Considerations and Potential Regulatory Applications for a Model Master File

In person (at The Universities at Shady Grove; Rockville, MD) and virtual workshop
May 2-3, 2024

The purpose of this workshop is to engage stakeholders among model developers, industry, and FDA in a discussion on the concept, scope, and regulatory application of a Model Master File (MMF). The goals of this workshop are to illustrate how MMFs can improve the efficiency with which evidence from modeling and simulation (M&S) can facilitate drug product development. Additionally, the workshop will explore how M&S can increase efficiency in application assessment and consistency in regulatory use and acceptance of established models.

Workshop link: https://www.complexgenerics.org/education-training/considerations-and-potential-regulatory-applications-for-a-model-master-file/
Registration link: https://www.eventbrite.com/e/considerations-and-potential-regulatory-applications-for-model-master-file-tickets-811540949827?aff=oddtdtcreator

The MMF framework has been introduced and discussed in two workshops co-hosted by the FDA and the Center for Research on Complex Generics (CRCG) in the past. For more information (agenda, speakers, presentation slides and recordings), refer to the links bellow:

- Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches. Co-hosted by FDA and the Center for Research on Complex Generics (CRCG) on September 30 and October 1, 2021 (https://www.complexgenerics.org/education-training/regulatory-utility-of-mechanistic-modeling-to-support-alternative-bioequivalence-approaches/)
- Best Practices for Utilizing Modeling Approaches to Support Generic Product Development. Co-hosted by FDA and the Center for Research on Complex Generics (CRCG) on October 27-28, 2022 (https://www.complexgenerics.org/education-training/best-practices-for-utilizing-modeling-approaches-to-support-generic-product-development/)
- Recently accepted manuscript: The Role of Model Master Files for Sharing, Acceptance, and Communication with FDA | The AAPS Journal (springer.com)

Small Group Discussion Session (in-person only)

Discussion Topics

Day 1 (2 hours)

1. Key considerations when developing an MMF: content and format.
    - What is an MMF (develop a definition), what are the type of MMFs and what type of (in silico) models could be considered MMFs?
    - What are the key components of an MMF for the preparation, validation and submission?
    - What will be your key considerations in the legal and/or financial aspects related to MMFs?
2. What are the potential benefits/incentives for stakeholders to develop and use an MMF? Based on the discussed cases, comment on how MMF enhances regulatory approval for product portfolios supported by M&S approaches:
    - How would an MMF streamline a regulatory submission?
    - How would an MMF increase regulatory acceptability of modeling and simulation approaches?
    - How could the MMF framework change the economic landscape of generic drug development?
3. What are the potential benefits/incentives for stakeholders to develop and use an MMF for oral dosage forms in the generics space?
    - How could the MMF help to address challenges with model validation for oral (and non-oral) dosage forms, especially in the absence of non-BE batches?
    - How could an MMF be applied to support modeling and simulation approaches on mitigating the risk for not conducting a fed study?
4. What are the potential benefits/incentives for stakeholders to develop and use an MMF for long acting injectables in the generics space?
    - How could an MMF be used to support alternative BE study design for LAIs?
    - What are the key elements that should be included in an MMF supporting a mechanistic IVIVC model for an LAI?
5. Summarize key conclusions/take home messages (20 minutes)

Day 2 (2 hours)

1. What are the potential benefits/incentives for stakeholders to develop and use an MMF for non-orally administered, locally acting drug products in the generics space?
    - How could an MMF be applied to support model validation for locally acting drug products in the absence of local bioavailability data, typically encountered with these products?

- What are some different considerations for an MMF of a computational fluid dynamics (CFD) model as compared with a physiologically based pharmacokinetic (PBPK) model?

2. Maximize the Benefit from Implementing the MMF Framework:
   - Which type of products or therapeutics areas may benefit the most from MMF applications?
   - Would specific considerations apply to MMF based on the delivery route?
   - How could an MMF be applied to support modeling and simulation approaches on alternative bioequivalence approaches for complex generics?
6. MMF versioning:
   - How to handle the dynamic nature of in silico models submitted under an MMF?
   - Under which scenarios (regulatory criteria) would an MMF revision or a submission of a new MMF be necessary?
   - What would be the mechanism or criteria for MMF upgrade?
   - Additional input on the mechanism that the FDA should consider?
3. Summarize key conclusions/take home messages (20-30 minutes)

Model Master File Definition:

MMF is a framework under which in silico models or methodologies/practices related to in silico models are viewed as portable, reusable, generalizable, and sharable after they have undergone sufficient Verification & Validation (V&V).

Model Master File Examples:

MMF Proposed Template:

1. MMF [Title]
2. MMF Type
3. Main Submission File
   - regulatory context of use of the MMF
   - scientific rationale supporting the MMF
   - Modeling Analysis Plan (MAP)/Modeling Analysis Report (MAR)
   - data analysis performed within the scope of the MMF
   - model files, datasets, literature and all sources of information used
4. Orientation File
   - list of version-controlled model files and supporting datasets and their sources (in-house, literature)
   - their role within the MMF

Case Studies

Case study 1

MMF Title: Systemic disposition model for active ingredient X

MMF Type: "Model development/verification/validation process for its intended purpose for an active ingredient"

Main Submission File:

- Regulatory context of use of the MMF: The regulatory purpose of this MMFXXX is to demonstrate the satisfactory performance of a systemic disposition PBPK model for active ingredient X describing the disposition and elimination of X following its intravenous administration.
- Scientific rationale supporting the MMF: For the purpose of submitting MMFXXX, a systemic disposition PBPK model for X was developed and validated using literature data and data generated within the scope of the drug product development program. The model was built by accounting for the physiochemical, ADME properties of X. It was validated against systemic PK data collected following the intravenous administration of X as a bolus dose or a continuous infusion (as a single/multiple dose). External validation was performed leveraging literature sources and in house data to demonstrate the acceptable performance of the model under informative scenarios (single dose vs steady state, dose proportionality/linearity over clinically relevant dose range, relevant virtual population). Model validation involved the comparison between the predicted and the observed systemic PK profiles for X.
  Model predictions were in good agreement with observed data.
  Therefore, the performance of the systemic disposition PBPK model for X was deemed overall satisfactory. The model is considered appropriate for the development of fit-for-purpose oral absorption PBPK models and PBPK models for locally acting drug products that carry X as their active ingredient.
- Data analysis performed within the scope of the MMF
  - MAP/MAR:
    - Model objective, model development, verification, validation
    - Summary of the performance assessment against selected criteria
  - Model(s) and data file(s) (in house and literature data), literature and other sources of information
    - Model 1, 2, ….
    - Data source 1, 2, …

Orientation File:

- list of version-controlled model files and supporting datasets, their sources (in-house, literature) and their role within the MMF

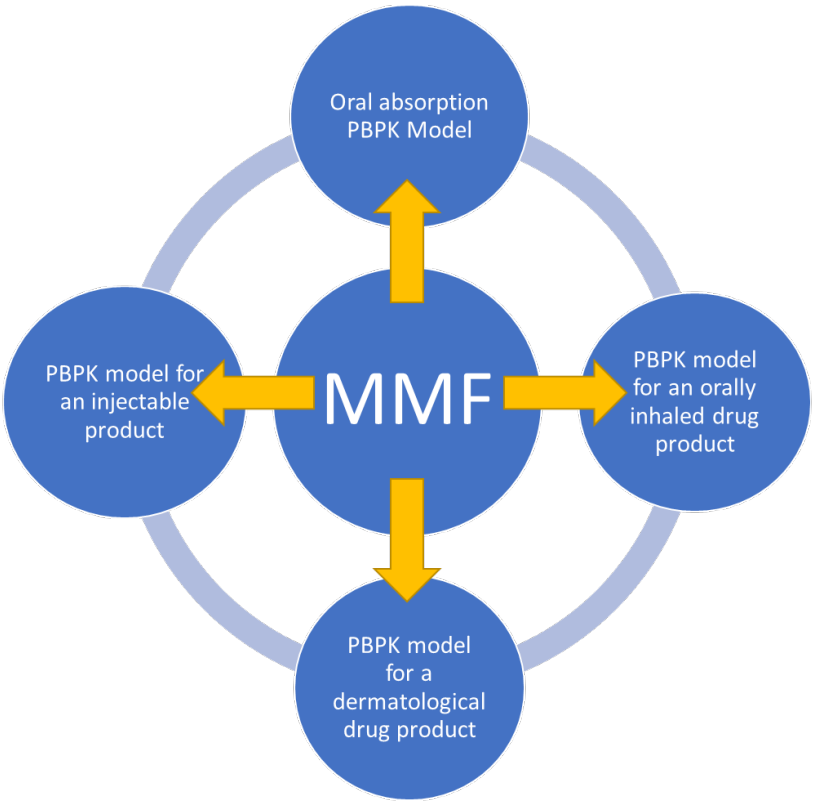

Figure 1: Graphical representation of the MMF on the systemic disposition model for active ingredient X across different products carrying the same active ingredient X.

Case study 2

MMF Title: 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 and its product"

Main Submission File:

- Regulatory context of use of the MMF: The regulatory purpose of this MMFXXX is to 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 supporting the MMF: For the purpose of submitting MMFXXX 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.
- Modeling files:
    - First, population PK informed clearance and compartmental parameters were incorporated into PBPK disposition model.

    - Secondly, physiochemical, ADME properties of drug Y and PSD data from different baches of soft gel capsules that cover a considerable range and relevant in vivo PK data were used to establish PBPK absorption model.
    - Sensitivity analysis found that PK parameters were sensitive to bile salt solubilization ratio, solubility and particle size distribution under fasting condition and sensitive to gastric transit time under fed condition. Bile salt solubilization ratio and solubility were then optimized for better model fitting under fasted conditions. Gastric transit time was optimized for better modeling fitting under fed condition.
    - The PBPK absorption model was built and internally validated using informative datasets including in vitro PSD and in vivo PK data from the different capsule strengths, if applicable, under fasted and fed conditions. External validation was performed using datasets that were not used for model building, including in vitro PSD and in vivo PK data from the different capsule strengths, if applicable, under fasted and fed conditions to demonstrate the acceptable performance of the model.
    - Model predictions were in good agreement with observed data obtained after the oral administration of drug Y soft gel capsule.
    - The performance of the oral PBPK model for the drug Y soft gel capsules was deemed overall satisfactory. This modeling methodology assessing the impact of PSD of drug Y soft gel capsules on bioequivalence (BE) was deemed satisfactory. The model was considered appropriate for the development of fit-for-purpose oral absorption PBPK models for assessing the impact of PSD of drug Y soft gel capsules on BE and support setting clinically relevant PSD specification.
- Data analysis performed within the scope of the MMF
    - MAP/MAR:
        - Model objective, model development, verification, validation
        - Summary of the performance assessment against selected criteria
    - Model(s) and data file(s) (in house and literature data), literature and other sources of information
        - Model version 1, 2, ….
        - Data source 1, 2, …

Orientation File:

- list of version-controlled model files and supporting datasets, their sources (in-house, literature) and their role within the MMF

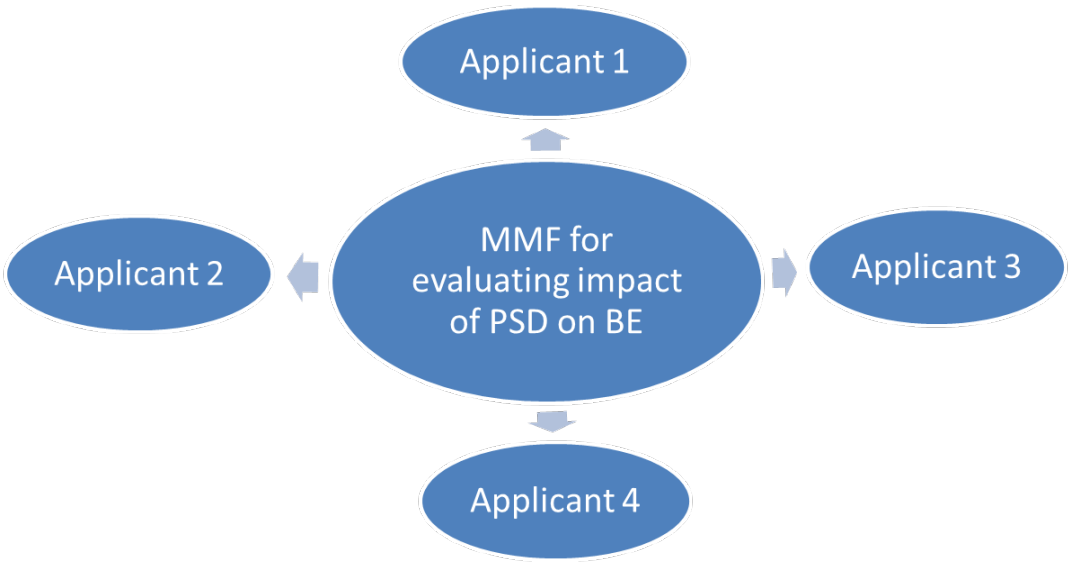

Figure 2: Graphical representation of the MMF on PBPK absorption modeling methodology of Drug Y to assess the impact of PSD (e.g., D10, D50 and D90) of drug Y soft gel capsules on BE and support setting clinically relevant PSD specification, which could be used by different applicants.