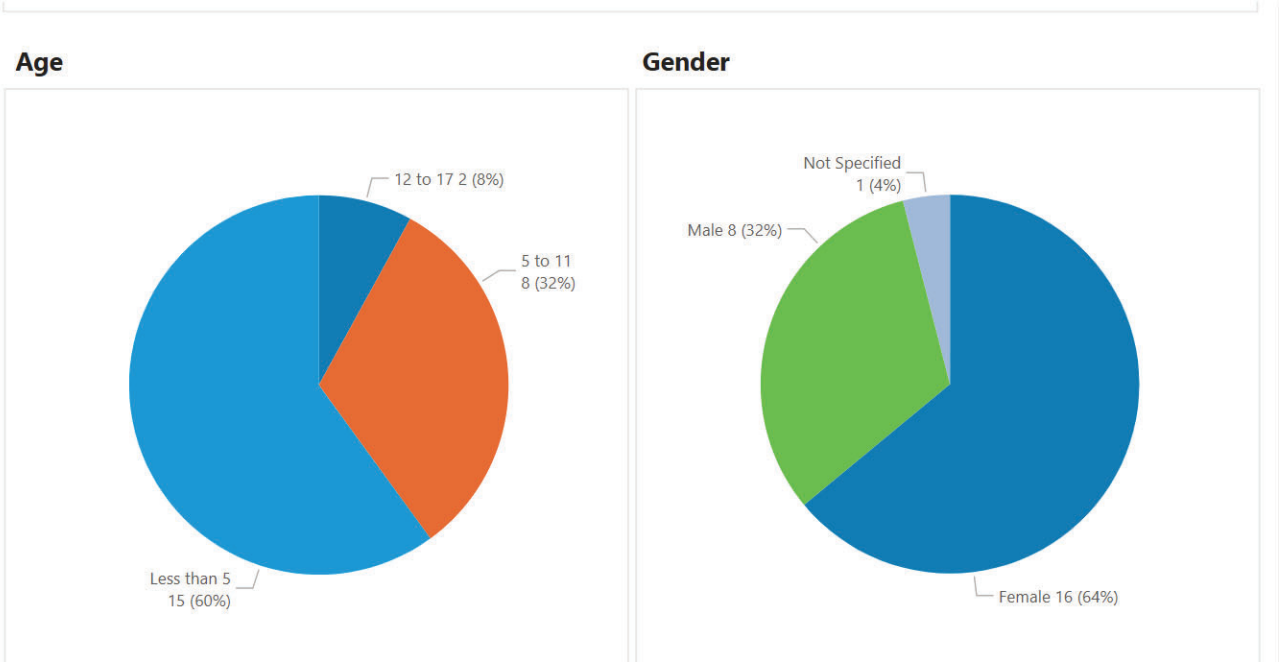
Gender



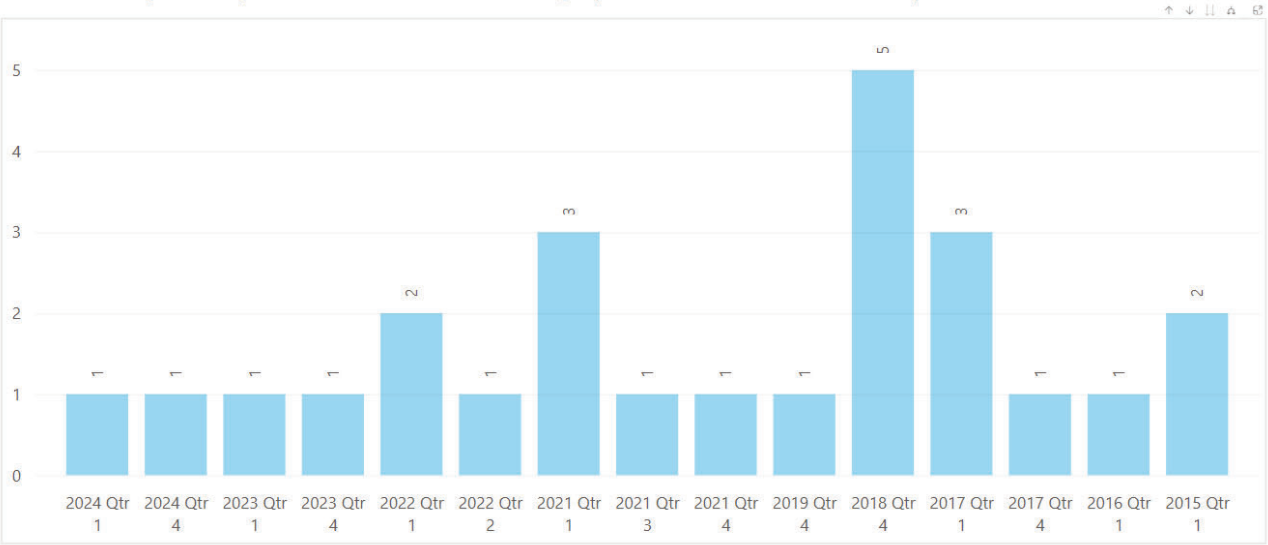


A summary of all DAEN product case reports with MedDRA reaction data is presented in Attachment 4. A DAEN Case Summary by MedDRA Reaction term and Organ Class by age less than 18 is provided in Attachment 5. A visual representation of all DAEN case data age <18 is presented below.





Case data by the report date – Hover over the graph to view data drill down options



2. Data Set Discrepancy

a. The file titled "Medicine Summary_04-Jan-2025_160805 1 BEMT AUSTRALIA 1" contains 65 reports though the query resulted in 92 reports. Include justification regarding why this original data set differs from the second data set which generated 92 reports with age information.

DSM RESPONSE:

DSM provided direct downloads of data collected by the Therapeutic Goods Administration (TGA) without altering any files. As a result, we have no control over the content reported by DAEN in publicly available downloads and cannot account for discrepancies.

However, as noted in our previous response, we revisited DAEN and conducted an additional search, which appears more accurate. The FDA is welcome to access the system directly, as various search parameters can be applied to the available data, which includes:

- Patient demographics (sex, date of birth/age, weight, ethnicity, state)
- Drug details (dose, frequency, form, route, start/stop dates, indication, batch number)
- Adverse reaction data (onset date, description, severity, treatment, outcome, sequelae)

3. Categorization of Adverse Events

a. The file titled "Medicine Summary_04-Jan-2025_160805 1 BEMT AUSTRALIA 2" contains 92 reports with ages included. Provide further categorization of these reports into system organ class (SOC) and preferred term (PT) for each event listed separately including severity.

DSM RESPONSE:

With the help of an artificial intelligence (AI) program (ChatGBT.com), we analyzed the DAEN case report dataset related to bemotrizinol, extracting relevant adverse event reaction terms from the MedDRA Reaction Terms column. Each reaction was categorized into:

- System Organ Class (SOC) – a broad classification of the affected system
- Preferred Term (PT) – the specific reaction name

Additionally, severity levels were assigned based on MedDRA classifications to provide a structured assessment of the reported adverse events.

Attachment 6 provides a categorization of each reaction term into its corresponding System Organ Class (SOC) and Preferred Term (PT) using MedDRA standards, including severity levels. Please note that each case may include multiple MedDRA reaction terms, and thus, the total number of categorizations exceeds the number of cases, as multiple adverse events may be reported for a single case.

DSM would like to emphasize the critical role of regulatory adverse event (AE) reporting systems, such as Australia's DAEN and the FDA's FAERS, in monitoring sunscreen safety. However, these systems have significant limitations in tracking AEs associated with multi-ingredient sunscreen formulations, particularly in identifying the causative ingredient and accurately assessing safety risks.

Key Limitations of AE Reporting Systems in Sunscreen Safety Assessment:

- ***Ingredient Attribution Challenges*** - Sunscreens contain a complex mix of UV filters and cosmetic excipients, making it difficult to determine whether an AE is caused by an active ingredient (e.g., bemotrizinol, avobenzone) or an inactive excipient (e.g., preservatives, emulsifiers, fragrances, silicones). Current AE reporting systems often lack full ingredient-level disclosure, leading to misclassification of the causative agent. Furthermore, actual ingredient concentrations are not readily available due to trade secret protections, further complicating causality assessments.

- ***Incomplete and Inconsistent Reporting*** - AE databases are limited by incomplete, inconsistent, and unverified consumer self-reports. Many reports lack medical confirmation, making it difficult to assess the severity and root cause of reactions. Mild cases are often underreported, while public awareness and media attention can skew reporting trends. Additionally, regulatory classification inconsistencies complicate data interpretation—reactions such as sunburn, phototoxicity, and contact dermatitis may be categorized under different System Organ Classes (SOCs) in MedDRA, reducing cross-product comparability.

- ***Regulatory Variability Across Regions*** - Sunscreen regulation differs globally, impacting AE reporting and safety assessments. In Europe, South America and Asia, sunscreens are classified as cosmetics, in Australia as therapeutic goods, whereas in the U.S., they fall under OTC drug regulations, leading to different safety assessment thresholds and pharmacovigilance requirements. These regulatory discrepancies affect how AEs are recorded, interpreted, and addressed in different markets.

Given these limitations, ingredient-specific safety data remain essential for ensuring accurate sunscreen safety assessments. Our OMOR submission (MGF-400105) supports the safety of Bemotrizinol (BEMT) for use in sunscreen formulations at a maximum level of 6%. As indicated in our OMOR submission, a primary rabbit eye irritation test demonstrated that BEMT is not corrosive or irritating to the eyes.

Furthermore, our submission includes comprehensive toxicological, clinical, and real-world exposure data to support a science-based assessment of BEMT's dermal and systemic safety profile. These data help bridge existing gaps in AE surveillance systems by providing ingredient-specific safety substantiation, ensuring consumer confidence and regulatory clarity regarding BEMT's suitability as a broad-spectrum UV filter.

4. Details of Specific Cases

a. For case 638629 (MedDRA term "third degree chemical burn of the skin"), provide details about the causative agent of the chemical burn and treatment received. Provide further case report information if available.

b. For cases 516049 and 709696 (MedDRA reaction term "burns third degree"), provide additional case report details.

c. For case 451537 (MedDRA reaction term "burns second degree"), provide additional case report details.

DSM RESPONSE:

Adverse events reported in the Database of Adverse Event Notifications (DAEN), including burns, are classified using standardized medical terminologies such as the Medical Dictionary for Regulatory Activities (MedDRA). Events are categorized into System Organ Classes (SOCs) and assigned Preferred Terms (PTs) to ensure consistency in reporting and analysis. The severity of each event is also assessed and recorded.

A third-degree burn, also known as a full-thickness burn, is one of the most severe types of burns (excluding fourth-degree burns). It destroys both the epidermis (outer layer of skin) and dermis (inner layer of skin) and may extend into the subcutaneous tissue, muscle, or bone.

In MedDRA, third-degree burns are classified under the System Organ Class (SOC) *"Injury, poisoning and procedural complications"* with the Preferred Term (PT) *"Burn third degree"*.

Access to Case Information, Safety Considerations & Reporting Accuracy

Further information related to Cases 638629, 516049, and 451537 is unavailable, as detailed case-specific data on adverse events related to bemotrizinol (BEMT) is subject to privacy and confidentiality regulations in Australia.

While the Therapeutic Goods Administration (TGA) manages the DAEN, which provides publicly available information on reported AEs, the publicly accessible data is de-identified to protect patient and reporter confidentiality. As a result, detailed case-specific information, including personal identifiers or sensitive details, is not publicly disclosed. This practice aligns with Australian privacy laws and ethical guidelines (TGA Database of Adverse Event Notifications).

Additionally, based on existing safety data, it is unlikely that third-degree burns or similar severe skin reactions would be caused by bemotrizinol (BEMT). Comprehensive toxicological and clinical safety studies have demonstrated that BEMT has a strong safety profile, with minimal skin penetration, low irritation potential, and no known phototoxic or sensitization effects. The occurrence of such severe burns in the DAEN database is more likely to be related to factors such as inadequate sun protection, pre-existing skin conditions, or other excipients within the product formulation rather than BEMT itself.

Furthermore, inaccurate or incomplete reporting of case data in adverse event databases such as DAEN may contribute to misclassification or overestimation of risks. Variability in how AEs are reported by consumers and healthcare professionals—including missing information on product use conditions, co-administered substances, or pre-existing skin conditions—can limit the ability to determine causality. Given these factors, reported third-degree burns in DAEN should be interpreted cautiously, particularly in the absence of substantiated clinical evidence linking BEMT to such severe skin effects.

5. Age Details for Reports

a. For cases where age values are listed as "<1", provide more specific details regarding the age in months.

DSM RESPONSE:

In the Database of Adverse Event Notifications, age data is often categorized into broad groups to protect patient confidentiality. For instance, individuals younger than one year old are typically labeled as "<1". Due to privacy regulations, more specific age details, such as the exact number of months, are not publicly disclosed. Consequently, obtaining precise age information beyond these general categories is not possible through publicly available DAEN data.

Review of January 15, 2025, Response

6. We received your response to the Information Request #9 regarding adverse events related to system organ class (SOC) "eye disorders," including Preferred Terms of "eye irritation, conjunctival hyperaemia, lacrimation increased, and eye discharge." You attributed these events to cross-contamination from the face or eye rubbing and stated that they are not considered a significant safety concern. However, the clinical study report documents in your OMOR submission specify study participants were instructed to wear eye goggles during the study. Provide further justification for your conclusion of cross-contamination in the context of study participants wearing eye protection. Include individual patient narratives as necessary to support your explanation.

DSM RESPONSE:

Eye protection was provided during the application phases but was not worn for the full study duration. While subjects were instructed to avoid touching their eyes, incidental contact through rubbing, sweating, or secondary transfer from hands or towels cannot be entirely ruled out. Given the lipophilic nature of sunscreen formulations, residual product on adjacent facial skin may have migrated toward the periocular region, increasing the likelihood of non-intentional exposure.

The reported eye-related adverse events were transient, mild, and self-resolving without requiring medical intervention, suggesting that these effects were minor and not indicative of true ocular toxicity. There were no severe or persistent cases of eye disorders linked to Bemotrizinol (BEMT), reinforcing the conclusion that the observed events were due to mechanical transfer rather than an inherent irritant effect of the ingredient.

We have included individual patient narratives to support our explanation in Table 1. Based on the documentation below, there is likely to be cross-contamination from areas of the face or from rubbing the eye, which would not be considered a significant safety concern. Of the 11 participants and 15 AEs noted below, all but three AEs have a report of self-contamination (rubbing, touching, or getting the product into the eyes) or product dripping.

Table 1. BEMT-001 Adverse Events Data – Individual Study Participant Narratives

Participant Number	Study Application Times	Adverse Event Details	Annotation Narrative
1006	2020-11-05T11:20:00, 2020-11-05T13:20:00, 2020-11-05T15:20:00, 2020-11-06T09:20:00, 2020-11-06T11:20:00, 2020-11-06T13:20:00, 2020-11-06T15:20:00	Bilateral watery eyes (05 Nov 2020 12:30:00 - 06 Nov 2020 23:30:00)	Subject reports watery eyes continue, increase noted when sunscreen is applied; improvement noted as sunscreen dries.
1-1012	2022-03-18T15:44:00	Bilateral Ocular Irritation (3/19/2022 9:44 - 3/21/2022 8:00:00 AM)	Subject reports mild irritation in both eyes since rubbing them this AM. Encouraged to avoid touching eyes.
1-1012	2022-03-18T15:44:00	Bilateral Conjunctival Injection (3/19/2022 9:41 - 3/21/2022 8:00:00 AM)	Subject reports mild irritation in both eyes since rubbing them this AM. Encouraged to avoid touching eyes.
1-1024	2022-03-15T16:32:00, 2022-03-16T10:32:00, 2022-03-16T12:32:00, 2022-03-16T14:32:01, 2022-03-16T16:32:00	Eye irritation (2022-03-15T17:00:00 - 2022-03-16T21:00:00)	Subject touched eyes after dose, irritation lasted ~30 minutes. No redness, no vision issues.
1-1033	2022-03-23T11:20:00, 2022-03-23T13:20:00	Eye irritation (2022-03-23T13:00:00 - 2022-03-23T14:00:00)	None available.
1-1034	2022-03-24T13:28:30, 2022-03-24T15:24:00	Left eye conjunctival injection (2022-03-24T13:45:00 - 2022-03-24T21:00:00)	Subject accidentally touched left eye after dose, mild injection, vision unaffected.
1-1043	2022-03-22T14:00:00, 2022-03-22T16:00:00,	Right Eye Irritation (3/22/2022 15:10 -	Felt sunscreen may have gotten in eye, wiped with

Participant Number	Study Application Times	Adverse Event Details	Annotation Narrative
	2022-03-23T10:00:00, 2022-03-23T12:00:00, 2022-03-23T14:00:00, 2022-03-23T16:00:00	3/22/2022 15:15:00 PM)	bedsheet, resolved quickly.
1-1043	Same as above	Left Eye Irritation (3/23/2022 14:54 - 3/23/2022 15:04)	Product dripped from forehead, resolved in 10 minutes after wiping.
1-1071	2022-03-30T10:04:00, 2022-03-30T12:04:00, 2022-03-30T14:04:00	Bilateral Ocular Irritation (3/30/2022 13:00 - 3/30/2022 13:15:00)	Subject believes IP got in eyes, resolved in 15 minutes.
1-1071	Same as above	Bilateral Epiphora (3/30/2022 13:00 - 3/30/2022 13:00)	Same as above.
1-1084	2022-04-07T15:28:00, 2022-04-08T09:28:00, 2022-04-08T11:28:00, 2022-04-08T13:28:00, 2022-04-08T15:28:00	Left eye irritation (4/7/2022 17:01:18 - 4/10/2022 08:00:00)	Mild burning, requested eye wash, improved with saline irrigation.
1-1090	2022-04-26T15:20:00, 2022-04-27T09:20:00	Left eye irritation (2022-04-26T16:15:00 - 2022-04-26T19:00:00)	Started after last dose, no visual changes, no tearing.
1-1092	2022-04-26T15:28:00	Left eye irritation (2022-04-26T16:00:00 - 2022-04-27T07:20:00)	Touched eye after last dose, no right eye issues.
1-1093	2022-04-26T15:32:00, 2022-04-27T09:32:45	Left Eye Redness (2022-04-27T06:15:00 - 2022-04-27T08:15:00)	None available.
1-1143	2022-09-20T11:08:00, 2022-	Eye Burning (2022-09-20T11:15:39 -	Product dripped into left eye, burning improved after wiping.

Participant Number	Study Application Times	Adverse Event Details	Annotation Narrative
	09-20T13:08:00, 2022-09-20T15:08:10	2022-09-20T17:00:00)	
1-1145	2022-09-28T15:04:00, 2022-09-29T09:04:00, 2022-09-29T11:04:00, 2022-09-29T13:04:00, 2022-09-29T15:04:00, 2022-09-30T09:04:00, 2022-09-30T11:04:00, 2022-09-30T13:04:00, 2022-09-30T15:04:00	Right Eye Rheum (9/28/2022 17:00:00 - 10/2/2022 18:00:00)	Dryness, redness, denies drug in eye, history of blepharitis.
1-1145	Same as above	Right Eye Epiphora (9/29/2022 11:30:57 - 9/30/2022 16:26:17)	Same as above.

As indicated in the OMOR submission (Attachment 7), results from a primary rabbit eye irritation test demonstrated that BEMT is not corrosive or irritating to the eyes. Additionally, post-marketing surveillance data from Australia's Therapeutic Goods Administration (TGA) does not indicate a pattern of significant ocular irritation complaints associated with BEMT-containing sunscreen products. Reports of sunscreen-related eye irritation are more commonly linked to other UV filters such as oxybenzone and homosalate, as well as inactive excipients including preservatives, emulsifiers, fragrances, and silicones.

Several inactive ingredients may cause eye irritation, including potassium cetyl phosphate and magnesium stearate, which were each present in the emulsion formulas applied during Part 2 of the pivotal MuST study (BEMT-001). These ingredients are commonly used emulsifiers but have been associated with mild ocular irritation when unintentionally introduced into the eyes. Given that subjects did not wear eye protection for the full study duration, the potential for inadvertent transfer of these excipients to the eye area through rubbing or sweating must be considered as a contributing factor.

Sunscreen-related eye irritation is generally attributed to accidental exposure rather than an inherent chemical effect. A chemical sunscreen active such as oxybenzone has been associated with tear film instability, leading to ocular discomfort in some individuals. Even physical sunscreen ingredients like zinc oxide and titanium dioxide, which are considered less irritating, can still cause mechanical irritation if rubbed into the eyes. Sunscreen formulations containing fragrances, alcohols, or gel-

based textures have been reported to increase the likelihood of eye irritation compared to fragrance-free or lotion-based formulations.

Given post-market surveillance trends and existing formulation considerations, sunscreen manufacturers commonly include explicit warnings on packaging advising consumers to avoid direct contact with the eyes. The study findings, in conjunction with preclinical safety data and broader post-marketing evidence, support the conclusion that the reported adverse events related to the "Eye Disorders" system organ class were most likely due to cross-contamination rather than a direct irritant effect of BEMT.

The response to this information request is being provided electronically under Mod 1 via FDA's NextGen portal MGF 400105.

Please contact me if you have any questions or need additional information.

Sincerely,

Carl D'Ruiz, MPH.
Senior Regulatory and Business Development Manager, Beauty & Care, NA