U.S. FOOD & DRUG ADMINISTRATION

Model Integrated Evidence for Bioequivalence Evaluation to Support Generic Drug Development and Regulatory Approval

Lanyan Lucy Fang, PhD

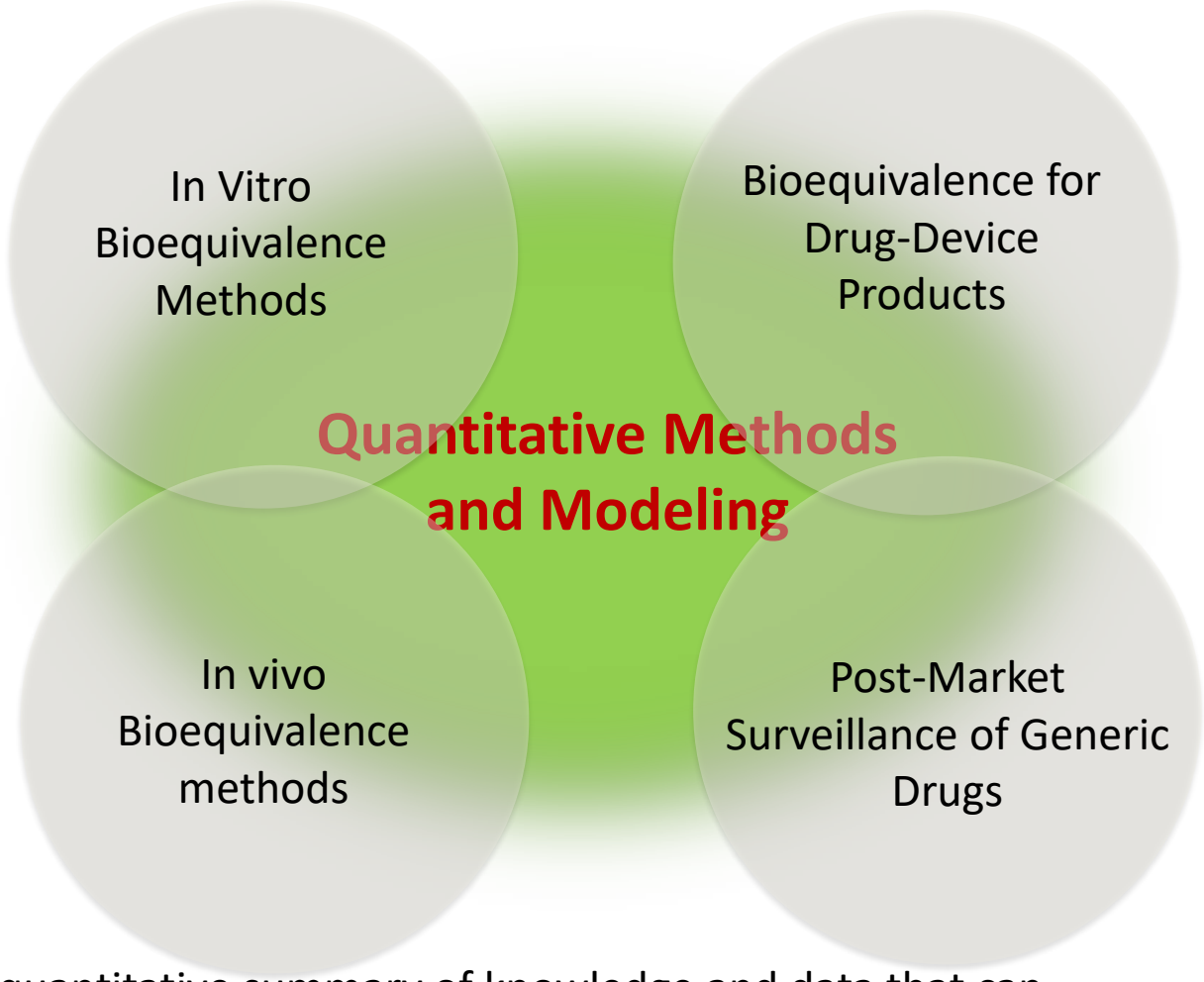
Division of Quantitative Methods & Modeling (DQMM)

Office of Research and Standards (ORS)

Office of Generic Drugs (OGD)

CDER, FDA

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

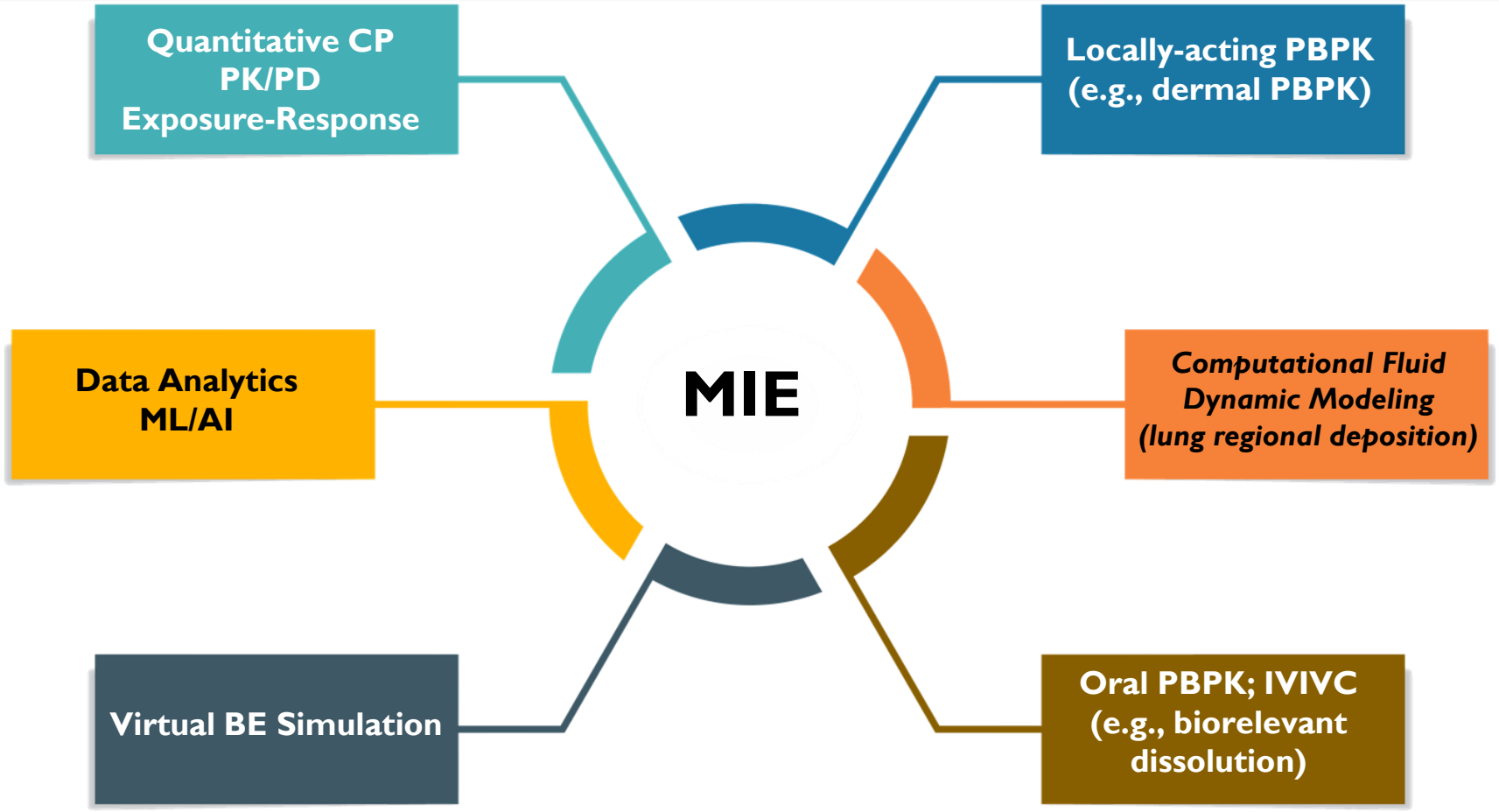


QMM is a quantitative summary of knowledge and data that can

- Drive a smart development program
- Serve as critical information or evidence for generic drug approval

Courtesy slide from Dr. Liang Zhao

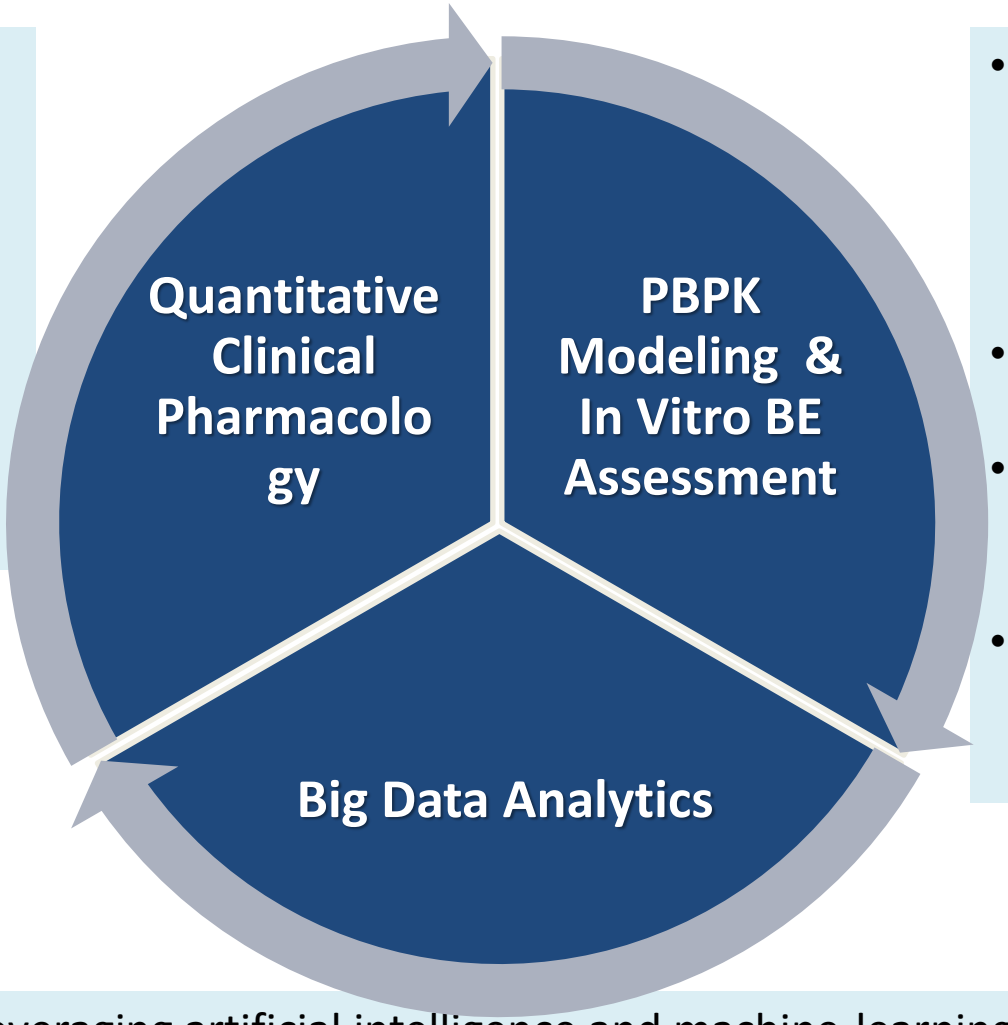
What is Model Integrated Evidence (MIE)?



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

Value/Impact of MIE

- **Efficient BE study design**
- Determination of PK metrics
- Clinical relevance of PK differences
- Evaluation of alternative BE approaches



- **Utilization of PBPK model as an alternative approach to the clinical endpoint BE Study**
- Clinical relevancy of in vitro BE studies
- Space determination for in vitro Characterization
- **Risk assessment of impact of food on BE and biowaiver**

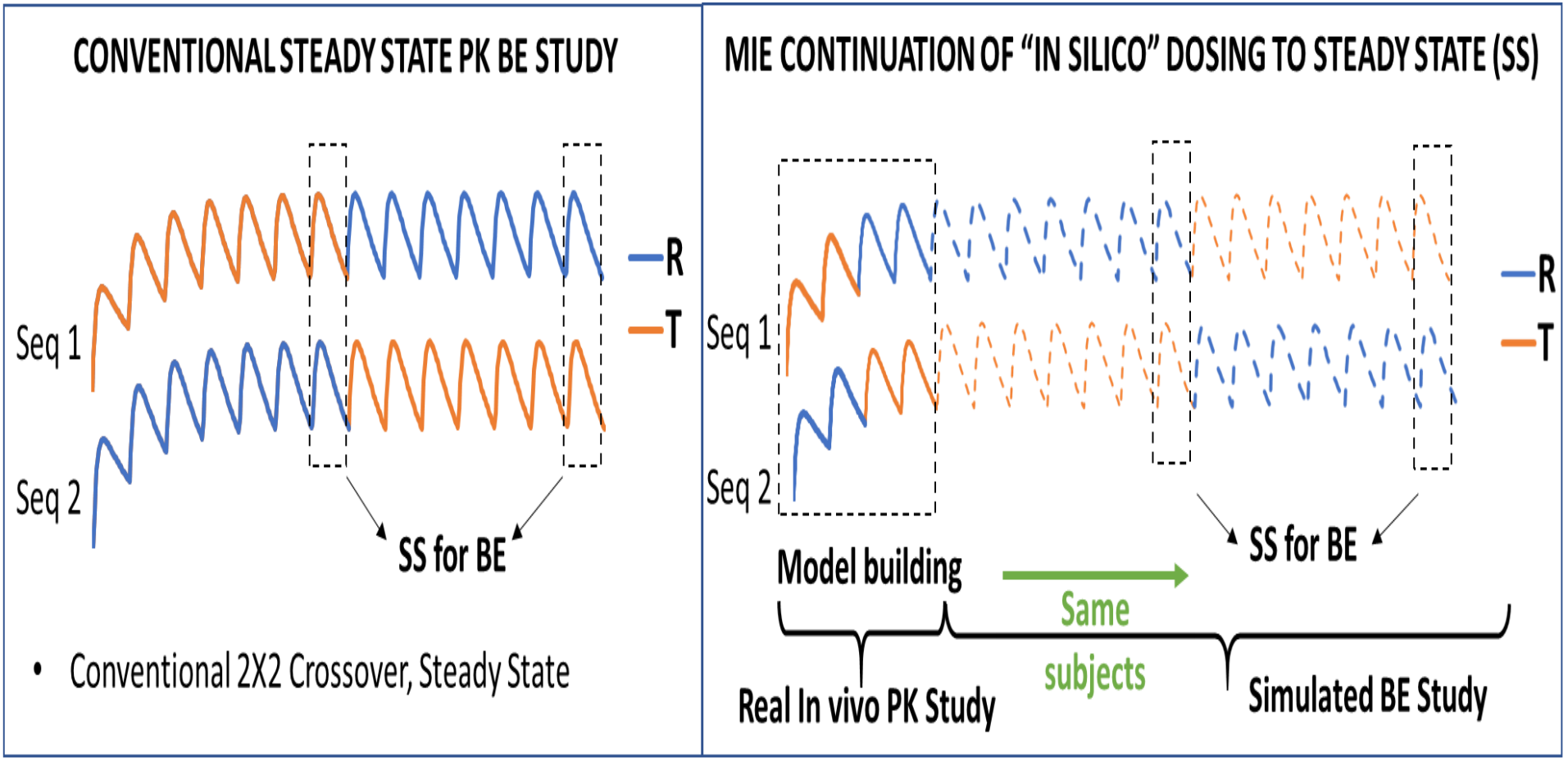
- Leveraging artificial intelligence and machine-learning technologies to enhance the ANDA review efficiency, quality, and consistency
- In vitro BE method development
- Post-Marketing surveillance

Courtesy slide from Dr. Liang Zhao

Opportunity Areas

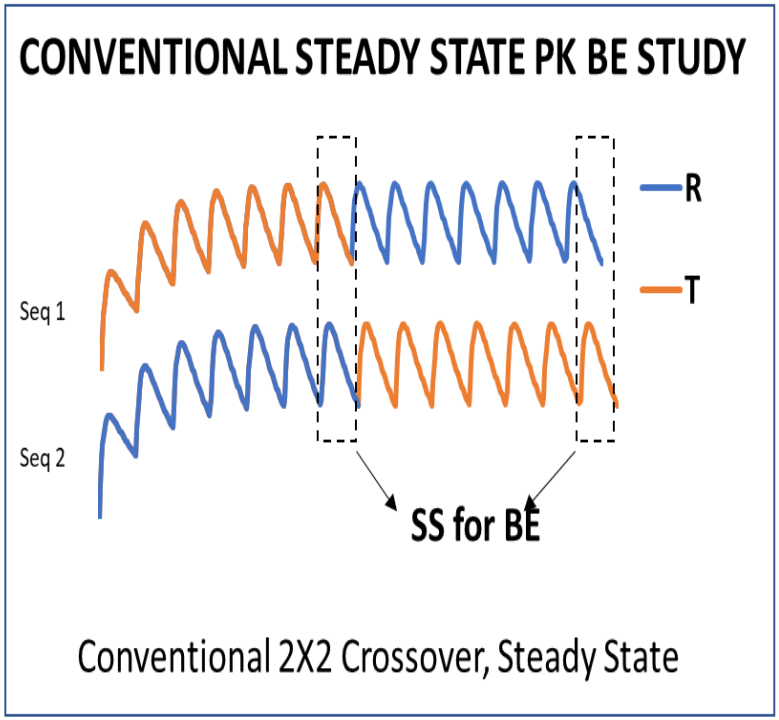
- Intends to illustrate some high impact opportunity areas that MIE can be used to facilitate generic drug development and regulatory decision making:
  - Ex 1: Shorter or smaller BE studies
  - Ex 2: Regional deposition + PBPK modeling serves as alternative BE approaches in lieu of clinical endpoint BE studies
  - Ex 3: PBPK absorption modeling to evaluate food impact on BE: support ICH (International Conference on Harmonization) M13 initiative

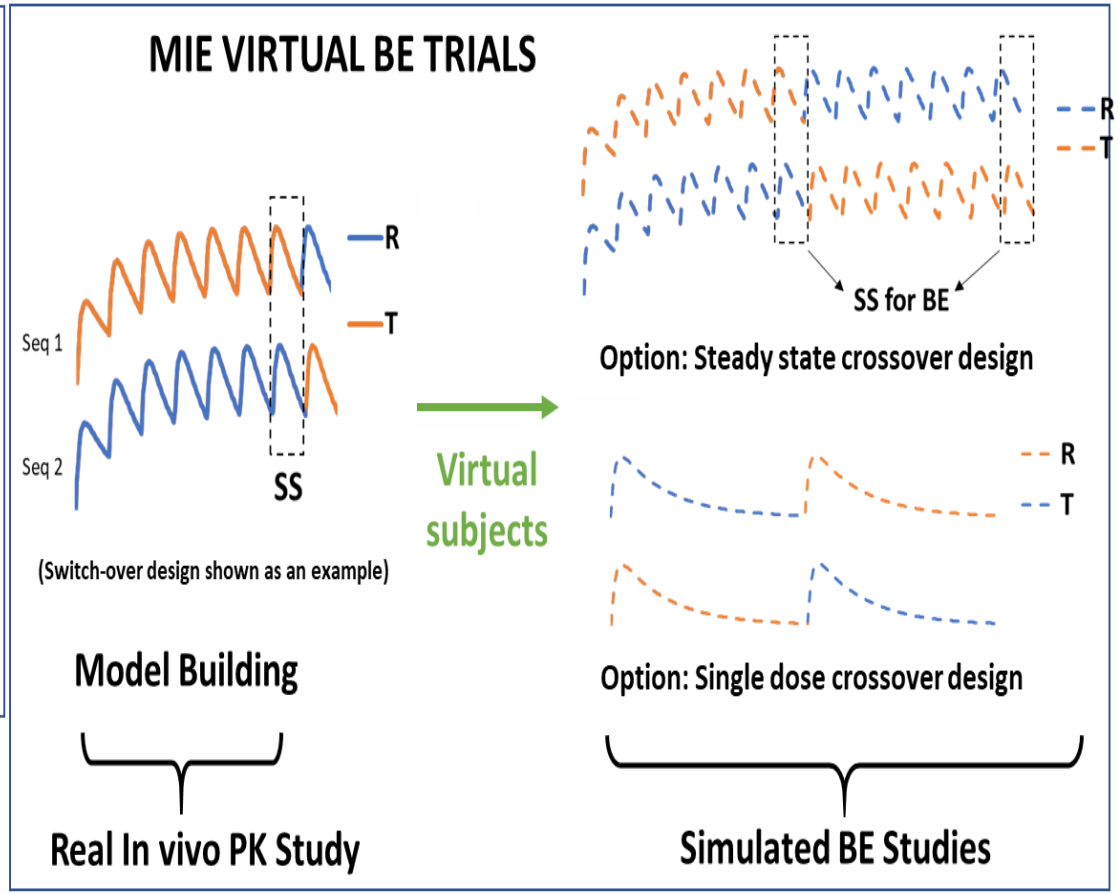
Ex 1: Shorter BE Study: “in silico” Dosing to Steady State



- for some long acting injectables (LAI), oncology, orphan drugs

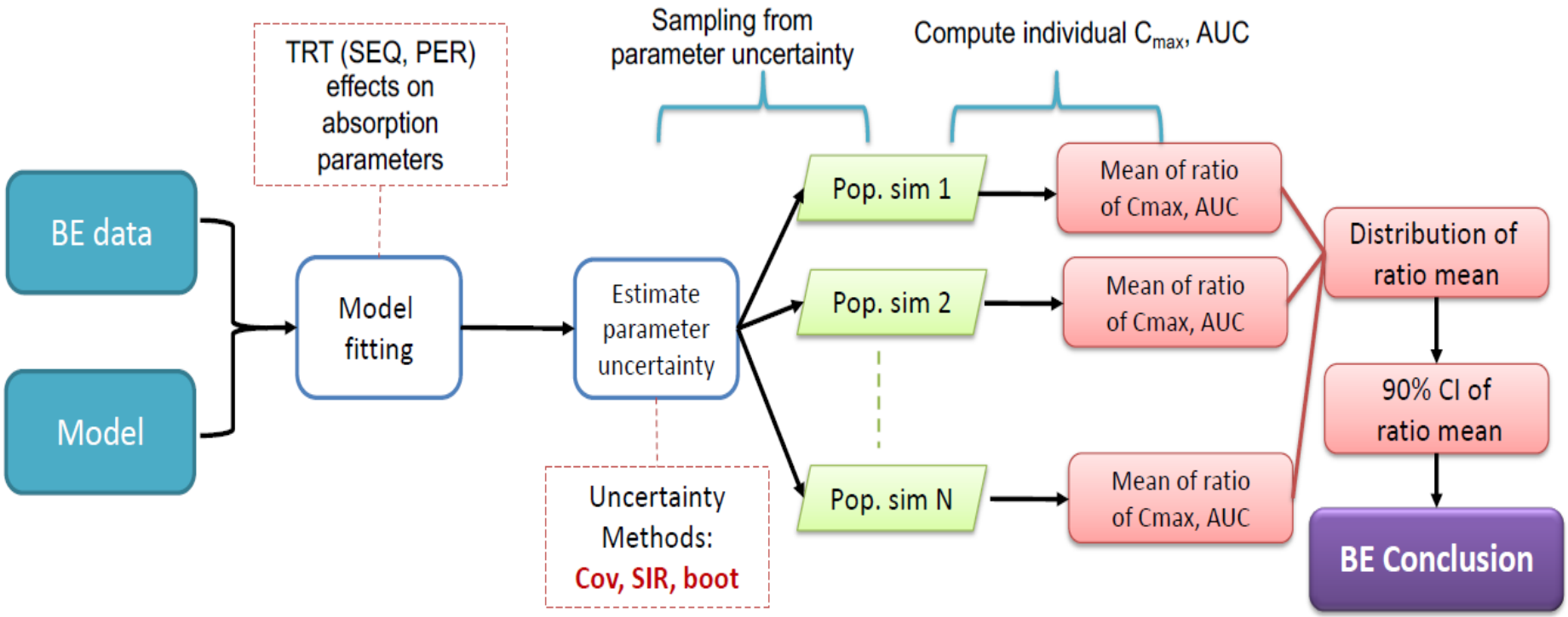
Ex 1: Smaller BE Study: Virtual BE Trials





- **Reduced sample size** and shorter duration in vivo PK studies
- Particularly useful for some oncology and orphan drugs

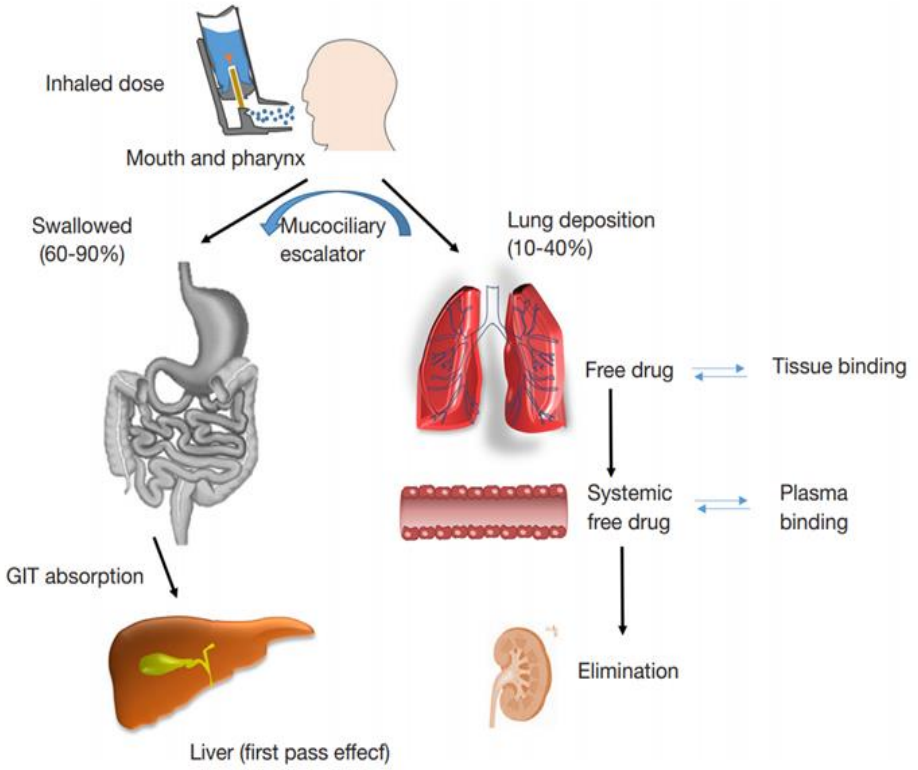
Ex 1: Virtual BE Framework



Slide adapted from ACOP presentation by Andrew Hooker 2019

Ex 2: Regional Deposition + PBPK Modeling: Alternative BE to Clinical Endpoint BE Studies

- For locally acting orally inhaled drug products (OIDPs), lung tissue concentration is the site of action
- Regional deposition is upstream of local tissue concentration and systemic pharmacokinetics (PK) is downstream
- Regional deposition modeling coupled with physiologically based pharmacokinetic (PBPK) modeling can connect in vitro metrics with lung tissue PK and systemic PK

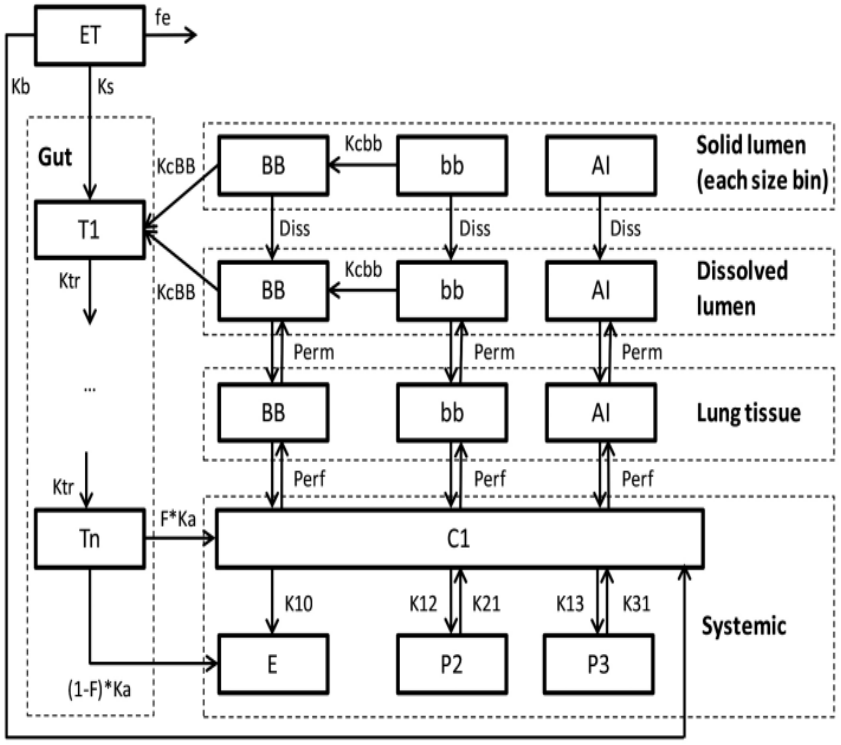


Drug delivery, absorption, distribution, metabolism, and elimination of OIDPs (Figure from de Pablo et al.[1])

de Pablo, etc., Annals of Translational Medicine. 2017 Nov;5(22).

Ex 2: Regulatory Utility of OIDP Modeling

- Several firms have contacted the Office of Generic Drugs (OGD) at FDA regarding alternative BE approaches for OIDPs in lieu of comparative clinical endpoint (CCEP) or pharmacodynamic BE studies
- Ideal approach is to validate both regional deposition and systemic PK predictions and bridge the two components to credibly predict local tissue PK
- Improvements are needed to model validation for regional deposition models that may use either semi-empirical or computational fluid dynamics (CFD) methods
- If successful, the use of modeling may help facilitate approval of generic OIDPs, because CCEP BE studies may require very large subject numbers and may then be difficult to conduct[2]



Lung PBPK model structure, where regional deposition predictions are used as inputs to the lumen of the extrathoracic (ET), tracheobronchial (BB), bronchiolar (bb) and alveolar-interstitial (AI) regions (Figure from Olsson and Bäckman[3])

[2]Lee J, etc., Clinical Pharmacology & Therapeutics, doi:10.1002/cpt.2553

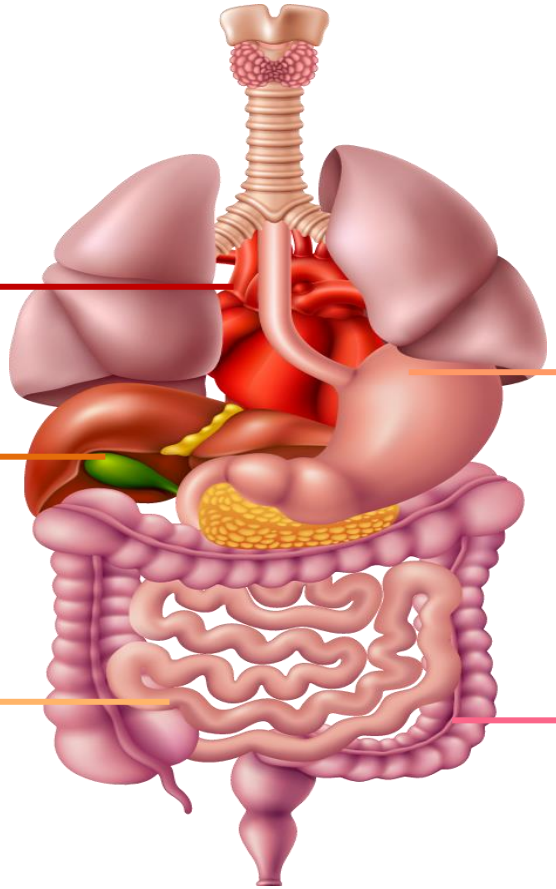
[3]Olsson B, etc., Respiratory Drug Delivery 2018 (Vol. 1, No. 2018, pp. 103-112)

Ex 3: Effect of Food on Gastrointestinal Physiology

Blood Flow
- Increased Liver and Portal Blood Flow

Gall Bladder
- Release of Bile Salt

Small Intestine
- Increased Bile Salt Conc.
- Increased Mortality
- Increased Viscosity
- Increased Volume
- Decreased pH
- Change in Enzyme and Transporter's Activity



Stomach
- Increased pH
- Increased Mortality
- Increased Acid Secretion
- Increased Volume
- Delayed Gastric Emptying

Colon
- Increased Buffer Capacity
- Increased Osmolarity
- Decreased pH

- ICH M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms
- Expert Working Group to reach technical consensus on challenging topics such as food impact on BE

Ex 3: PBPK Absorption Modeling: Food Impact on BE

Research Background

- Both fasting and fed in vivo BE study are recommended for immediate release (IR) product unless the product should be taken only on an empty stomach or when serious adverse events are anticipated under fed conditions.
- Can PBPK model be used to evaluate the BE of proposed generic product in the fed state using virtual BE (VBE) simulation?

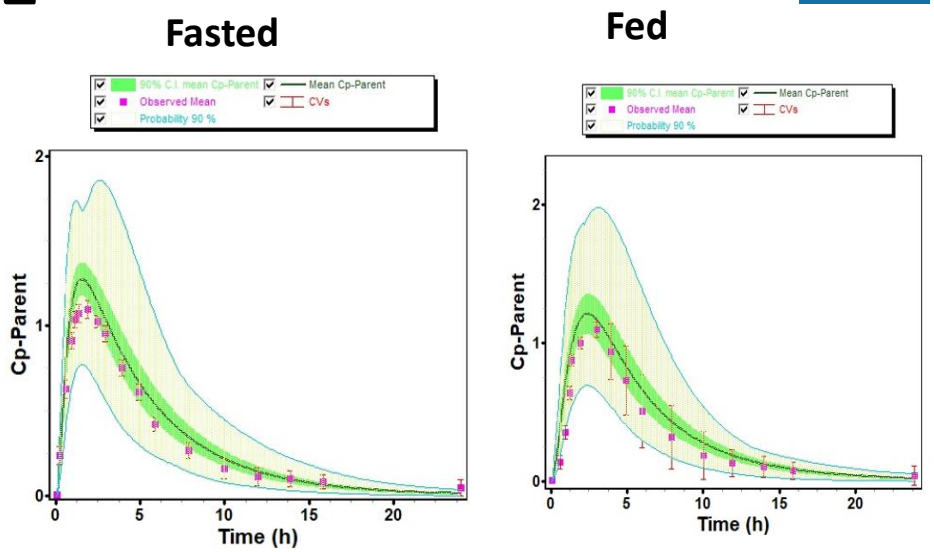


Figure. PBPK Model Simulation for Acyclovir IR Product 800 mg

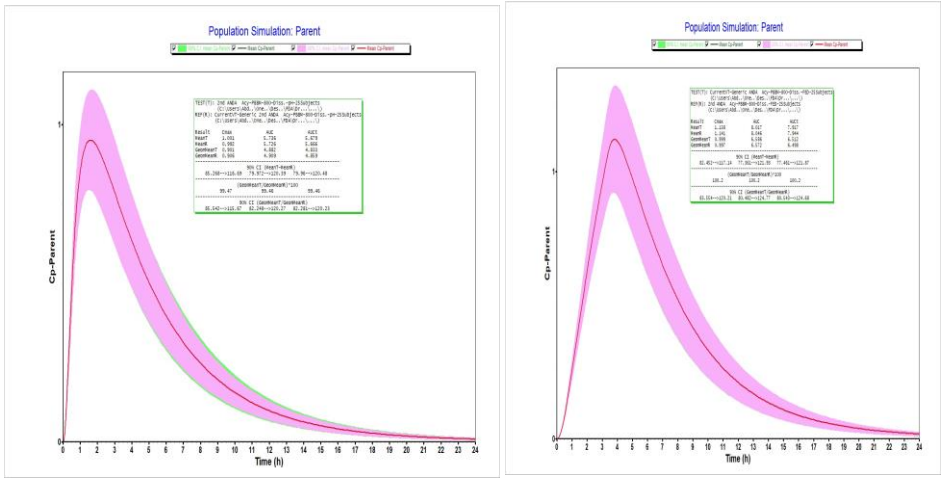


Figure. VBE of Acyclovir IR Product 800 mg

Outcome

- VBE indicated that food appears not to impact the BE results for this case

Ex 3: PBPK Absorption Modeling: Food Impact on BE

Regulatory Case

- Drug X oral tablets include API with amorphous solid dispersion form. The Firm developed a mechanistic absorption model for oral tablet based on literature data and results from pilot BE studies (different formulations) in the fasted and fed state and pivotal BE study in the fasted state, comparing the Test formulations and the RLD.
- PBPK modeling is used to assess risk of bio-inequivalence with food intake

Gaps in PBPK Model

- Lack of supporting information related to formulation design, manufacturing process, API characteristics (e.g., particle size or percentage of amorphous form vs crystallization form), excipients and quality attributes of the drug product that may significantly impact the in vivo dissolution and bioavailability (BA) of drug.
- Lack of correlation between generated in vitro dissolution profiles and in vivo dissolution (or release)
- Uncertain model sensitivity to formulation differences: model validated with BA/BE data which demonstrated BE of tested batches; need to challenge the model with data which showed lack of BE and/or batches with different release rate

Summary

- MIE is an integrative approach to address the challenges of generic drug development
  - Integrate data (formulation, dissolution, PK, etc.) throughout product life cycle
  - Different modeling approaches demonstrated tangible benefit to generic drug development and regulatory decision making
  - We see a clear demand: increasing use of modeling approaches in Pre-ANDA MPs and ANDA submissions
- Next step is to engage stakeholders and develop best practices

Thank You!

Acknowledgements

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