Model Master File:
How to Develop and Submit One?

CDER SBIA | Model Master Files: Advancing Modeling and Simulation in Generic Drug Development and Regulatory Submissions

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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.

Overview

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

What is an MMF?

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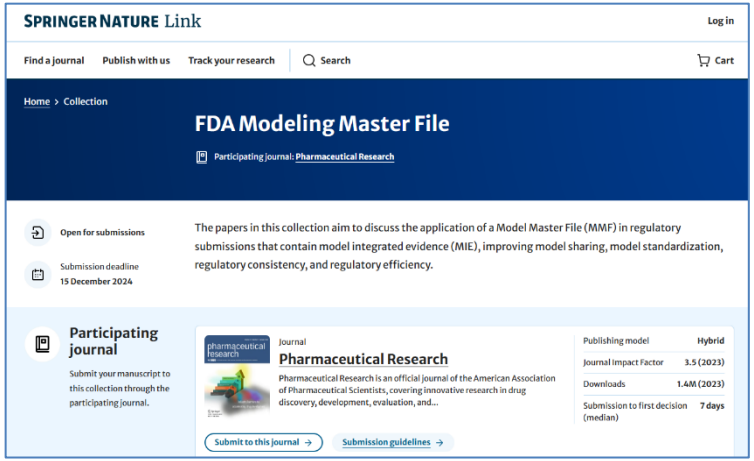
MEETING REPORT

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?



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

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."

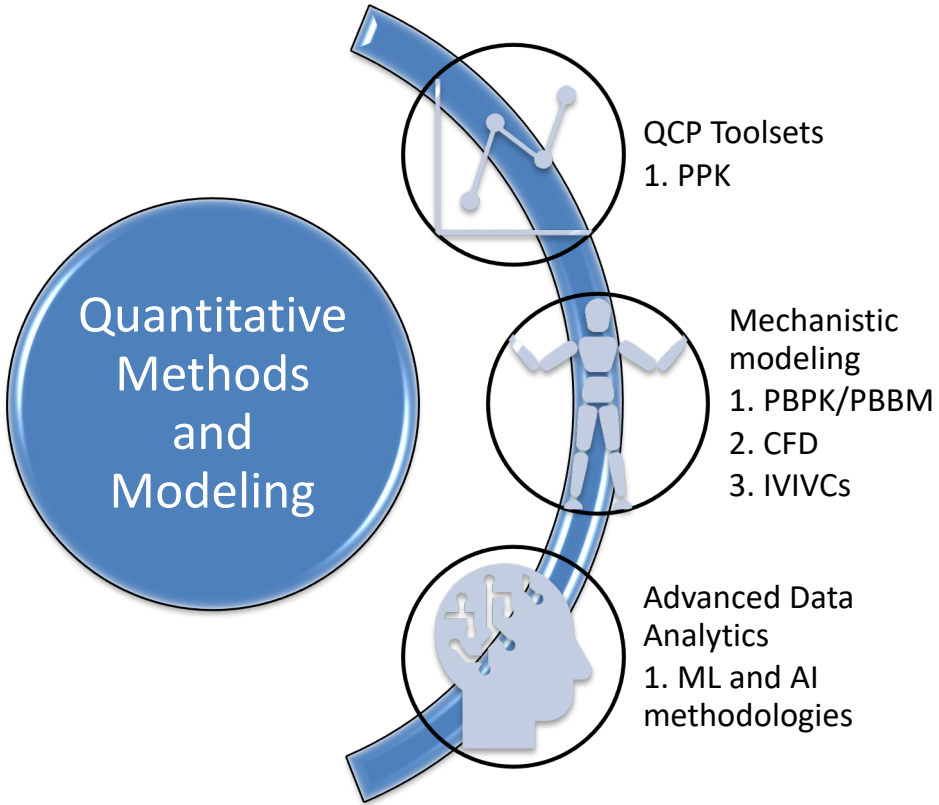
V&V: verification and validation, MIE: model-integrated evidence; PBPK: physiologically based pharmacokinetic, CFD: computation fluid dynamics, PPK: population pharmacokinetic

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?

MMFs support

- model integrated evidence (MIE) approaches

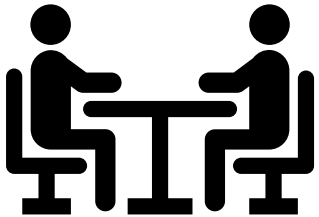


QCP: quantitative clinical pharmacology, PBBM: physiological biopharmaceutics modeling, IVIVC: in vitro in vivo correlation, ML: machine learning, AI: artificial intelligence

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

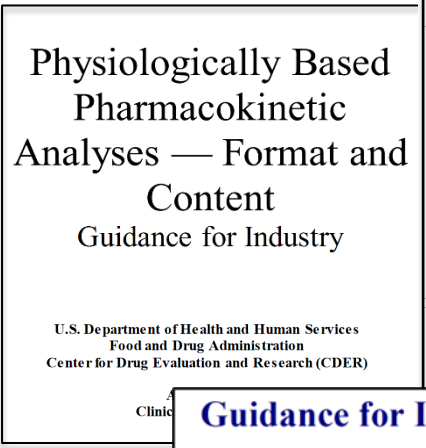
- Reduce time, cost and other resources related to development and regulatory submission of M&S approaches
- Reduce data redundancy
- Improve M&S availability

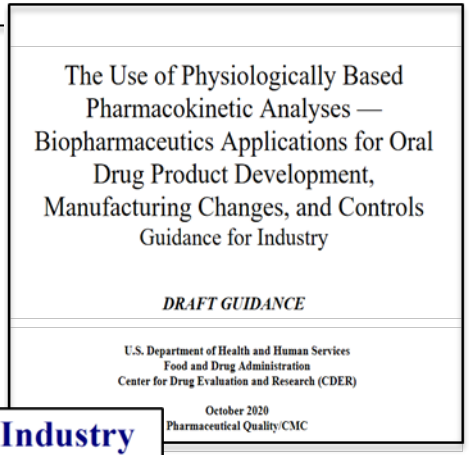
M&S: modeling and simulation

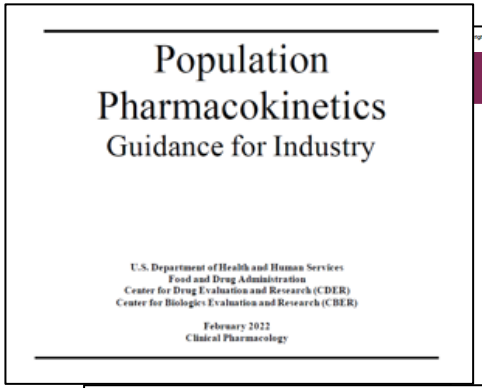
How to Develop an MMF?

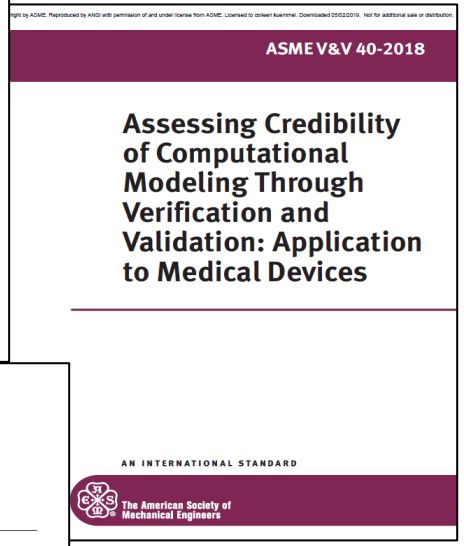
MMF Title*	
MMF Type	
Main Submission File	
M&S Approach submitted within the MMF	
1. Regulatory context of use	
2. Scientific rationale supporting the M&S approach	
3. Data Analysis	
MAR	• Model objective (question of interest) • Model development, verification, validation • Summary of the model performance 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**	

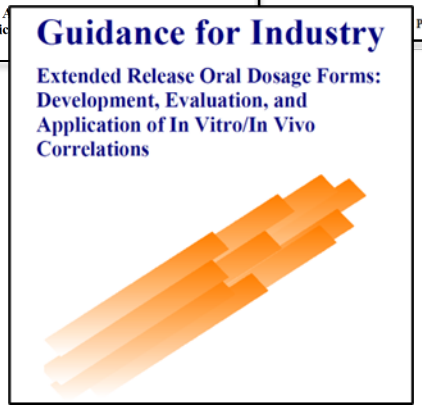
Applicants are encouraged to follow best practices when documenting M&S approaches in regulatory submissions

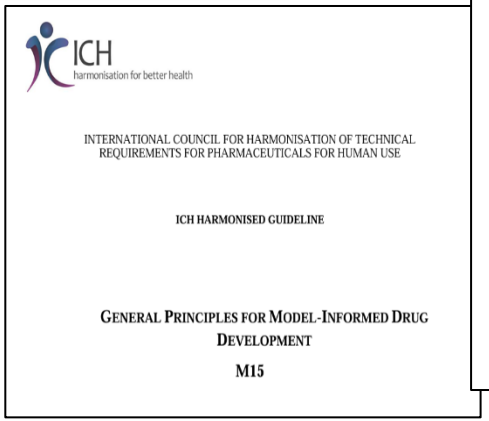


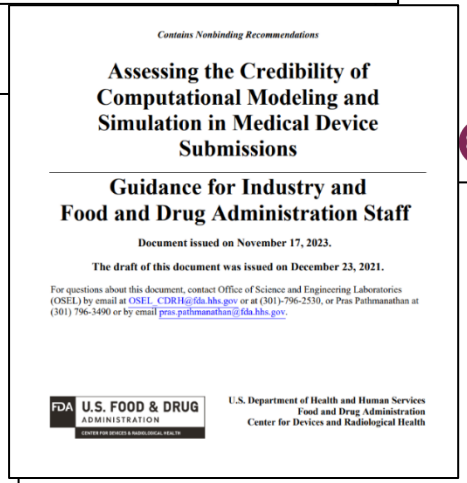












MMF Mock Examples

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 of Drug Y to assess the impact of Particle Size Distribution (PSD) of drug Y soft gel capsules on bioequivalence (BE)
3. Modeling methodology on an MIE-supported alternative BE study design for one or more long acting injectables (LAIs)
4. In silico model for predicting immunogenicity risks in peptide- and protein-based therapeutics across different regulatory submission

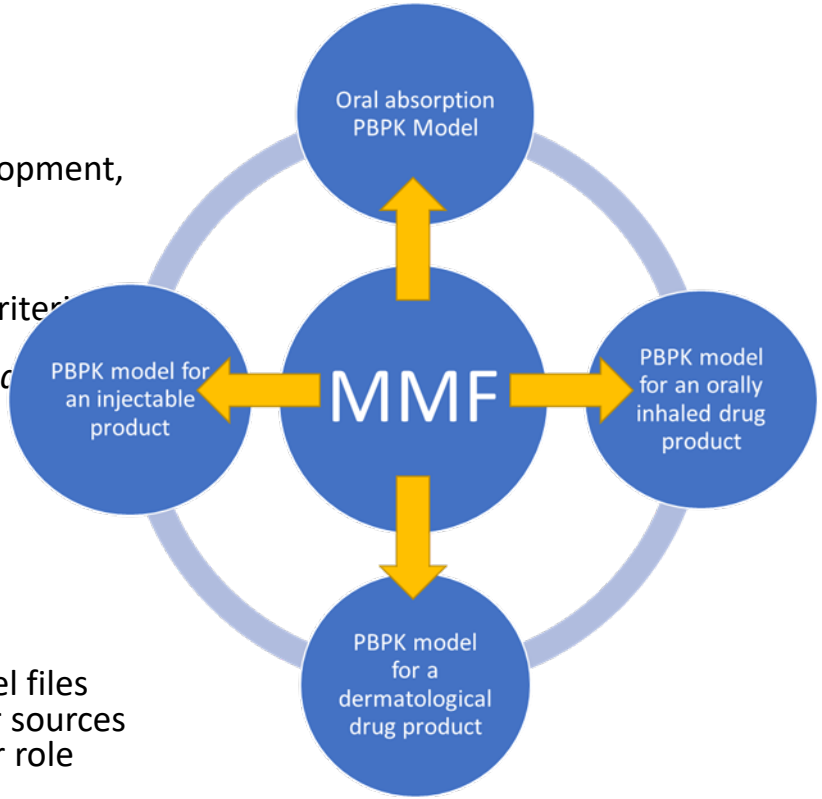
Mock Example 1

- *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.

ADME: absorption, disposition, metabolism, excretion

Mock Example 1

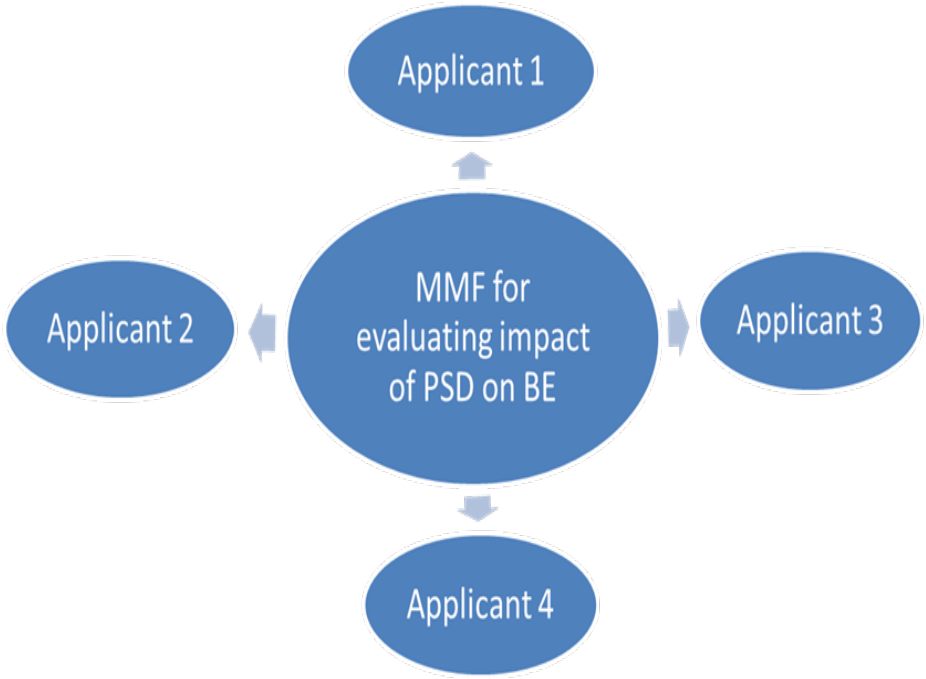
- *Data analysis:*
  - **DMF#-MAR**:
    - Model objective, model development, verification, validation
    - Summary of the performance assessment against selected criteri
  - *Model(s) and data file(s), literature d sources of information*
    - **DMF#-Model 1, 2, ….**
    - **DMF#-Data source 1, 2, …**
  - **DMF#-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** -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

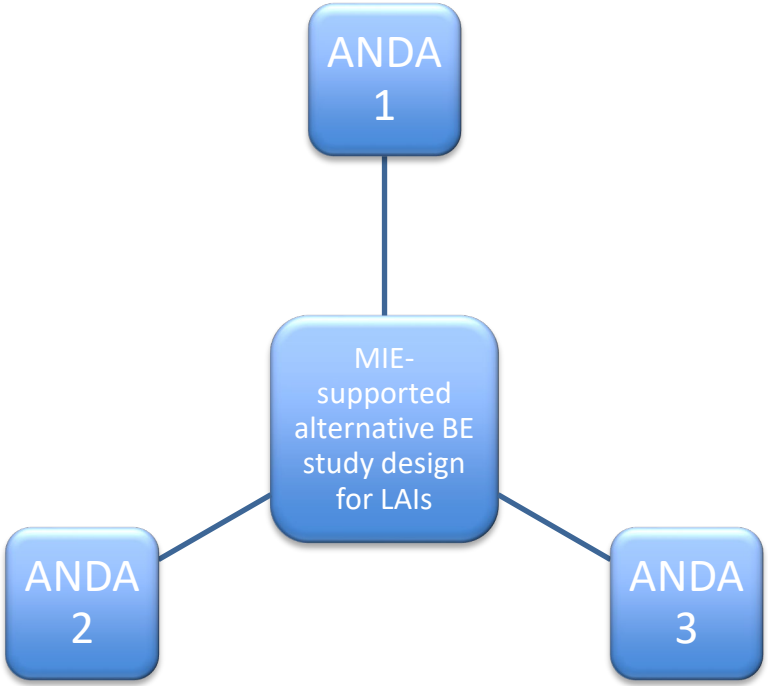
Mock Example 2



Mock Example 3

- *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

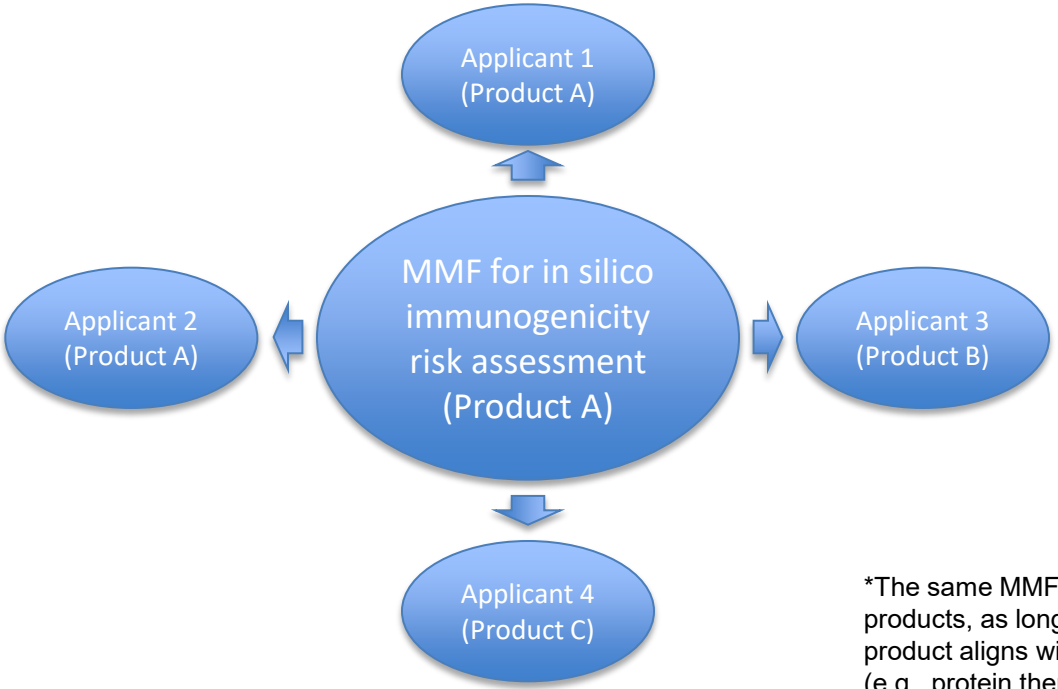
Mock Example 3



Mock Example 4

- *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 4



*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.

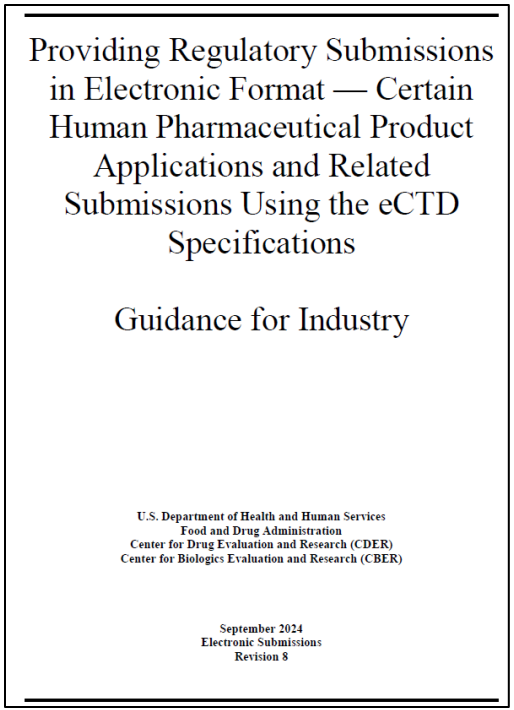
How to Submit an MMF?

- 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.

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 Submit an MMF?

Submit the Type V DMF in the [Electronic Common Technical Document (eCTD) format]

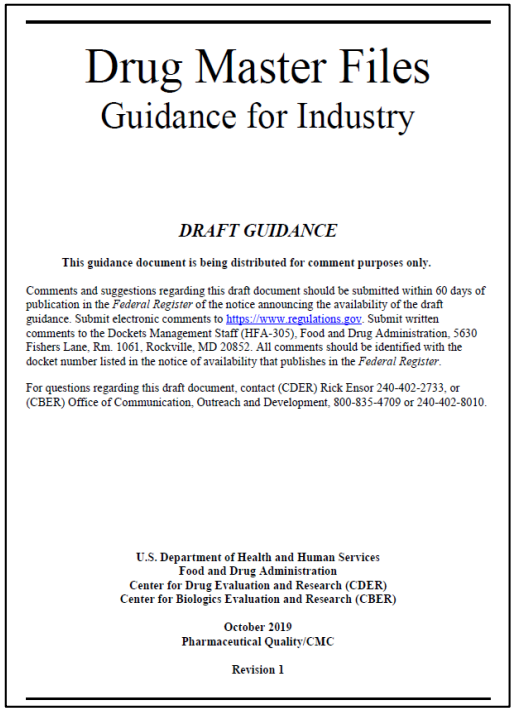


Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

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)

September 2024
Electronic Submissions
Revision 8



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

How to Submit an MMF?

Step 1:

Interested parties must provide a letter of intent (LOI) to submit a Type V DMF for an MMF submission to the DMF staff at dmfquestion@fda.hhs.gov

- Please include a clearly stated subject field and other necessary information.* For example: “Letter of Intent to Submit Type V DMF for MMF Submission to Support ANDAs”
- You may want to include a brief description of: i) the MMF context of use (i.e., question of interest, model influence, and decision consequences) of the MMF; ii) the scientific rationale supporting the MMF; iii) the modeling analysis report relevant to the MMF; and iv) data analysis performed within the scope of the MMF

*See FDA Draft Guidance for Industry “Drug Master Files”; see also 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 Submit an MMF?

Step 2:

Submit your Type V DMF according to the FDA Draft Guidance for Industry "Drug Master Files" and the FDA's DMF web page, available at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

- Please submit your Type V DMF for an MMF following the Electronic Common Technical Document (eCTD) format. Module selection should be based on the context of use of the M&S approach contained in the MMF.
- Please include "MMF" or "Model Master File" in the subject line of your main submission
- Please include the "DMF#" in the file name of each file included in the submission

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 Submit an MMF?

For Questions: mmf@fda.hhs.gov

For additional information:

Lanyan (Lucy) Fang
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 75, Rm. 4686
Silver Spring, MD 20993-0002

How to get the FDA's Early Input?

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

- Industry Meeting Pilot MIE program
  - Submit a meeting request with your questions
- Controlled correspondence
  - An option for further discussion

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FDA/CDER/OGD/ORS/DQMM

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- Jae (Mike) Lee

FDA/CDER/OGD/ORS

- Lanyan (Lucy) Fang
- Andrew Babiskin
- Lei Zhang
- Robert Lionberger

FDA/CDER/OPQ/OPQAIII/DPQAXVIII

- Erin Skoda

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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