U.S. FOOD & DRUG ADMINISTRATION

Leveraging Model-Integrated Evidence for Generic Drug Development and Approval

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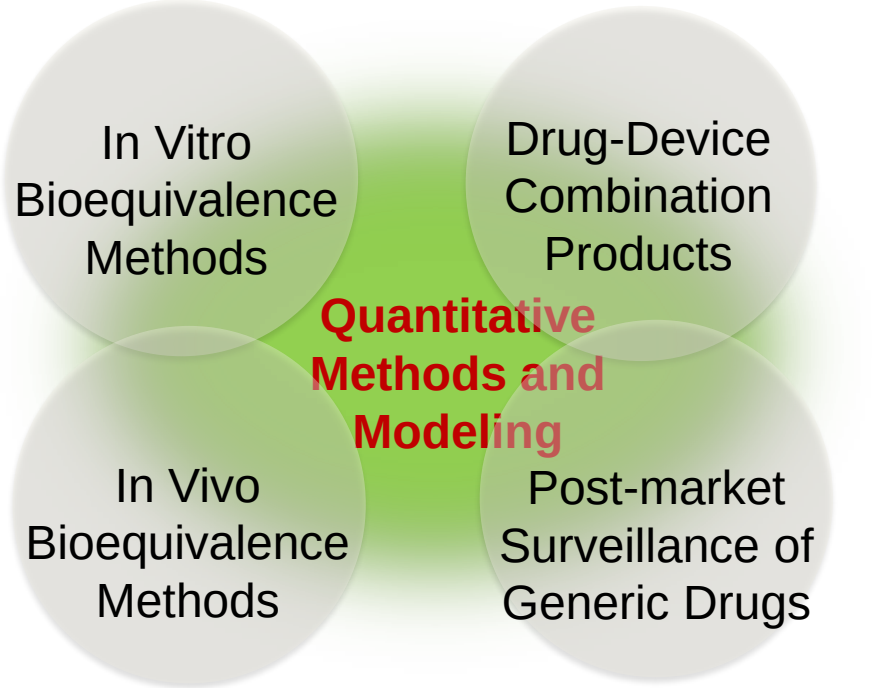
The Global Bioequivalence Harmonization Initiative

September 28th, 2022

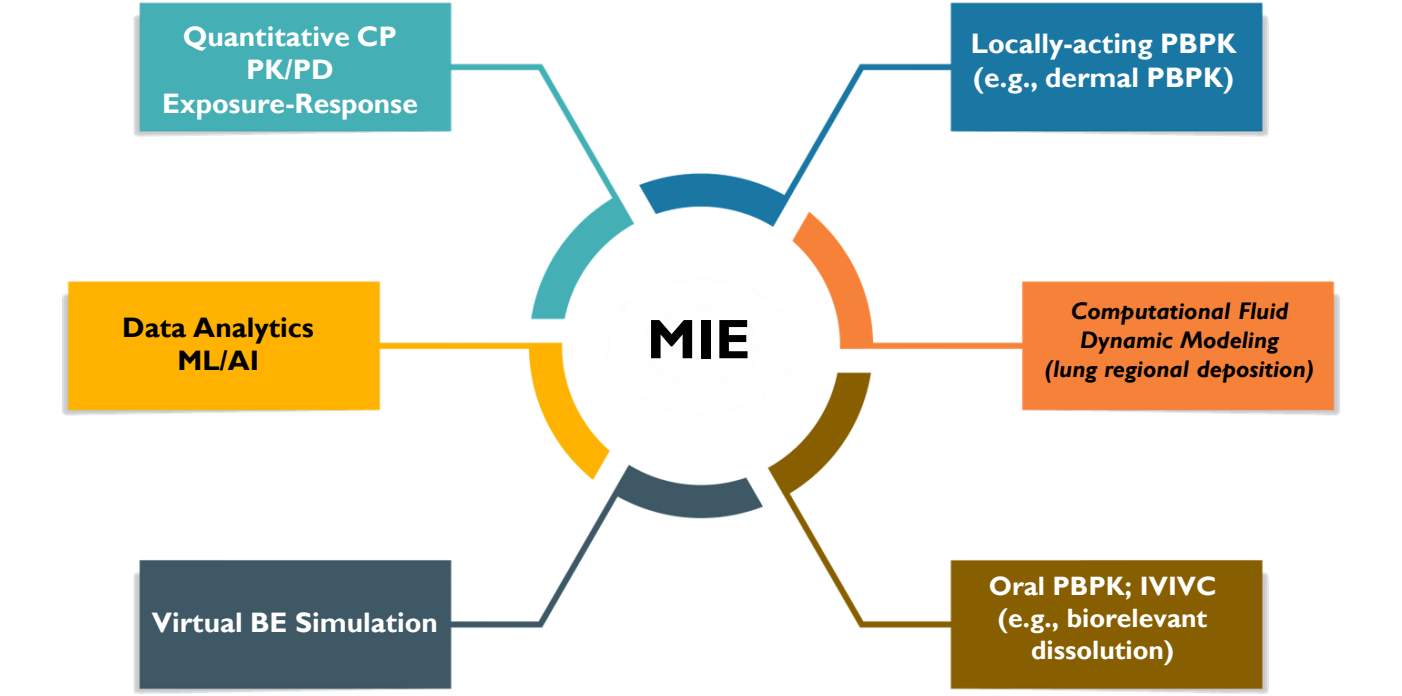
Quantitative Methods & Modeling (QMM) for Generic Drug Development and Approval



QMM tools can be used to support regulatory assessment of generic drug products in multiple categories

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

What is Model Integrated Evidence (MIE)?



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

CP – Clinical Pharmacology; PBPK – Physiologically-based pharmacokinetics; BE – Bioequivalence
PK/PD – Pharmacokinetics/Pharmacodynamics; ML – Machine Learning; AI – Artificial Intelligence
IVIVC – In Vitro-In Vivo Correlations; BE – Bioequivalence

Quick Overview on QMM Activities in the Office of Generic Drugs

Regulatory Activities in CY 2021 and New Grants and Contracts in GDUFA II

	Type	No.	Examples
Regulatory	**ANDA Review Consults**	23	❖ Using in vitro-in vivo modeling and simulation to support accessibility of dissolution profiles ❖ Topical dermatological/orally inhaled/long-acting injectable products ❖ Evaluation of alternative BE approaches to the CE study for locally acting products
	Pre-ANDA Meetings	29	
	Controlled Correspondences	24	
	BE Guidance	10+	❖ PSGs: use of pAUC as an additional BE metrics
Research	**Internal Regulatory Research Projects**	36	❖ Assessment of API sameness ❖ BE evaluation methods (e.g., higher-order crossover design, group/batch effects) ❖ Modeling and simulation to support PSG development for liposome injection
	New Contracts and Grants in GDUFA II since 10/2017	42	❖ Hybrid CFD-PBPK models for prediction of nasal corticosteroid deposition ❖ CFD models to aid the development of generic metered dose inhalers ❖ Modeling platform development (e.g., long acting injectables, sparse sampling) ❖ Integrated multiscale-multiphysics modeling framework for locally acting products ❖ Characterizing safety and efficacy of generic drugs, and expanding BCS class 3 waivers

ANDA, abbreviated new drug application; API, active pharmaceutical ingredient; BE, bioequivalence; CE, clinical endpoint; CFD, computational fluid dynamics; PBPK, physiologically based PK; PSG, product-specific guidance; BCS, Biopharmaceutics Classification System; pAUC, partial area under the curve.

Case 1: PBPK Model to Support Locally Acting Product Approval

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

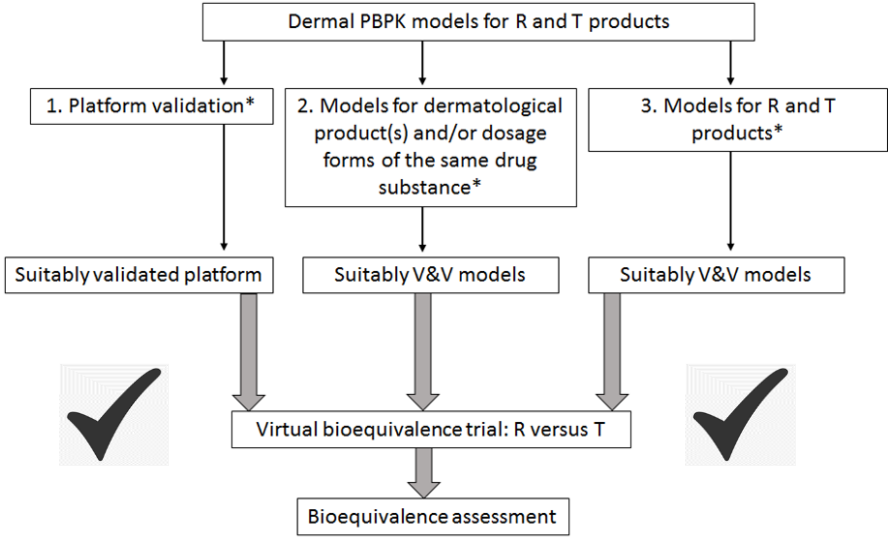
- Satisfactory model performance for all data evaluated

MIE impact

- Model generated virtual drug exposure at site of action supported drug approval in lieu of a comparative clinical endpoint study

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



*Simulations in healthy or diseased population

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.

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.

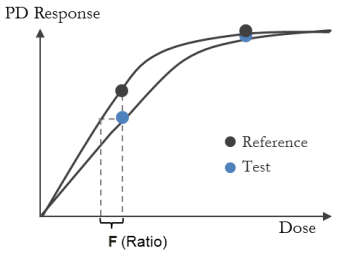
Background: PD BE bronchoprovocation study conducted by the applicant included considerable amount of censored values (out of detection limit) in PC20 data.

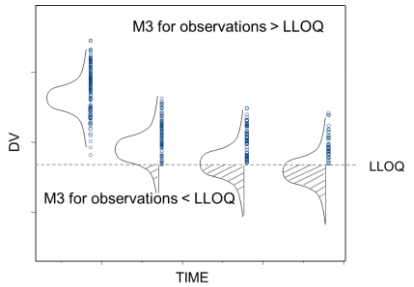
Question: How to assess PD BE given the high percentage of censored values in the study data?

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

MIE 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.





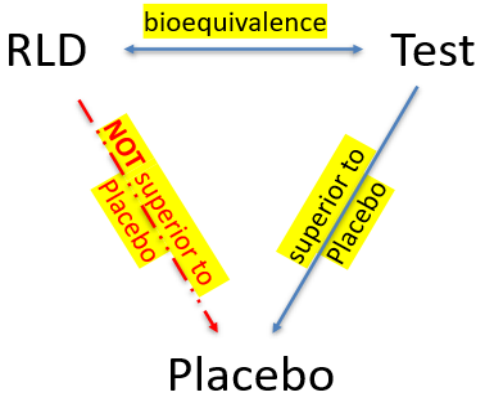
Case 3: Use of Modeling & Simulation to Support BE Decision with a Clinical Endpoint BE study that failed Superiority

Background: Applicant's 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.

MIE impact: Model generated study results showed large size study would demonstrate superiority of RLD against placebo. It 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.

MIE impact: Model generated virtual PK data following formulations with different particle size distributions supported low risk of bioinequivalence and a satisfactory BE assessment of this ANDA.

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

Advancing MIE for Complex Products

- Model-informed development of in vitro (only) BE approaches
  - Identification of clinically relevant attributes and the associated BE space
  - Countering challenges conducting in vitro testing studies. E.g., In Vitro Permeation Testing
- Alternative approach to replace comparative pharmacodynamic/clinical endpoint BE studies as appropriate
  - Correlate PK metrics based on systemic PK exposure to action site exposure and/or clinical response
  - Modeling for regional drug depositions for orally inhaled products
- Model-integrated evidence for generic drug approvals
  - Platform for virtual BE simulations
  - Sufficiently verified and validated model to generate virtual BE results
  - E.g., Long-acting injectables

Advancing MIE for non-Complex Products

- Support a further abbreviated in vivo program for BE assessment
  - BCS 3 Biowaivers for more general cases
  - Lower strength waiver under special conditions
    - Risk assessment for modified release products
- Modernize the in vivo BE programs with MIE support
    - BE assessment based on steady state PKs (e.g., long-acting injectables + oncology)
  - Risk assessment for BE across different populations
    - Healthy adult volunteers-> pediatric and geriatric
    - Healthy adult volunteers-> patient population

Introducing Artificial Intelligence and Machine Learning to Generic Drug Development and Regulatory Assessment

- In vitro-in vivo connections
  - Formulation effects on dissolution profiles and PK exposure
  - In vitro-in vivo correlations
  - Effect of manufacturing process
- Improving conventional pharmacometrics toolsets
  - Model building and model selection
- Machine learning and natural language processing for knowledge management
  - Knowledge collection for FDA assessors
  - PK data warehouse
  - Review automation
    - Text mining and text generation
  - Tools to enhance review efficiency, consistency, and quality

Industrial Implementation and Use of Quantitative Methods and Modeling

- Sufficient communication between the agency and industry in terms of expectation in the modeling package is key to successful implementation

- Awareness of value creation by using modeling and simulation toolsets to support regulatory decision making is an important start

Seeking Your Input on Using MIE to Support Generic Drug Approvals

- Alternative BE pathway to replace comparative pharmacodynamic/clinical endpoint BE studies as appropriate
- Biowaivers (BCS, lower strength under special conditions)
- Model supported in vitro characterizations
  - BE space for testing parameters
- Novel BE study designs

Acknowledgement

- Case Contributors
  - –All DQMM scientists
- ORS/OGD
  - – Robert Lionberger, PhD
  - – Lei Zhang, PhD