



Introduction and Overview of the Model Master File

Lanyan (Lucy) Fang, PhD

Division of Quantitative Methods & Modeling
Office of Research and Standards, Office of Generic Drugs, CDER/FDA

CDER SBIA | Model Master Files: Advancing Modeling and Simulation in
Generic Drug Development and Regulatory Submissions (13 March 2025)

Disclaimer



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

Modeling and Simulation as Modern Tools for Drug Development



- Modeling and simulation (M&S) makes drug product development and regulatory assessment more efficient
 - New drug development: M&S is an integral part for almost all NME NDAs and BLAs
 - Generic drug development: there are more opportunities for M&S given that generics are approved based on abbreviated pathways, but less utilization!

MIE Pilot Program

FDA

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

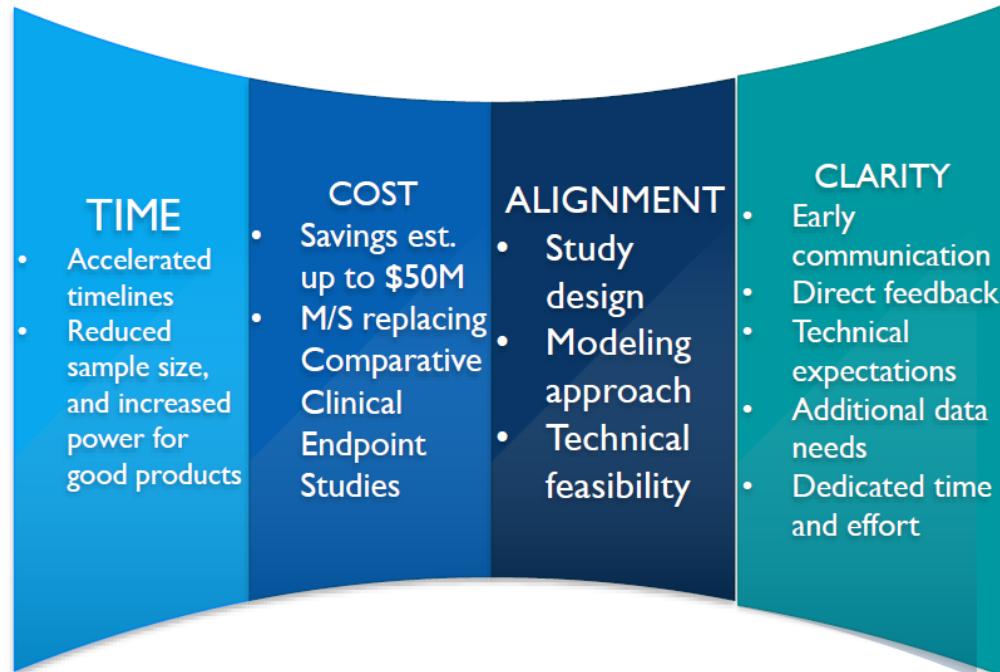
Expected Benefits

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



What If Models Can Be Reused?



- Shared models (or commonly used models) would make it easier and less risky for applicants to use M&S approaches
- Shared models will make regulatory assessment more efficient and consistent

Model Master File (MMF)



- Use of the Type V Drug Master File (DMF) for MMF submissions aims at model-sharing and model-reusability
- MMF submission through Type V DMF allows the owner of model(s) to submit data/info that multiple applicants can cross-reference/use the same model(s)



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 .

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.

Considerations and Potential Regulatory Applications for a Model Master File

(FDA/CRCG Workshop, May 2nd, 2024)

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

MEETING REPORT

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 Fang¹ · Yuqing Gong¹ · Andrew C. Hooker² · Viera Lukacova³ · Amin Rostami-Hodjegan^{4,5} · Mark Sale⁵ ·
Stella Grosser⁶ · Rebeka Jereb⁷ · Rada Savic⁹ · Carl Peck^{8,9} · Liang Zhao¹

 Sections ▾  Browse ▾  Search ▾  Reader Aids ▾  My FR ▾  Search Documents 

FEDERAL REGISTER
The Daily Journal of the United States Government



 Notice

Use of a Type V Drug Master File for Model Master File Submissions To Support Abbreviated New Drug Applications; Establishment of a Public Docket; Request for Comments

FDA-2024-N-5975, accepting comments by April 17, 2025

[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 - The Center for Research on Complex Generics \(CRCG\)](#)

[Considerations and Potential Regulatory Applications for a Model Master File - The Center for Research on Complex Generics \(CRCG\)](#)

<https://www.federalregister.gov/documents/2025/01/17/2025-01182/use-of-a-type-v-drug-master-file-for-model-master-file-submissions-to-support-abbreviated-new-drug>

What is in an MMF?

“ ... an ‘MMF’ or ‘MMF submission’ refers to a set of information and data on an in silico quantitative model or modeling platform supported by sufficient [verification and validation (V&V)]. MMFs can be established to support MIE in a broad range of quantitative models, including, but not limited to, PBPK, CFD, PPK, and mechanistic in vitro in vivo correlation models.”

PBPK: physiologically based pharmacokinetic, CFD: computation fluid dynamics, PPK: population pharmacokinetic

<https://www.federalregister.gov/documents/2025/01/17/2025-01182/use-of-a-type-v-drug-master-file-for-model-master-file-submissions-to-support-abbreviated-new-drug>

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 on modeling approaches
 - Increased confidence in the use of modeling approaches for developing complex drug products
- 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

MMF in the Generic Drug Program



- Scale: nearly 1000 generic drug application submissions per year
- M&S streamlines generic drug development program, via integrating in vitro characterization and in vivo performance as well as efficient and sensitive studies
- Efficiency is essential!
 - Generic drug development builds on the established safety and efficacy of an approved new drug product
 - Same model(s) can be used in the development of different products

MMF in the Generic Drug Program



- Many reference listed drugs have multiple ANDA submissions
- Consistency is essential!
 - M&S should be evaluated similarly for all similarly situated applicants
 - MMFs can be referenced by multiple applications for a similar purpose of use, thus improving model sharing, model standardization, and regulatory consistency

Lower the Risk to Innovation

- Inclusion of a modeling approach in applications to FDA has some risk as related to the model V&V and relevance for the intended use
 - Pre-ANDA product development meetings and Model Informed Evidence pilot
 - Model Master Files can build confidence that the approach has been documented appropriately and has been used successfully

Summary

- M&S makes drug product development more efficient, particularly for generic drugs
 - MMFs can advance the use of M&S in generic drug development program
- Type V DMF for MMF submissions provides a regulatory mechanism aimed at model-sharing and model-reusability
 - Improving regulatory efficiency and consistency

Acknowledgments



- ORS/OGD/CDER/FDA
 - Robert Lionberger
 - Lei Zhang
- Division of Quantitative Methods and Modeling, ORS/OGD/CDER/FDA
 - Liang Zhao (currently works at UCSF)
 - Eleftheria Tsakalozou, Andrew Babiskin, Ross Walenga, Yuqing Gong, Fang Wu, Meng Hu
 - All scientific leads and scientists
- OGDP/OGD/CDER/FDA
 - Daniel Ritterbeck
 - Martha Nguyen
- ONDP/OPQ/CDER/FDA
 - Rebecca Moody
 - Bhagwant Rege
- OB/OGD/CDER/FDA
 - Partha Roy
- OCP/OTS/CDER/FDA
 - Issam Zineh
 - 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!