Considerations for Using Model Master Files

FDA/M-CERSI PBBM Best Scientific Practices to Drive Drug Product Quality: Latest Regulatory and Industry Perspectives

Day 2, Breakout Session J: PBBM modeling report requirements and consideration for using model master files

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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.

Model Master Files

Draft Guidance for Industry: Drug Master Files (October 2019)
https://www.fda.gov/media/131861/download

- Analogy to Drug Master File for API:
  - "Provide confidential, detail information" about production of API and its qualities
  - "Can authorize one or more applicants or sponsors"
  - Does not need to be re-reviewed unless modified since last assessment
- Model Master Files (MMF) – What Can They Be?
  - Can be viewed as a portable, re-usable, generalizable, and shareable model
  - Can be submitted to FDA separately from application
  - Can include description of the model with implementation details, validation data, and purpose of use; e.g., types
    - Novel in silico methodologies
    - Model verification and validation (V&V)
    - Platform V&V (i.e., for physiologically based pharmacokinetic [PBPK] models)

API: active pharmaceutical ingredient

MMF Benefits - Industry

- Communication on model acceptance for industry awareness
- Access to models for smaller firms with less in-house expertise
- Interaction between model developers and FDA SMEs during MMF assessment process
- Cost savings due to:
  - Model standardization
  - Model re-use
  - Review time and consistency
  - Managing model update upon new advancements/enhancements
  - Reduce duplicative efforts

MMF Benefits - FDA

- Coordination on MMF assessments across relevant CDER offices
- Development of institutional knowledge (particularly around novel applications)
- Minimize duplicative assessment work
- Provide access to critical platform V&V data/activities that the applicant may not be aware of or have access to

Platform Performance Assessment – PBPK MMF Type

Basic Principles

- PBPK Platform: a system of databases and differential equations defining movement of drug through ADME processes defined by anatomy and physiology
- Platform credibility is independent of the proposed implementation of that platform for a specific drug product
- A sufficient number of drug compounds/products ranging in physiochemical and PK properties with observed outcomes predicted with adequate precision
- Should not only include compounds/products used for platform development

ADME: absorption, distribution, metabolism & excretion

Derived from:
Zhao, L., Seo, P., and Lionberger, R. *CPT: pharmacometrics & systems pharmacology* 8.6 (2019): 347
Tsakalozou, E., Alam, K., Babiskin, A., and Zhao, L. CPT (2021), https://doi.org/10.1002/cpt.2356

Dermal PBPK Model Supporting ANDA Approval: PPA MMF Case Study

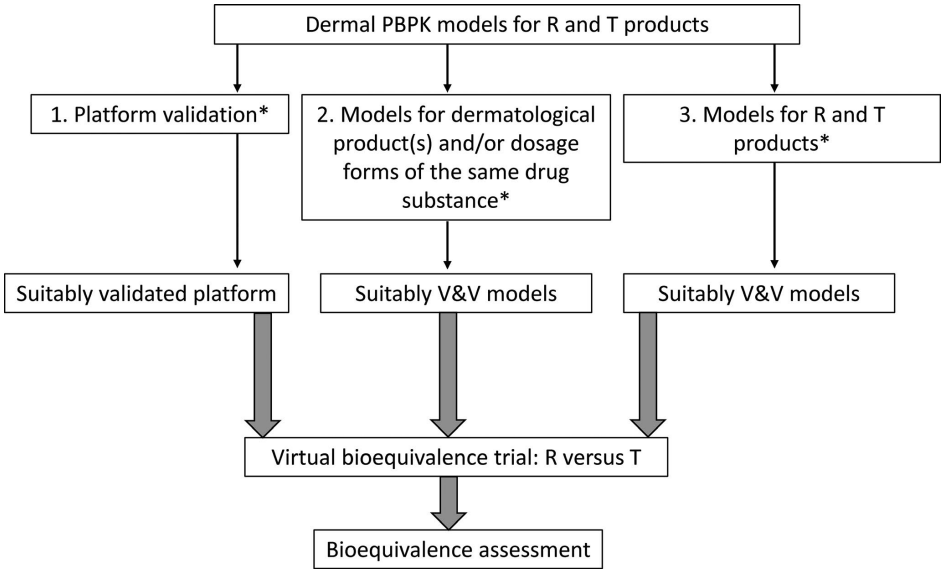
Diclofenac topical gel, 1%: Dermal PBPK model supporting ANDA approval for a generic. Virtual PBPK based BE studies in lieu of a comparative clinical endpoint study supported the product approval.

Data for model V&V

- Data from 10+ dermal for TDS and topical products with multiple doses/product strengths, dosing regimens, age, and anatomical locations
- Systemic and local bioavailability (skin biopsy, IVPT, dermal microdialysis) data

Model performance evaluation

- Satisfactory model performance for all data evaluated



Tsakalozou, E et al. CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.
Tsakalozou, E et al. Clin Pharmacol Ther. 2021 July; 111(5):1036-1049.

Adapted from Eleftheria Tsakalozou, Ph.D. and Liang Zhao, Ph.D.

TDS: Transdermal Delivery Systems, IVPT: in vitro permeation testing

Scope of Platform V&V Activities Contained

TABLE 3 Overview of the platform performance assessment conducted by the applicant in support of the dermal PBPK model for diclofenac sodium topical gel, 1%, developed in MPML MechDermA within the Simcyp Simulator, version 17

Active ingredient[a]											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Dosage form/products[b]	TDS	TDS	TDS	Solution	TDS	Cream	Gel ointment cream	TDS cream	Gel Solution Nanoparticles TDS	Gel	Solution
Verification matrix	Plasma	Plasma	Plasma	Plasma	Plasma	IVPT	Plasma	Plasma	Plasma Synovial fluid Subcutis Muscle Dermis Stratum corneum	Plasma Synovial fluid	Skin biopsy (stratum corneum, viable epidermis, dermis)
Number of literature sources for validation of the systemic disposition PBPK model	4	1	1	c	1	c	3	c	4	2	c
Number of literature sources for validation of the dermal PBPK model	8	2	1	1	1	1	1/1/1	1/1	6/1/1/1	2	1

Abbreviations: IVPT, in vitro permeation testing; MPML, multi-phase multi-layer; PBPK, physiologically-based pharmacokinetic; TDS, transdermal delivery system.

[a]The selected active ingredients differed in terms of their physicochemical properties (lipophilicity and ionization potential) and pharmacokinetic characteristics (protein binding, extent of distribution in the human body, route of elimination, and blood-to-plasma partitioning among others). More specifically, the molecular weight, logP (lipophilicity), blood to plasma ratio, fraction unbound in plasma, volume of distribution at steady-state and total systemic clearance of the selected active pharmaceutical ingredients ranged from 162 to 468 g/mol, from −1.6 to 6.4, from 0.55 to 1.107, from 0.003 to 0.95, from 0.123 L/Kg to 48.8 L/Kg and from 1.6 L/h to 71.5 L/h, respectively. The selected active ingredients were acids, bases, and ampholytes.

[b]Product-specific dermal PBPK models were developed for each of these dosage forms.

[c]Not provided in the submission or refers to a drug substance that is not given by other than the topical route.

Tsakalozou, E et al. CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.

Slide courtesy of Eleftheria Tsakalozou, Ph.D.

Potential for MMF

- In this case, the application contained:
  - High-level data for model and platform validation
  - Product-specific modeling parameters for diclofenac topical gel
  - A platform for dermal PBPK models
  - A practice for model building, V&V, and simulation for a well-defined regulatory use
- These components can be done in a MMF framework
- FDA can review the PPA for dermatological topical products in the form of a MMF and/or the diclofenac model separately from the application itself.
- Once found adequate/accepted, MMF is recognized as having/containing sufficient verification and validation (V&V) for the intended purpose. Future applications can refer to the MMF for then same regulatory use.

Slide adapted from Liang Zhao, Ph.D.

Practical Considerations for Model Reuse/Referencing for a PPA-based MMF

- Is the intended purpose of modeling & simulation consistent with the previous case or with other V&V cases in the PPA/MMF?
- Is the drug substance within the range of physiochemical properties utilized in the PPA/MMF? Does the drug substance go through ADME processes not considered in the PPA/MMF (e.g., metabolism)?
- Are the critical physiochemical attributes of the drug product consistent with those utilized in the PPA/MMF?
- Data for validation of the drug product of interest (e.g., systemic PK, local PK, …) that can support parameterization
- Any platform enhancements/versioning that has occurred since the MMF was last used?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