

The Development and Framework of Model Master Files as a Regulatory Initiative

American Society of Pharmacometrics 2025

"Ascending New Heights: Envisioning The Future Landscape of Quantitative Pharmacology"

C5B: FDA's Model Master Files: Paving the Path for Innovative Technologies and Increased Regulatory Acceptance of Modeling and Simulation Approaches

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Office of Generic Drugs | CDER | U.S. FDA

21 October 2025

Disclaimer



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



Overview

- What is a Model Master File (MMF)?
- MMF Utility in the Regulatory Space
- How to Develop an MMF?
 - Type
 - Content
 - Structure
- MMF Mock Examples
- How to Submit an MMF?

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?

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 

What is an MMF?



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](#)

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.

[Submission deadline](#)
15 December 2024

[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

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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

What is an MMF?

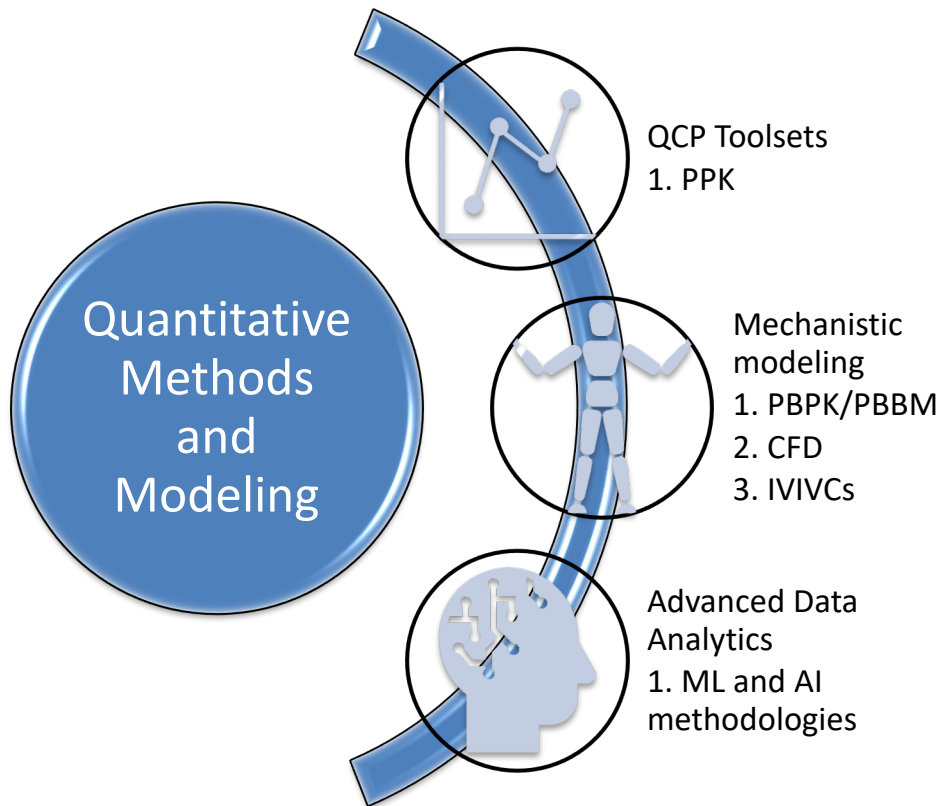


- Describe the purpose, benefits, and challenges of MMFs
- Understand how to navigate the process for using the Type V DMF for MMF submissions to support ANDAs
- Recognize the value MMFs provide to the development, assessment, and approval of high-quality generic drugs
- Implement best practices for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

What is an MMF?

MMFs support

- model integrated evidence (MIE) approaches



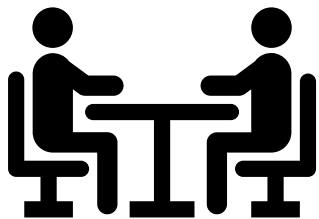
Types of MMF

Drug product-specific models

In silico framework for products following the same route of administration

Modeling methodology or framework for a particular 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 for development and regulatory submission of M&S approaches
- Reduce data redundancy
- Improve M&S availability

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) - Model development, verification, validation - 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 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

DRAFT GUIDANCE

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

Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices

ASME V&V 40-2018

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

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

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

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 Prus Pathmanathan at (301) 796-3490 or by email prus.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

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

AN INTERNATIONAL STANDARD

The American Society of Mechanical Engineers

MMF Mock Examples

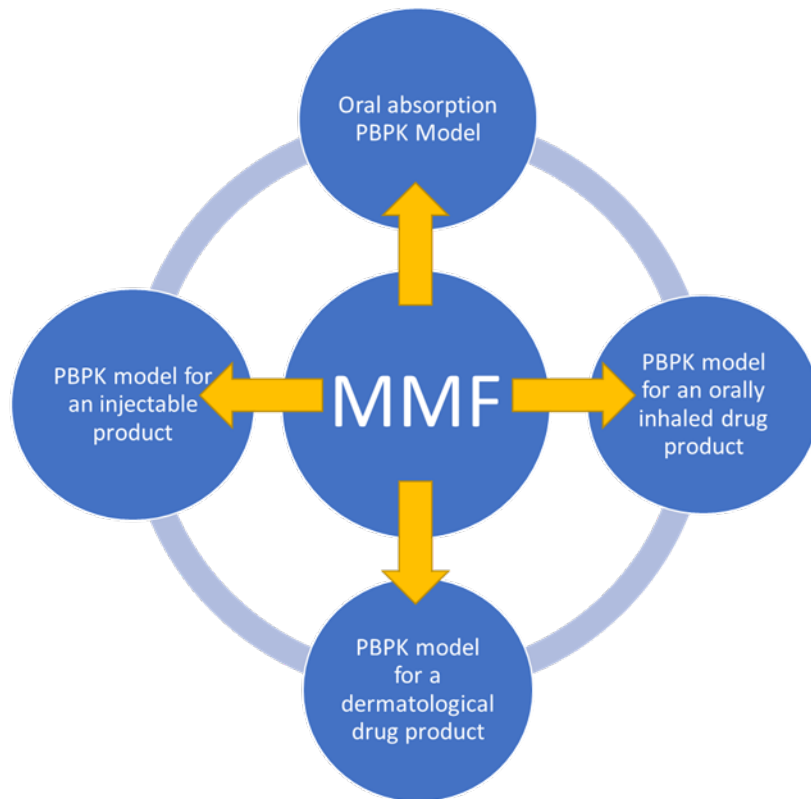
1. Systemic disposition model for active ingredient X supporting the development of fit-for-purpose PBPK models for oral and non-oral routes of administration
2. Modeling methodology on an MIE-supported alternative BE study design for one or more long acting injectables (LAIs)
3. In silico model for predicting immunogenicity risks in peptide- and protein-based therapeutics across different regulatory submissions

Mock Example 1

- *MMF Title:* **Model Master File** - Systemic disposition model for active ingredient X
- *MMF Type:* “Model development/verification/validation process for its intended purpose for an active ingredient”
- *Regulatory context of use of the MMF:* Systemic disposition PBPK model for active ingredient X describing the disposition and elimination of X following its intravenous administration. This model can support the development of fit-for-purpose PBPK models for oral and non-oral routes of administration.
- *Scientific rationale:* The model itself captured the physicochemical properties and the ADME characteristics of drug X and was appropriately verified/validated with data extracted from publicly available sources or in house data. Internal and external validation was performed at the sufficient level of detail and demonstrated the satisfactory performance of the systemic disposition PBPK model. Potential applications involve coupling the systemic disposition PBPK model to oral absorption PBPK models or PBPK models for locally acting drug products for active ingredient X.

Mock Example 1

- *Data analysis:*
 - **MMF#-MAR:**
 - Model objective, model development, verification, validation
 - Summary of the performance assessment against selected criteria
 - *Model(s) and data file(s), literature and other sources of information*
 - **MMF#-Model 1, 2,**
 - **MMF#-Data source 1, 2, ...**
 - **MMF#-Orientation File:**
 - list of version-controlled model files and supporting datasets, their sources (in-house, literature) and their role within the MMF

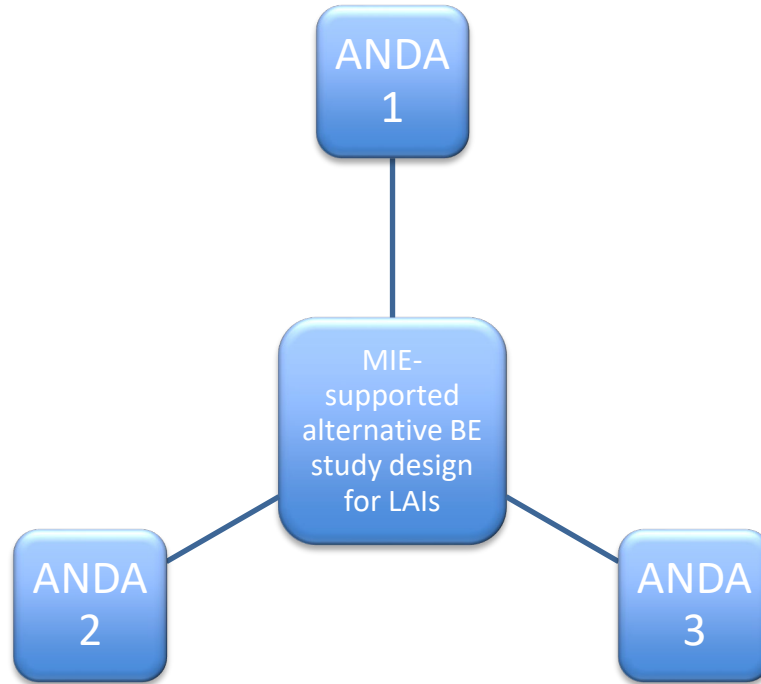


Mock Example 2



- *MMF Title:* **Model Master File** -MIE-supported alternative BE study design for LAIs
- *MMF Type:* MIE method validation for its intended purpose for one or more LAIs
- *Regulatory context of use of the MMF:* Demonstrate the validity of an MIE-supported alternative BE study design (e.g., “in silico” continuation of PK profile using PPK modeling for a shorter BE study) of one or more LAIs. Once validated, the established MIE-supported alternative study design can be applied across a range of products.
- *Scientific rationale:* The MIE-supported alternative BE study design was validated through virtual trial simulations of selected LAI(s) using PPK models available in literature or model developed within the scope of the drug product development program. The established method was able to control the overall Type-1 error rate at a regulatory-accepted level.
- *Data analysis:* MAR, model and data files, orientation file

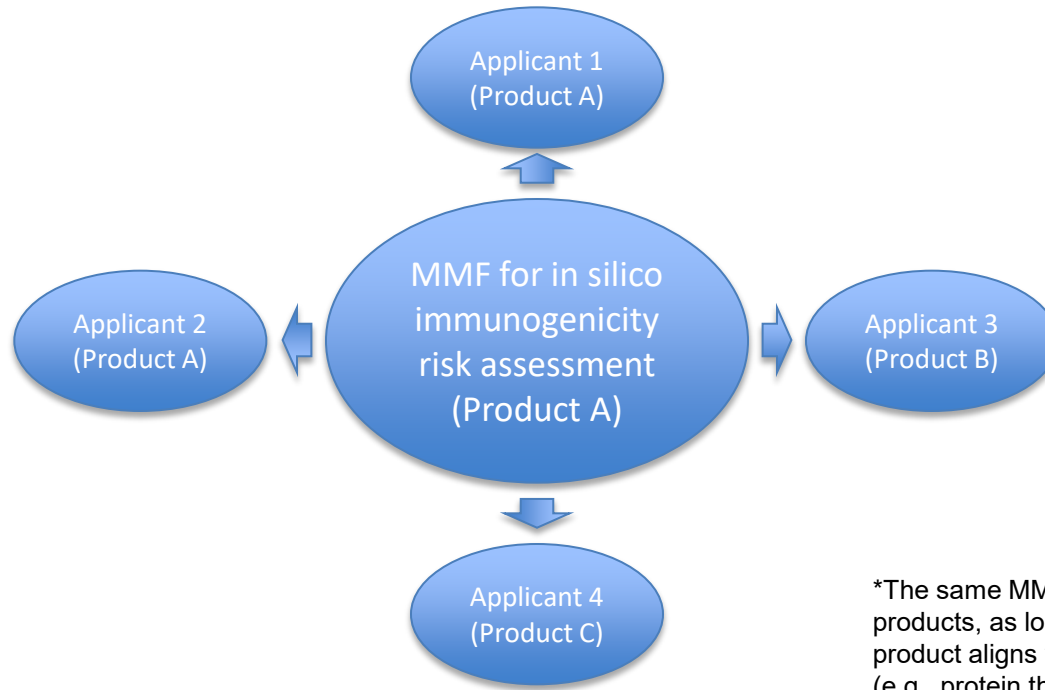
Mock Example 2



Mock Example 3

- *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 3

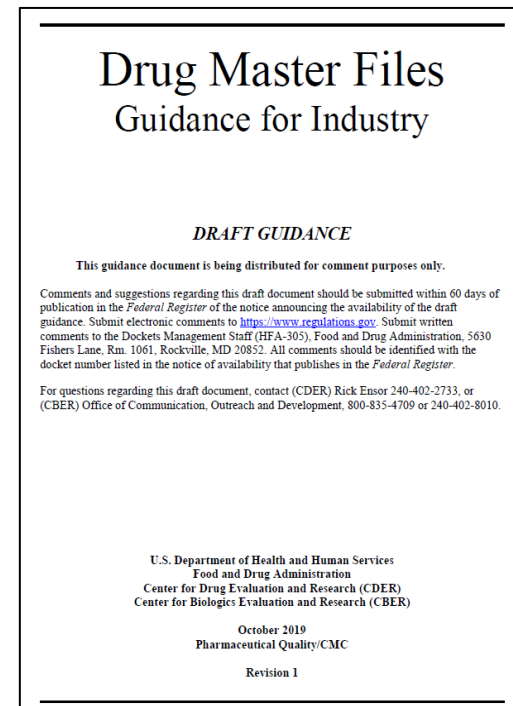


*The same MMF can be used across multiple products, as long as the context of use for each product aligns with what is described in the MMF (e.g., protein therapeutics). A novel molecular modification may need additional data.

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](https://www.fda.gov/oc/ohrt/eCTD/eCTDFAQ.htm)





How to get the FDA's Early Input?

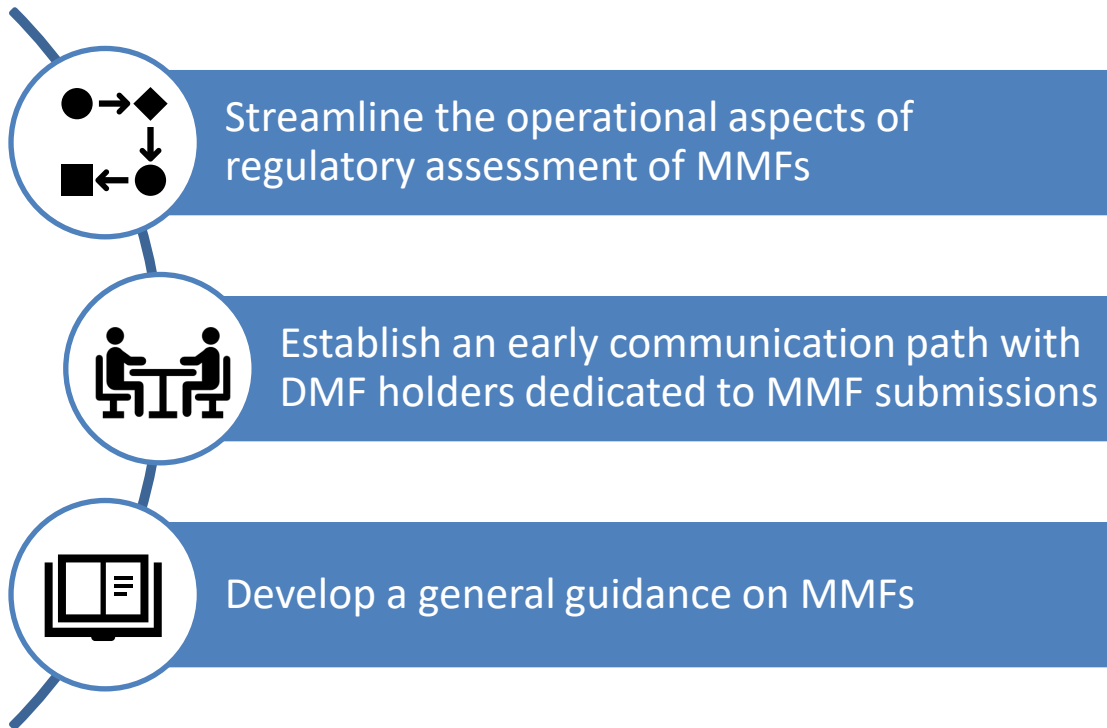
To start the discussion with the FDA on the development of an MMF:

- [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 DMFs
 - hold incentives for both regulatory agencies and pharmaceutical industry
 - advance the role of M&S in drug development and regulatory approval

- Next steps for the FDA:



Acknowledgements



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- Lei Zhang
- Robert Lionberger

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FDA/CDER/OGD/OB

- Partha Roy

FDA/CDER/OTS/OCP

- Rajanikanth Madabushi
- Hao Zhu

Questions?

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Division of Quantitative Methods and Modeling
Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA



Mock Example 2



- *MMF Title:* **Model Master File** -Modeling methodology of Drug Y to assess the impact of Particle Size Distribution (PSD) of drug Y soft gel capsules on bioequivalence (BE)
- *MMF Type:* “Model development/verification/validation process for its intended purpose for an active ingredient”
- *Regulatory context of use:* Demonstrate the satisfactory performance of a PBPK absorption modeling methodology of Drug Y assessing the impact of PSD (e.g., D10, D50 and D90) of drug Y soft gel capsules on BE to support setting clinically relevant PSD specification.
- *Scientific rationale:* To assess the impact of PSD of drug Y soft gel capsules on BE, a PBPK model for drug Y and its soft gel capsule drug products was developed and validated using literature data and data generated within the scope of the drug product development program.
- *Data analysis:* MAR, model and data files, orientation file

Mock Example 2

