Potential Types of Model Master Files

Liang Zhao, PhD

Division Director

Division of Quantitative Methods & Modeling

Office of Research and Standards, Office of Generic Drugs, CDER/FDA

FDA-CRCG Workshop on Best Practices for Utilizing Modeling Approaches to Support Generic Product Development

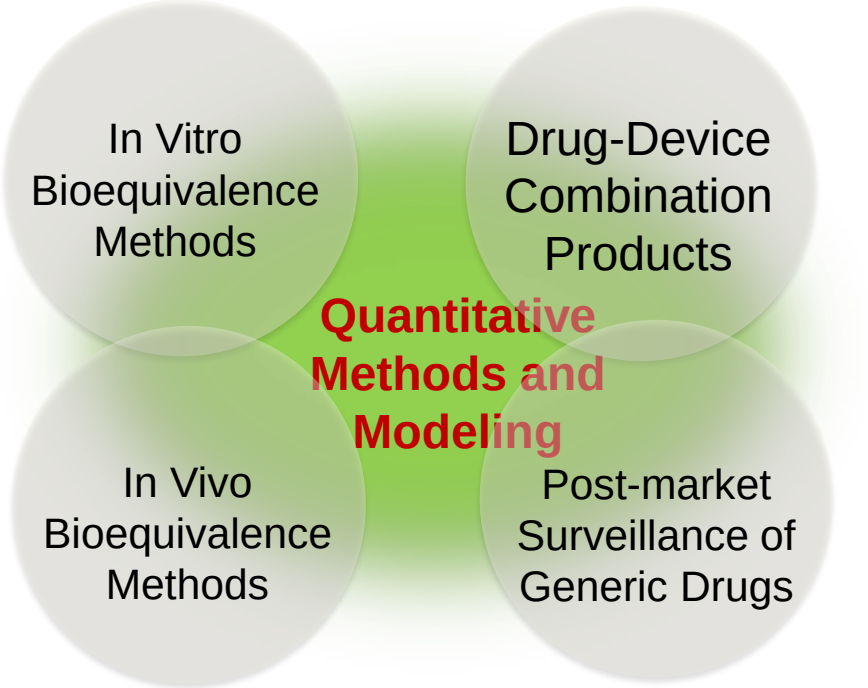
October 28th, 2022

Disclaimer

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

The presenter is offering his perspective based upon his experiences during regulatory decision-making

Quantitative Methods & Modeling (QMM) for Generic Drug Development and Approval



Model-integrated evidence (MIE) refers to using model-generated information such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence

Clin Pharmacol Ther. 2019 Feb;105(2):338-349

Contextual Analysis to Use Models to Support Drug Development

- Significant value generation for efficiently bringing high quality drug product to the market
- Challenges:
  - Knowledge/technical barrier
  - Novelty vs standardization
  - Lack of data to verify and validate models
- Opportunities:
  - Model sharing
  - Model Master File
    - portable, re-usable, generalizable, and sharable models
  - Targeted researches to address development need

Benefits for Developing Model Master Files (MMFs)

- Industry awareness on
  - Regulatory acceptance on utility of certain models
  - How to sufficiently verify and validate (V&V) a model for regulatory use
- Model access for “unprivileged” firms
- Cost saving on
  - Model standardization – model building and model V&V
  - Model re-use for the same purpose
  - Review time and review consistency
- Benchmark for further model advance
- Knowledge/Platform sharing to the scientific community

Types of Models Currently Used

- Models (1) with challenging-to-get/proprietary information and/or (2) that need large datasets from other sources to verify and validate may benefit from having Master files
  - Physiologically based pharmacokinetic (PBPK) models
  - Systems pharmacology
  - In vitro-in vivo correlation models
  - Other types of mechanistic models
- Models that can be easily duplicated from scientific publications may not necessarily need Master Files
  - Population PK
  - Exposure-response analysis
  - Pharmacokinetics-Pharmacodynamics (PK-PD) relationships

Legal Considerations

- When can a model be considered as trade secret?
  - Proprietary info; Genuine and not obvious; providing a competitive and economic advantage and having value to the owner; reasonably protected from disclosure
- Models may be treated as trade secret if conditions are met
  - ~~Based on~~ See comments from Dr. David Feigal, Jr., MD, MPH in the Fiscal Year (FY) 2022 Generic Drug Science and Research Initiatives Public Workshop
- However, we encourage all models to be publicly disclosed

Types of Drug Master Files (DMFs)

- Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel
- Type II: Drug Substance, Drug Substance Intermediate, and Material Used in their Preparation, or Drug Product
- Type III: Packaging Material
- Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in their Preparation
- Type V: FDA Accepted Reference Information

Examples

- PBPK model for locally acting products
  - E.g., the PBPK support for the approval of diclofenac
- Oral absorption PBPK models to
  - Justify Q3 parameter deviation and safe space
  - Justify BCS biowaivers and not to conduct fed BE studies
- Quantitative clinical pharmacology models
  - E.g., M3 model for dose scale analysis
  - Exposure-response model to assist comparative clinical endpoint analysis

Case 1: PBPK Model to Support Locally Acting Product Approval

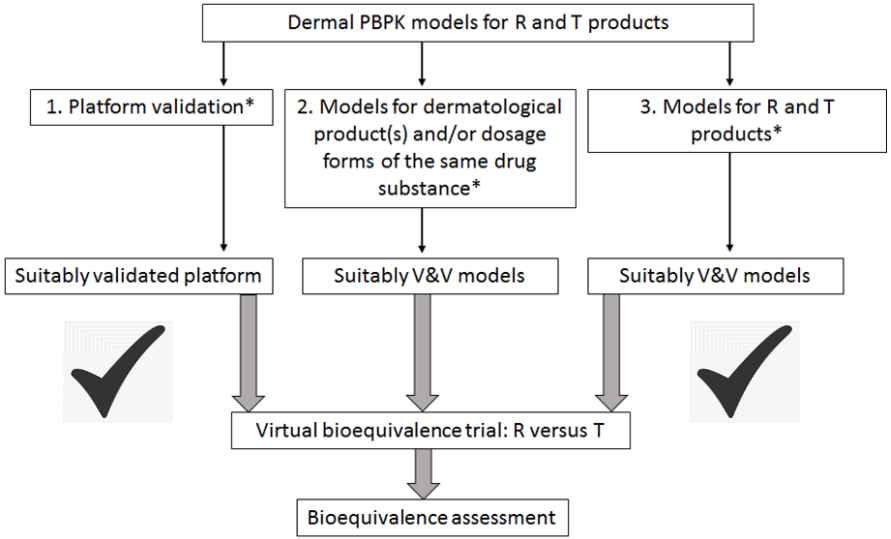
Diclofenac topical gel, 1%: Dermal PBPK model supporting ANDA approval for a generic

Platform performance assessment

>10 dermal PBPK models for TDS and topical products

- Multiple doses/product strengths and dosing regiments, age, and anatomical locations
- Systemic and local bioavailability (skin biopsy, IVPT, dermal microdialysis) data
- Satisfactory model performance

V&V methodology in support of fit-for-purpose dermal PBPK models



TDS: Transdermal Delivery Systems, IVPT: in vitro permeation testing, M&S: Modeling and Simulation

Tsakalozou, E et al. CPT Pharmacometrics Syst Pharmacol. 2021 May;10(5):399-411.
Tsakalozou, E et al. Clin Pharmacol Ther. 2021 Jul 7. doi: 10.1002/cpt.2356.

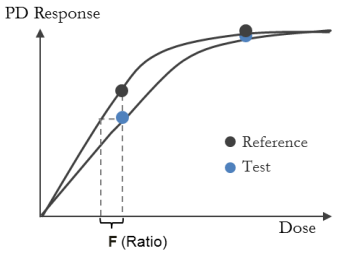
Potential MMF Types Involved

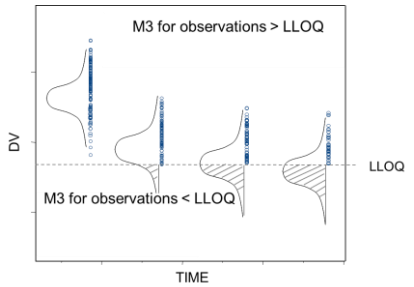
- A good practice to bring a generic topical product on the market that has been acceptable by the agency
- A platform for dermal PBPK models
- Product specific modeling parameters for diclofenac topical gel

Case 2: Likelihood Model Based Data Imputation to Support BE Evaluation for Albuterol Sulfate Inhalation Aerosol

Albuterol Sulfate Inhalation Aerosol: a beta$_2$-adrenergic agonist indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older.

- PD bioequivalence (BE) bronchoprovocation study conducted by the applicant included considerable amount of censored values (out of detection limit) in PC20 data
- Modeling approach improved the credibility of the PD model and provided model-integrated evidence to support the final ANDA approval as one of the first generics in 2020
- FDA's internal analysis adopted a modern likelihood-based modeling approach (M3 model) to perform data imputation for censored values.





Potential MMF Types Involved

- A good practice for data imputation that has been acceptable by the A~~a~~gency
- A transferable algorithm that has been used to impute values below Lower Limit of Quantitation

Case 3: PBPK Absorption Model in Assessing the Impact of Particle Size Distribution (PSD) on BE

A Capsule Product: PK parameters, e.g., Cmax and AUC, are found to be sensitive to changes in mean particle size of the active pharmaceutical ingredient under fasting condition

- There is a PSD deviation in terms of D90 between test and reference products
- PBPK modeling and simulation suggested that the test vs reference PK metrics showed a low risk of non-BE when D90 varied over a wide range with a certain fixed value of D50 for all strengths
- The modeling results supported a satisfactory BE assessment of this ANDA and setting a clinically relevant PSD specification

Formulation	D10	D50	D90	Test/Reference Ratios			BE
				Cmax	AUCt	AUCinf	
Refence	X10	X50	X90				
Test 1	X10--	X50	X90--	107	105	106	Pass
Test 2	X10-	X50	X90-	1	98.3	98.2	Pass
Test 3	X10+	X50	X90++	81.2	81.5	81.3	Pass
Test 4	X10+	X50	X90+++	80.3	79.8	80.3	Fail

Simulation results with fixed D50 and changed D10 and D90 using the reference upper bound PSD

Potential MMF Types Involved

- A good practice for dissolution profile justification
- Product specific PBPK parameters for the product involved following oral administration

Summary: Potential Types of MMFs

DMF

- Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel
- Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
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MMF

- Modeling platform or best practices including automation procedures and data sources to qualify the platform
- Product specific models and modeling parameters including substance and formulation parameters and relevant data records
- User friendly interfaces
- Computational method including optimization routines and automation procedures if situation applies

MMFs Should

- Have multiple types
- Increase modeling, knowledge, and information sharing
- Be upgradable for enhancement/improvement
- Be portable and transferrable
- Not be limited to one kind of model for a particular purpose

MMFs Should Not

- Prohibit knowledge and information sharing
- Be used in the place of a patent
  - Others can establish the same thing and publish it to the public
  - Can only be protected from being acquired through improper means or a breach of confidence

To Do List for MMFs

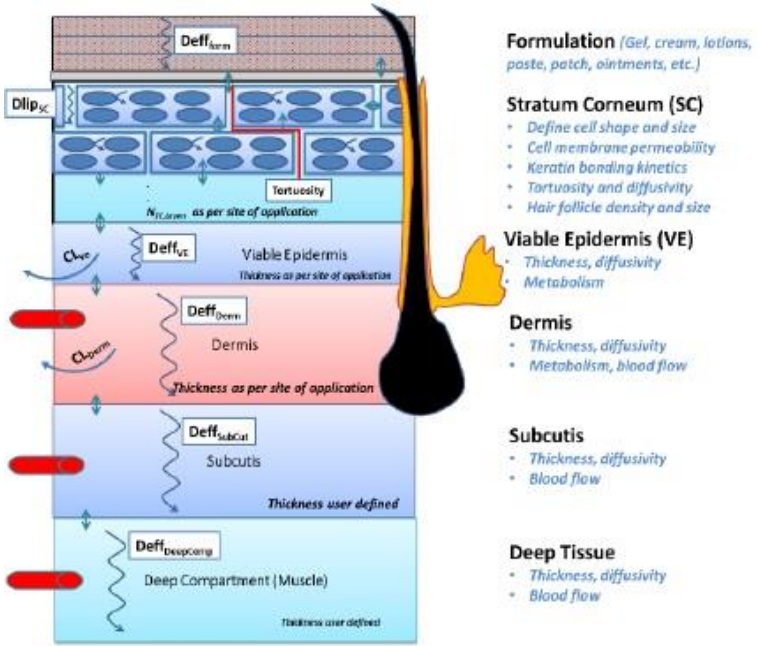
- How to
  - share MMFs?
  - deal with proprietary information?
  - reconcile with ~~Ɛ~~commercial interest?
  - navigate the legal implications?
- Where and who to host MMFs?
- What is the best process to publish and announce MMFs?

U.S. FOOD & DRUG ADMINISTRATION

Back ups

Case Example

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval



- Diclofenac sodium topical gel, 1%
- Alternative BE approach for a Q1/Q2/Q3 formulation: dermal PBPK model supported alternative to in vivo comparative clinical endpoint BE study
- Model development:
  - API physicochemical properties
  - API ADME properties
  - Formulation attributes for Reference and Test drug products (e.g., viscosity, globule size, pH)

API: active pharmaceutical ingredient; ADME: absorption, distribution, metabolism, and elimination

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case Example

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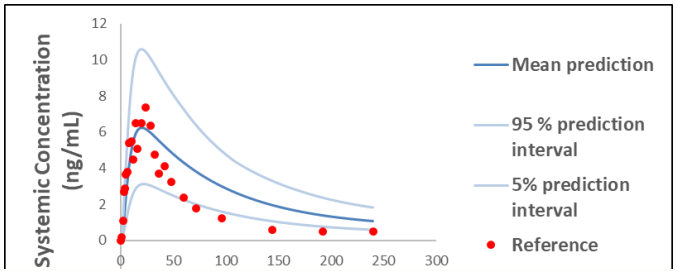
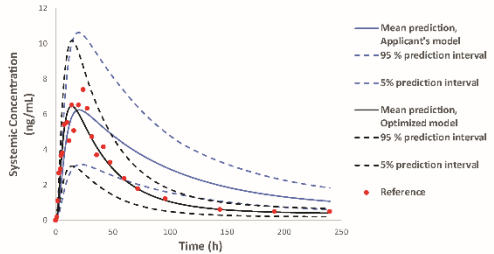




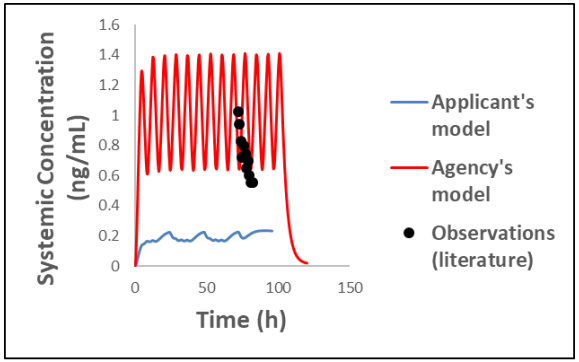
- Platform performance assessment:
  - >10 PBPK models for TDS and topical products
  - Multiple doses/product strengths and dosing regiments
  - Satisfactory model performance
- Model performance assessment for diclofenac sodium topical gel, 1%:
  - Literature and application data on doses, product strengths, dosing regiments, routes of administration and local/systemic exposure data
  - Formulation attributes for R and T
  - Good predictions of systemic exposure

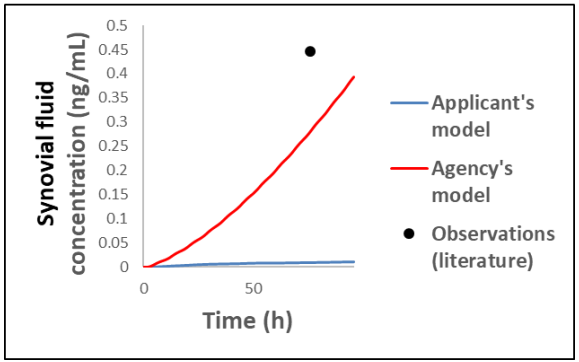
R: Reference, T: Test, TDS: Transdermal Delivery System

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case Example

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval





- Refined model to improve synovial fluid exposure predictions (by the Agency)
  - Protein binding in all skin layers
  - Drug product attributes updated
  - Partition coefficients modified leveraging observed local drug amounts

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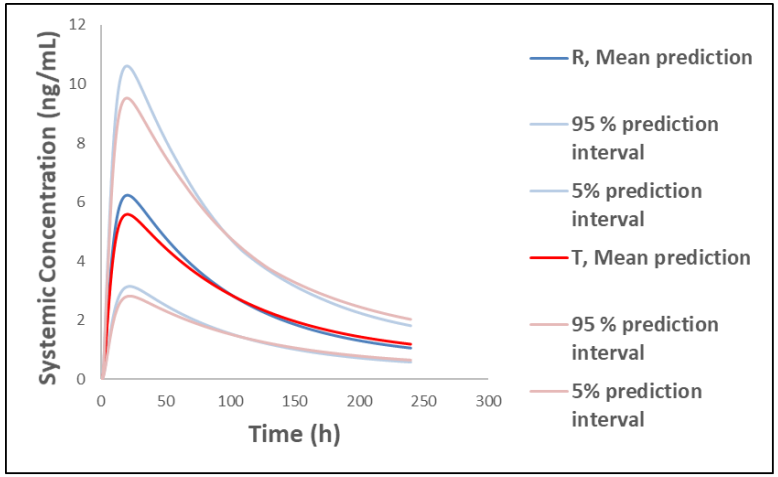
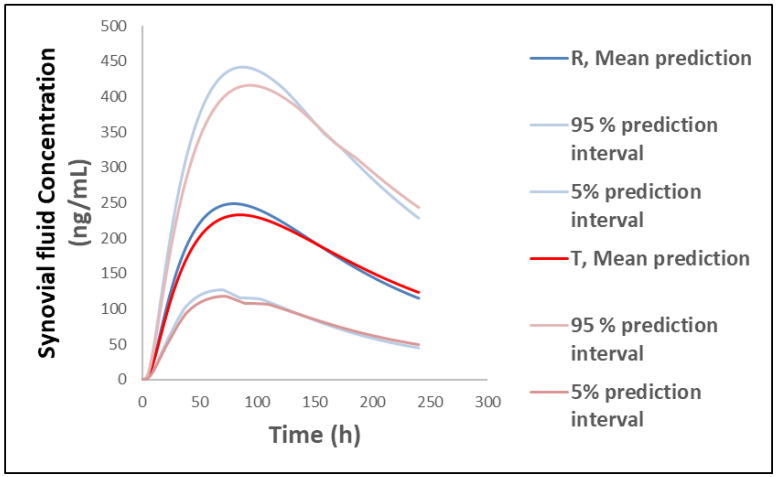
Case Example

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval

- Conducted virtual BE assessments on predicted systemic and local exposure data
- Sensitivity analysis to check on effect of changing parameters values on conclusion
  - ✓ **R and T drug products were found bioequivalent**





R: Reference, T: Test

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Case Example Summary

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval

- First case for using PBPK model to directly approve a product.
- PBPK models can be used to inform product development decisions and support alternative BE approaches for generic locally-acting drug products.
- Applicants are encouraged to follow best practices when developing PBPK models for generic locally-acting drug products as these are communicated by the Agency in guidances and other public forums.
- Applicants are encouraged to engage with the Agency early in their product development program by making use of the pre-ANDA meeting request program (GDUFA II) – case example of the approved ANDA for a complex topical drug product.

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Characteristics of a Model Master File

- Has explicit regulatory purpose
- Has received regulatory acceptance for the purpose
- Includes all technical details
  - Data/software/platform
  - Scope of use
  - Model building
  - Model V&V
  - Simulated results
- Includes modeling and simulation practices that can be duplicated, cross-referenced, and inter/extrapolated within the scientific scope of use