dsm-firmenich

DSM Nutritional Products LLC
45 Waterview Boulevard
Parsippany, NJ 07054-1298, USA
+1 201.400.9376
Carl.d-ruiz@dsm-firmenich.com

16 January 2025

CDR Trang Tran, PharmD, MBA, BCPS **CONFIDENTIAL INFORMATION**

Senior Regulatory Project Manager
Division of Regulatory Operations for Nonprescription Drugs I
Office of Regulatory Operations
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Subject: MGF 400105 – Final Response to Filing Communication Information Request

Dear CDR Tran,

Reference is made to FDA's Filing Communication (FC) letter dated December 06, 2024, related to our OMOR submission of September 23 and subsequent amendments dated October 07, October 18, October 28, November 07, November 12, and November 21, 2024, in response to our information request correspondences issued on October 1, October 16, October 24, and November 5, 2024. Further reference is made to DSM's MGF 400105 – Partial Response to Filing Communication Information Request letter of January 10, 2025.

In its Filing Communication correspondence, the FDA confirmed that our OMOR submission is sufficiently complete and properly formatted to proceed with a substantive review. The FDA has officially filed the submission and requested additional data to address four potential review areas: interdisciplinary science, clinical, clinical pharmacology, and Chemistry, Manufacturing, and Controls (CMC).

Our responses to the identified interdisciplinary science, clinical, and CMC issues were submitted on January 10, 2025. In that correspondence, we noted the need for additional time to compile the requested clinical pharmacology information. Below is our response addressing this remaining information request.

CLINICAL PHARMACOLOGY

1. *Submit the method validation summary and reports for bioanalytical method(s) used to analyze in vitro permeation test (IVPT) samples.*

DSM Response:

A formal bioanalytical method development and validation report for the IVPT analyte, 14C-BEMT, was not prepared because standard methodologies for radiolabeled test substances in IVPT studies do not require separate method development and validation. The approaches used at the testing facilities cited in the DSM-submitted final reports—Innovative Environmental Services, Ltd. and BASF Testing Services—are consistent with these standards. Unlike LC-MS methodologies, radiochemical LSC chromatography is not classified as a bioanalytical method requiring validation.

We also wish to clarify that the Innovative Environmental Services, Ltd. IVPT study was not pivotal to the clinical studies. This study was repeated at the FDA's request due to the presence of BOS. As a result, the IVPT formulations were reformulated and subsequently tested in the pivotal BASF study, which informed the selection of market-image formulations used in the pilot and pivotal MUsT studies.

Both test laboratories routinely perform IVPT studies using positive control substances with established performance characteristics within their respective systems. To support this, we are providing example reports from BASF's pivotal IVPT study as attachments to this response. These reports include data on 14C-labeled positive control substances, demonstrating the performance and reliability of their IVPT systems.

Several additional considerations further underscore the robustness and representativeness of the BEMT percutaneous penetration results obtained in BASF's pivotal IVPT study. These considerations also extend to the original IVPT study conducted by Innovative Environmental Services, Ltd.:

1. **Standardized Protocols**: Each study protocol adheres to recognized test guidelines, including OECD Test No. 428, European Commission Method B.45, and the European Food Safety Authority. All studies are conducted in compliance with the relevant GLP-compliant Standard Operating Procedures of each laboratory.
2. **Quality Assurance**: Results are validated through study phase inspections, auditing by the laboratories' Quality Assurance Units, and verification by the Study Director.
3. **Representative Validation**: The IVPT final reports include:
    - Certificates of Analysis for both the non-labeled and 14C-labeled BEMT test items.
    - Chromatograms comparing HPLC and LSC elution times, demonstrating the coincidence of labeled and non-labeled molecular entities, thereby confirming their representativeness.

The criteria outlined in the ICH M10 Bioanalytical Method Validation Guidance for Industry (2018) (M10 Bioanalytical Method Validation And Study Sample Analysis) are addressed and satisfied within the IVPT methodologies and analytical results presented in the study final reports.

Consequently, a separate method development and validation report for 14C-BEMT is deemed unnecessary.

Additionally, HPLC elution was employed to verify the representativeness of the radiolabeled test item relative to BEMT. The HPLC method has been submitted as part of the Bemotrizinol USP monograph. Reviewers are referred to the proposed USP monograph file for BEMT, included as an attachment to this letter (https://online.usppf.com/usppf/document/GUID-C54FF151-CCCF-4FD1-80BA-7DE764908314_10201_en-US).

To further elaborate on the radiochemical detection and sample analysis process:
Bemotrizinol ([triazine-U-^{14}C]BEMT) was the target analyte in the submitted study reports. As a radiolabeled chemical, BEMT determination involves a straightforward analytical process that quantifies radioactive disintegrations of the analyte in a sample. Background radioactivity is measured and used to correct the total disintegration counts. This automated, machine-controlled process also includes counting efficiency determination and relies on the instrument's calculation software and radiation detector, tuned specifically to the energy emitted by ^{14}C. Instrument reliability and performance are validated independently of the sample as part of the laboratory's GLP compliance processes, including equipment maintenance logs.

Using radiolabeled chemicals in IVPT protocols allows for a comprehensive mass balance of the applied test substance, ensuring the overall study integrity and representativeness of skin penetration results.

Given the detailed and comprehensive nature of the submitted data and analyses, separate validation reports are unnecessary. The information provided in the MGF 400105 submission files sufficiently addresses these requirements in an effective and thorough manner.

We thank FDA for providing additional time to address this potential issue. 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 further questions or need additional information.

Sincerely,

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