# Adopting the Model Master File Framework to Enhance Modeling and Simulations Approaches for Regulatory Use

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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.***

# 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!



NME: new drug molecule; NDA: new drug application; BLA: Biologics license agreement

# 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)

# What is an MMF?

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 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]

# What is an MMF?

CENTER FOR RESEARCH ON COMPLEX GENERICS

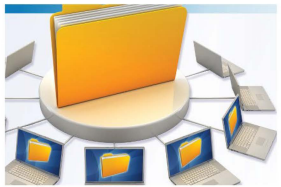
## Considerations and Potential Regulatory Applications for a Model Master File

Home / Education and Training / Past Events

**Date and Time:** May 2, 8:30 am – 5:35 pm,
May 3, 8:30 am – 3:50 pm

**Co-hosts:** FDA and the Center for Research on Complex Generics (CRCG)

In person (at The Universities at Shady Grove; Rockville, MD) and virtual workshop.



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## FDA Modeling Master File

Participating journal: Pharmaceutical Research

Open for submissions

Submission deadline
15 December 2024

The papers in this collection aim to discuss the application of a Model Master File (MMF) in regulatory submissions that contain model integrated evidence (MIE), improving model sharing, model standardization, regulatory consistency, and regulatory efficiency.

**Participating journal**

Submit your manuscript to this collection through the participating journal.

Journal
**Pharmaceutical Research**

Pharmaceutical Research is an official journal of the American Association of Pharmaceutical Scientists, covering innovative research in drug discovery, development, evaluation, and...

| | |
|---|---|
| Publishing model | Hybrid |
| Journal Impact Factor | 3.5 (2023) |
| Downloads | 1.4M (2023) |
| Submission to first decision (median) | 7 days |

Submit to this journal → | Submission guidelines →

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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

# What is an MMF?


- Describe the purpose, benefits, and challenges of MMFs
- Understand how to navigate the process for using the Type V DMF for MMF submissions to support ANDAs
- Recognize the value MMFs provide to the development, assessment, and approval of high-quality generic drugs
- Implement best practices for MMF submissions in your work

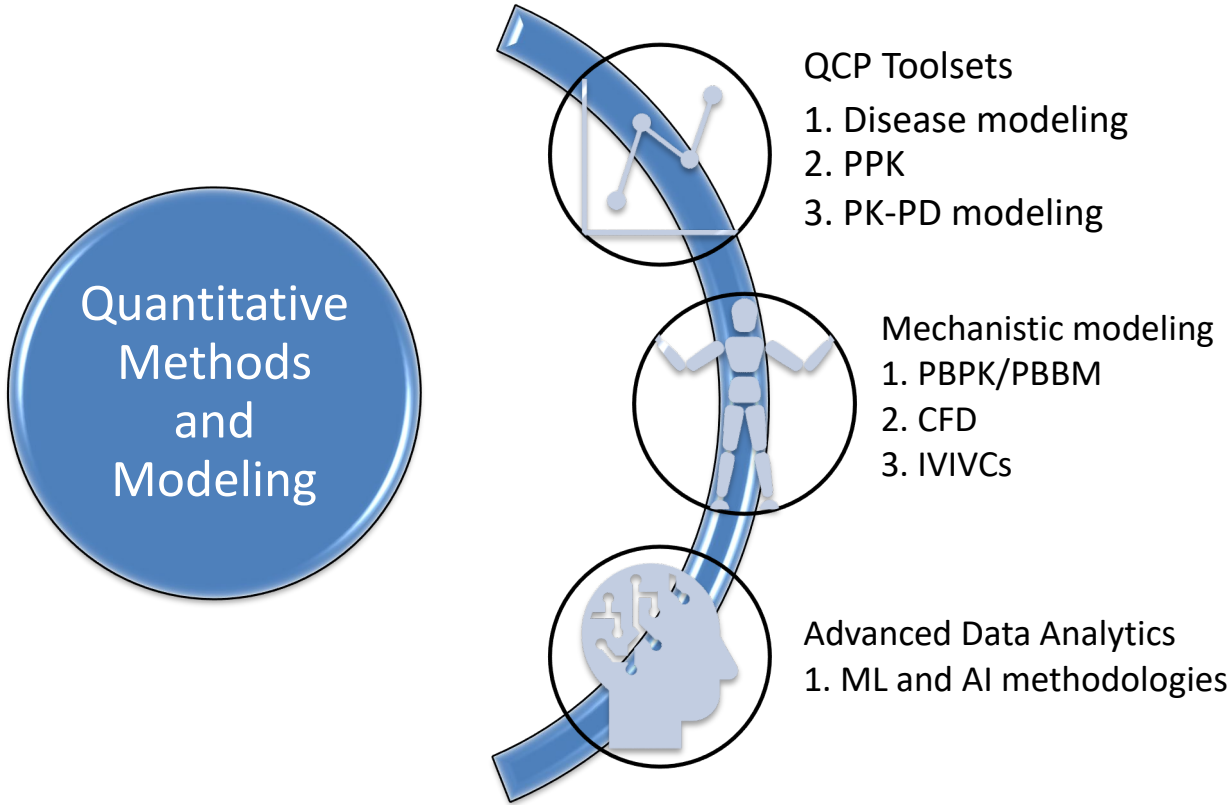
# What is an MMF?

" … 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 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."

V&V: verification and validation, MIE: model-integrated evidence; 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
https://pubmed.ncbi.nlm.nih.gov/38413548/

# What is an MMF?




QCP: quantitative clinical pharmacology, PBBM: physiological biopharmaceutics modeling, PK-PD: pharmacokinetics-pharmacodynamics, IVIVC: in vitro in vivo correlation, ML: machine learning, AI: artificial intelligence

# Example Types of MMF

Drug product-specific models: reusable throughout product life cycle, with adequate V&V for intended COU

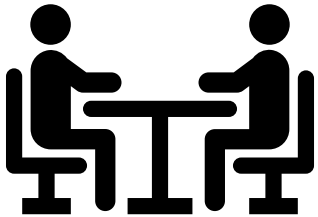
In silico framework for products following the same route of administration: reusable for different products if the framework is qualified for the COU

Modeling methodology or framework for a particular context of use: reusable for different products if the framework is qualified for the COU



COU: context of use

# MMF Utility



**Regulatory Agencies**

- Improve efficiency and consistency
- Improve interdisciplinary communication
- Institutional knowledge
- Ensure the confidentiality of sensitive proprietary information

**Pharmaceutical Industry**

- Reduce time, cost and other resources related to development and regulatory submission of M&S approaches
- Increase confidence: M&S has been documented appropriately and has been used successfully
- Reduce data redundancy & improve M&S availability

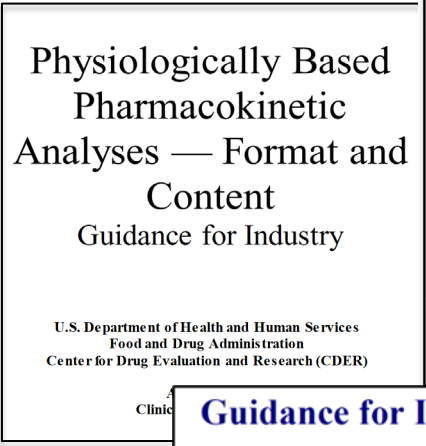


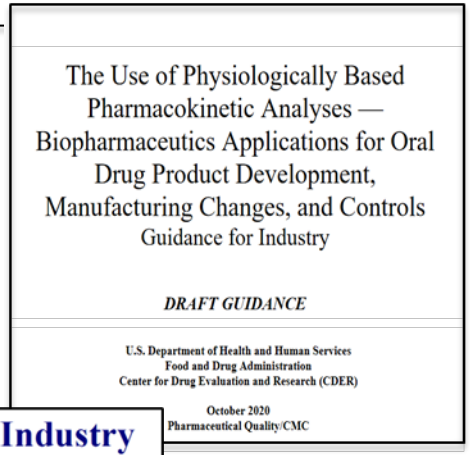
M&S: modeling and simulation

# How to Develop an MMF?

| | |
|---|---|
| **MMF Title*** | |
| **MMF Type** | |
| **Main Submission File** | |
| **M&S Approach submitted within the MMF** | |
| **1. Regulatory context of use** | |
| **2. Scientific rationale supporting the M&S approach** | |
| **3. Data Analysis** | |
| **MAR** | • Model objective (question of interest)<br>• Model development, verification, validation<br>• Summary of the model performance assessment against preselected criteria |
| **4. Model(s) and data file(s)** | Model(s) and data file(s) (in house and literature data), literature and other sources of information |
| **5. Orientation file** | List of version-controlled model files and supporting datasets, their sources (in-house, literature) and their role within the MMF |
| ***provided by the Drug Master File (DMF) holder**<br>**M&S: modeling and simulation, MAR: modeling analysis report** | |

# Applicants are encouraged to follow best practices when documenting M&S approaches in regulatory submissions


Physiologically Based Pharmacokinetic Analyses — Format and Content
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)


The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls
Guidance for Industry
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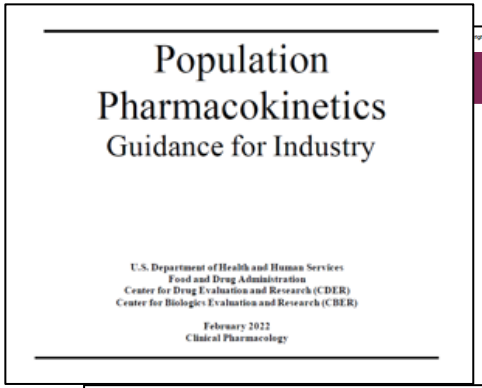
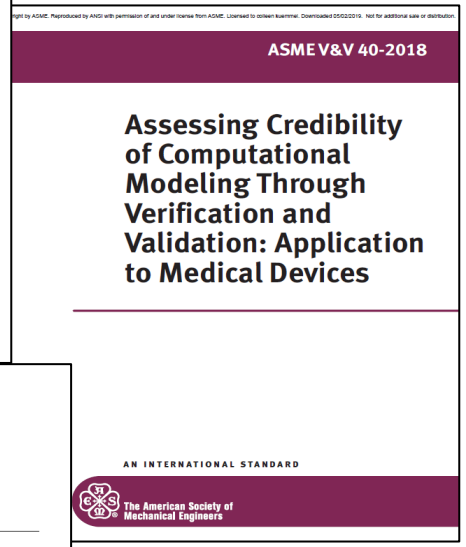
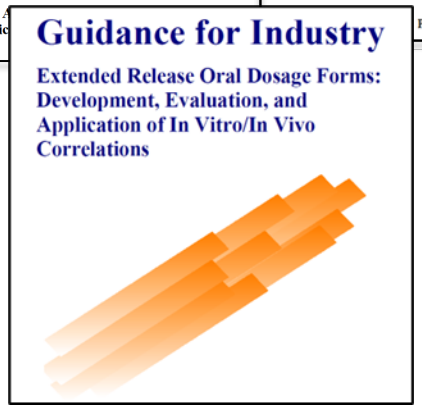
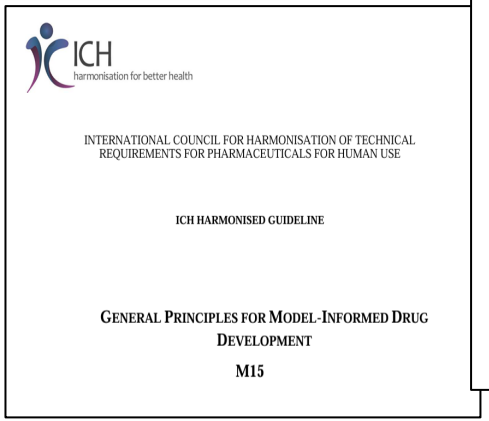
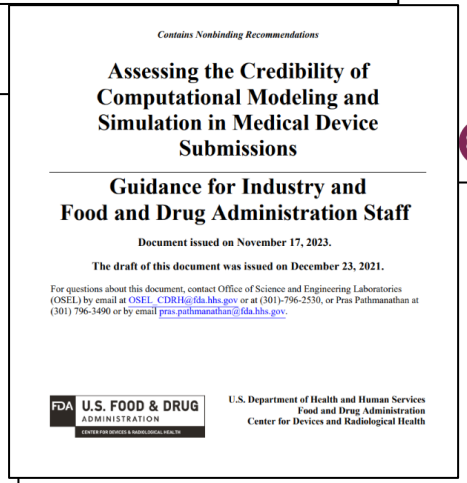
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2020
Pharmaceutical Quality/CMC


Population Pharmacokinetics
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
February 2022
Clinical Pharmacology


ASME V&V 40-2018
Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices
AN INTERNATIONAL STANDARD
The American Society of Mechanical Engineers


Guidance for Industry
Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

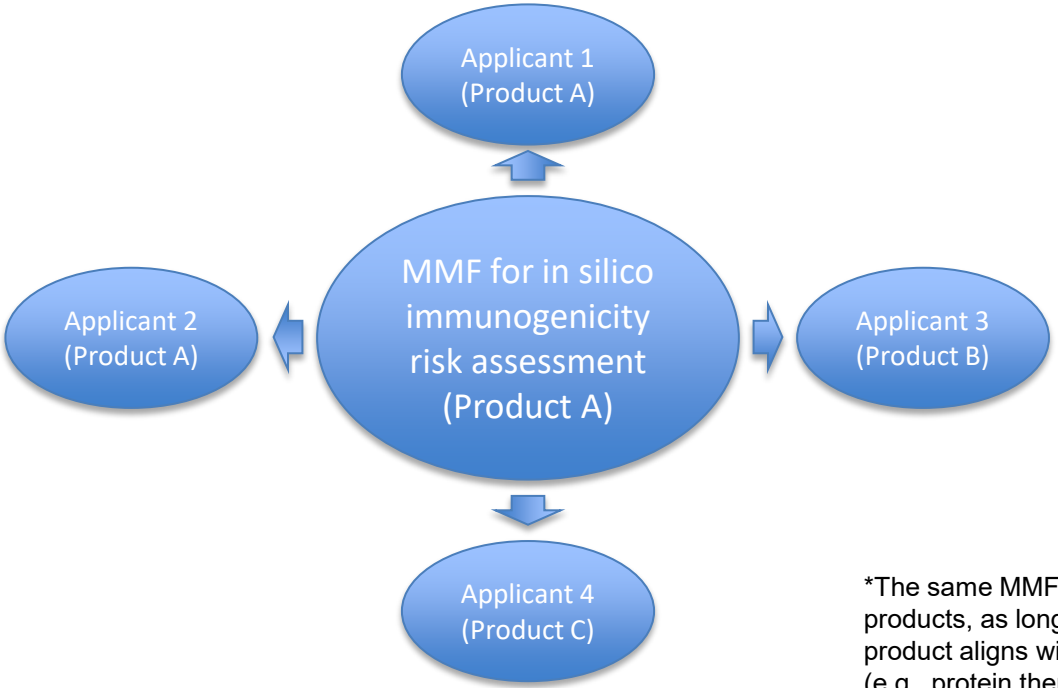

ICH
harmonisation for better health
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE
ICH HARMONISED GUIDELINE
GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG DEVELOPMENT
M15


Contains Nonbinding Recommendations
Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions
Guidance for Industry and Food and Drug Administration Staff
Document issued on November 17, 2023.
The draft of this document was issued on December 23, 2021.
For questions about this document, contact Office of Science and Engineering Laboratories (OSEL) by email at OSEL_CDRH@fda.hhs.gov or at (301)-796-2530, or Pras Pathmanathan at (301) 796-3490 or by email pras.pathmanathan@fda.hhs.gov.
FDA U.S. FOOD & DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

# Mock Example

- *MMF Title:* **Model Master File** - In silico immunogenicity risk assessment model for peptide and protein-based therapeutics
- *MMF Type:* "Model development/verification/validation process for its intended purpose for an active ingredient"
- *Regulatory context of use of the MMF:* A validated in silico model for predicting immunogenicity risks in peptide- and protein-based therapeutics. The model evaluates amino acid sequences to generate quantitative risk scores and identify regions of concern for immunogenicity. This provides a complementary tool to in vitro assays and clinical immunogenicity studies, reducing the experimental burden while maintaining confidence in risk assessments.
- *Scientific rationale:* The model's predictive performance was validated against in vitro assays, clinical immunogenicity data, and historical data to ensure accuracy and consistency across multiple submissions.
- *Data analysis:* MAR, model and data files, orientation file

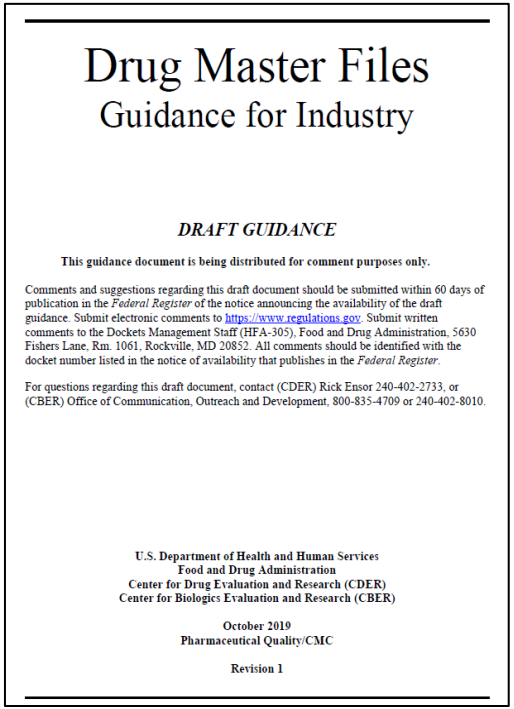
# Mock Example




*The same MMF can be used across multiple products, as long as the context of use for each product aligns with what is described in the MMF (e.g., protein therapeutics). A novel molecular modification may need additional data.

# How to Submit an MMF?

- MMFs can be submitted as Type V DMFs
  - Type V is used for “FDA-accepted reference information.” (21 CFR 314.420(a)(5))
    - A DMF is neither approved nor disapproved
    - The DMF technical content (in this case, the MMF) is typically reviewed by FDA only in connection with the review of a premarket application.
    - Type V DMFs for MMF submissions to support an ANDA may be submitted on an ongoing basis.
    - Submit the Type V DMF in the Electronic Common Technical Document (eCTD) format



Drug Master Files
Guidance for Industry

*DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Rick Ensor 240-402-2733, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019
Pharmaceutical Quality/CMC

Revision 1



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

# How to get the FDA's Early Input?

To start the discussion with the FDA on the development of an MMF:

- Industry Meeting Pilot MIE program
  – submit a meeting request with questions
- Controlled correspondence
  – an option for further discussion

# Take Home Messages

- MMF submissions
  - involve M&S approaches submitted as Type V DMFs
  - hold incentives for both regulatory agencies and pharmaceutical industry
  - advance the role of M&S in drug development and regulatory approval

# Acknowledgements


FDA/CDER/OGD/ORS/DQMM
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- Bhagwant Rege
- Qi Liu

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# Questions?

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