The Development and Framework of MMF as a Regulatory Initiative

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MHRA/APS Workshop (Nov 7-8, 2024)

Disclaimer

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

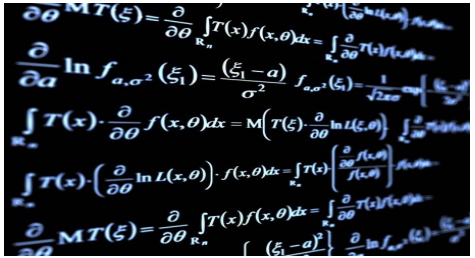
Division of Quantitative Methods and Modeling

Non-Oral Drug

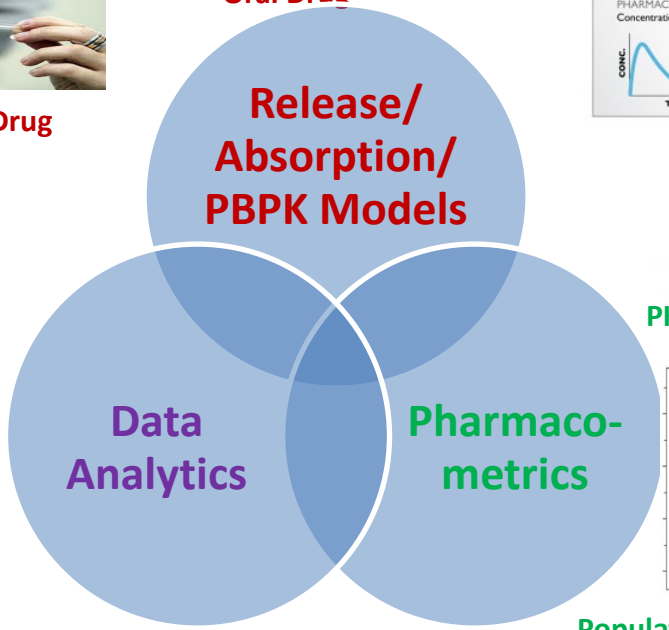
Oral Drug

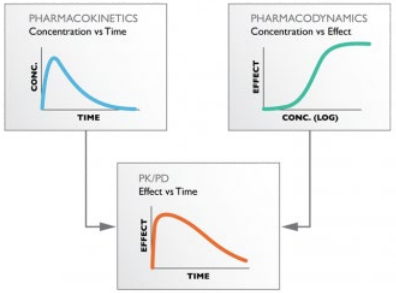
Our goal is to facilitate

- Generic drug development/review
- Policy development
- Regulatory decisions

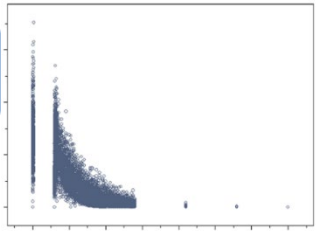


Machine learning toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models





PK-PD model



Population based model

PBPK: Physiologically Based Pharmacokinetics
Courtesy slide from Liang Zhao, Ph.D.

Modeling and Simulation as Modern Tools for Drug Development

- Modeling and simulation makes drug product development and regulatory assessment more efficient
  - MIDD: M&S an integral part of new drug development for almost all NME NDAs and BLAs
    - PDUFA VI: MIDD paired meeting pilot
    - PDUFA VII: Officially part of the user fee act
  - MIE: Can cover all challenging areas for generic drug development, especially for complex generics
    - GDUFA III: MIE Industry Meeting pilot launched on October 1st, 2023
- New modeling types and utilities (e.g., QSP and AI/ML, etc.)

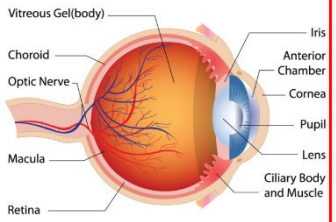
MIDD: Model-Informed Drug Development; **MIE: Model-Integrated Evidence**; QSP: Quantitative Systems Pharmacology; AI/ML: Artificial Intelligence/Machine Learning
MIE pilot: https://www.fda.gov/media/172028/download?attachment

Mechanistic Modeling and Simulation Tools for Non-Orally Administered Drug Products

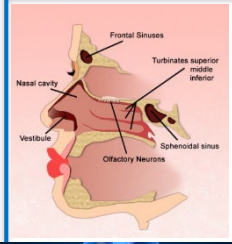
Drug Substance Formulation CQAs → **Physiological System** → **In vivo Performance**

Predict **systemic** AND **local** concentrations

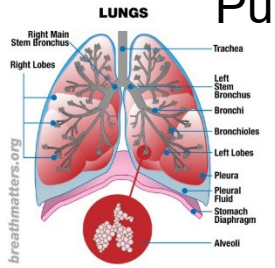
Ocular

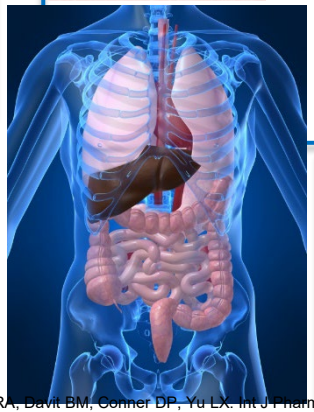


Nasal

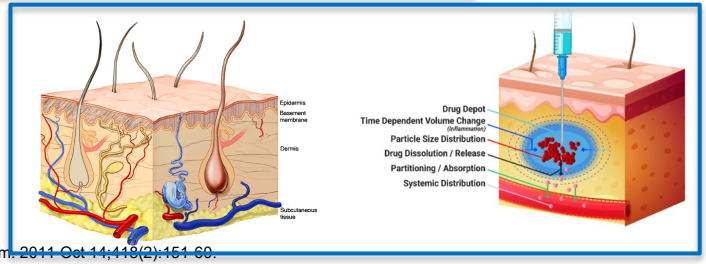


Pulmonary

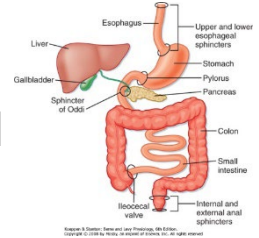




Dermal
Long-acting injectables



GI



Adapted from Dr. Liang Zhao

Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60. https://pubmed.ncbi.nlm.nih.gov/38675213/

Purposes for OIDP Modeling

- Regional deposition models, using computational fluid dynamics (CFD) or semi-empirical methods, can predict the impact of device or formulation changes prior to in vivo or in vitro testing.
  - May accelerate product development by avoiding unnecessary testing.
  - For generic OIDPs, modeling may be used to justify biorelevant bioequivalence (BE) limits for relevant in vitro studies.
- Physiologically based pharmacokinetic (PBPK) models can examine relationships between in vivo plasma concentration pharmacokinetics (PK) data and regional absorption.
  - May be used to make decisions about product development based on PK data.

Purposes for Modeling Ophthalmic Products

- Ocular PBPK models can mechanistically describe active ingredient release from drug products administered to eye and permeation through different eye tissues.
  - Correlate in vitro metrics to the in vivo exposure in ocular tissues
  - Assess BE between the reference listed drug (RLD) and a proposed drug product in the target eye tissues
  - Utilize preclinical data to inform product development by performing interspecies model extrapolation mechanistically

Purposes for Modeling Products Applied on the Skin

- Dermal PBPK models can mechanistically describe active ingredient release from the drug product post application on the skin and permeation through the skin under in vivo and ex vivo scenarios.
  - Identify a “safe space” for in vitro metrics related to the quality of the RLD and assess their impact on an in vivo performance of potential deviations in these characteristics between the RLD and the proposed drug product
  - Predict skin permeation for low permeation active ingredients using in silico in vitro permeation test (IVPT) models
  - Asses BE between the RLD and the proposed drug product locally in the skin or in the systemic circulation instead of conducting in vivo studies to establish BE when such studies are challenging, thus decreasing unnecessary human testing

Highlights of Oral PBPK Absorption Modeling Impacts on Regulatory Decision Making in OGD

Category	Impact on regulatory decision making
Risk assessment of the impact of Particle Size Distribution (PSD) on BE	Evaluate the impact of PSD on BE and support setting a clinically relevant 3 tier PSD specification
Risk assessment of deviation of dissolution profiles on BE	Using IVIVC and PBPK absorption model to evaluate the impact of non-comparable dissolution profiles of the proposed drug product and the RLD for lower strengths in multi-media (pH 1.2, pH 4.5, and pH 6.8 buffers) on their in vivo performance
Biowaiver assessment	Justify BCS biowaivers and not to conduct fed BE studies
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

IVIVC: In vitro in vivo correlation; BCS: Biopharmaceutics Classification System

Case 1: PBPK Model to Support Locally Acting Product Approval

Diclofenac topical gel, 1%: Dermal PBPK model supporting ANDA approval for a generic

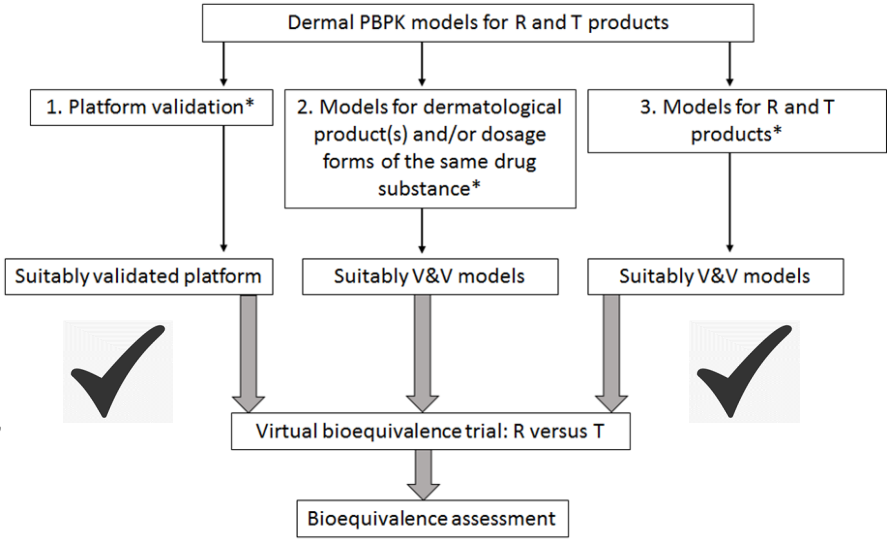
- Virtual BE assessment leveraging dermal PBPK modeling and simulation in lieu of a comparative clinical end point study in patients

- Platform performance assessment

>10 dermal PBPK models for TDS and topical products

- Multiple doses/product strengths and dosing regiments, age and anatomical locations
- Systemic and local bioavailability (skin biopsy, IVPT, dermal microdialysis) data
- Satisfactory model performance

V&V methodology in support of fit-for-purpose dermal PBPK models



TDS: Transdermal Delivery Systems, IVPT: in vitro permeation testing, M&S: Modeling and Simulation

Tsakalozou, E et al. CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.
Tsakalozou, E et al. Clin Pharmacol Ther. 2021 Jul 7. doi: 10.1002/cpt.2356.

Case 2: PBPK Absorption Model in Assessing the Impact of Particle Size Distribution (PSD) on BE

A Capsule Product: PK parameters, e.g., Cmax and AUC, are found to be sensitive to changes in mean particle size of the active pharmaceutical ingredient under fasting condition

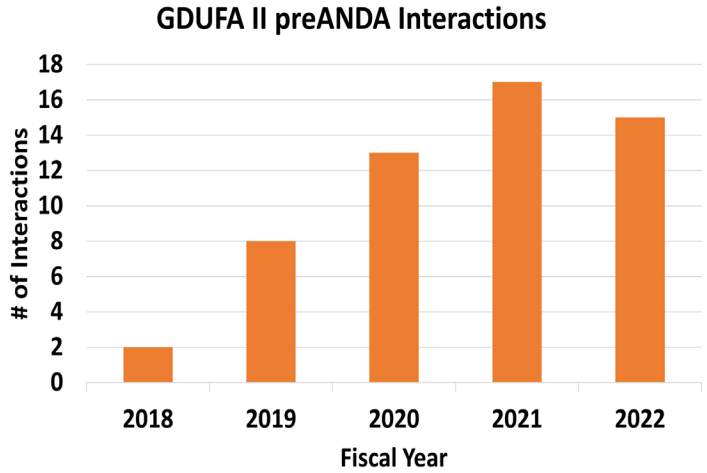
- There is a PSD deviation in terms of D90 between test and reference products
- PBPK modeling and simulation suggested that the test vs reference PK metrics showed a low risk of non-BE when D90 varied over a wide range with a certain fixed value of D50 for all strengths
- The modeling results supported a satisfactory BE assessment of this ANDA and setting a clinically relevant PSD specification

Formulation	D10	D50	D90	Test/Reference Ratios			BE
				Cmax	AUCt	AUCinf	
Refence	X10	X50	X90				
Test 1	X10--	X50	X90--	107	105	106	Pass
Test 2	X10-	X50	X90-	1	98.3	98.2	Pass
Test 3	X10+	X50	X90++	81.2	81.5	81.3	Pass
Test 4	X10+	X50	X90+++	80.3	79.8	80.3	Fail

Simulation results with fixed D50 and changed D10 and D90 using the reference upper bound PSD

Increasing Impact of MIE Approaches in Generic Drug Development

- FDA has been openly encouraging the use of quantitative methods and modeling approaches with MIE to support the development and approval of generic drug products.



Number of pre-ANDA interactions with industry proposed MIE during GDUFA II.

ANDA, abbreviated new drug application; GDUFA, Generic Drug User Fee Amendments

Yoon M, et al. CPT Pharmacometrics Syst Pharmacol. 2023 May;12 (5):552-555. doi: 10.1002/psp4.12930

MIE Pilot Program

Launched on October 1st, 2023

The pilot program allows enhanced scientific communications on a broad range of quantitative methods and modeling techniques to address generic drug development issues or questions that are either out of the scope of or cannot be sufficiently addressed by the existing pre-ANDA and ANDA scientific meetings. E.g.,

- Common modeling issues across multiple products
- Complex modeling approaches for non-complex products

A dedicated regulatory platform for interactions on MIE

- To foster early and focused interactions between industry and FDA on MIE approaches for establishing bioequivalence (BE) in generic drug development

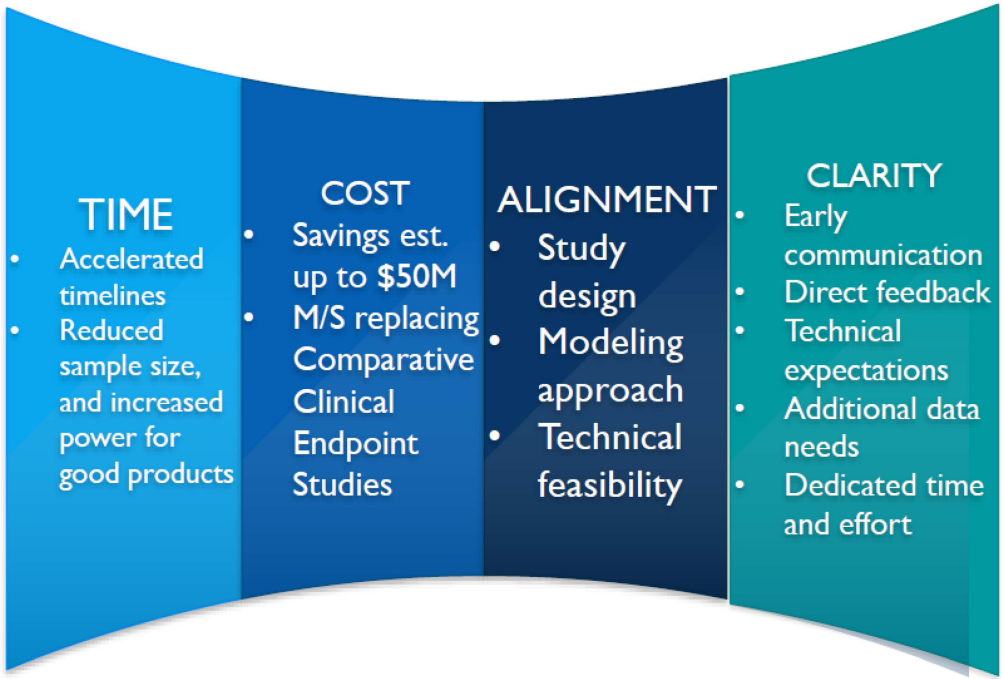
MIE Pilot Program General Principles document

Situations that A Meeting May Be Granted

- 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., machine learning and artificial intelligence) for BE establishment and assessment

Expected Benefits

Industrial Benefit →



Agency Benefit

- Efficiency to handle multiple products
- Reducing number of cycles for drug approval
- Eco-system with industry to develop effective BE approaches

Slide adapted from CDER SBIA Presentation by Liang Zhao, Ph.D., MIE Industry Meeting Pilot Program for Generic Drugs: Introduction, 1/18/2024

Benefits for Model Sharing, Standardization, and Archiving in Regulatory Submissions

- Regulatory Agencies:
  - Breaking down organizational silos when conducting M&S assessments, by allowing access to previous comments on the same subject and/or M&S practice with a similar regulatory use
  - Enhancing review consistency, quality, and efficiency
- Regulated Industry:
  - Saving effort to duplicate the same model(s) and/or modeling practices
  - Reducing communication cost with FDA
  - Enhanced and informed awareness of M&S advancement and use in the regulatory setting
- All:
  - Building a transparent and positive eco-system for the use of the models (e.g., by benchmarking modeling progress and standardizing modeling practices)
  - Maximizing impact of M&S approaches, especially for regulatory use
  - Incentivizing the community to develop models with practical regulatory impacts

Courtesy slide from Liang Zhao, Ph.D.

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

(FDA/CRCG Workshop, September 30-October 1, 2021)

Symposium III on Day 2: Challenges and Opportunities to Enhance Model Sharing upon Regulatory Use

Aimed to discuss what can be a Model Master File (MMF) and how to share it .

Agenda, meeting materials and recording available at:
Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches - The Center for Research on Complex Generics (CRCG)

Best Practices for Utilizing Modeling Approaches to Support Generic Product Development

(FDA/CRCG Workshop, October 27-28, 2022)

Symposium II on Day 2: Model Sharing, Acceptance, and Communication with FDA

Aimed to explore practical and efficient ways to facilitate the development of an MMF as part of best practices in MIE implementation.

Agenda, meeting materials and recording available at:
Best Practices for Utilizing Modeling Approaches to Support Generic Product Development - The Center for Research on Complex Generics (CRCG)

Considerations and Potential Regulatory Applications for a Model Master File

FDA/CRCG Workshop, May 2nd, 2024

Agenda, meeting materials and recording available at:
Considerations and Potential Regulatory Applications for a Model Master File - The Center for Research on Complex Generics (CRCG)

What is an MMF?

"Model Master File (MMF) MMFs are information and data on a quantitative model or modeling platform that have undergone sufficient verification and validation (V&V) to be viewed as portable, reusable, generalizable, and sharable from an FDA regulatory perspective.

The AAPS Journal (2024) 26:28
https://doi.org/10.1208/s12248-024-00897-8

MEETING REPORT

Check for updates

Best Practices for Utilizing Modeling Approaches to Support Generic Product Development: A Series of Workshop Summary Reports

The Role of Model Master Files for Sharing, Acceptance, and Communication with FDA

Lanyan Fang[1] · Yuqing Gong[1] · Andrew C. Hooker[2] · Viera Lukacova[3] · Amin Rostami-Hodjegan[4,5] · Mark Sale[5] · Stella Grosser[6] · Rebeka Jereb[7] · Rada Savic[9] · Carl Peck[8,9] · Liang Zhao[1]

MMF Advantages

- Reusable
    - Efficient product development and application assessment
    - Don’t duplicate review
- Scalable
    - More model submissions in the future
- Support an “Eco-system” for model development
    - Models are not just for applicants with “in-house” expertise
- Consistency
    - FDA assessment questions are consistent across applicants
- Support Innovative Approaches
    - Regulatory risk of using novel approaches

Courtesy slide from Robert Lionberger, Ph.D.

Build Mechanism to Manage Unintended Impacts

- Accommodating the dynamic nature of models and data:
  - Setting up mechanisms to get model updated based on latest knowledge and availability of more data
- Allowing multiple models for the same use:
  - Allowing and advocating modeling DEI (diversity, equity, and inclusion to address the same regulatory need)
- Eliminating “monopoly”
  - Encouraging scientific publications and building venues and platform for public access to non-proprietary knowledge/information

Utilizing Drug Master File (DMF)

- A standing regulatory mechanism
  - For sharing files of different types
  - In good management of potential downsides associated with file sharing
  - With realized benefits for both industry and the FDA
- With established guidance/policy and infrastructure(s)
- Use an electronic Type V DMF (see 21 CFR 314.420(a)(5)) to submit MMF information and data to the Agency

DMF Characteristics

- DMF are submissions to FDA that may be used to provide confidential, detailed information about certain aspects of drug products.
- DMF holders “can authorize one or more applicants or sponsors to incorporate by reference information contained in the DMF without having to disclose that information to the applicants or sponsors”
- Typically, DMFs are reviewed “in connection with the review of applications that reference them”
- A DMF can include the proprietary information about synthetic chemistry process to produce a drug substance and then subsequent purification steps
- Multiple DMFs with the same regulatory use
- Owners can update DMFs at any time
- DMF can assume multiple types

https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs
Draft Guidance for Industry: Drug Master Files (October 2019) https://www.fda.gov/media/131861/download

Some Potential Types of MMF

- A product- or an API-specific model
- A methodology or a good modeling practice that can be applied to multiple products for the same purpose of use
- A verified and validated virtual physiological organ or system that can be subsequently connected with drug product specific information for the established use

Main MMF Submission Files

- Regulatory context of use (question of interest, model influence, and decision consequences) of the MMF
- Scientific rationale supporting the MMF
- Modeling Analysis Plan and Report relevant to the MMF
- Data analysis performed within the scope of the MMF
- Model files, datasets, literature and all sources of information that have been developed and have been utilized to support the development of the MMF

When to Consider an MMF?

- Models (1) with proprietary information, (2) verified and validated with large data and knowledge that incur high cost, and/or (3) representing a highly reusable method or practice, may benefit from having Master Files, e.g.,
  - Virtual physiological organs/systems for purpose of use
  - Niche physiologically based pharmacokinetic (PBPK) models
  - Certain systems pharmacology models
  - In vitro-in vivo correlation models
- Models that can be easily duplicated from scientific publications may not necessarily need Master Files, e.g.,
  - Conventional population PK models
  - Routine exposure-response analysis
  - Conventional pharmacokinetics-pharmacodynamics (PK-PD) relationships

Courtesy slide from Liang Zhao, Ph.D.

Welcome Your Thoughts on

- Further define MMFs
- Potential types of MMFs
- What to include in the MMFs
- How to maximize the benefits and impacts of MMFs
- How to build the most positive and productive eco-system
- How to mitigate unintended consequences

Acknowledgments

- ORS/OGD/CDER/FDA
  - Robert Lionberger
  - Lei Zhang
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  - Liang Zhao (currently works at UCSF)
  - Eleftheria Tsakalozou, Andrew Babiskin, Ross Walenga, Yuqing Gong, Fang Wu, Meng Hu
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  - Shiew Mei Huang
  - Rajanikanth Madabushi
  - Hao Zhu
- External contributors including
  - Carl Peck
  - Amin Rostami
  - Previous workshop contributors to MMF

All modelers in field from the agency and industry made contributions to this subject!

U.S. FOOD & DRUG ADMINISTRATION

Back ups