

1.6 Meetings

1.6.1 Communications Between FDA and DSM

During the development of BEMT, regulatory guidance on the clinical, nonclinical, and efficacy approach required to support a GRASE determination was obtained from the FDA. A summary of key interactions during the clinical development program for BEMT 6% is presented in [Table 1](#). Complete copies of the meeting materials and correspondence are available in [Module 1.6.3](#). Copies of meeting background material provided to FDA may be found in [Module 1.6.2](#). Correspondence regarding BEMT Pre-IND (PIND) meetings can be found in [Module 1.12.1](#).

Table 1 Summary of Key Interactions with FDA during BEMT Development

Date(s)	Type of Meeting/Correspondence: Purpose/Summary
January 29, 2019	The purpose of this meeting request was to introduce DSM as an Interested Party to the OTC listing of BEMT and obtain FDA feedback on DSM's proposed approach for submitting the additionally required safety and efficacy data needed to support a generally recognized as safe and effective (GRASE) determination for BEMT under the OTC Sunscreen Monograph via the Sunscreen Innovation Act (SIA) regulatory process.
April 24, 2019	DSM submitted the confidential meeting package for BEMT to OTC Docket FDA-2005-N-0453.
April 30, 2019	FDA issued the Meeting Request Granted letter for a non-public teleconference on Jun 7, 2019 to discuss the pending Time and Extent Application (TEA) and FDA's Proposed Sunscreen Order for BEMT.
June 7, 2019	FDA held the teleconference with DSM.
July 16, 2019 and August 9, 2019, respectively	FDA issued non-public and public meeting minutes providing feedback on meeting questions related to clinical, nonclinical and administrative data requirements needed to support a positive GRASE determination for BEMT
November 7, 2019	DSM sent an email correspondence to CDR Kristin Haslam requesting clarification on how to import formulations containing BEMT for use in US clinical MUSt studies given that it is an unapproved new sunscreen active ingredient not subject to an IND, but rather SIA regulatory requirements (i.e., time and extent application (TEA) active ingredient for inclusion onto sunscreen monograph).
November 11, 2019	Dr. Theresa Michele sent an e-mail correspondence to DSM indicating that based on further FDA review, an IND would be needed prior to the initiation of the clinical MUSt studies. Subsequent verbal communications with CDRs Trang Tran and Kristen Haslam indicated that due to this determination, there would be a need to submit a pre-IND submission in order to obtain FDA feedback regarding IVPT test results, proposed pilot MUSt study formulations and draft Pilot MUSt study protocol.
December 4, 2019	DSM submitted a pre-IND Type B meeting request and data package for BEMT. Submission contained: June 7, 2019 meeting minutes and information; IVPT study test results and reports associated with the proposed Pilot MUSt study formulations; a summary of the rationale for a proposed Pilot MUSt study design for BEMT based on IVPT test results; a draft clinical study protocol for the proposed Pilot trial; and a list of questions by discipline.
December 4, 2019	DSM submitted the information regarding the IVPT test results, proposed pilot MUSt study formulations and draft pilot MUSt study protocol to solicit FDA's written feedback prior to submitting it for review to support a determination that BEMT is GRASE for sunscreen use under the OTC Sunscreen Monograph.
February 7, 2020	FDA issued Type B Pre-IND Written Responses Only. The letter provided responses to questions related to non-clinical IVPT test results; clinical MUSt protocol design; the need to conduct a market survey of BEMT-containing formulations used in the IVPT and

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	MUsT studies; CMC and administrative clarifications; and a notification that all BEMT IND submissions needed to be in eCTD format.
June 10, 2020	DSM submitted an investigational new drug application (IND 146892) to conduct a pilot clinical pharmacokinetic (PK) investigation of BEMT at a maximum concentration of 6% in a topical sunscreen maximal use trial (MUsT) in support of its inclusion as a sunscreen active ingredient in FDA's OTC Monograph M020: Sunscreen Drug Products for OTC Human Use.
July 9, 2020	FDA and DSM had a teleconference to discuss modification needed for clinical pilot MUsT study.
August 3, 2020	FDA issued a 'Study May Proceed' letter for IND 146892 with non-hold clinical, clinical pharmacology, chemistry (CMC), and pharmacology/toxicology (P/T) comments. FDA's P/T comments indicated that the identification and quantification of potential metabolites of concern that necessitate nonclinical safety assessment (if any) and the submission of adequate pharmacokinetic, absorption, distribution, metabolism and excretion (PK/ADME), and toxicokinetic (TK) data were needed to support a future GRASE determination for BEMT.
October 30, 2020	DSM submitted a protocol amendment for IND 146892 that included the following information: (1) modifications made to the clinical investigation for sunburn prevention (BEMT-001) in follow-up to the agreed upon changes made during the teleconference of July 9, 2020; (2) scientific rationale to support the in vitro permeation testing (IVPT) results for the MUsT in light of the formulations change between those used in the IVPT and those proposed for the MUsT; (3) four new dermal safety clinical protocols for FDA review and comment; (4) rationale for not conducting a systemic carcinogenicity test for BEMT; and (5) responses to the clinical, clinical pharmacology, CMC, and P/T comments made in the Study May Proceed letter of August 3, 2020.
January 28, 2021	FDA issued a general advice letter for IND 146892 to provide comments/recommendations for the Part 2 pivotal MUsT study, excipient used in IVPT tests, and draft dermal safety protocols. Regarding DSM's request not to conduct a systemic carcinogenicity test for BEMT, FDA indicated that such a request was premature prior to receipt of results from DSM's pilot and pivotal clinical MUsT studies. FDA also reiterated that data from adequately designed and conducted TK/ADME studies in appropriate animal models administered BEMT by both the oral and the dermal routes would be pivotal to any ultimate GRASE determination for BEMT.
February 26, 2021	DSM submitted a protocol amendment, which included a response to FDA's request for further information, a request for a Type A teleconference meeting (with a meeting package) to discuss the timeframe and design of the studies that remained to be conducted under the BEMT general investigational plan to support a GRASE determination for BEMT, and a request for special protocol assessment for a new carcinogenicity study protocol for IND 146892.
April 6, 2021	DSM submitted a request for advice on the proposals for the new IVPT test, butyloctyl salicylate contribution to overall activity, formulations for MUsT and dermal studies, Part 2 MUsT, and a carcinogenicity study for IND 146892.
April 12, 2021	The CDER Executive Carcinogenicity Assessment Committee issued a 'Special Protocol – No Agreement' Correspondence for IND 146892 that included recommendations and conclusions regarding DSM's new carcinogenicity study protocol. The Committee was unable to agree to DSM's proposed doses in male or female mice based on the available information submitted. The available supporting data did not provide a sufficient basis upon which to recommend alternative doses for a definitive 26-week study. The Committee concluded that additional data and justification were needed.
August 13, 2021	FDA issued a Type C Written Responses Only (WRO) Letter for IND 146892 that included the responses to DSM's questions from the February 26, 2021, meeting request and April 6, 2021, request for advice.
February 22, 2022	DSM submitted an information amendment and general correspondence to provide an update of the progress being made with IND 146892 based on FDA's recommendations

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	provided in the January 28, 2021, general advice letter and August 13, 2021, Type C WRO Letter.
September 8, 2023	DSM submitted an annual report that included an update on the status of its general investigational plan. DSM notified FDA of the completion of all planned clinical and nonclinical studies, requested not to conduct a systemic oral carcinogenicity test, provided IND amendments, provided a response to FDA’s request for additional CMC information, and general correspondence, to IND 146892. DSM also included several questions with this submission.
October 4, 2023	DSM received an email communication from CDR Trang Q. Tran, the Project Officer, acknowledging receipt of the DSM annual report and the included questions. Also stated was the following: <i>“To allow us to best respond to these questions, we recommend DSM to submit a pre-OMOR Type Y meeting request, following the guidance for industry Formal Meetings Between the Food and Drug Administration and Sponsors or Requestors of Over-the-Counter Monograph Drugs FDA.”</i>
November 13, 2023	DSM submitted a request for a Type Y face-to-face meeting (MGF 400083) for bemotrizinol (BEMT) 6%. The purpose of this meeting was to discuss DSM’s upcoming OMOR request for a GRASE determination for BEMT 6% as a sunscreen active ingredient under FDA’s OTC Monograph M020: Sunscreen Drug Products for OTC Human Use, and questions regarding the completion of DSM’s drug development plan.
November 22, 2023	DSM received a Type Y meeting request granted letter from FDA.
December 12, 2023	FDA received a meeting Type Y meeting package from DSM.
January 2, 2024	DSM received a CMC/drug substance advice/information request related the CMC section IND 146892 from Esther W. Jones, BSN, RN, Regulatory Business Process Manager, DRBPMI, Office of Program and Regulatory Operations Office of Pharmaceutical Quality, CDE. The request concerned the justification of impurity specification limits, batch analyses showing compliance, validation of test methods for detecting various impurities, and whether the starting material was available in the non-pharmaceutical market.
January 3, 2024	DSM received a CMC/drug substance advice/information request from Esther W. Jones, BSN, RN, Regulatory Business Process Manager Division of Regulatory and Business Process Management I (DRBPMI), modifying the response date associated with the January 2, 2024 letter.
January 16, 2024	DSM provided the FDA with a response to its request for additional CMC information in the request letter dated January 3, 2024.
January 29, 2024	DSM received FDA’s preliminary responses to the questions raised in DSM’s December 12, 2023 Type Y meeting package.
January 31, 2024	<p>In response to the FDA's Meeting Preliminary Responses correspondence of January 29, 2024, DSM submitted a letter indicating that a meeting was still needed on February 5, 2024 (3-4 pm ET) to discuss and clarify the responses provided to several questions. DSM also submitted a revised agenda that included pre-meeting comments addressing the FDA’s preliminary responses to questions 4, 9, 10, 12, and 13, along with additional comments. Key agreements and outcomes:</p> <ul style="list-style-type: none"> • <i>All information and complete study results, both positive and negative, that are relevant to the GRASE determination for BEMT 6% will be included in OMOR submission.</i> • <i>OMOR submission will include full study reports from any legacy studies submitted under the Time and Extent Application (TEA) process that will be relied upon to support a GRASE determination of BEMT 6%.</i> • <i>Any safety or efficacy concerns regarding combining BEMT with other sunscreen active ingredients will be addressed in the OMOR submission.</i> • <i>Determination of whether the scientific justification for not conducting a systemic carcinogenicity study is adequate to support OMOR will be a review issue.</i> • <i>DSM will address why certain PK study timepoints concentrations were above 0.5 ng/ml for some subjects in OMOR.</i>

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	<ul style="list-style-type: none"> • <i>DSM will provide any updates regarding the ingredient's current marketing status.</i> • <i>FDA plans to determine whether the OMOR is sufficiently complete and formatted to permit a substantive review within 60 days after receipt (i.e., filing determination).</i> • <i>DSM will the proposed age group for BEMT and discuss the rationale for the chosen age group in the OMOR.</i>
February 12, 2024	Following DSM's January 16, 2024, IND 146892 amendment, which responded to the Agency's January 3, 2024, request for CMC information for BEMT synthesis, DSM received a request from Esther W. Jones, BSN, RN, Regulatory Business Process Manager at DRBPMI, for additional CMC/drug substance information.
March 6, 2024	<p>DSM received a copy of the official meeting minutes from the Type Y meeting between the DSM and the FDA on February 5, 2024. Key agreements and outcomes:</p> <ul style="list-style-type: none"> • <i>All efficacy and safety data sets, analysis plans, case report forms for adverse events, investigator disclosure information, postmarketing data presentations by source, literature review indexed or hyperlinked, and other relevant information will be provided in OMOR submission.</i> • <i>DSM will clarify which efficacy studies were conducted on BEMT in combination with other sunscreen active ingredients.</i> • <i>If major human metabolites are identified, DSM will identify disproportionate metabolites based on comparison of human and animal metabolites (in vivo) to determine if any additional animal testing is warranted.</i> • <i>DSM will submit a copy of draft USP monograph for BEMT and resolve any remaining issues related to starting materials and specification limits for impurities.</i> • <i>FDA noted that the new PK studies that DSM conducted are expected to be considered human studies for exclusivity purposes under the CARES Act. FDA advised DSM to submit the request for an exclusivity determination as part of its OMOR submission along with appropriate justification.</i> • <i>DSM confirmed that its intention is to market sunscreen products containing BEMT for adults and children 6 months of age and older and will revise the Drug Facts Label so that it is consistent with FDA's sunscreen labeling requirements.</i> • <i>FDA stated that there are no PREA requirements for monograph products. According to the 2019 Sunscreen Proposed Rule and 2021 Sunscreen Proposed Order, as long as the margin of safety is wide, FDA is unlikely to ask for additional pediatric information beyond the required clinical data. In addition, FDA advised DSM to provide any available pediatric data from the European market in its OMOR submission, including postmarketing safety reports and indicated that FDA is not looking for any specific pediatric studies.</i>
July 15, 2024	DSM submitted a quality information amendment in response to FDA's February 12, 2024 Advice/Information Request letter for additional CMC information.
August 27, 2023	DSM obtains new reassigned MFG # 400105 for BEMT OMOR Submission via FDA NextGen Portal following telephone conversation with CMDR Tran Trang.