Overview of Recent Model-Integrated Evidence (MIE) Submissions to Support Generic Drug Development: What We've Received and What It Tells Us

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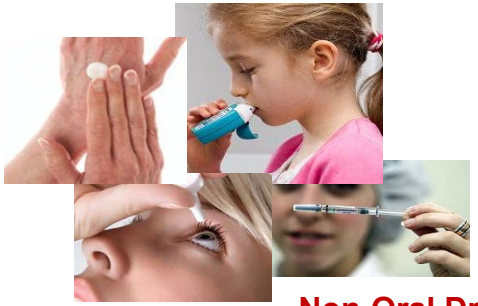
Advancing Generic Drug Development (AGDD): Leveraging Model-Integrated Evidence (MIE) in the Development & Approval of Generic Drugs – August 27, 2026

Learning Objectives

- Provide an overview of model-integrated evidence (MIE) industry meeting pilot program
- Review topics discussed through MIE meetings
- Learn to prepare an effective meeting request package that includes modeling

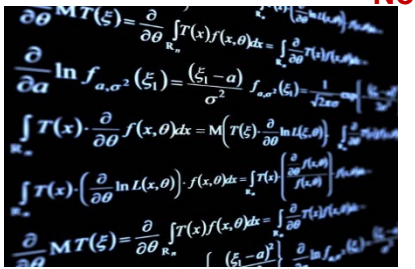
Quantitative Methods and Modeling in Office of Generic Drugs

PK – pharmacokinetics
PD – pharmacodynamics
PBPK – physiologically based PK
CFD – computational fluid dynamics
QCP – quantitative clinical pharmacology
PopPK – population PK

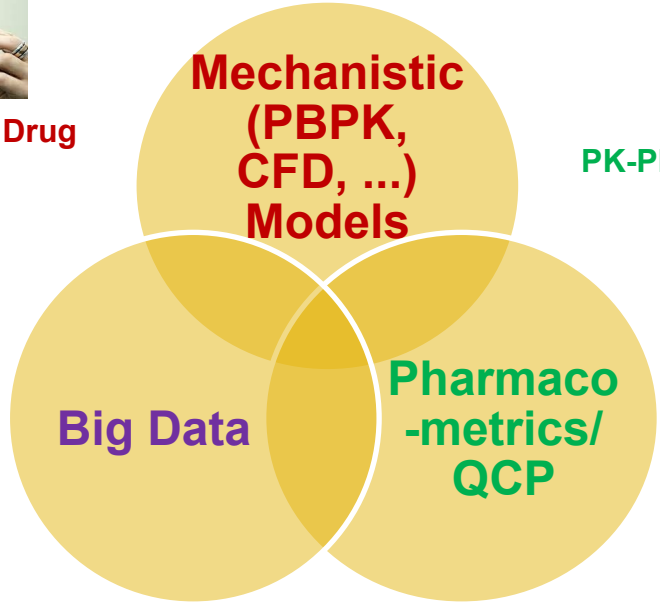


Non-Oral Drug

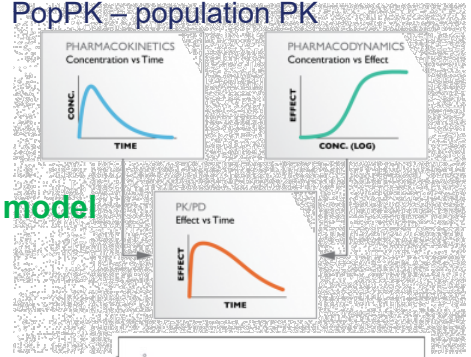
Oral Drug

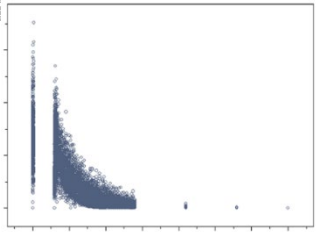


Artificial Intelligence (AI)
Machine learning (ML)
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models



PK-PD model





popPK model

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MIE Pilot Program

Launched on October 1st, 2023

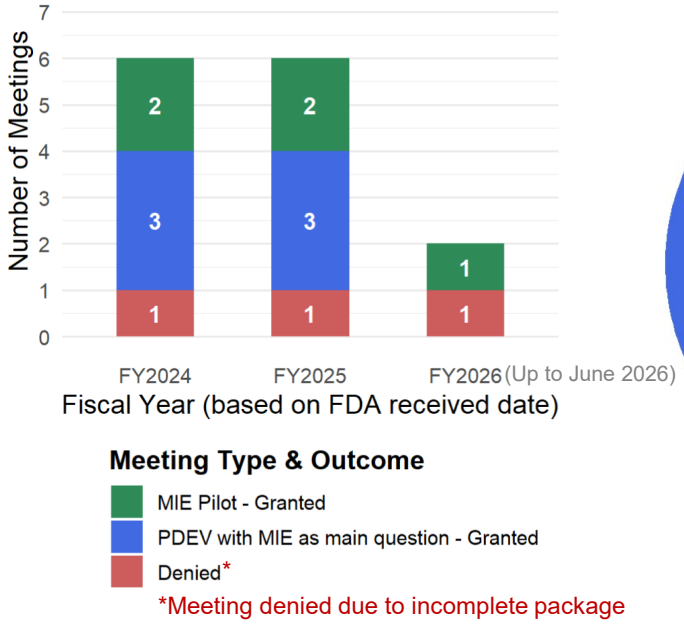
- To foster early and focused interactions between industry and FDA on MIE approaches for establishing bioequivalence (BE) in generic drug development.
- Under the MIE Pilot Program, a meeting may be granted if it pertains to:
  - Innovative MIE-focused approaches for BE establishment that cannot be effectively addressed under the existing GDUFA scientific meetings.
  - Non-complex products with complex modeling approaches.
  - Novel data analytics tools and approaches (e.g., AI and ML) for BE establishment and assessment.

FDA Website: MIE Industry Meeting Pilot Between FDA and Generic Drug Applicants

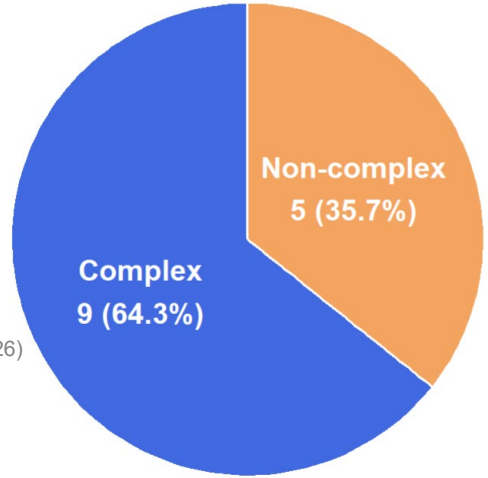
MIE Meeting Experience

(Since 10/1/2023, FY 2024)

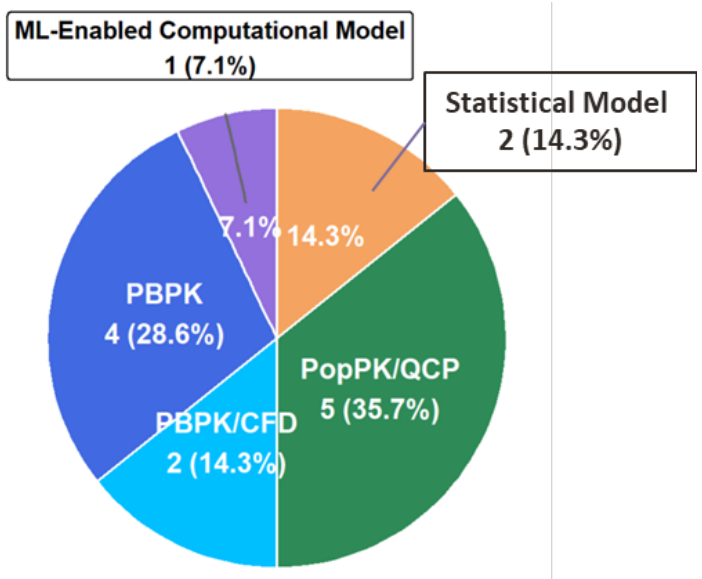
Number of Received MIE Meetings (Total: 14)



Meetings by Product Category



Meetings by MIE Methodology



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PDEV: Pre-ANDA Product Development (PDEV) meeting

MIE Meeting – Complex Product Long-Acting Injectables (LAIs)

- PopPK/PBPK was proposed to either perform virtual BE simulations or leverage modeling results as supportive information to reduce the sample size required for a PK BE study.
  - Mechanistic PBPK modeling, informed by in vitro characterization data and a small-scale PK validation study, together serve as a totality of evidence approach
  - PopPK modeling to support the use of a small-scale abbreviated PK study to support BE demonstration
- Key topics discussed during these meetings included:
  - Detailed technical discussion regarding modeling method and model validation strategy
  - In vitro experimental methodologies for PBPK model development and validation purposes
  - 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)

MIE Meeting – Statistical Modeling for LAIs

- Statistical modeling and simulation were used to support proposed adaptive study designs that integrated prospectively planned modifications to one or more aspects of the trial based on accumulating data from study subjects.
  - Modeling and simulation results were submitted by the applicant to demonstrate Type I error for the proposed design.
- The proposed design deviated from published Potvin methods, such as such as multi-center study configurations and applicant-defined interim analysis criteria.
- During the MIE meeting, FDA reviewers assessed the submitted simulation codes and results and provided specific feedback to the applicant on additional simulations and statistical models to be evaluated going forward.

MIE Meeting – Complex Product Orally Inhaled Drug Products (OIDPs)

- Regional deposition model (e.g., CFD models) and PBPK were proposed to
  - Assess the need for a PK study with a charcoal block
  - Identify systemic PK metrics that are related to reginal drug delivery in the lung to serve as alternatives of not conducting a charcoal block PK BE study
  - Justify biorelevant BE limits for relevant in vitro studies
- Key topics discussed during these meetings included:
  - Model parameterization: data source used to support the CFD/PBPK model
  - Model verification and validation
  - The utility/purpose of the modeling to support BE

The use of a regional deposition or PBPK modeling to support BE is discussed in: Product Specific Guidance (PSG) on Formoterol Fumarate; Glycopyrrolate (NDA 208294)

MIE Meeting – Non-complex Products with Complex Modeling Approaches

- MIE to provide a PK bridge between two oral dosage forms
  - MIEs were used to characterize PK differences between available and discontinued products, providing a scientific bridge for BE demonstration in circumstances where neither the Reference Listed Drug (RLD) nor the Reference Standard (RS) was available.
  - MIE meetings facilitated in-depth technical discussions on data sources, bridging strategies, and modeling techniques. As an outcome, alternative approaches that allow to extrapolate BE with an alternative comparator were recommended in the PSGs for
    - Trazodone Hydrochloride Extended Release Oral Tablet
    - Potassium Chloride Extended Release Oral Suspension

Lessons Learned from Previous Meetings

- Include any preliminary or pilot data currently available, along with a plan for future data generation.
- If pilot data is unavailable, submit an MIE proposal that includes the proposed modeling approach with sufficient technical detail, underlying assumptions and justifications for model building, and model verification and validation strategies—even if complete validation data is not yet available.
- If available, case studies or proof-of-concept analyses demonstrating the proposed MIE approach would strengthen meeting package.

Lessons Learned from Previous Meetings

Include sufficient modeling details in the meeting request package:

- Question of interest, context of use, and model influence within the scope of the proposed BE approach.
- Model parameterization: sufficient details for underlying assumptions and model building process
- Clear model verification and validation strategies including current and future data support. The model should be sufficiently validated for its context of use.
- If applicable, include a risk-based assessment plan addressing a regulatory acceptable Type I error rate.

Summary

- The MIE pilot program has helped FDA understand how to more effectively use meetings to provide feedback on model development, model performance, and the use of modeling to address a specific issues in generic drug development.
- Generic applicants are encouraged to develop alternative BE approaches supported by MIE and engage with the Agency early during drug product development.

Acknowledgement

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