Regulatory Perspective on Modeling Strategies Across Multiple Submissions

2022 Workshop: Best Practices for Utilizing Modeling Approaches to Support Generic Product Development

Day 1, Session 2: Use of the Same Model or Modeling Strategy Across Multiple Submissions: Focus on Complex Drug Products

Andrew Babiskin, Ph.D. & Miyoung Yoon, Ph.D.

Team Leads (Locally-Acting PBPK Modeling and Quantitative Clinical Pharmacology)
Division of Quantitative Methods and Modeling,
Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

October 27, 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 presenter's perspective based upon presenter's experiences during regulatory decision-making

Role of Modeling and Simulation – Complex Generic Drug Products

- Address challenges with comparative in vivo clinical endpoint and pharmacokinetic (PK) endpoint bioequivalence (BE) studies
  - Study design
  - Predictions on probability of success of in vivo study (e.g., support product development)
  - Evaluation of outcomes for BE
- Support or serve as a basis for alternative BE approaches that either do not include certain in vivo studies or include such a study with a modified design
- Supplement in vitro characterization-based BE approach with model-based evaluation of in vitro metrics
- Support biopredictiveness of in vitro methodologies
- From regulatory side, support product-specific guidance (PSG) development

Mechanistic Modeling & Simulation

- Includes physiologically based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD) modeling
- Advantages for complex generic drug products:
  - Integrate information on physiology (population and subpopulations), drug substance (e.g., physiochemical properties), drug product attributes (e.g., in vitro release testing, particle size distribution), and device parameters to provide informed predictions on in vivo performance
  - Predict exposure of drug substance and/or active moiety at or close to the site of action/application where in vivo sampling is not feasible, not ethical, and/or challenging due to study cost, limited sample size, and variability
  - Decrease the need for human studies, which may be costly, not feasible, or not the most sensitive or discriminatory method for detecting formulation differences that would impact local bioavailability/BE

Factors for Success for Mechanistic Modeling in a Single Submission (e.g., PBPK)

- Quality of data used for model development and V&V activities
- Are justifications scientifically sound? Is parameter selection/optimization appropriate? Have all relevant **A**DME processes been considered?
- For BE purposes, how are test and reference listed drug defined in the model? Is that appropriate? How are products compared, including statistical approach?
- In validation cases, how well is PK data and local exposure being predicted?
  - Includes platform performance assessment
- Considerations on population (healthy vs. patient) when used for either virtual BE or for model V&V

V&V: verification and validation
ADME: absorption, distribution, metabolism & excretion

Model Reuse

- “Reuse”: can I (or other applicant) utilize the same modeling approach for a different product/ANDA?
- Define: PBPK Platform - a system of databases and differential equations defining movement of drug through ADME processes defined by anatomy and physiology
- Scenario for this presentation:
  - Same platform + Same modeling purpose
  - Different active ingredient and/or dosage form/formulation (i.e., different reference product) + Different model (i.e., implementation of the platform for the product-of-interest)
- Benefits of Reuse
  - Increased confidence on acceptability of further application of the approach
  - For the applicant, more streamlined regulatory submission and reduction in V&V activities
  - For the FDA, the platform would not need to be reassessed in every submission

Platform in Model Reuse

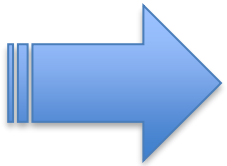
- Acceptance of PBPK models for regulatory decision-making (NDAs and ANDAs) for certain purposes supported by a history of predicting successful outcomes across multiple drug products and drug substances in commercially available platforms
- i.e., Platform Performance Assessment (PPA). For example, for PBPK,
  - 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
- For complex locally-acting products, V&V activities center on predictions at the site of action/administration

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

Platform

- >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



Suitably validated platform

Adapted from Eleftheria Tsakalozou, Ph.D.

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

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

Dermal PBPK Model Supporting ANDA Approval: PPA

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.

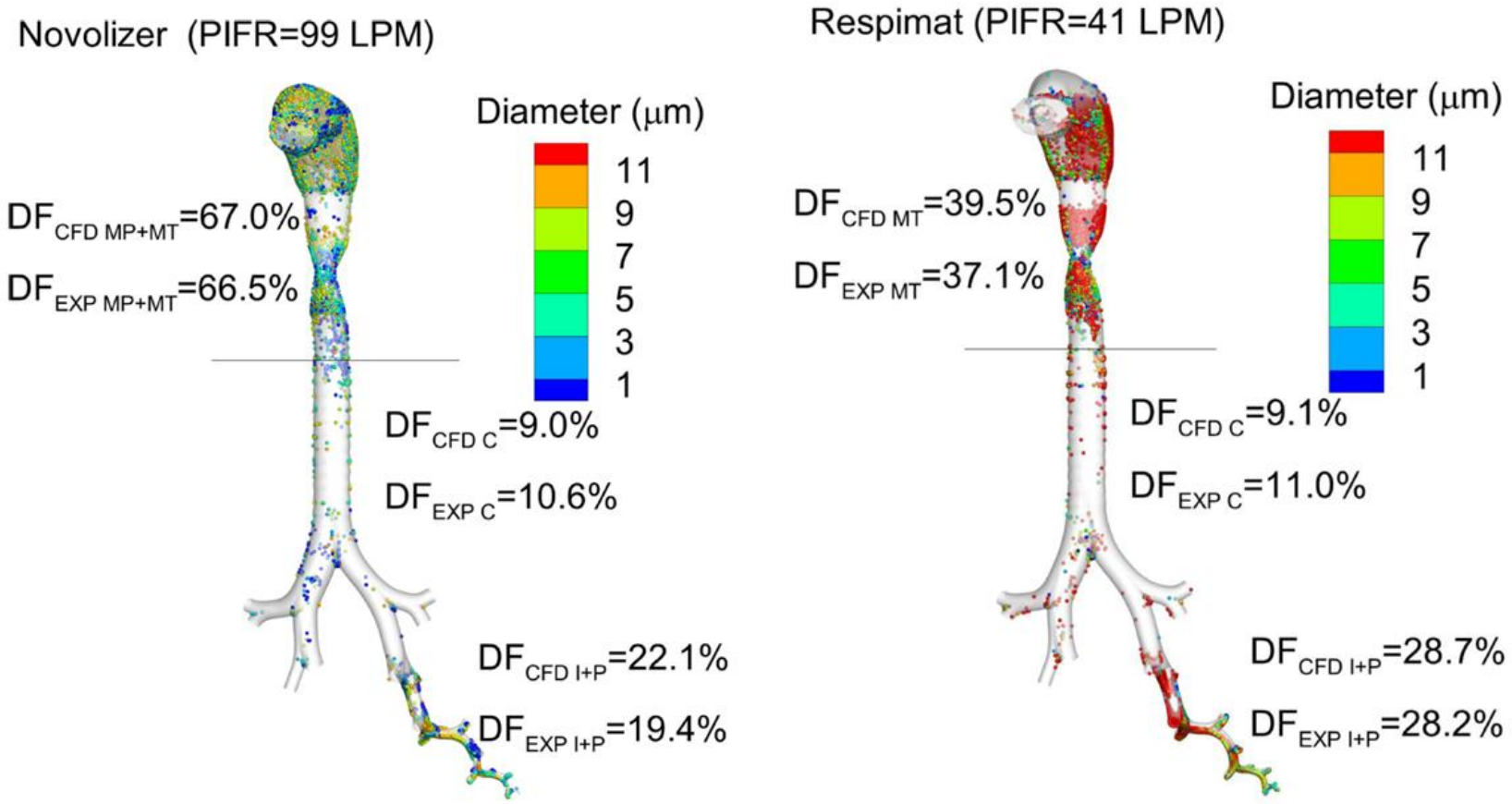
[c]Not provided in the submission or refers to a drug substance that is not given by other than the topical route.

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

Slide courtesy of Eleftheria Tsakalozou, Ph.D.

Regional Deposition Predictions with CFD

- Dry powder inhaler (budesonide inhalation powder [Novolizer]) and Soft Mist™ inhaler (fenoterol inhalation metered spray using Respimat® device)
- Predictions are compared against in vivo gamma scintigraphy data from literature
- More results would be needed to thoroughly conduct a PPA (was not the purpose of this study)



Figures 6 and 9 from Tian et al. (2015), showing deposition fraction (DF) for CFD predictions as compared with experimental (EXP) data

Slide courtesy of Ross Walenga, Ph.D.

Tian G, Hindle M, Lee S, Longest P. Validating CFD predictions of pharmaceutical aerosol deposition with in vivo data. Pharmaceutical research. 2015;32(10):3170-87.

Practical Considerations for Model Reuse

- Hypothetical scenario: Topical product – intent of model is to justify that a deviation in an identified critical attribute (i.e., Q3 difference) is still BE under an in vitro characterization based BE approach

  - Is the intended purpose of modeling & simulation consistent with the previous case or with other V&V cases in the PPA?

  - Is the drug substance within the range of physiochemical properties utilized in the PPA? Does the drug substance go through ADME processes not considered in the PPA (e.g., metabolism)?

  - Are the critical physiochemical attributes of the drug product consistent with those utilized in the PPA?

  - Data for validation of the drug product of interest (e.g., systemic PK, local PK, …) that can support parameterization

Model-Integrated Evidence (MIE) BE with Quantitative Clinical Pharmacology

- Utilities of population PK (pop-PK) models for MIE include:
  - To predict PK under different study design (e.g., study duration, sample size) based on the available in vivo PK data
  - To support alternative BE metrics (e.g., partial AUCs, residual drug amounts in implant)
  - To support alternative BE criteria (e.g., alternative limits along with shorter study duration) alone or in combination with other BE tools (e.g., in vitro, mechanistic modeling etc.)
  - To help reduce/replace in vivo studies for certain products, especially patient BE studies
- Increasing proposals of pop-PK-MIE submitted by generic drug industry

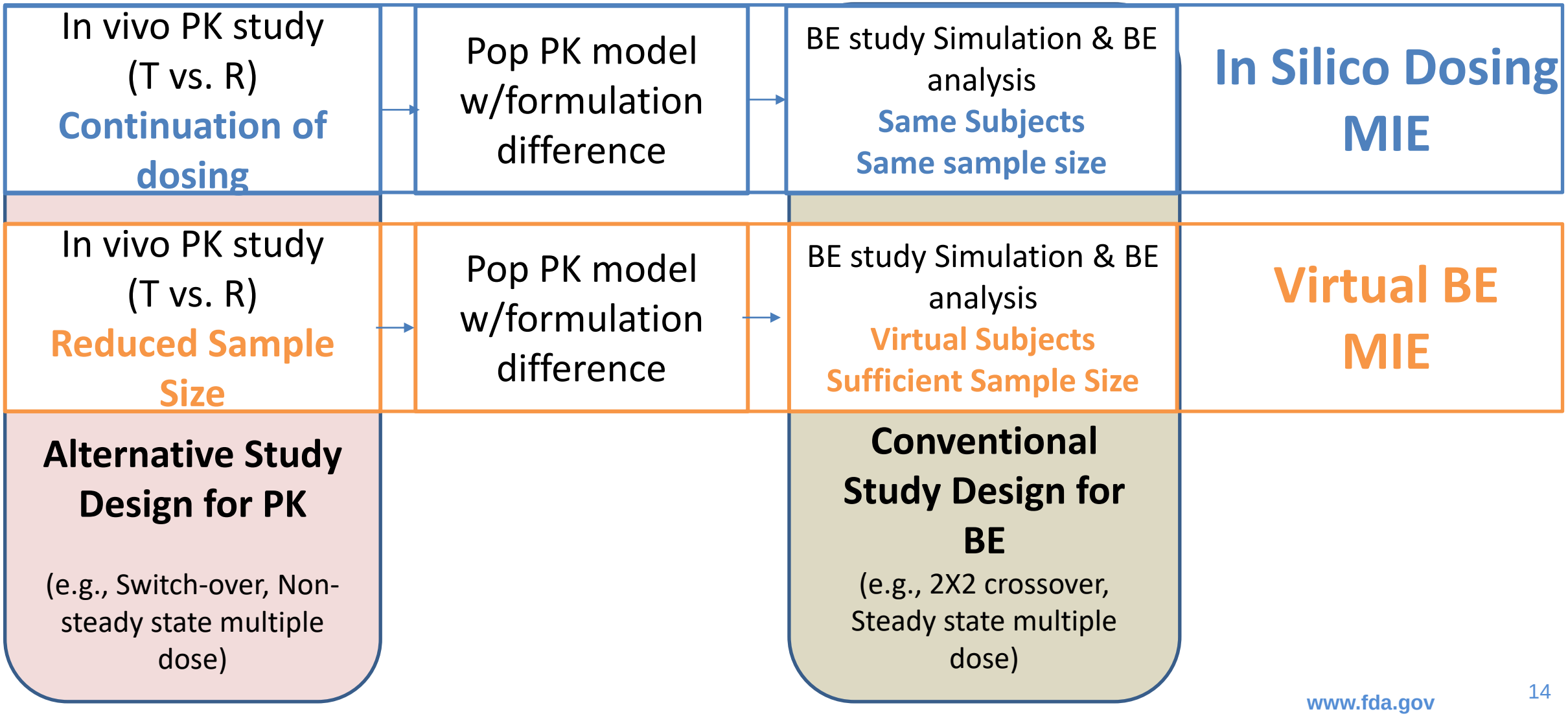
Industry's Keen Interest on MIE as Reflected in Their Feedback on Research Priorities*

- Strong interest in MIE as promising tools for the current challenges in both complex and non-complex generics
  - e.g., long acting injectables, orally inhaled drug products, oncology/rare disease drug products

- Recognized gaps/priority areas for investment
  - Expectations for MIE for the purpose of regulatory BE decision
  - Validation/verification criteria for MIE in lieu of in vivo BE studies
  - Facilitation via product-specific guidances
    - MIE validation and verification criteria, study designs, templates for submission
  - Standardization of MIE approaches

*FY 2022 Generic Drug Science and Research Initiatives Workshop

Types and Typical Processes of Population PK-MIE for BE: Examples



Examples of Population PK-MIE for Complex Products

- Potential applications for some long-acting injectable drug products, oncology and orphan drug products
- **Shorter duration** in vivo PK studies
- Reduced sample size and treatment cycle-compatible in vivo PK studies

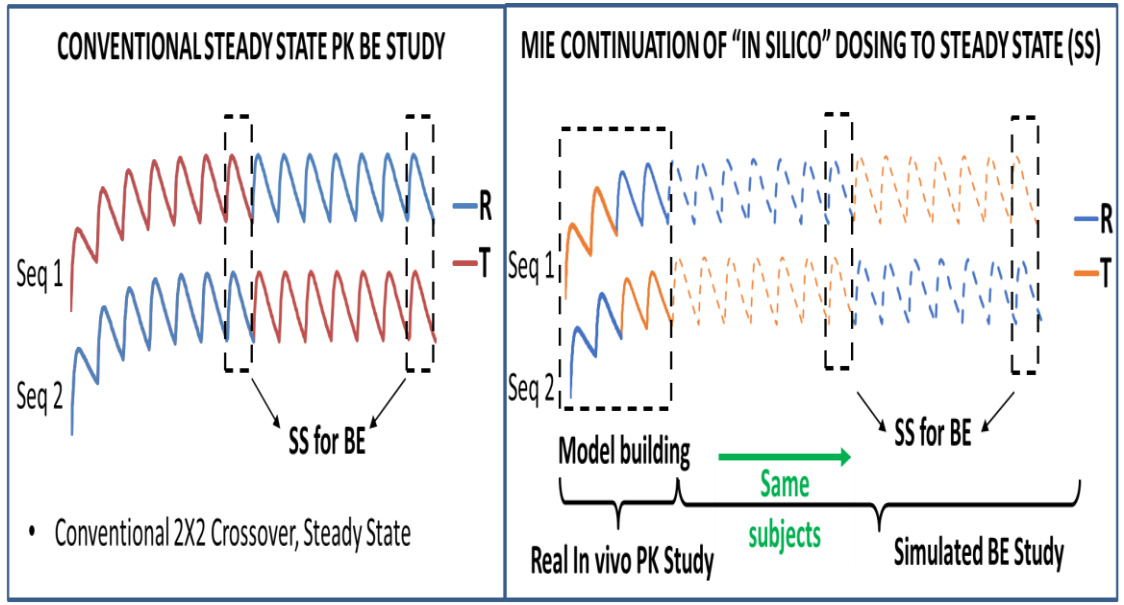


Illustration of In silico Dosing MIE for LAI products

- Potential applications for some oncology and orphan drug products
- **Reduced sample size** and shorter duration in vivo PK studies
- MIE framework for LAIs by Uppsala University (GDUFA research*) can be applied

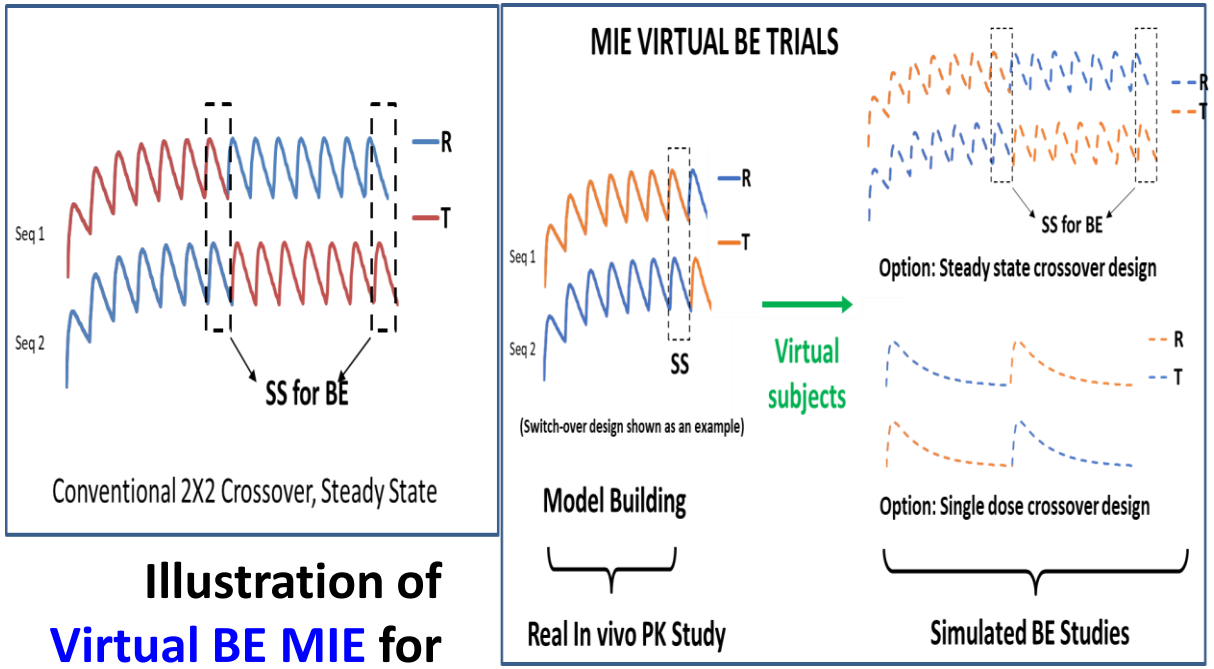
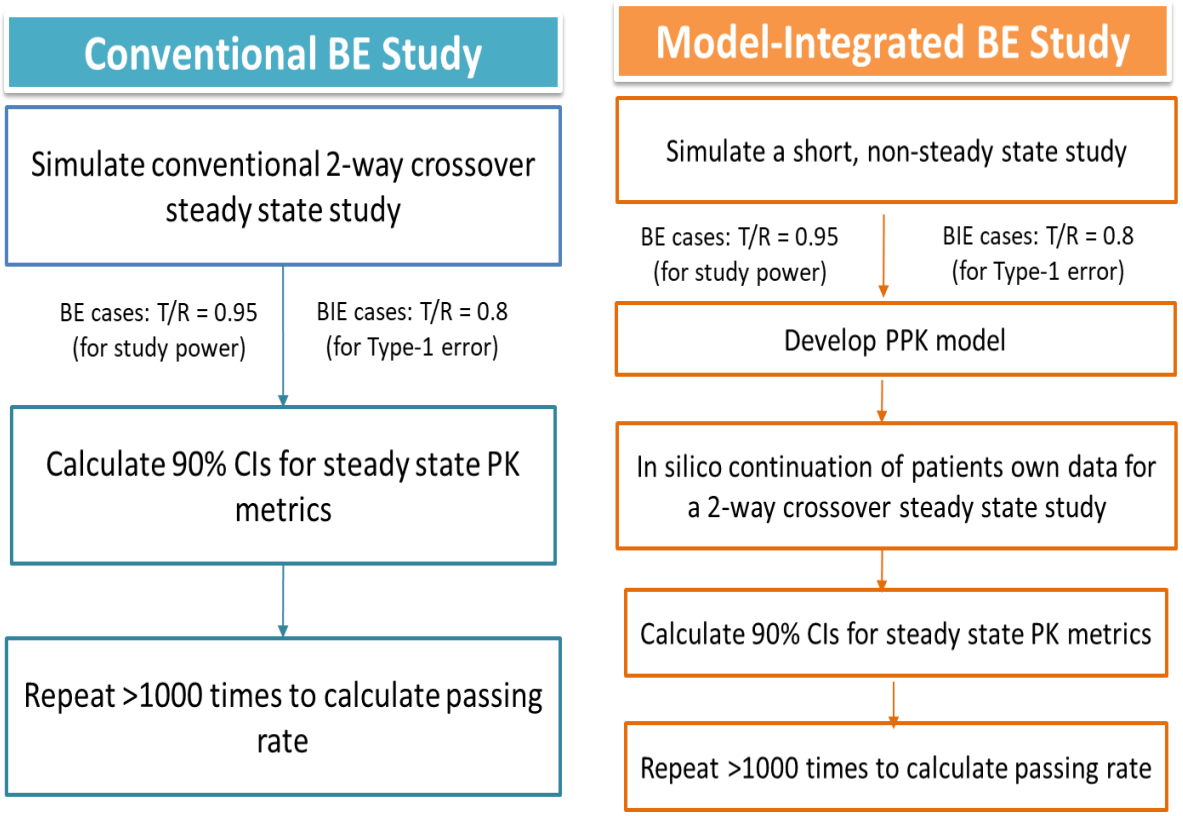


Illustration of Virtual BE MIE for LAI products

*FDA Research Contrac#75F40119C10018

Selection of a Model-based Study Design for In Silico Dosing: An example for a LAI Drug Product

A Clinical Trial Simulation Process to Evaluate Power and Type-1 Error



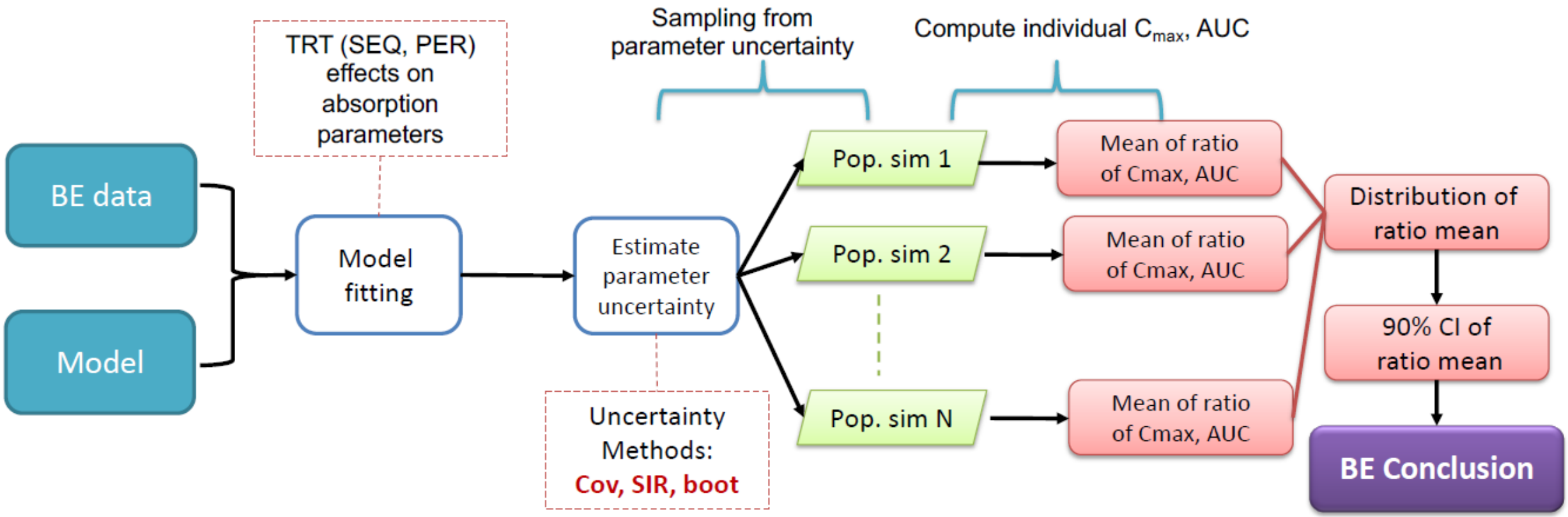
Power and Type-1 Comparisons for conventional and in silico continuation approach

Study Design	Design Description	In Vivo Study Duration	Study Power (%)	Type-1 Error (%)
Conventional, 2-way crossover study (N=X)	7 dosing interval/trt period + simulation to SS	14 X Dosing Interval	> 80	< 5
Shortened 2-way crossover study with "in silico" continuation (N=X)	5 dosing interval/trt period + simulation to SS	10 X Dosing Interval	> 80	< 5
	3 dosing interval/trt period + simulation to SS	6 X Dosing Interval	> 80	< 5
	2 dosing interval/trt period + simulation to SS	4 X Dosing Interval	> 80	< 5
	1 dosing interval/trt period + simulation to SS	1 X Dosing Interval	< 80	> 5

Justifying the selection of a suitable in vivo study design based on good Power and Type-1 control in MIE BE.

Slide provided by Courtesy of Dr. Yuqing Gong

Model Building, Validation and Virtual BE Simulation



Slide adapted from ACOP presentation by Andrew Hooker 2019

Regulatory Considerations – Examples with In Silico Dosing

- Should be accompanied with adequate scientific justifications
  - Perform a clinical trial simulation process using available data/literature information to show the proposed approach is capable to discern formulation difference and comparable to the conventional approach
    - Clarify how to include formulation difference in the model and simulate test and reference products
  - Evaluate different clinical study designs (e.g., different study durations in non-steady state) and evaluate which design would be the most sensitive and efficient to detect the formulation differences and not lead to biased equivalence determination for the subsequent BE study simulation (e.g., steady state)
  - Indicate how the proposed approach can properly characterize the uncertainty and the impact on BE determination
  - Propose sufficient model verification and validation plan for the intended regulatory use
  - Consider exploring the feasibility to assess BE using observed data from clinical BE study as supportive information
- Should be pre-specified in the modeling analysis plan (MAP) prior to data unblinding

Regulatory Considerations – based on Common Deficiencies in Virtual BE

- Model is not able to detect potential formulation difference between test and reference product
- Not evaluating type I error before virtual BE simulation
- A substantially larger sample size in virtual BE simulation than the sample size of in vivo BE study for model building without sufficient justifications
- Not understanding additional considerations are needed for MIE BE in the model building and validation compared to the pop-PK modeling in new drug development
- Not submitting a modeling analysis plan (MAP)

Applying MIE to Regulatory BE Decision – Reusing the Strategy Across Multiple Submissions

Pop-PK guidance

Variability

Between-Subject
Within-Subject (e.g., occasion, period)
Residual error (e.g., measurement)
Covariates

Detect formulation difference

TRT (SEQ, PER) effects on absorption parameters

Modeling Uncertainty Estimation

Numerical

Convergence
Parameter SE (%)
Shrinkage (%) etc.

Graphical diagnostic

Obs vs. IPRED
CWRES vs. Time
VPC for T&R, PER, etc.

PK metrics

Cmax, AUCt, AUCinf
Obs. within simulated [5%, 95%] for T&R, Per, etc.

Model Validation

Type I Error

Sensitive to detect formulation difference

Identify parameters for T/R ratio of all PK metrics
T/R ratio at boundary of 80% and 125%

Type II Error

Applicant's responsibility
Power and sample size

e.g., T/R ratio at 95%, 100%, 111.11% etc.

Type I and Type II Error

Sampling

Parameter uncertainty

PK metrics

All PK metrics
NCA method
Simulated method

Possible approaches

Model-based BE
Conventional Model Averaging
Bootstrap Model Selection
Model-informed (Switch study, covariates effect)

Simulation

Data sources

Clinical studies +
Data imputation
Simulation

Model uncertainty

Sufficient replicate simulations

PK metrics

90% CI of T/R ratio for all PK metrics should fall within [80%, 125%].

BE Conclusion

Adapted from the SBIA presentation in September 2022, Courtesy of Dr. Kairui (Kevin Feng)

MIE Utility Can be Cross-Referenced

- Common benefit of cost saving in in vivo BE study (i.e., reduced sample size, study duration)

- Model validation and verification can be standardized (i.e., reused) based on common key regulatory considerations

Looking into the Future

- Effective communication of the use of same model or same MIE BE strategy across multiple submissions

- Standardization of model sharing, submission, communication
  - Modeling Analysis Plan
  - Model Master files (*Symposium II, Oct. 28, 2022)*

Acknowledgments

QCP Team, DQMM/ORS/OGD

- Yuqing Gong
- Kairui (Kevin) Feng
- Quantitative Clinical Pharmacology (QCP) Team members

Locally-acting PBPK Team, DQMM/ORS/OGD

- Eleftheria Tsakalozou
- Ross Walenga
- Locally-acting PBPK Team members

DQMM/ORS/OGD

- Lanyan (Lucy) Fang
- Liang Zhao

OGD/ORS/IO

- Rob Lionberger
- Lei Zhang

FDA GDUFA Research Collaborators

- Uppsala University Team


FDA
U.S. FOOD & DRUG
ADMINISTRATION