



15 January 2025

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10903 New Hampshire Avenue
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Subject: MGF 400105 – Response to Information Request Letter #9 [3261]

Dear CDR Tran,

Reference is made to FDA’s Information Request (IR) letter dated January 09, 2025, related to DSM’s MGF 400105 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.

In its January 09th correspondence, the FDA provided the following comments and IR’s related to our BEMT-001 clinical study. The FDA requested that we submit a written response to the CDER NextGen Portal by January 15, 2025. Below is our response to this IR.

Clinical:

- 1. A review of your adverse events dataset for BEMT-001 shows 14 adverse events related to the system organ class (SOC) “eye disorders” out of 176 total adverse events. These Preferred Terms include eye irritation, conjunctival hyperaemia, lacrimation increased, and eye discharge. Provide justification for this, supplying patient narratives as necessary.*

DSM Response:

For ocular adverse events, the study product Bemotrizinol (BEMT) was applied to the entire body, including the face, brow, and up to the wrists bilaterally. All participants underwent 16 total applications of the study product. Adverse events were transient, did not occur with every dose, and no visual disturbances were noted. All adverse events resolved with continued dosing, except for participant 1006, who experienced no ocular events during the first 10 doses. Based on these facts, the event is more likely attributable to cross-contamination from the face or eye rubbing and is not considered a significant safety concern.

The inclusion of a warning statement regarding eye safety is a critical component of OTC sunscreen labeling, as mandated by the FDA. In our OMOR submission (section 1.14.1.1), the proposed labeling reflects this requirement: **“When using this product, keep out of eyes. Rinse with water to remove.”** This warning mitigates the potential for irritation from accidental exposure to sensitive areas, ensuring the responsible use of BEMT-based formulations. By including this universally recognized statement, our labeling demonstrates a commitment to regulatory compliance and consumer safety, offering clear guidance to minimize risks and enhance user experience.

From a post-marketing perspective, sunscreens containing BEMT have a low potential for eye irritation. This is supported by data from the Australian Database of Adverse Event Notifications (DAEN), summarized in our MGF 400105 – Partial Response to Filing Communication Information Request submitted on January 10, 2025. In this DAEN summary, eye irritation was not identified except for a few isolated cases of eye swelling, none of which were directly associated with BEMT in applied sunscreen products.

- 2. In addition, for the SOC “general disorders and administration site conditions”, there are several events related to “infusion site,” for example, hemorrhage, irritation, and pain. There are also several events related to “vessel puncture site,” for example: pain, bruise, reaction, and swelling. Provide justification for use of the term “infusion site” as there was no mention of IV placement or infusion as part of BEMT-001. Additionally, explain how you differentiated between “infusion site” reactions and “vessel puncture site” reactions.*

DSM Response:

The MedDRA version 23.1 dictionary does not have a Lowest Level Term (LLT) that directly translates to “phlebotomy site” as recorded in the AE Terms. Spaulding Clinical LLC’s coding process, at the time of this study, used a coding program that related the recorded AE Term as closely as possible to an available LLT. In the specifics of this case – phlebotomy site pain, bruise, reaction, and swelling coded to the LLT of ‘venipuncture site’ because venipuncture is a catch-all term for puncturing a vein for a medical procedure. The following Preferred Term (PT) of ‘Vessel Puncture Site’ is just the standard coding pathway per the MedDRA dictionary (please see the standard pathway below):

Bemotrizinol (BEMT)

The MedDRA version 23.1 dictionary does not include a Lowest Level Term (LLT) that directly corresponds to "phlebotomy site" as recorded in the Adverse Event (AE) Terms. At the time of this study, Spaulding Clinical LLC's coding process utilized a program that assigned the recorded AE Term to the closest matching LLT available. In this case, terms such as **phlebotomy site pain, bruise, reaction, and swelling** were coded to the LLT '**venipuncture site**'. This is because "venipuncture" is commonly used as an umbrella term to describe vein puncture for medical procedures.

Following standard MedDRA coding pathways, the LLT '**venipuncture site**' maps to the Preferred Term (PT) '**Vessel Puncture Site**', which reflects the standardized hierarchy in the MedDRA dictionary. The pathway is as follows:

- **LLT:** Venipuncture site pain
- **PT:** Vessel puncture site pain
- **HLT:** Administration site reactions NEC
- **HLGT:** Administration site reactions
- **SOC:** General disorders and administration site conditions

In the case of the Adverse Event (AE) Terms recorded as '**phlebotomy site hemorrhage,**' '**phlebotomy site irritation,**' '**phlebotomy site tenderness,**' or '**phlebotomy site ecchymosis,**' there was no corresponding Lowest Level Term (LLT) of '**venipuncture site**' with the accompanying descriptors of hemorrhage, irritation, tenderness, or ecchymosis in the MedDRA version 23.1 dictionary. While we recognize that more precise terms could have been selected, the coding team at the time opted to use '**infusion site**' followed by the specific descriptors of hemorrhage, irritation, tenderness, or ecchymosis as the closest match to accurately capture these adverse events.

This approach was based on the team's assessment of the available LLTs and their alignment with the reported AE Terms. The hierarchy pathway for the chosen LLT is as follows:

- **LLT:** Infusion site irritation
- **PT:** Infusion site irritation
- **HLT:** Infusion site reactions
- **HLGT:** Administration site reactions
- **SOC:** General disorders and administration site conditions

While this coding choice may not have been ideal, it reflects the limitations of the MedDRA dictionary at the time and the team's effort to select terms that most closely captured the nature of the reported events.

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

MGF-400105

Bemotrizinol (BEMT)

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

Sincerely,

A handwritten signature in black ink, appearing to read "Carl D'Ruiz". The signature is written in a cursive style with a large initial "C".

Carl D'Ruiz, MPH.

Senior Regulatory and Business Development Manager, Beauty & Care, NA