Potential Topics for Discussion Through the MIE Industry Meeting Pilot Program

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Model-Integrated Evidence (MIE) Industry Meeting Pilot Program for Generic Drug**s**
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Disclaimer

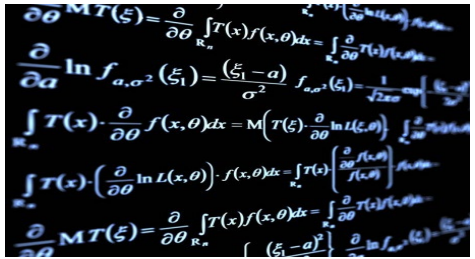
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

MIE Areas

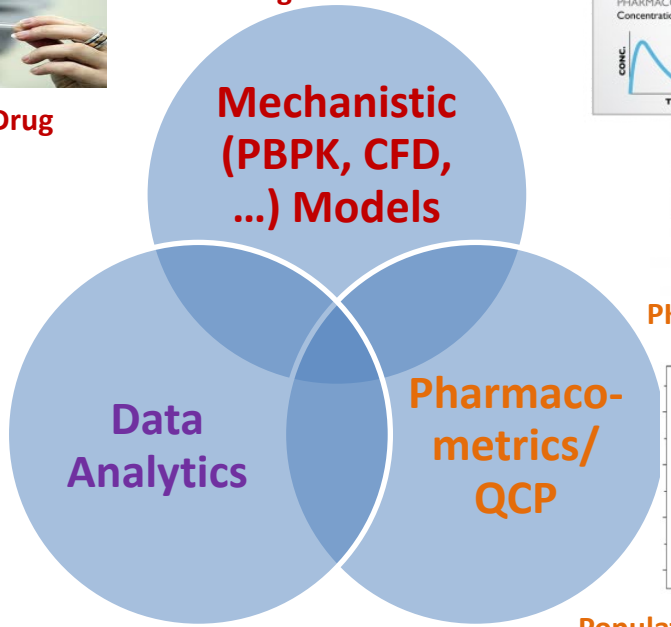
PK – pharmacokinetics
PD - pharmacodynamics
PBPK – physiologically based PK
CFD – computational fluid dynamics
QCP – quantitative clinical pharmacology

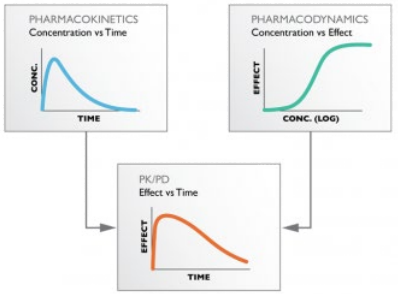
Non-Oral Drug

Oral Drug

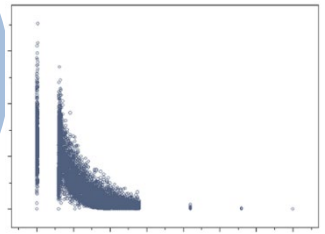


Machine learning (ML) toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models





PK-PD model



Population based model

Slide adapted from Liang Zhao, Ph.D.

Goals of the MIE Industry Meeting Pilot Program

The new MIE pilot program intends 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"
- "Support drug development by offering prospective ANDA applicants and ANDA applicants an opportunity for early, focused, and enhanced interactions with FDA"

Meeting participants can obtain 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"
- "How to address complex issues as they arise and implement innovative approaches in the development of non-complex products"

MIE Industry Meeting Pilot – General Principles, Sept. 12, 2023
https://www.fda.gov/media/172028/download?attachment

Situations that a Meeting may be Granted

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 approaches/modeling for Biopharmaceutics Classification System (BCS)--based biowaivers and/or other study waivers", and
- "Novel data analytics tools and approaches (e.g., machine learning and artificial intelligence) for BE establishment and assessment"

MIE Industry Meeting Pilot – General Principles, Sept. 12, 2023
https://www.fda.gov/media/172028/download?attachment

Potential Topics - Primer

- All topics gathered by the four quantitative disciplines in the Division of Quantitative Methods and Modeling (DQMM) –

  oral PBPK, non-oral PBPK, QCP and data analytics

- Topics will be presented in the same order as above
- Topics are not meant to be an exhaustive list, but were curated from previous industry interactions with DQMM, including pre-ANDA meetings, CCs, ANDA assessment, and post-submission meetings

Topics Related to Use of PBPK for Oral Drug Products

Topics Related to Use of PBPK for Oral Drug Products

Category	Potential discussion topics
Risk assessment of deviation of dissolution profiles on BE	Using PBPK absorption model to evaluate the impact of non-comparable dissolution profiles of lower strength on BE and support biowaiver for oral products including immediate release (IR) and extended release (ER) products
Risk assessment of the impact of Particle Size Distribution (PSD) on BE	Using PBPK modeling to evaluate the risk of impact of Particle Size Distribution (PSD) on BE and support setting a clinically relevant PSD specification for a generic product
Risk assessment of non-comparable in vitro alcohol dose dumping studies	PBPK modeling to evaluate the impact of in vitro alcohol dose dumping on BE study
Identify biopredictive dissolution and support BE evaluation	PBPK absorption modeling to help identify biopredictive dissolution and support BE evaluation for a gastrointestinal (GI) locally acting product

Topics Related to Use of PBPK for Oral Drug Products (cont.)

Category	Potential discussion topics
Support waiver of fed BE study for high-risk product	Using PBPK modeling to evaluate the impact of food on BE for high-risk products
Support waiver of BE study in subjects with gastric pH change	Using PBPK modeling to evaluate the impact of gastric pH on BE
Support BCS based biowaiver	PBPK modeling to evaluate the impact of excipients on bioequivalence of BCS class III drug products
Justify BE study design	• PBPK modeling to evaluate the impact of including single-sex subjects on BE • PBPK modeling to evaluate the sensitivity of BE analyte (parent vs. metabolite)

Topics Related to Use of PBPK for Non-Oral Drug Products

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Category	Potential discussion topics
Model Validation for OIDPs	Validation of regional deposition models for orally inhaled drug products (OIDPs)
Describe drug delivery to the site of action for OIDPs	Application of PBPK modeling to understand relationships of in vitro and in vivo metrics with drug delivery to the site of action for OIDPs
Model validation for topical dermatological drug products	Validation of in vivo dermal PBPK models and in silico IVPT models using percutaneous pharmacokinetic (IVPT, dermal microdialysis and dOFM) or systemic PK data: considerations for RLD and T products based on formulation composition differences
Model platform development and validation	Platform validation for locally acting drug products: considerations for in vivo PBPK models for locally acting drug products or in silico IVPT models for topical dermatological drug products supporting platform validation

IVPT: in vitro permeation test
dOFM: dermal open-flow microperfusion

Topics Related to Use of PBPK for Non-Oral Drug Products (cont.)

Category	Potential discussion topics
In silico IVPT model	Methodology on the development and validation of the in silico IVPT model for topical dermatological drug products with API of low skin permeation or products with IVPT study challenges
	Application of the validated in silico IVPT model to inform in vivo dermal models through validated IVIVEs for topical dermatological drug products
Models on drug release for drug products with unique formulation characteristics	Development and validation of drug release models for drug products with unique formulation characteristics (topical dermatological drug products: microsphere formulations, PLGA-based LAIs, ophthalmic (biodegradable) inserts, etc.) that may require innovative approaches
Model-based interspecies scaling	Interspecies model extrapolations to humans for ophthalmic and LAI drug products: usage of PBPK modeling approach
LAI PBPK model	Development of LAI PBPK model accounting formulation attributes, local physiology and their interplay to describe the in vivo release and subsequent absorption of API from the injection site

IVIVE: in vitro to in vivo extrapolation

Topics Related to Use of QCP & VBE

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Category		Potential discussion topics
Alternative Study Designs …		
	with shortened overall duration (e.g., for LAIs, for studies in sensitive patient populations)	In silico continuation – population PK (popPK) to continue in silico dosing of a non-steady state study and evaluate BE at steady state
		Carryover adjustment – popPK-based adjustment for carryover effect in patient single-dose crossover studies with no washout period
		popPK-based support of AUC truncation
		popPK-based support of truncated study design with alternative evaluation criteria (e.g., narrowed BE limits)
		popPK-based support for alternative study designs such as switch-over study designs and repeated designs
	with decreased number of subjects (e.g., for orphan drugs, for studies in sensitive patient populations)	Along with shortened study designs (i.e., non-steady state studies), additional incorporation of replicate reference sequences for use of reference-scaling
		Sparse or reduced sampling optimized design strategies supported by model-based BE evaluation

Topics Related to Use of QCP & VBE (cont.)

Category	Potential discussion topics
Practical study considerations & BE assessment challenges	Assessment of steady state attainment through popPK modeling
	Accounting for missed samples (in PK or PD) through popPK modeling; data imputation approaches
	Model-based adaptive design
	Justification in deviations in PK profiles (e.g., Tmax, Tlag) through popPK and PK/PD modeling
	Model-based Emax determination in dose-scale PD studies
PK/BE bridging	Bridging to alternative product when reference standard is discontinued

Topics Related to Use of Data Analytics/ML

Topics Related to Data Analytics/ML

Category	Potential discussion topics
Complex comparative profile analysis	Equivalence analysis of complex particle size distribution; Comparative analysis of LC/MS profile
Complex substance analysis	Novel quantitative modeling and methods for complex substance analysis
Novel data analytic tool	Utilization of artificial intelligence (such as machine learning) to support data analysis and/or model building in the submission

Topics Can Focus on the Following Modeling Steps:

Category	Potential discussion topics
Model or platform development	E.g., Justification of model input parameters
Model or platform validation	E.g., Sufficient validation of PBPK and popPK models for the intended regulatory use
Model application (e.g., VBE simulations)	E.g., Appropriate design of virtual BE simulations

Refer to presentation *Considerations and Expectations when Meeting with the FDA under the Industry Meeting Pilot MIE program* for more information

Take Home Messages

- The pilot includes both complex and non-complex products
- Meeting topics can be specific to a single product or a class of products
- Meeting topics include applications utilizing:
  - PBPK for oral products
  - PBPK for non-oral/locally-acting products
  - Quantitative pharmacology (popK, PK/PD, VBE)
  - Data analytics/ML
- The potential topics presented here are not exhaustive and it is anticipated that the generic industry may have further MIE use cases for discussion

Questions?

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