Enabling the Conduct of Patient Pharmacokinetics Bioequivalence Studies Using Model-Integrated Evidence

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Increasing Impact of Modeling and Simulation in Generic Drug Development

- **Model integrated evidence (MIE)** refers to using model generated information not just to plan a study but to serve as pivotal evidence to support bioequivalence (BE). [1]
- FDA is working on advancing research to facilitate the utility of MIE to support demonstrations of BE.
- Research related to the utility of MIE were identified in **GDUFA Science and Research Priorities.**

FY 2025 GDUFA Science and Research Priorities

7. Facilitate the Utility of Model-Integrated Evidence (MIE) to Support Demonstrations of BE:

A. Advancing complementary approaches using MIE to support an efficient demonstration of BE specifically for drugs with complex routes of delivery (e.g., inhalation and topical routes of delivery) as well as for LAI products
B. Establishing best practices for model standardization, validation, acceptance, and sharing (e.g., using model master files) that improve the reproducibility and reusability of quantitative pharmacology information used in BE study simulations
C. Developing innovative study designs for PK BE studies in patients, such as those with reduced or sparse sampling for oncology products, and adaptive designs

https://www.fda.gov/drugs/generic-drugs/fy-2025-gdufa-science-and-research-priorities

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

MIE Industry Meeting Pilot Program

Launched on October 1st, 2023

The pilot program allows enhanced scientific communications on a broad range of quantitative methods and modeling techniques to address generic drug development issues or questions that are either out of the scope of or cannot be sufficiently addressed by the existing pre-ANDA and ANDA scientific meetings. E.g.,

- Common modeling issues across multiple products
- Complex modeling approaches for non-complex products

A dedicated regulatory platform for interactions on MIE

- To foster early and focused interactions between industry and FDA on MIE approaches for establishing bioequivalence (BE) in generic drug development

Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants

MIE Pilot Program General Principles document

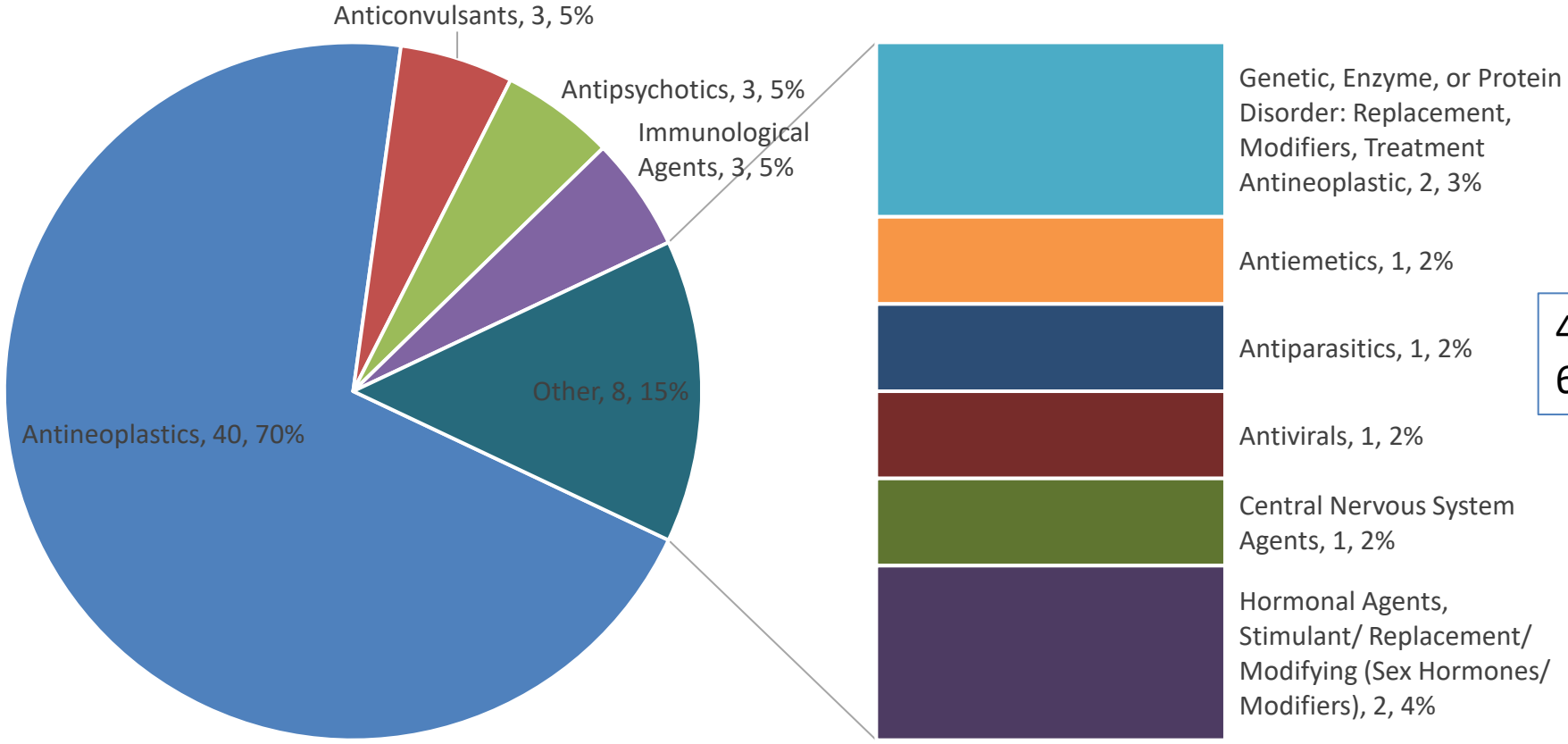
Pharmacokinetics (PK) BE Studies in Patients

- Sometimes, safety considerations preclude the use of healthy subjects in PK BE studies.[1]
- In such situations, BE studies should enroll patients for whom the drug is intended to treat without disruption patients' ongoing treatment.[1]
  - Antineoplastics (anticancer drugs), antipsychotics, immunological agents, anticonvulsants, etc.
- Challenges in patient PK BE study
  - Difficulties in collecting intensive sampling in patients
  - High variability/large sample size
  - Recruiting difficulty
  - High dropout

[1]Guidance for Industry, Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (August 2021)

Patients BE Studies Recommended in Product Specific Guidance (PSG) for Oral Drugs

- 57 PSGs for oral drug products recommended conducting PK BE studies in patients (based on FDA PSG database search as of May 2023).



40% - single dose study
60% - multiple dose study

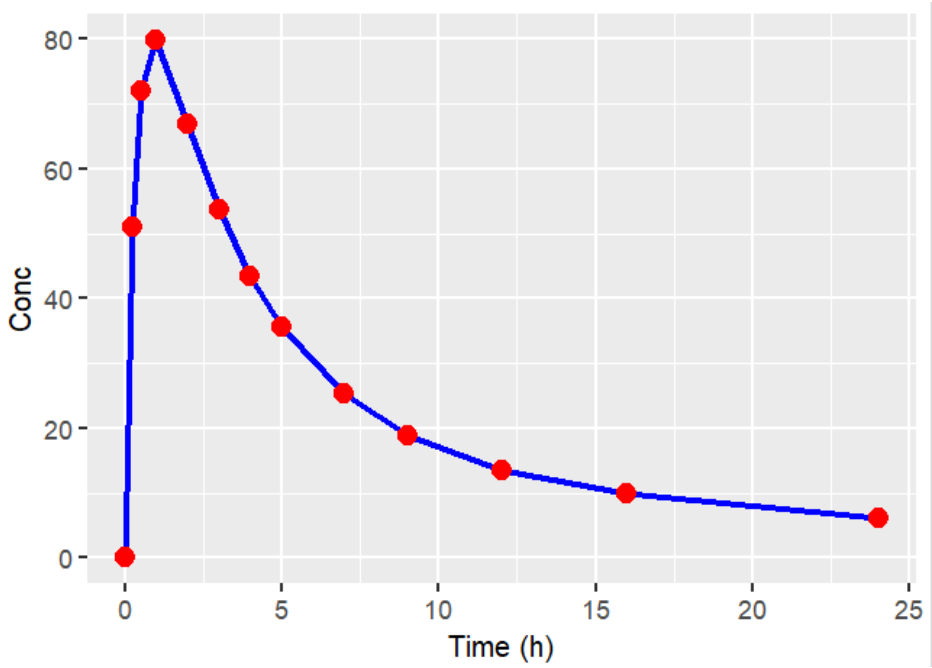
Adapted from Tran et. al. Safety Considerations of Subject Population Selection in Bioequivalence Studies for Generic Drug Development. Poster at American Society for Clinical Pharmacology & Therapeutics (ASCPT), March 28, 2024

Opportunities for MIE in Generic Development

- Generate pivotal evidence for BE decision
- Develop more efficient and feasible patient BE studies
  - Reduced or sparse sampling
  - Alternative BE study design (e.g., crossover study without washout)
  - MIE BE framework
  - Adaptive design
  - Shorter study duration (e.g., non-steady state study)
- We see a clear demand: increased use of modeling approaches in pre-abbreviated new drug application (pre-ANDA) interactions and ANDA submissions.

Example 1 – MIE to Support Sparse PK Sampling Design

Simulated time-concentration profile for demonstration purpose



Group	pre-dose	post-dose (h)											
		0.25	0.5	1	2	3	4	5	7	9	12	16	24
1	x	x	x	x					x				
2	x		x	x	x					x			
3	x		x	x		x					x		
4	x		x	x			x					x	
5	x		x	x				x					x

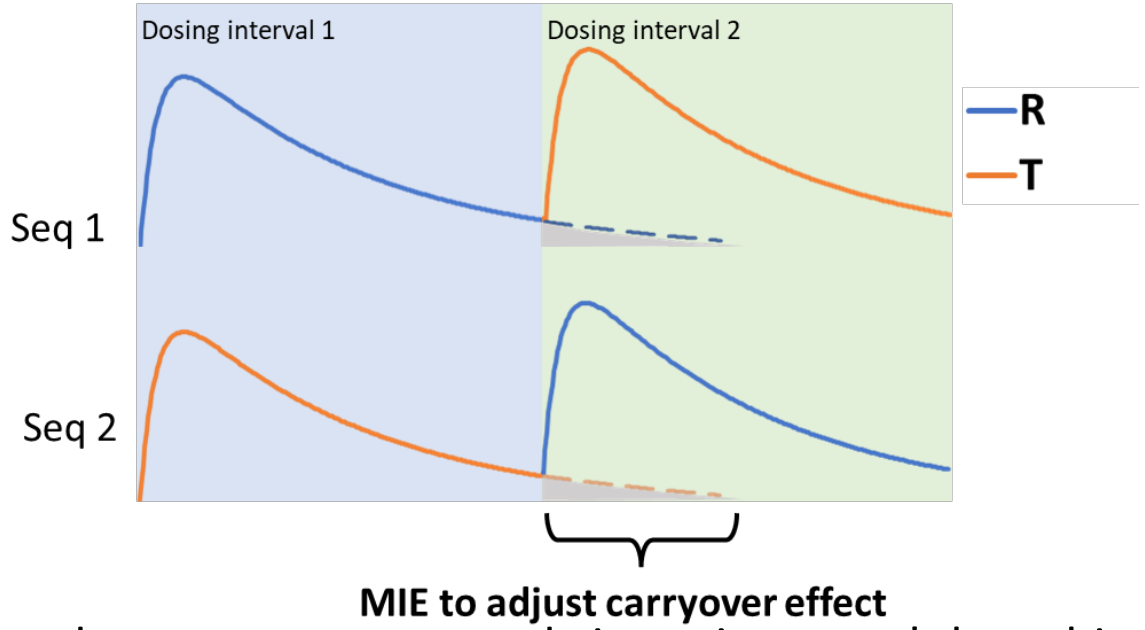
- Sparsely sampled population by groups to help characterize the full PK profile
- More sampling around Tmax but reduced sampling for other timepoints

- Population PK modeling allows pooling data from sparsely sampled populations, as it can recognize sources of variability and incorporate covariates to better characterize and compare drug exposure from sparse datasets.

Example 2 - MIE to Support Alternative Crossover Design

Alternative crossover BE study

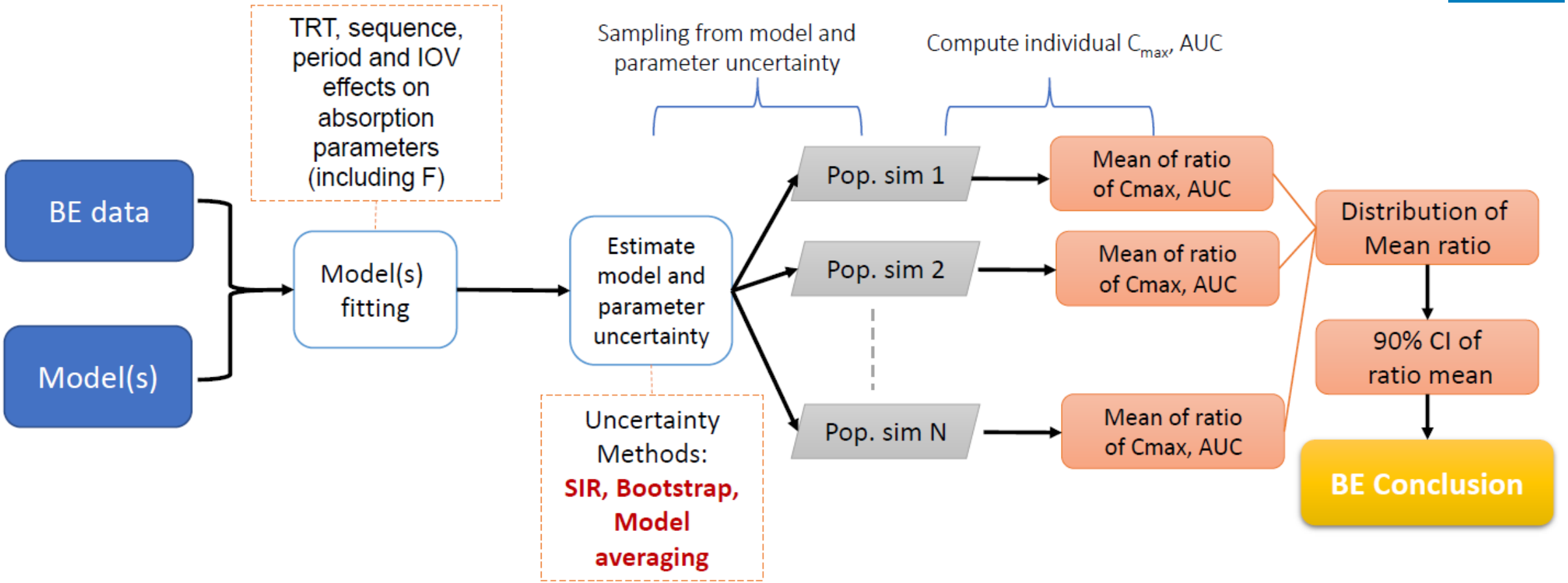
No washout per dosing regimen



- In some cases, steady state crossover study in patients can't be achieved either due to irregular dosing frequency or length of treatment.
- Adjusting carryover in a crossover study when the washout is not feasible – removing carryover via population PK modeling
  - Do not disturb patients' dosing regimen
  - Allow crossover BE comparison with smaller sample size (compared to a parallel study)

Example 3 – MIE BE Framework

(Developed by Uppsala University Research Team (Andrew Hooker & Mats Karlsson))



Slide adapted from FDA-CRCG Workshop Presentation by Andrew Hooker, Model Integrated Methods and Innovative Study Designs for Generic LAI Product Development and Regulatory Assessment, 11/30/2021.

Potential Applications of the Developed MIE Framework

- BE evaluation for highly variable drugs with an incomplete washout design (FDA contract: 75F40122C00139)
  - *Huang Z, et al. Model-Integrated Bioequivalence Method for Highly Variable Drugs with Long Half-Life: a Simulation Study Comparing Complete Washout and Incomplete Washout Designs. Poster Presentation at the Population Approach Group Europe (PAGE) Annual Meeting. Rome, Italy, Jun. 26, 2024.*
- BE evaluation with sparse data (FDA contract: HHSF223201710015C)
  - *Chen X, Nyberg HB, Donnelly M, Zhao L, Fang L, Karlsson MO, Hooker AC. Development and comparison of model-integrated evidence approaches for bioequivalence studies with pharmacokinetic end points. CPT Pharmacometrics Syst Pharmacol. 2024 Aug 23. doi: 10.1002/psp4.13216. Epub ahead of print. PMID: 39177211.*
  - *Bjugård Nyberg H, Chen X, Donnelly M, Fang L, Zhao L, Karlsson MO, Hooker AC. Evaluation of model-integrated evidence approaches for pharmacokinetic bioequivalence studies using model averaging methods. CPT Pharmacometrics Syst Pharmacol. 2024; 00: 1-14. doi:10.1002/psp4.13217*
- BE evaluation at non-steady state PK (e.g., switch design) (FDA contract: 75F40119C10018)
  - *Gong Y, Zhang P, Yoon M, et al. Establishing the suitability of model-integrated evidence to demonstrate bioequivalence for long-acting injectable and implantable drug products: Summary of workshop. CPT Pharmacometrics Syst Pharmacol. 2023; 12: 624-630. doi:10.1002/psp4.12931*

Example 4 - Adaptive Design

- **Adaptive Design:** a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.
- An adaptive design can be a group sequential design, or other design with one or more adaptive features
  - The possibilities of stopping a study earlier or adjusting the sample size during the conduct of a study (e.g., Potvin's methods)
- Model-based approach for group sequential and adaptive designs (FDA contract: 75F40119C10111)
  - *France Mentré, Model-based statistical approaches for pharmacokinetic bioequivalence studies with sparse sampling and extension to two-stage designs. Presentation at American Conference on Pharmacometrics (ACOP) 2019*

Regulatory Considerations/Research Gaps for Using MIE

- Meeting regulatory standards to generate BE evidence
  - How to ensure unbiased equivalence determination for formulation differences assessment?
  - How to characterize the uncertainty and propose an appropriate BE statistical method?
- Sufficient verification and validation
  - What would be the appropriate model validation strategy? Additional model validation strategies may be needed using more quantitative measures beyond the general predictive/diagnostics checks.
  - How much prior data are needed to propose and evaluate an MIE approach?
- The model development and validation process and criteria should be pre-specified.
  - Using MIE approach in BE assessment should not be interpreted as post-hoc analyses that may lead biased BE results.
- Best practice of MIE approach in regulatory submission
- Standardization of model sharing, submission, communication (Model Master File)

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