Best Practices to Leverage Model-Integrated Evidence and Model Master File Packages to Bring Complex Generics to Market

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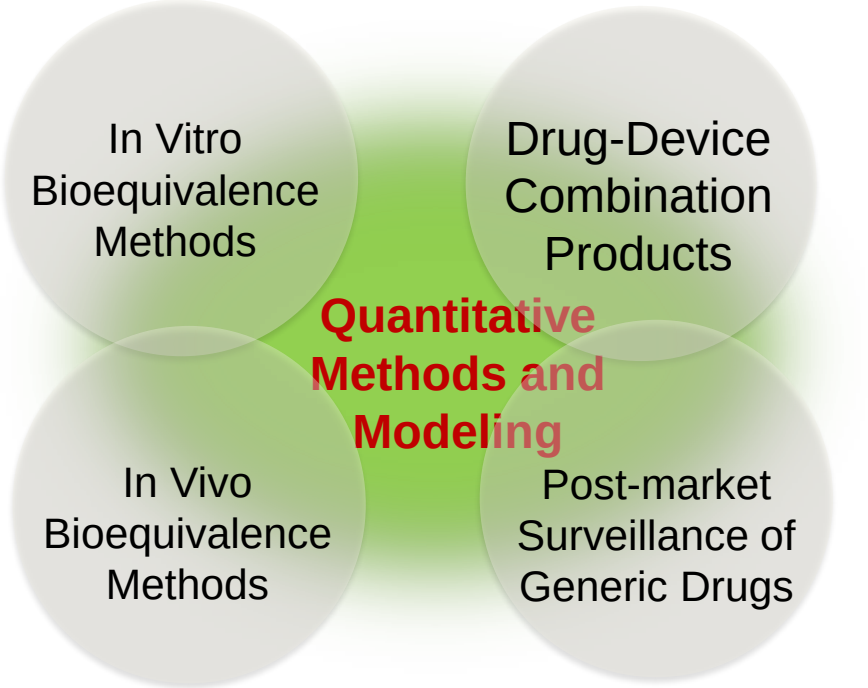
Disclaimer

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

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

MIE Contextual Analysis

- Significant value generation for bringing high quality generics to the market
- Challenges:
  - Knowledge/technical barrier
  - A developing ecosystem and culture for modeling & simulation
  - Novelty vs standardization
  - Lack of data to verify and validate models
- Opportunities:
  - Model sharing
  - Model Master File
  - Targeted researches to address development need

Drug Master File (DMF) Characteristics

- DMF holders “can authorize one or more applicants or sponsors to incorporate reference information contained in the DMF without having to disclose that information to the applicants or sponsors”
- DMFs are reviewed “in connection with the review of applications that reference them”
- DMF does not need to be re-reviewed for subsequent applications unless DMF has been modified since last assessment
- A DMF can include the proprietary information about synthetic chemistry process to produce a drug substance and then subsequent purification steps

https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs
Draft Guidance for Industry: Drug Master Files (October 2019) https://www.fda.gov/media/131861/download

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

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

Cases

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

Case 1: PBPK Model to Support Locally Acting Product Approval

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

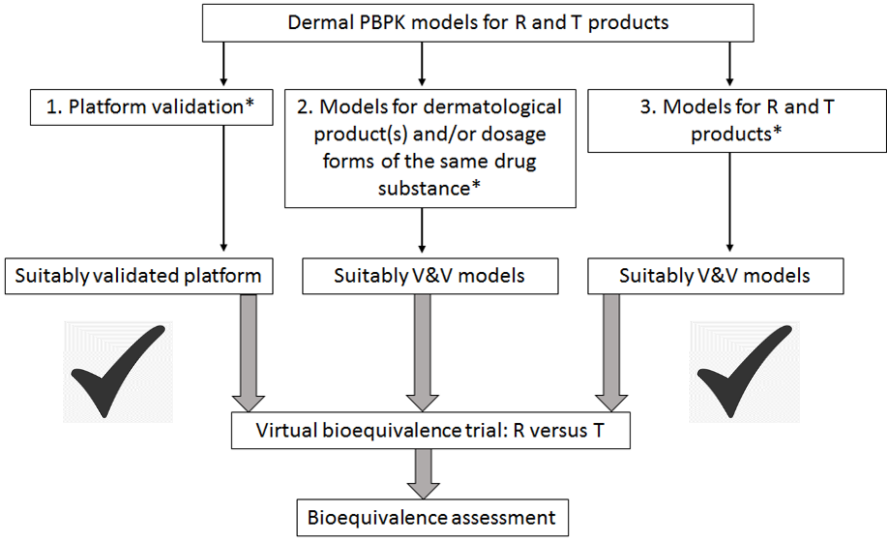
Platform performance assessment

>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

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

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



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

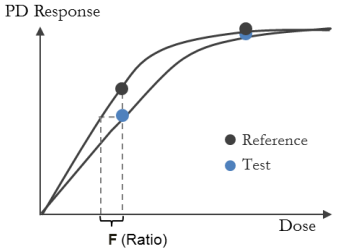
- **First Generic Priority ANDA**

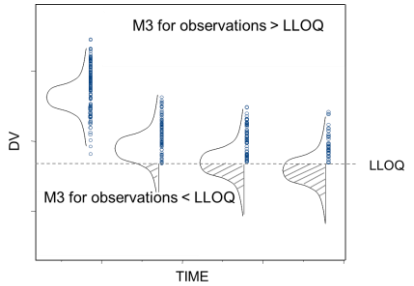
Background: PD BE bronchoprovocation study conducted by the applicant included considerable amount of censored values (out of detection limit) in PC20 data.

Question: How to assess PD BE given the high percentage of censored values in the study data?

Solution: FDA's internal analysis adopted a modern likelihood-based modeling approach (M3 model) to perform data imputation for censored values.

Regulatory Impact: This 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.





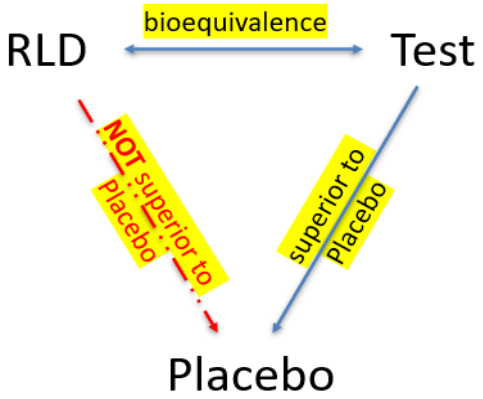
Case 3: Use of Modeling & Simulation to Support BE Decision with a Comparative Clinical Endpoint BE study that failed Superiority

Background: Applicant's comparative clinical endpoint BE study for a topical drug product demonstrated equivalence between T and R, but failed to demonstrate superiority over placebo for R.

Question: Can we assess the probability of study success if the study was conducted with a larger sample size?

Solution: FDA assessor developed a model that captures the time-profiles of clinical effects and used it for simulation of clinical BE studies with varying numbers of subjects. The results showed that with a larger sample size, superiority would have demonstrated, and BE would have been established.

Regulatory impact: Modeling and simulation allowed scientific evaluation of the acceptability of BE conclusion in this ANDA by demonstrating that the risk of bio-inequivalence is low.



Case 4: PBPK Absorption Model in Assessing the Impact of Particle Size Distribution (PSD) on BE

A Capsule Product: efficacy related to systemic drug exposure.

Background: 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 product.

Question: What is the effect of PSD deviation on bioequivalence?

Solution: PBPK modeling and simulation by the FDA assessor 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.

Regulatory Impact: The modeling results supported a satisfactory BE assessment of this ANDA and setting a clinically relevant 3 tier 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

Key Questions and Inputs Needed

- How to:
  - define MMFs?
  - share MMFs?
  - deal with proprietary information?
  - reconcile with Commercial interest?
- What are:
  - the legal implications?
  - the potential investment to make it happen?
  - the platforms to host MMFs?
  - the process to publish MMFs?
- Who should develop and host the MMFs?
- Where should we invest first?

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Back ups

Model Master File Within the PBPK M&S Regulatory Space

Platform performance assessment for locally acting drug products

- Challenge: observed data on local bioavailability not available or sparse or of high variability/uncertainty
- PBPK models developed and validated for drug products of an array of formulation complexity and in vivo performance against a multitude of observed data types and sources

Base model describing systemic disposition for systemically acting or locally acting drug products

- **Development of a PBPK model for API of interest with minimal drug product information accounted for (note: ideally with clinical PK data from IV studies)**

Disease or Special Population PBPK models

- Develop and validate a disease model by taking into account (patho)physiology information
- Validate how well the disease-drug product interplay is captured in the model (note: drug product complexity or unique features to be taken into account)

IVIVE methodology for population predictions using a PBPK model

- Develop computational models describing the experimental set up and incorporate in vitro data (e.g., IVPT studies for dermatological products)
- Inform relevant model parameters (i.e., formulation attributes)
- Extrapolate the acquired information to an in vivo model capable for population predictions

M&S: Modeling and Simulation API: active pharmaceutical ingredient, IV: intravenous, IVPT: in vitro permeation testing, IVIVE: in vitro-in vivo extrapolation

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Mechanistic Models in ANDAs

- Commercial vs. in-house modeling packages:
  - Oral and dermal PBPK and inhalation SERDM - commercial packages
  - Inhalation PBPK or compartment-based models – in-house
  - Computational Fluid Dynamics – commercial and in-house software

- Modeling purpose:
  - Address aberrations with in vitro, pharmacokinetic (PK), or comparative clinical endpoint (CCE) bioequivalence (BE) studies
  - Waive follow-up study
  - Provide alternative BE approaches in lieu of CCE BE study

- Regulatory use: One example of generic approval – ANDA 211253 for diclofenac sodium topical gel

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