Considerations and Expectations when Meeting with the FDA under the Industry Meeting Pilot MIE program

Eleftheria Tsakalozou, PhD
Senior Pharmacologist
Division of Quantitative Methods and Modeling, Office of Research and Standards
Office of Generic Drugs| CDER | U.S. FDA

Model-Integrated Evidence (MIE) Industry Meeting Pilot Program for Generic Drugs
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Disclaimer

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Overview

- Components of an effective FDA-Industry meeting
  - Meeting process stages
  - How to maximize the impact of the Model Integrated Evidence (MIE) pilot program meeting?
    - What, Who, When?
- Pre-ANDA PDEV vs. MIE Pilot Program Meetings
  - Which one is right for you?

ANDA: Abbreviated New Drug Application, PDEV: product development.

MIE Industry Meeting Pilot Program

- " … 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 … "
- " … obtain FDA's advice on

  if and/or how the proposed modeling approaches can be used in a specific drug development program,

  how to advance modeling methodology to address common issues of multiple products from the same applicant, and/or

  how to address complex issues as they arise and implement innovative approaches in the development of non-complex products … "

Gained Experiences Through Industry Meetings

Under GDUFA I-III, DQMM has led or supported several FDA-industry interactions on M&S approaches

- Pre-ANDA PDEV and PSUB meetings
- (Enhanced) Mid-Cycle Review meetings
- Post-CRL Scientific (clarification) meetings
- PSG Teleconference meetings
- Other interactions (CCs, ANDA assessments)

GDUFA: Generic Drug User Fee Amendment, DQMM: Division of Quantitative Methods and Modeling, M&S: Modeling and Simulation, ANDA: Abbreviated New Drug Applications, PDEV: product development, PSUB: product submission, CRL: complete response letter, PSG: product-specific guidance, CC: controlled correspondence.

Overview

- Components of an effective FDA-Industry meeting
  - Meeting phases
  - How to maximize the impact of the MIE pilot program meeting?
    - What, Who, When?

Effective FDA-industry meeting

- Pre-meeting phase*:
  - Industry: Comprehensive meeting package/IR
  - FDA: Preliminary responses are concise and informative
  - Meeting held at agreed and reasonable timeframe allowing FDA assessment
- Meeting phase:
  - All parties join the meeting with the intention to share all relevant information
  - Open discussion within the scope of the meeting objective
  - Parties have achieved clarity on the critical aspects of the discussion and are satisfied with the responses they received
- Post-meeting phase:
  - Meeting outcomes are documented

IR: Information request

* After the grant-deny decision

MIE Industry Meeting Pilot Program

How to make your meeting under the MIE Pilot Program successful?

- Meeting package preparation: what to include in the meeting package – **what?**
- Meeting attendees: who should be invited to the meeting – **who?**
- When to submit a meeting request? – **when?**

Meeting package preparation

- Sufficiently developed scientific proposal
  - Meeting questions are relevant, critical, and clearly stated
- Adequate documentation of the modeling approach
  - Model objective clearly documented
  - Assumptions and justifications related to model building are included
  - Risk analysis/assessment
  - Case studies to demonstrate the modeling approach

Meeting package preparation

- Adequate documentation of the modeling approach for the proposed regulatory use
  - Model validation appropriate for the proposed modeling approach
    - *Model validation often focuses on only one drug product, but validation is needed for multiple products to demonstrate model sensitivity to product differences*
    - *Model validation may occur using a different drug product or product type (DPI vs. MDI)*
  - Model application scope clearly defined/described for the product of interest and future model uses
  - Approach for virtual BE analysis (e.g., selection of subjects, power of study, variability) and risk assessment (e.g., type I and II error analysis)

DPI: dry powder inhaler, MDI: metered dose inhaler, BE: bioequivalence

Meeting package preparation

- Error-free information, sufficient to replicate the analysis
  - Limit the need for IR
  - Limit the need for orientation meetings extending assessment time
- Components of the meeting package:
  - Model analysis plan and modeling report supporting its regulatory use
    - pre-specification of model verification and validation criteria
    - pre-specification of modeling building/development criteria including formulation effect
  - Model files – provided in organized fashion for accessibility
  - Datasets (summary/individual level data)
  - Supporting data study synopsis/reports

Meeting attendees

Open discussion within a multidisciplinary team from the FDA and Industry

Attendees should be:

- Knowledgeable of the technical details related to the proposed modeling approach
- Familiar with the drug product(s) of interest
- Familiar with the regulatory context

When to meet?

Engage early in the drug development program

- Low burden on preliminary data accompanying the package
- Role of the MIE approach on the overall regulatory program is necessary
  - Meeting scope: scientific discussion on novel model-based BE approaches
  - Meeting package should be complete
- Meeting outcomes may be generalizable across more than one products in the pipeline

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Pre-ANDA PDEV vs. MIE Pilot Program Meetings

Meeting scope

- Modeling approaches for non-complex products with complex approaches
- Model-engaged biowaiver approaches for a certain type of products or study
- Innovative MIE-focused approaches for BE establishment to address complex issues for a single product or multiple products
- Novel data analytics tools such as modeling methodology advancement or new applications of a modeling approach, new quantitative approaches for comparative analysis, and application of novel data analytics approaches for equivalence assessment
- Communication model on opportunities and challenges with MMF
- Discuss in vitro experimental methodologies for model development and validation purposes

Q1: qualitative sameness between the reference listed drug and the prospective generic, Q2: quantitative sameness between the reference listed drug and the prospective generic, BCS: Biopharmaceutical Classification System

Samples of potential deficiency language

- We recommended you use a biopredictive dissolution method to mimic fasted condition and use appropriate approach to incorporate dissolution data into your PBPK model
- You did not challenge the model with (in vitro and in vivo) data which showed lack of BE and/or batches with different release rate to support the robustness of the established PBPK model
- You should evaluate different clinical study designs and determine which one(s) would be the most sensitive and efficient for the PPK model to detect the formulation differences and would not lead to biased equivalence determination for the subsequent BE study simulation
- You should indicate how the proposed MIE approach can properly characterize the uncertainty and propose the most appropriate BE statistical method
- You should pre-specify the model analysis plan. Sufficient model verification and validation should be included for the intended regulatory purpose
- Within the scope of the platform validation process, the drug products selected should involve APIs with a range of physicochemical properties containing the API of interest
- Your proposed VBE trial lacks information on the study design, the virtual population, the sample size, the incorporation of inter- and intra-subject variability as applicable, the statistical analysis you intend to perform for BE testing

PBPK: physiologically based pharmacokinetic, PPK: population pharmacokinetic, API: active pharmaceutical ingredient, VBE: virtual bioequivalence

Pre-ANDA PDEV vs. MIE Pilot Program Meetings

Meeting process

- Orientation meetings available at the FDA's discretion

Meeting time

- Early engagement
  - Burden for generating preliminary data in the package could be lower than in the pre-ANDA PDEV meeting
  - Complete alternative BE approach on the comparison between RLD and Test is not necessary
  - Meeting scope on modeling considerations on the RLD alone

RLD: reference listed drug

Take Home Messages

- To maximize outcomes from the MIE pilot program
  - Sufficiently develop and adequately document your scientific proposal
  - Work with a multidisciplinary team
  - Engage with the FDA early in your product development program
  - Understand how the MIE pilot meeting program may be a suitable choice for your needs

Closing Thought

Consider the Industry Meeting Pilot MIE program when requesting a meeting with the FDA

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Questions?

Eleftheria Tsakalozou, PhD
Eleftheria.Tsakalozou@fda.hhs.gov

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