12 September, 2023

GENERAL PRINCIPLES
MODEL-INTEGRATED EVIDENCE (MIE) INDUSTRY MEETING PILOT BETWEEN FDA AND GENERIC DRUG APPLICANTS

The U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services has established a pilot program to provide industry with opportunities for early and focused interactions for science-driven topics using model-integrated evidence (MIE) approaches for bioequivalence (BE) establishment to facilitate generic drug development and regulatory decision making. The goal of the pilot program is to enhance scientific communications between generic drug developers and FDA on using a broad range of quantitative methods and modeling techniques to address generic drug development issues or questions that are either out of the scope or cannot be sufficiently and efficiently addressed by the pre-abbreviated new drug application (pre-ANDA) and ANDA meetings established under the Generic Drug User Fee Amendments (GDUFA) III. Overall, industry is seeking FDA's feedback on establishing best practices for MIE and outcome communication to help implement MIE in their development processes. Thus, this pilot program aims to support drug development by offering prospective ANDA applicants and ANDA applicants[1] an opportunity for early, focused, and enhanced interactions with FDA. Meetings granted under this pilot program will serve as a dedicated forum for interactions with the FDA on MIE approaches to obtain FDA's advice on 1) if and/or how the proposed modeling approaches can be used in a specific drug development program, 2) how to advance modeling methodology to address common issues of multiple products from the same applicant, and/or 3) how to address complex issues as they arise and implement innovative approaches in the development of non-complex products. Scientific issues for non-complex products are currently not the main focus in existing meetings.[2]

FDA has the following principles for the pilot program. Posting this "General Principles" document on the website will make the MIE program's process and goals more transparent and

[1] Applicant is defined as "any person who submits an…ANDA…under this part to obtain FDA approval of a new drug and any person who owns an approved…ANDA." 21 CFR 314.3(b). The term "prospective ANDA applicant" is used when meetings occur before an ANDA is received and the term "ANDA applicant" is used when meetings occur after an ANDA is received. This document uses the term "applicants" to refer to both prospective ANDA applicants and ANDA applicants.

[2] FDA Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (October 2022, Revision 1). Available at: https://www.fda.gov/media/107626/download

help answer questions about the program. This document is posted in accordance with FDA procedures.

FDA will start receiving meeting requests under the MIE pilot program on October 1, 2023. FDA will continue to receive meeting requests under the MIE pilot program until a sufficient number of MIE meetings are held. FDA will evaluate the pilot program at the end of year one (1) or after five (5) meetings have been held, whichever occurs first to determine the next phase of the pilot program.

Specifically, to optimize time and resources of the pilot program, a priority will be given to meeting requests focusing on:

- Innovative MIE-focused approaches for BE establishment that cannot be effectively addressed under the existing GDUFA scientific meetings
- Non-complex products with complex approaches/modeling
- Novel data analytics tools and approaches (e.g., machine learning and artificial intelligence) for BE establishment and assessment

As described below, there are a total of three stages in this pilot MIE meeting process (**Appendix**):

1) Stage 1, applicant requests a meeting with FDA
2) Stage 2, FDA assesses the meeting request, determines the need for an optional orientation meeting, and conducts a final meeting with the applicant
3) Stage 3, FDA communicates the final discussion held during the MIE meeting

During and after the conclusion of the pilot, FDA will evaluate the benefits and challenges of the program, including the resources required, and determine next steps.

1. The MIE pilot program is voluntary. To participate in the MIE pilot program, applicant submits a meeting request to FDA following the process delineated in this document.

2. Under the MIE pilot program, candidates include product development programs that may benefit from early and focused communication with FDA on their MIE approach for BE, and such approaches cannot be effectively addressed under the existing GDUFA scientific meetings. For example, the prospective applicant may use the MIE pilot program to discuss MIE-focused approaches that are innovative in nature for BE establishment and are not eligible under the pre-ANDA program to address complex issues pertinent to a singular product or multiple products from the same applicant, non-complex products with complex approaches or modeling simulations for Biopharmaceutics Classification System (BCS)-based biowaivers or other study waivers, and novel data analytics tools such as modeling methodology advancement or new applications of a modeling approach.

MIE-focused regulatory pathways for complex products can also be considered for the pilot program. While such approaches can be eligible for discussion with the existing GDFUA scientific meeting process (e.g., pre-ANDA product development meetings), the pilot MIE meeting is valuable that will focus on discussing scientific and technical topics of using MIE strategies for BE establishment (e.g., feasibility of the MIE approach, details in model building, and/or model verification and validation data and strategies for the intended purpose).

3. Requests for MIE meetings will be granted based on meeting eligibility criteria, anticipated value to the MIE program, and available resources. For each request, FDA will hold at a minimum one, one-hour, (1) MIE meeting with the applicant focused on the specific development questions raised.
   - For each request, FDA will also evaluate the need for one (1) optional (at FDA's discretion) one-hour orientation meeting prior to the MIE meeting, where the applicant can further explain their MIE approach.

Stage 1: MIE Meeting Requests

4. Applicants submitting an MIE meeting request should:

   - As a general matter, focus on and develop specific and technical questions on the utilization of MIE approaches to establish BE for complex or non-complex products.

     Applicants should not submit multiple meeting requests or controlled correspondence at or around the same time with the same or similar questions. If FDA receives multiple meeting requests or controlled correspondence that contain the same or similar question(s), FDA will determine which meeting to grant or controlled correspondence to answer and may deny the other(s); however, the pilot MIE meetings are a potential avenue for discussion on modeling-related topics during a product development cycle.

   - Submit one single "Request for MIE" along with the meeting package to FDA at MIE@fda.hhs.gov. In the meeting package, provide the following information:

     - Cover Letter
       - The cover letter should include ANDA number and product name, the main meeting objective, and applicant information (see below).
     - Pre-assigned ANDA number[3]
     - Applicant information
       - If the applicant is not based in the United States, also provide the U.S. agent information; if the applicant is based in the United States, provide a statement

[3] See FDA's website for information on requesting a pre-assigned application number: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number.

indicating whether the submission is being made by the ANDA applicant or by a U.S. agent on behalf of the ANDA applicant.
        - Contact person for the meeting (i.e., the person submitting the request), with their title and affiliation, secure email address, and phone number. This is the person FDA will communicate with about the meeting.
    - Information and context on the product in development and the reference listed drug (RLD)
    - Information on previous interactions with FDA, for example, to include controlled correspondences (CCs) and/or pre-ANDA product development or pre-submission meetings
    - A brief statement on the purpose and objective of the meeting, including why an MIE meeting would be beneficial to the product's development
    - Specific questions for discussion about the MIE approaches to establish BE for the applicable drug development program
    - A brief statement of the questions of interest in the study or development program, underlaying the agenda
    - A brief statement on the purpose of use: model-integrated BE approach(es) considered for the product under development and how it will be used to address the question of interest and inform regulatory decision-making
    - Sufficient details for underlying assumptions and building process[4]
    - Clear model verification and validation strategies including current and future data support
    - Meeting information to include:[5]
        - Proposed agenda
        - Meeting participants
        - Dates which will not be suitable for a meeting

5. Upon receipt of the meeting package, the applicant will receive a confirmation of meeting package receipt by FDA.

6. Within 14 days of the meeting package receipt date, FDA will evaluate and assess the meeting package submission. FDA, at its sole discretion, will determine if the MIE meeting request will be granted or denied.

7. A MIE request does not guarantee that the MIE meeting will be granted. For a variety of reasons, FDA may decline to participate in such meeting.[6] If an applicant's request for a MIE meeting is not granted, the applicant will receive a formal meeting denial letter via email.

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[4] A full data set is not required at this time, however, can be requested by FDA if a meeting is granted. If a request is made, the applicant should be prepared to provide the full data set to FDA within a reasonable amount of time, as determined by FDA at their sole discretion.

[5] For the MIE pilot program, all meeting requests granted will be granted as a videoconference.

[6] FDA will generally follow the principles, as relevant, outlined in the Manual of Policies and Procedures (MAPP) 5220.8 (Rev.1), titled "Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings," available at: https://www.fda.gov/media/130874/download

The applicant can pursue other communication pathways in alignment with FDA's normal procedures.[7]

Stage 2: Meeting Preparation and Conduct

8. If FDA grants the applicant's MIE request, the applicant will receive an email from FDA, pursuant to FDA's standard procedures, acknowledging such decision and indicating the primary contact person at the Agency.

9. Stage 2 of the MIE process can consist of up to two (2) meetings with the applicant. The MIE process is generally comprised of a 120-day timeline from the date the meeting is granted. The primary contact person from FDA will liaise and agree on a schedule for meetings with the applicant.

    - During the initial assessment of the MIE meeting package, FDA may determine to schedule and host an optional orientation meeting (via videoconference)[8] with the applicant generally within 30 days of the grant decision date. During this meeting, the applicant will present to FDA its MIE approach and provide additional background and context into its generic drug development process.

    - Regardless if an optional orientation videoconference is scheduled, the applicant will participate in a final meeting via videoconference with FDA. The final meeting will usually be scheduled around 120 days after the grant decision is made.[9] FDA's preliminary responses for discussion will be shared approximately 5 days before the final meeting. The designated primary contact for FDA will coordinate the final meeting logistics with the applicant via email.

        - Upon receipt of the preliminary responses, the applicant can notify the FDA point of contact via email that the preliminary written responses provide a meaningful written response and a meeting with FDA is not needed. FDA will close the meeting request and consider the preliminary written responses as the final meeting responses.

        - Upon receipt of the preliminary responses, if the applicant determines that discussion is needed for only some of the original questions, the applicant has the option of updating the agenda. The updated agenda should list the questions for discussion and order of priority. The updated agenda should be sent no later than 48 hours prior to the meeting via email to MIE@fda.hhs.gov and copied to the assigned FDA point of contact.

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[7] For information on submitting controlled correspondence or a GDUFA scientific meeting request to FDA, see FDA's guidance for industry, Controlled Correspondence Related to Generic Drug Development (Dec. 2022) and Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (Oct. 2022).

[8] The optional orientation videoconference will be hosted at FDA's sole discretion as determined during the initial assessment stage of the meeting package. If an optional orientation videoconference is warranted, FDA's point of contact will communicate with the applicant's point of contact via email to schedule the meeting.

[9] If an optional orientation videoconference is scheduled, FDA, at its sole discretion, can request an additional 30 days to schedule the final meeting. In such case, FDA generally will notify the applicant by Day 60, from the grant date. The additional 30 days will bring the total review date to 150 days from the grant decision.

Stage 3: Post-Meeting FDA Communication

10. Documentation of the MIE meeting outcomes, agreements and disagreements, issues for further discussion, and action items is critical to ensuring that the information is preserved for meeting attendees and for future reference.

    - The applicant can submit a meeting summary of their understanding of the meeting discussion via email to MIE@fda.hhs.gov and the FDA point of contact within 7 calendar days of the final meeting.

    - FDA meeting minutes are the official record of the meeting. FDA generally will issue the official, finalized meeting minutes to the applicant within 30 days of the final meeting via email.

11. MIE meetings are not GDUFA meetings and are not subject to the performance goals for scheduling and conducting GDUFA meetings.

12. FDA remains committed to the individual process and timeframes. The MIE pilot program should not adversely impact the FDA's ability to meet its individual performance expectations.

Appendix. Procedure and Timeline for Evaluating Requests and Conducting MIE Meetings