Computational Pharmaceutics: Scientific Gaps and Forthcoming Research to Modernize Regulatory Science

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The Disclaimer

- This presentation represents the views and perspectives of the speaker and does not necessarily reflect the views of the U.S. FDA

Agenda

- Introduction
- Challenges and opportunities in regulatory science for computational pharmaceutics
  - FY 2020 Generic Drug Regulatory Science Initiatives Public workshop on May 4, 2020
  - Current status quo, scientific gaps, opportunities, and next steps
- Summary

Computational Pharmaceutics

- Computational characterization of drug delivery and formulation development
- Regulatory impacts: bioequivalence (BE) establishment for new formulations, local drug delivery and manufacturing control

Key Questions Reviewed in FDA May 4th Public Workshop for GDUFA Science and Research Priority Initiatives

- How to evaluate data from in vitro studies and which in vivo studies are clinically relevant (e.g., how to justify Q1/Q2/Q3 deviation for equivalence assessment)?
- What are the challenges for industry in implementing modeling and simulation methods to support more efficient regulatory BE pathways?
- What are the emerging expertise/tools in implementing new BE approaches?

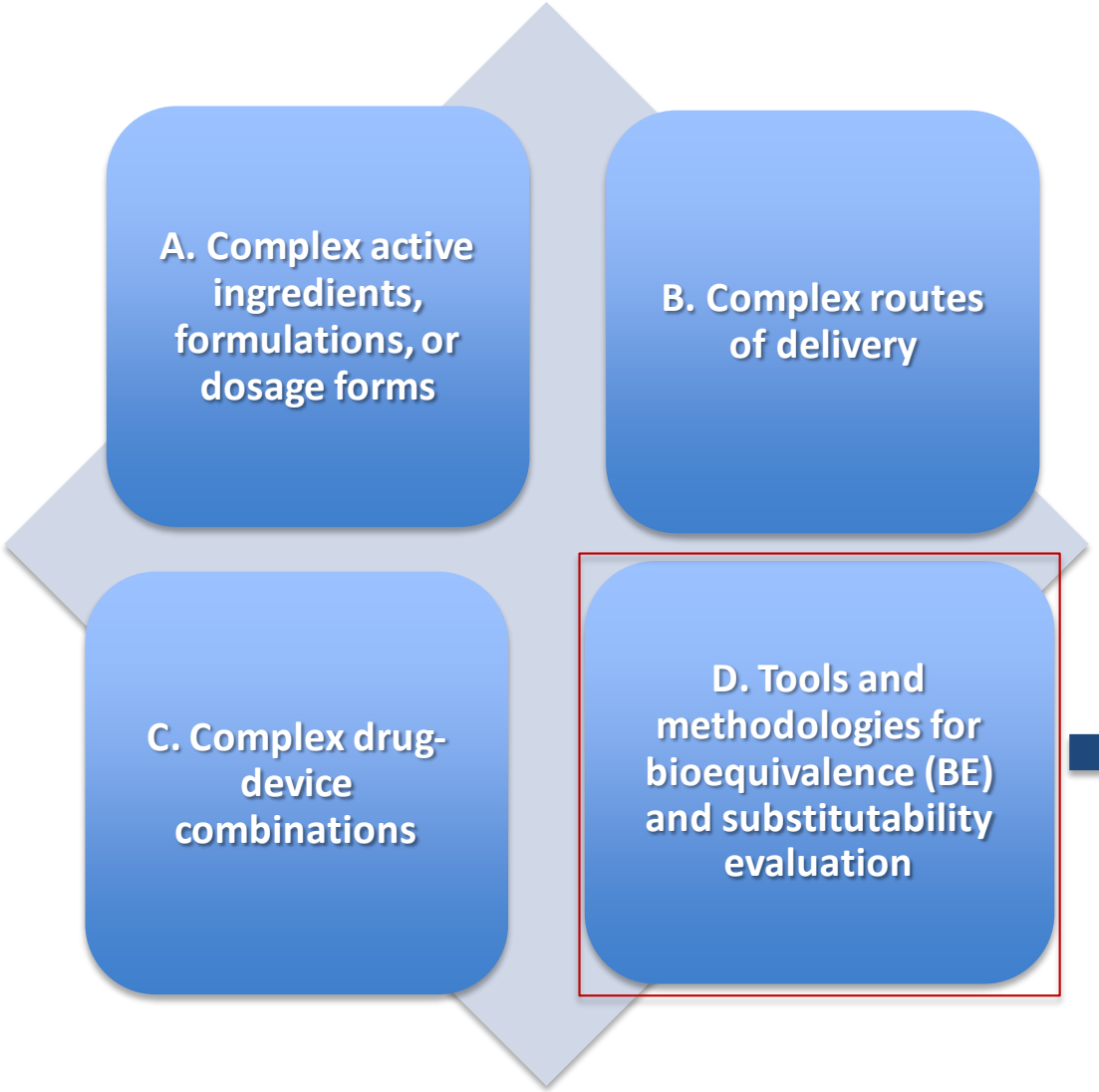
Q1, qualitative sameness; Q2, quantitative sameness; Q3, microstructure/physicochemical sameness/similarity

Expert Discussants In May 4th FDA Workshop

- **Liang Zhao, PhD** – FDA, CDER/OGD/ORS/DQMM, Session moderator
- **Amin Rostami, PhD** – University of Manchester, Centre for Applied Pharmacokinetic Research
- **Andrew Hooker, PhD** – Uppsala University, Department of Pharmaceutical Biosciences
- **Charlie DiLiberti** – Montclair Bioequivalence Services, LLC
- **Glenys Barber, PhD** – University of Manchester
- **Sandra Suarez-Sharp, PhD** – Simulations Plus, Inc.
- **Viera Lukacova, PhD** – Simulations Plus, Inc.
- **Stella C. Grosser, PhD** – FDA, CDER/OTS/OB (Office of Biostatistics)/DBVIII
- **Stephan Schmidt, PhD** – University of Florida, Center for Pharmacometrics & Systems Pharmacology
- **Sid Bhoopathy, PhD** – Absorption Systems
- **Raja Velagapudi, PhD** – Sandoz Pharmaceuticals, Clinical Development (US)
- **Lanyan (Lucy) Fang, PhD** – FDA, CDER/OGD/ORS/DQMM
- **All break out session participants**

Review of FY2020 GDUFA Research Science Priorities

that are most relevant to Data Analysis and Model-Based Bioequivalence



- D1. Improve **quantitative pharmacology and BE trial simulation** to optimize design of BE studies for complex generic drug products
- D2. **Integrate predictive dissolution, physiologicaly based Pharmacokinetic (PBPK) and Pharmacokinetic/Pharmacodynamic (PK/PD) models** establishing generic drug bioequivalence standards
- D3. Expand the scientific understanding of the role of excipients in generic drug products to support **the expansion of BCS Class 3 biowaivers** to drug products with differences in formulations larger than currently recommended in FDA guidance
- D4. **Develop methods and integrated technological solutions that will allow FDA to leverage large data sets** (such as bioequivalence study submissions, electronic health records, substitution/utilization patterns, drug safety data, and drug quality data) to support regulatory decisions and improve post-market surveillance of generic drug substitution

https://www.fda.gov/media/132370/download

Key Questions to Address

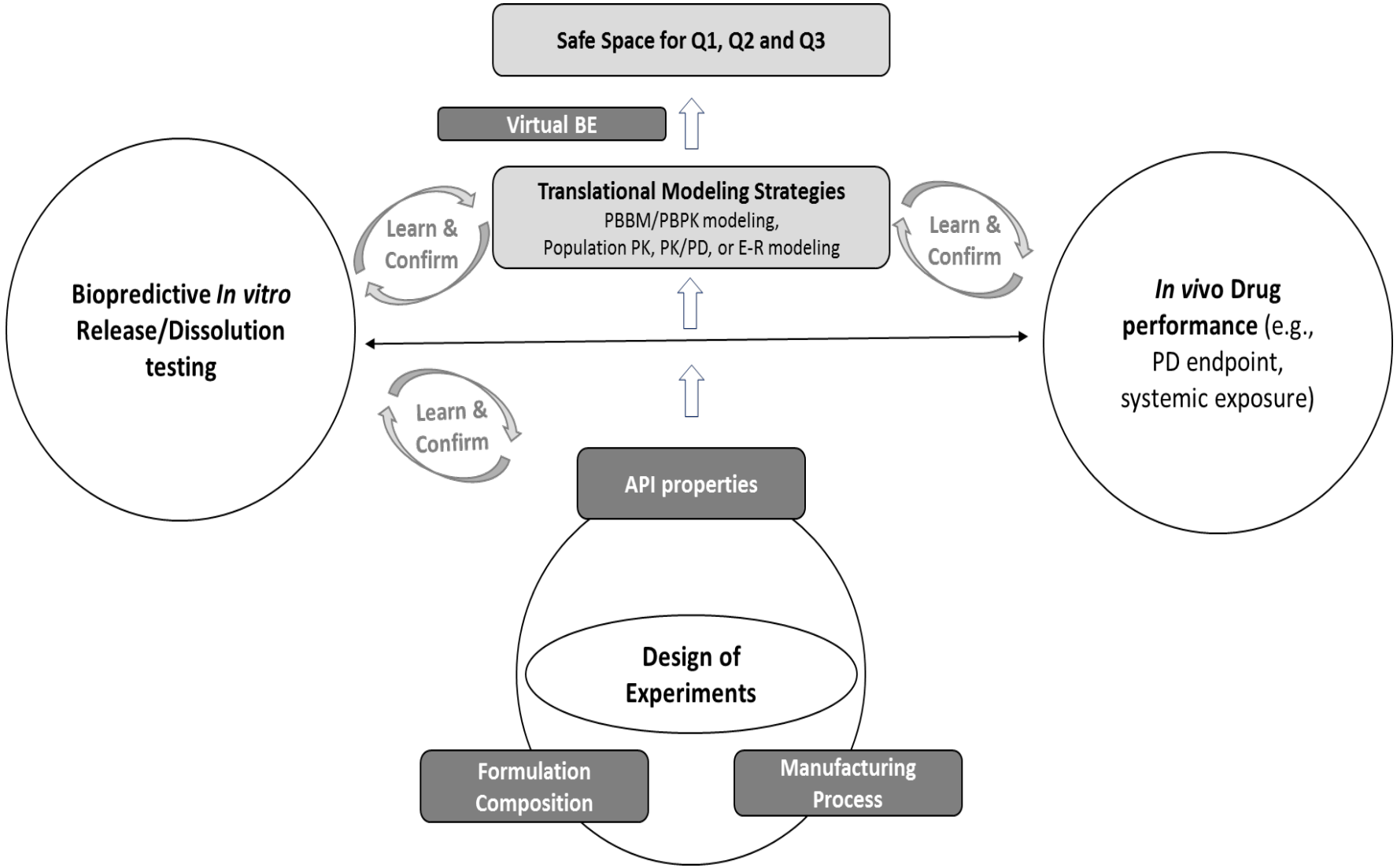
- **How to evaluate data from *in vitro* studies and which *in vivo* studies are clinically relevant (e.g., how to justify Q1/Q2/Q3 deviation for equivalence assessment)?**

Q1, qualitative sameness; Q2, quantitative sameness; Q3, microstructure/physicochemical sameness/similarity

Current Challenges and Need

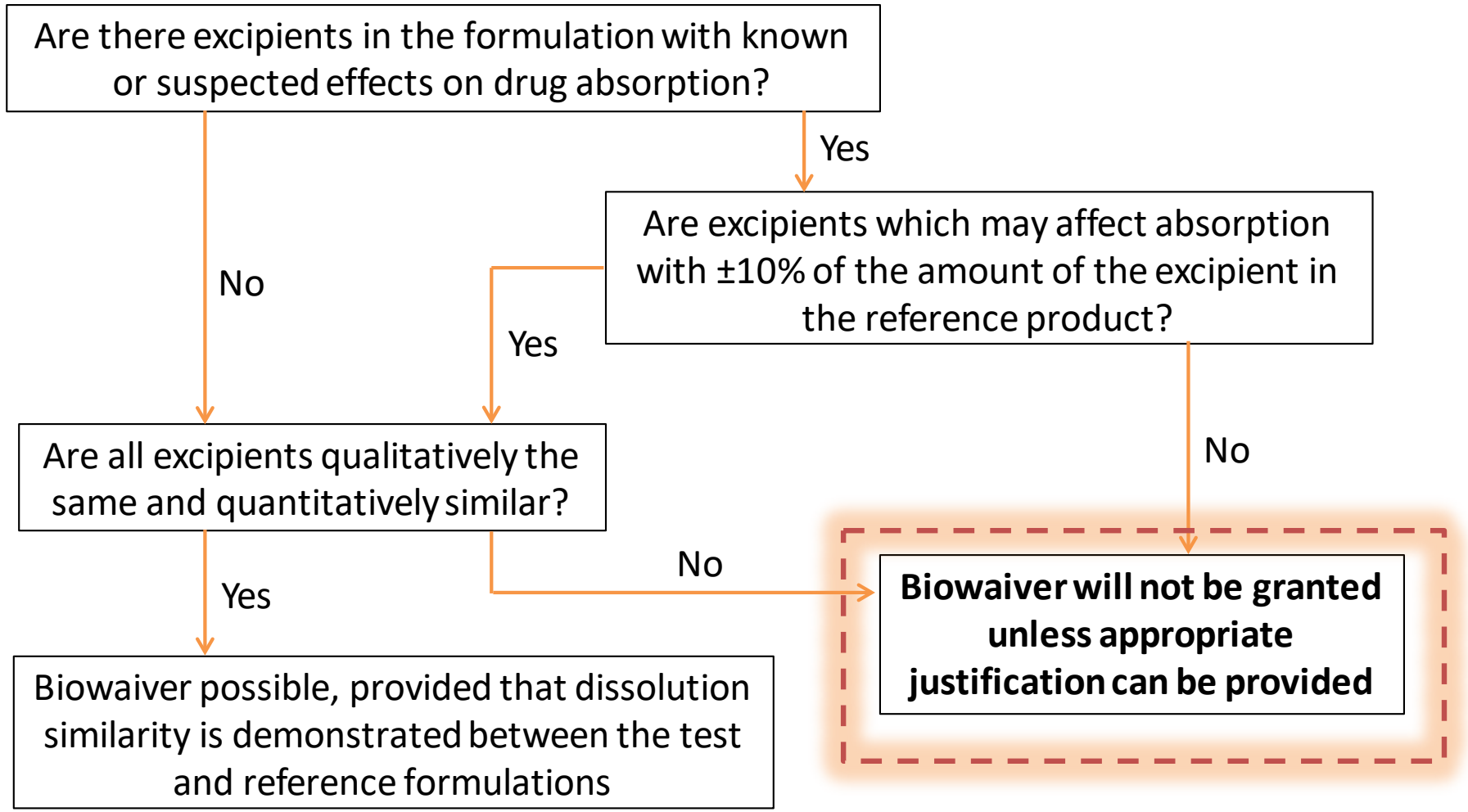
- For in vitro only approaches, narrow Q1/Q2/Q3 standards often requires exhaustive reverse engineering of the reference product using state-of-the-art analytical techniques
- Patents sometimes block the ability to use a Q1/Q2/Q3 formulation
- A significant need to develop modeling approaches to justify relaxation of the narrow and probably overly conservative compositional and microstructural requirements
  - In vitro in vivo correlation (IVIVC) using PBPK models to set clinically relevant space (also known as safe space) in terms of Q2 differences for these products
  - Setting-up excipient exception categories for class 3 biowaivers, and providing alternative pathways for data evaluation when justifying the lack of impact of excipient change on class 3 product BE

A Proposed In Vitro- In Vivo Link to Assess the Clinical Relevance of Critical Variables and to Establish the Safe Space for Q1/Q2/Q3



Jieon Lee et al. Clin Pharmacol Ther. doi: 10.1002/cpt.2120

BCS Class 3 Drug Substances



ICH M9 on biopharmaceutics classification system-based biowaivers
EMA/CHMP/ICH/493213/2018
Date for coming into effect – 30 July 2020

Continue working towards – Exception categories, alternative pathways for evaluation, expanded tolerance ranges

Adapted from Presentation by Dr. Bhoopathy in May 4th 2020 Public Workshop

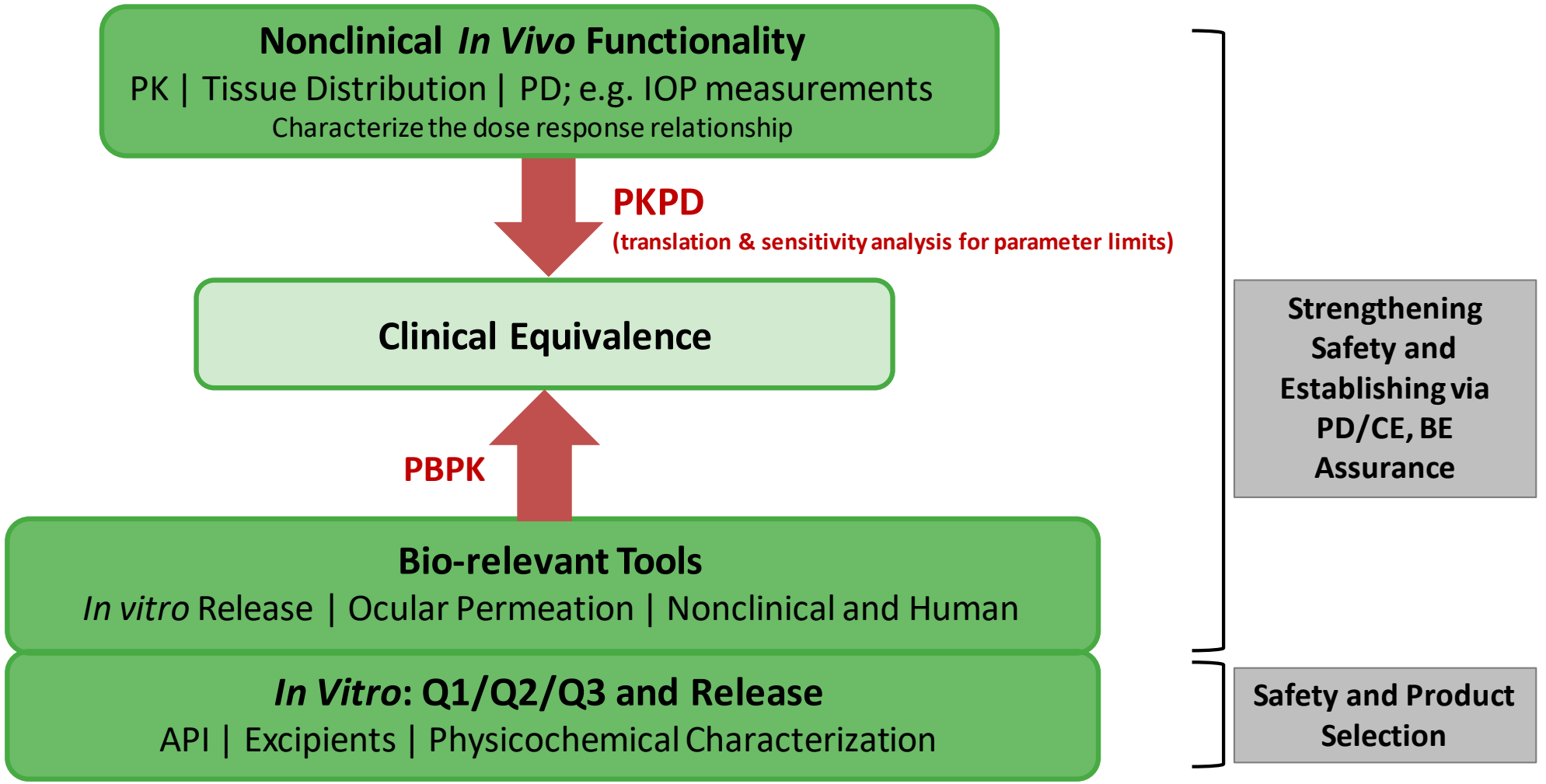
BCS Class 3 Oral Drug Product Biowaivers

- Must be very rapidly dissolving (≥ 85% dissolved in 15 minutes)
- Test product must have same excipients as reference product except for changes in the technical grade
- Quantitatively similar to the reference product:
- Test-reference differences in excipient content, expressed as percent (w/w) of the total formulation less than or equal to the following percent ranges:
  - Filler (± 10%)
  - Disintegrant, Starch (± 6%)
  - Disintegrant, Other (± 2%)
  - Binder (± 1%)
  - Lubricant, Calcium or Magnesium Stearate (± 0.5%)
  - Lubricant, Other (± 2%)
  - Glidant, Talc (± 2%)
  - Glidant, Other (± 0.2%)
  - Film Coat (± 2%)
- The total additive effect of all excipient differences should not be more than 10 percent.
- Some other conditions, e.g., NTI drugs, combination products, absorption through oral mucosa, etc.

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, December 2017

Adapted from Presentation by Dr. DiLiberti in May 4th 2020 Public Workshop

Example: Chronic Complex Ophthalmics: Opportunity for Innovation



Modified from by Dr. Bhoopathy in May 4th 2020 Public Workshop

Potential Outcomes and Challenges for Ophthalmic Products

- An alternative in-vitro, model informed BE approach for chronic complex ophthalmic products

- *Establishing IVIVC for the identified ophthalmic product CQAs (lack of human in vivo data on local BA, what are possible surrogate measures, model validation for regulatory acceptance)?**

Potential areas for FY 2021 research priorities

Challenges from Industry Perspective

- Streamlined BE approaches have, in principal, been welcomed by the industry, however:
- Meeting compositional/microstructural requirements can be so challenging that sponsors frequently abandon streamlined BE pathway and follow traditional BE approaches:
  - Conduct human BE studies for BCS class 3 drugs
  - Conduct comparative clinical endpoint BE studies for locally-acting drug products
- Sponsors sometimes also shy away from developing their own novel streamlined BE pathway for similar reasons
- Dilemma between extreme BE approaches with too much or too little sensitivity
  - Current compositional/microstructural criteria are extremely narrow (conservative) due to lack of understanding of relationships between these criteria and clinical effect (i.e., they are too sensitive to product differences that may be clinically irrelevant)
  - Comparative clinical endpoint BE studies are extremely insensitive even toward product differences that may be clinically relevant

Adapted from Presentation by Dr. DiLiberti in May 4th 2020 Public Workshop

View of Opportunities from ANDA Applicants

- Significant opportunities exist to apply modeling methods to justify relaxation of existing narrow compositional/microstructural requirements to qualify for streamlined BE pathway
- Many reference product drugs are locally-acting drugs and have no (or few) approved generics, at least in part because of the difficulties in qualifying for streamlined BE pathways
- Opportunity to facilitate the development of generics by relaxing the compositional/microstructural criteria to qualify for streamlined BE approaches, **using modeling methods to probe the effect of deviations** from narrow compositional/microstructural criteria on expected product performance *in vivo*
- Developing such modeling approaches should be an important GDUFA FY 2021 research priority, because the results of such research would act directly to remove major impediments to the development of the most-needed generics

Adapted from Presentation by Dr. DiLiberti in May 4th 2020 Public Workshop

Opportunities in Regulatory Science (1)

- The quantitative connection and interaction among critical formulation and manufacturing variables (CFMV), dissolution, and *in vivo* performance is the *in vivo* evaluation of variables
- The clinical relevance of these critical variables and their ranges can then be assessed once an *in vitro-in vivo* link and safe space has been established via e.g., PBPK absorption modeling

Key Questions to Address

- **What are the challenges for industry in implementing modeling and simulation methods to support more efficient regulatory BE pathways?**

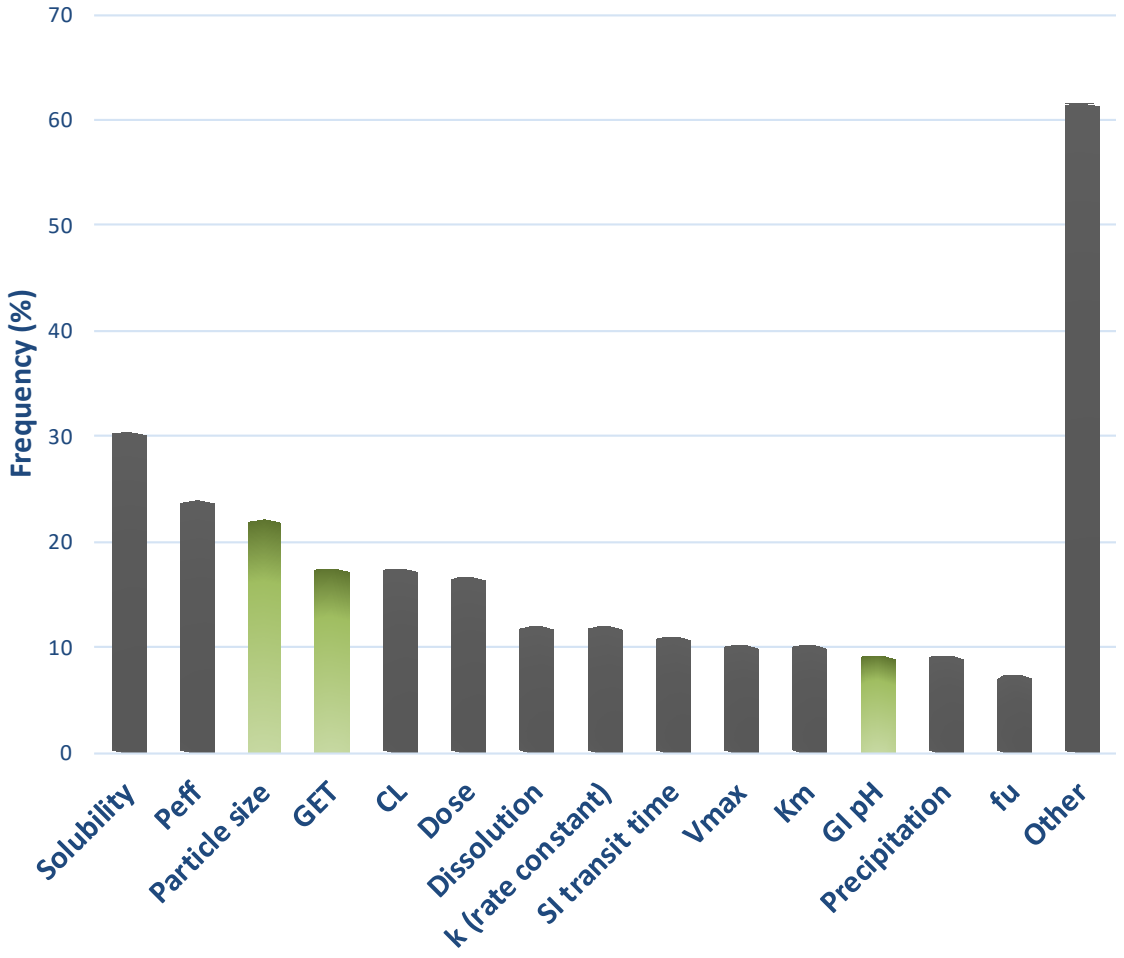
Current Challenges and Need

- There are many pharmaceutical companies where model-informed drug development (MIDD) is not common practice or is not even known as a path for drug development
- Virtual bioequivalence (VBE) requirements for prudent use of PBPK in uncharted territories
  - System parameters related to absorption of the drugs (that concerns generic drugs) in the gastrointestinal system and other routes of entry are not well defined
  - Inter-occasion variability (IOV) is rarely known for physiological parameters concerning various routes of administration
  - Effects of excipients on the physiologic system (i.e., permeability, transporters and enzymes, transit time, pH, and food effect) are not well understood

Gaps and Sensitivity Analysis

Most used sensitivity analysis input parameters in the literature

- Pubmed search: **Simcyp**, **Gastroplus** and **PBPK**, **Oral drug absorption**
- 109 out of 257 studies (42.4%) performed a sensitivity analysis
- Frequency of the parameters appearing in the 109 studies are shown to the right
- *GET*, *particle size*, *duodenal pH* and *bile acid concentration* were explored in this study



FDA, Cder, Permutt, and Thomas J, "E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials," 2017.
EMA, "Committee for Medicinal Products for Human Use (CHMP) Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation," 2018.

Adapted from Presentation by Dr. DiLiberti in May 4th 2020 Public Workshop

Bayesian Framework for Fitting: Using Prior Information

Incorporation of stochastic variability in mechanistic population pharmacokinetic models: handling the physiological constraints using normal transformations

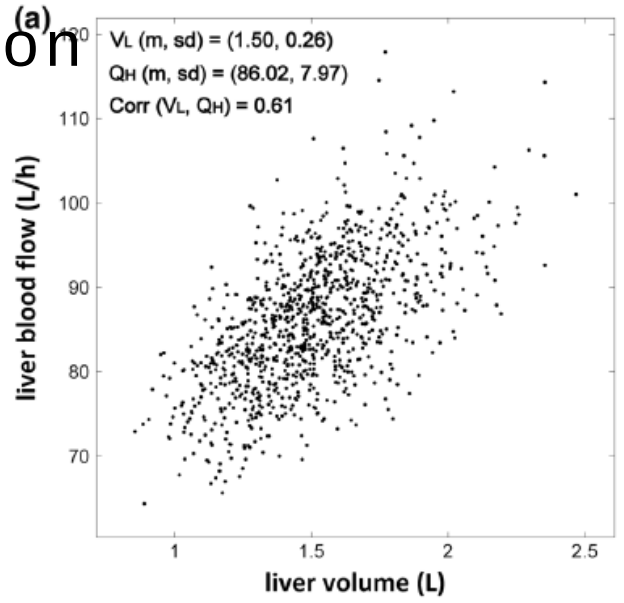
Nikolaos Tsamandouras[1] · Thierry Wendling[1] · Amin Rostami-Hodjegan[1,2] · Aleksandra Galetin[1] · Leon Aarons[1]

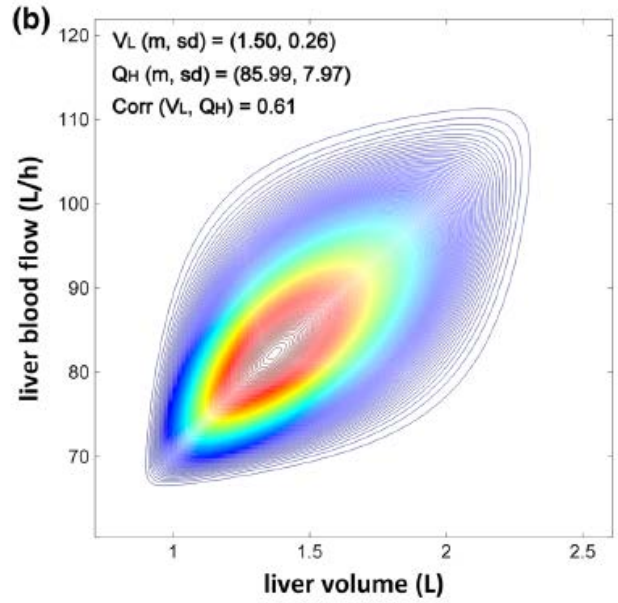
Application of a Bayesian approach to physiological modelling of mavoglurant population pharmacokinetics

Thierry Wendling[1,2] · Swati Dumitras[2] · Kayode Ogungbenro[1] · Leon Aarons[1]

Model-Based Evaluation of the Impact of Formulation and Food Intake on the Complex Oral Absorption of Mavoglurant in Healthy Subjects

Thierry Wendling • Kayode Ogungbenro • Etienne Pigeolet • Swati Dumitras • Ralph Woessner • Leon Aarons





***J Pharmacokins Pharmacodyn* 2015 x 2 ; *Pharm Res* 2014**

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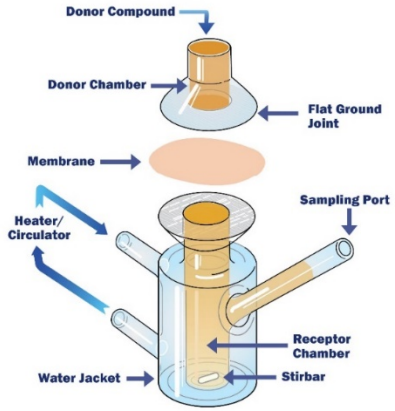
Dermal IVIVE – A Step Towards Virtual Bioequivalence for Complex Topical/Transdermal Products

Input



***In vitro* Release/Permeation Studies**

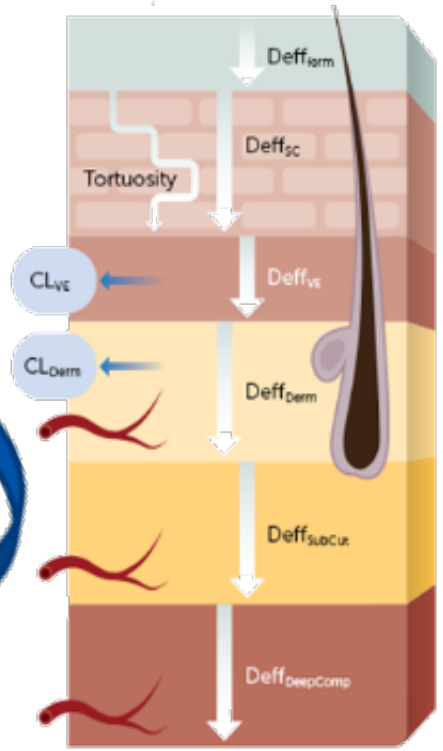
+

Understanding Q1, Q2 and Q3 properties various of topical/transdermal products (i.e. patches, creams, ointments, gels, etc.)

- **Composition**
- **Drug Solubility in different phases**
- **Drying Rate (weight loss)**
- **Specific gravity**
- **Particle size (solid particles/droplets)**
- **Rheology**
- **Precipitation characterization**
- **Excipient penetration**

Confirm & Learn Approach

Verify

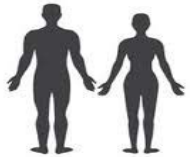


Mechanistic Dermal Absorption Model

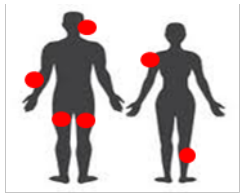
- **Confirm key drug/formulation parameters: partition and diffusion coefficients**
- **Verify model performance with challenge formulations (different strengths, non-Q1, Q2, Q3 formulation)**

Combine with *in vivo* physiology to predict *in vivo* local and systemic exposure

Extrapolate



Healthy NEurCaucasian



Diseased Population

Elderly Subjects

Paediatric Population

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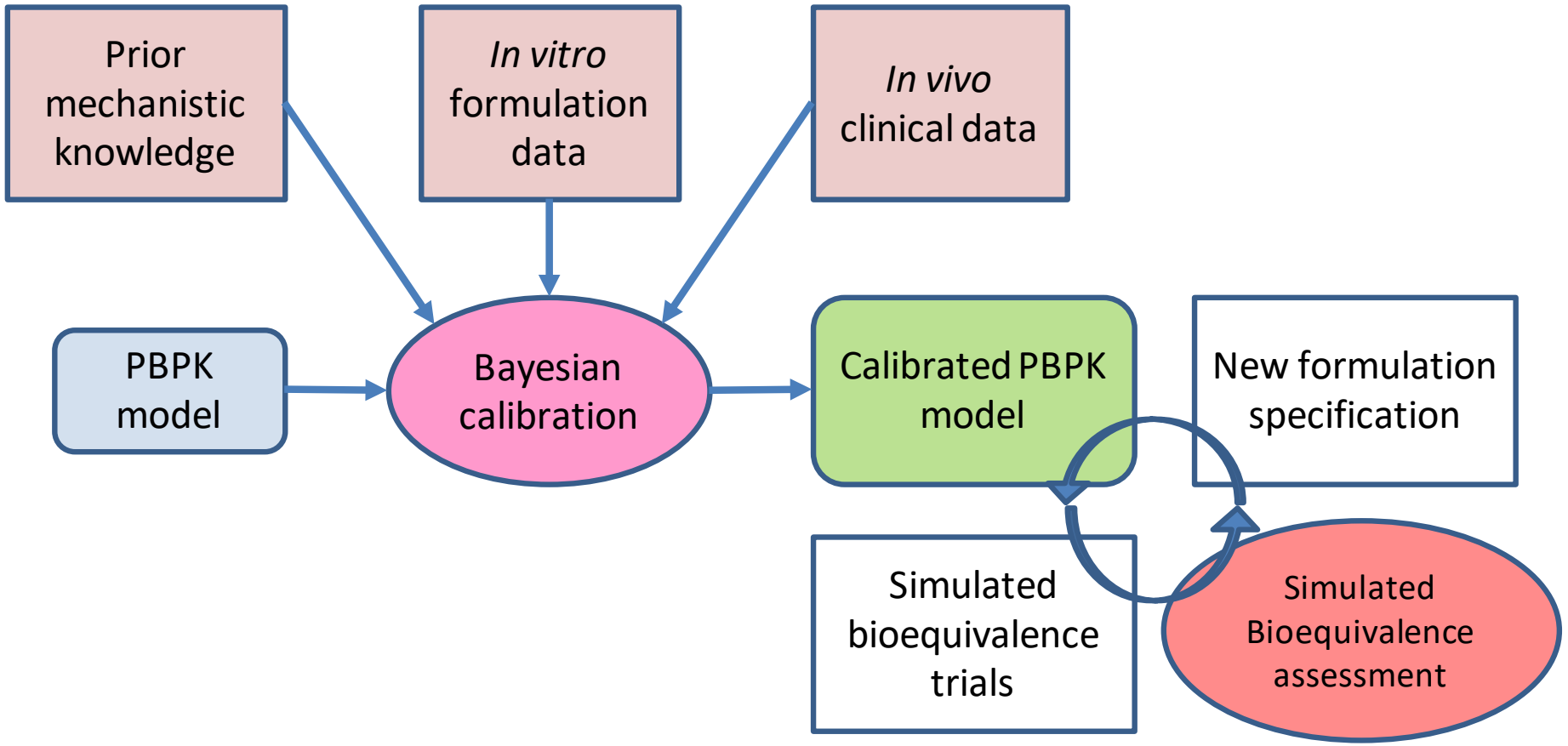
Integrating in vitro Formulation Data and in vivo Clinical Evidence to Simulate Realistic Trials for Product Development



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Opportunities in Regulatory Science (2)

- PBPK models to (1) incorporate mechanistic understanding of absorption and drug disposition and (2) address the "inter-play" between drug, formulation, and attributes of physiology and biology in each set of patients (target population)
  - Multiple dose PK studies with various classes of drugs (e.g., replicate BE studies) may help to construct the best estimates for IOV of physiological values for a wide range of drugs and formulations
- A well-established *in vitro* modeling could help determine the food effect which potentially helps to determine the waiver of doing only fasting BE study
- Availability of ready-made and user-friendly tools plays a big role in moving modeling and simulation approaches from a luxurious nice-to-have tool to a must-have kit

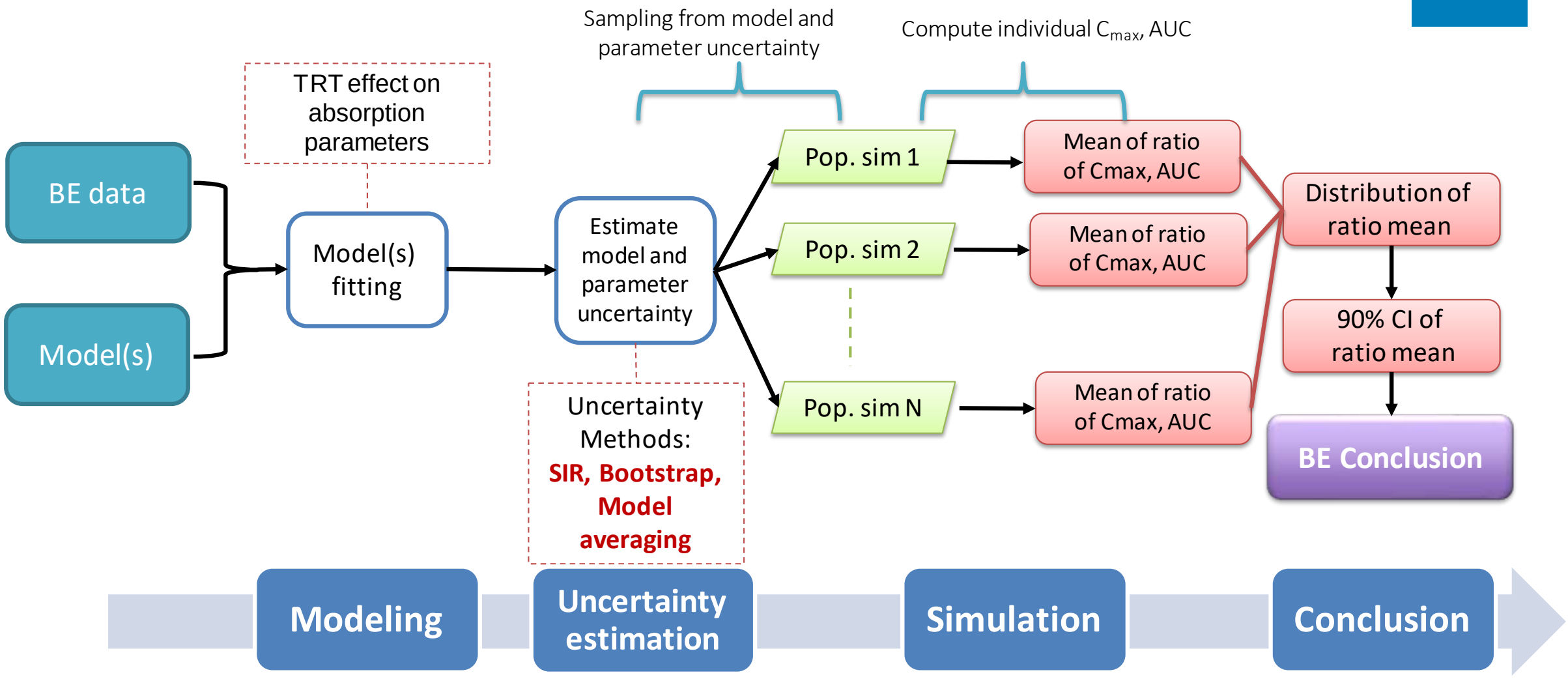
Key Questions to Address

- **What are the emerging expertise/tools in implementing new BE approaches?**

Current Challenges and Need

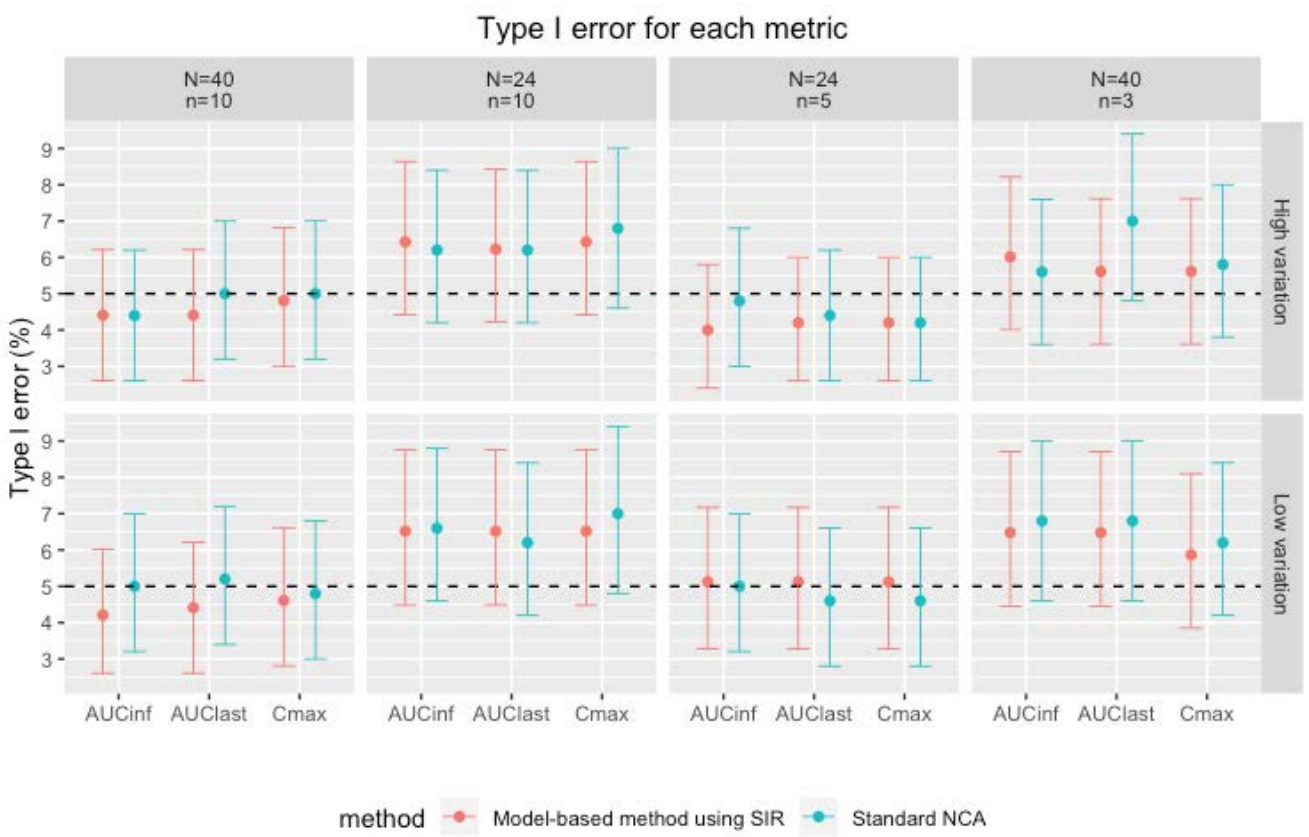
- Challenges to bring complex generics or new drugs in the 505(b)(2) route with challenging clinical programs
- Insensitive pharmacodynamic and/or clinical endpoints to detect formulation differences

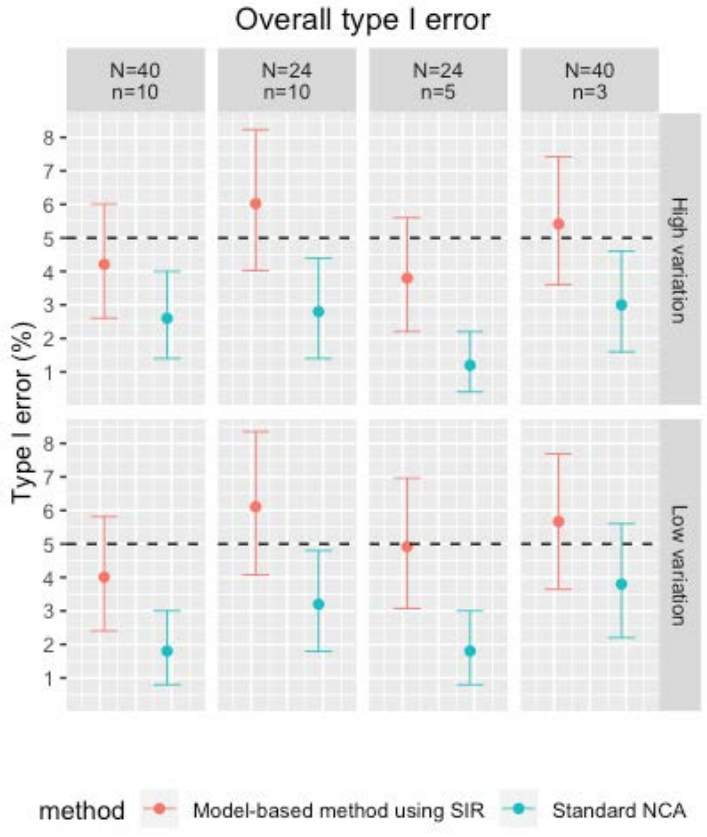
Developed Model-based BE Method



- ACOP 2019, Andrew Hooker, Development and comparison of model-based bioequivalence analysis methods on sparse data.
- ACOP 2019, Xiaomei Chen, Model-based bioequivalence evaluation for ophthalmic products using model averaging approaches.

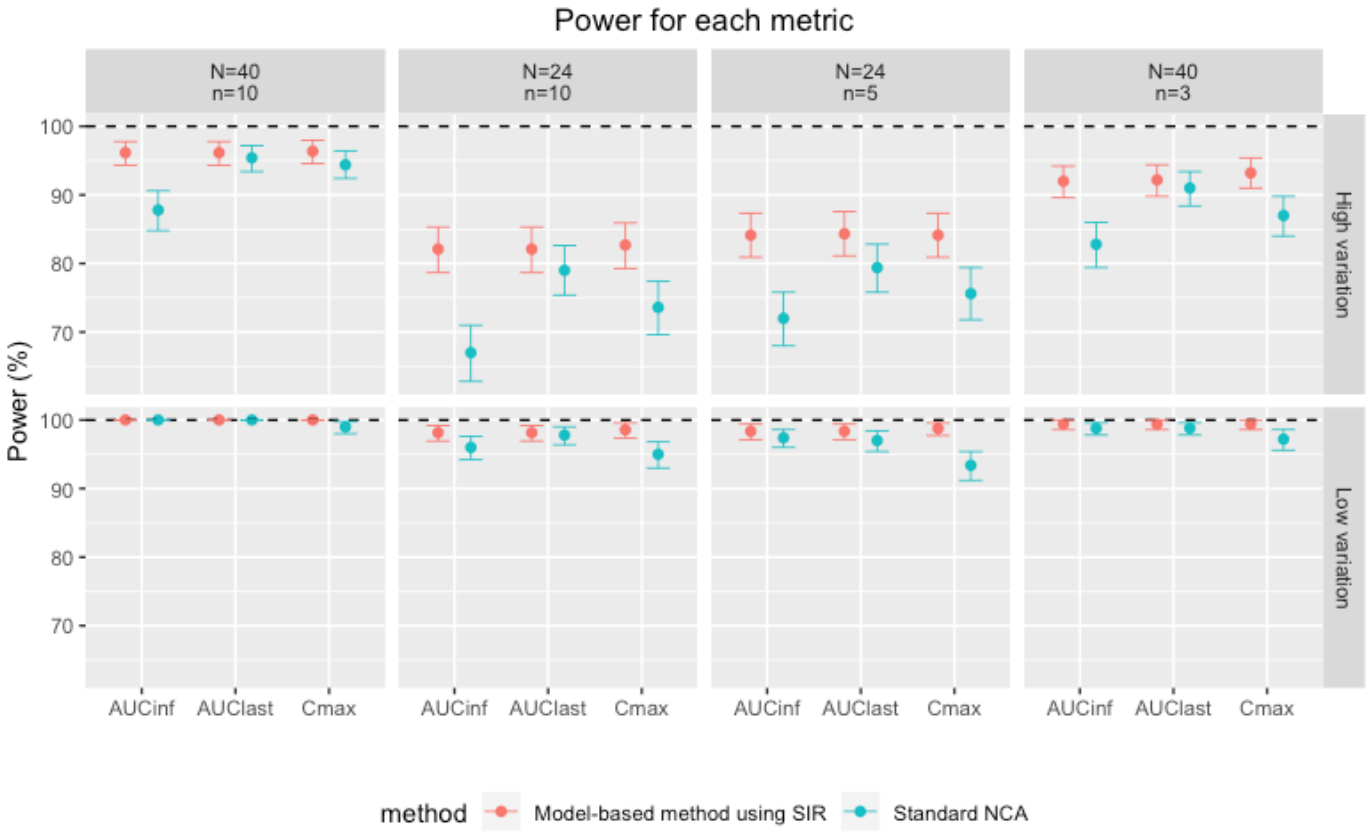
Type I Error Control by Model-based BE Method

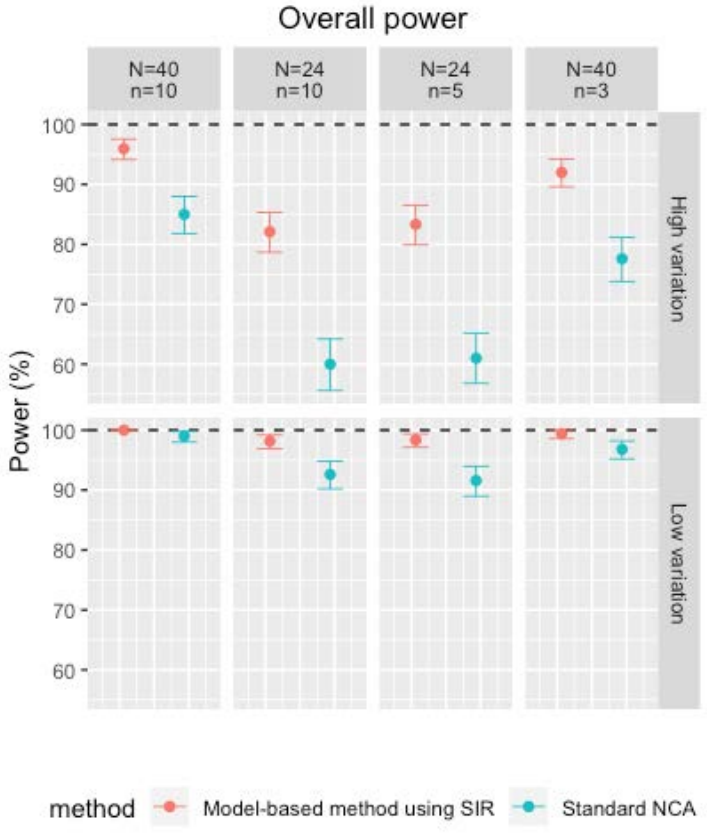




Model based method using SIR can control type I error in a reasonable range

Higher Power with Model-based Method than NCA-based Method

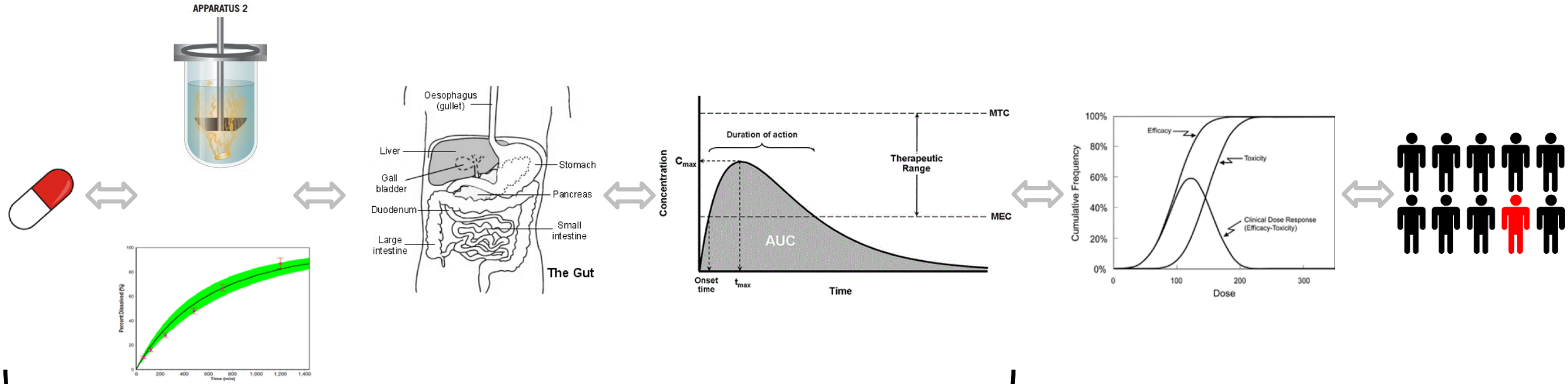




Modified from Presentation by Dr. Hooker in May 4th 2020 Public Workshop

A Model- and Systems-Based Approach to Efficacy and Safety Questions Related to Generic Substitution

Formulation | ***In vitro* and *in silico* dissolution testing** | ***In vivo* dissolution and *in silico* absorption modeling** | ***In silico* bioequivalence testing** | **Exposure-response analysis** | **Real world evidence**



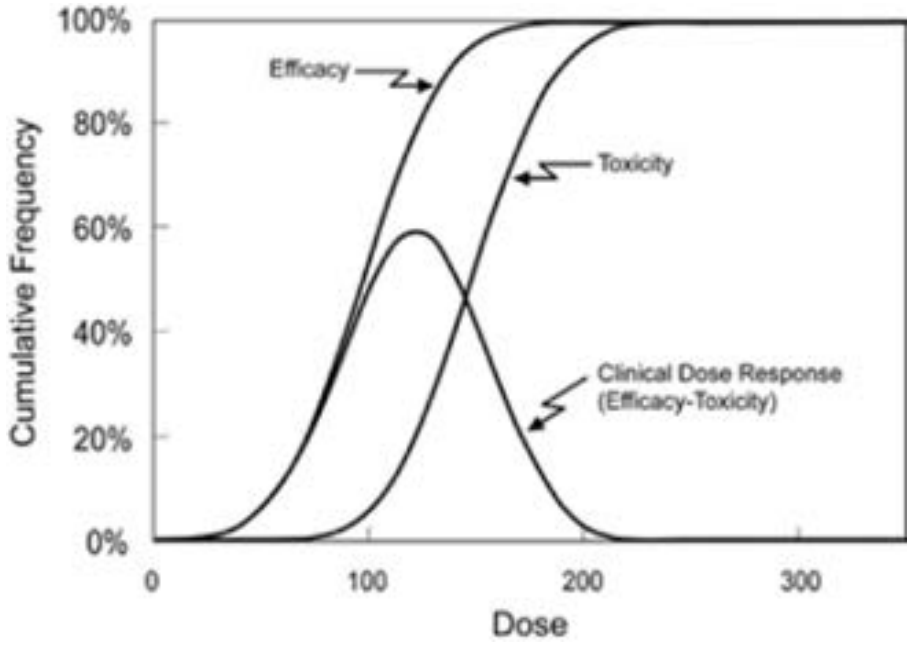
Virtual bioequivalence (PBPK)

(PBPK + Pop-PK/PD)

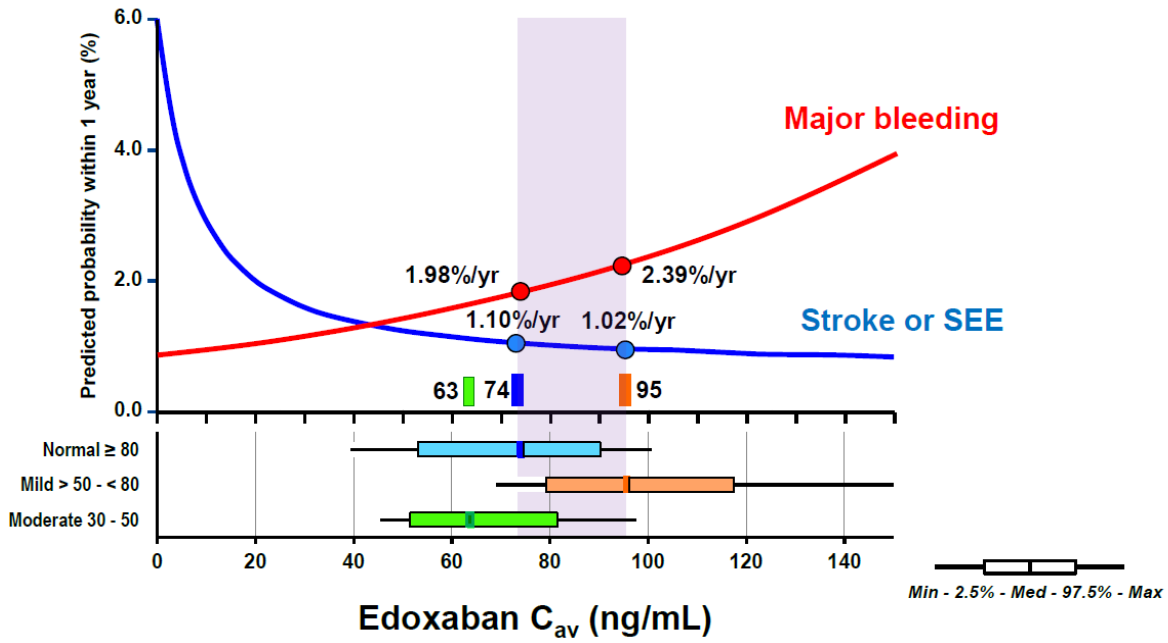
Virtual therapeutic outcome (PBPK + Pop-PK/PD + RWE)

Impact of Exposure-Response on Bioequivalence Assessment – Example: Edoxaban

General



Drug (class) specific



https://wayback.archive-it.org/7993/20170405211301/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421613.pdf

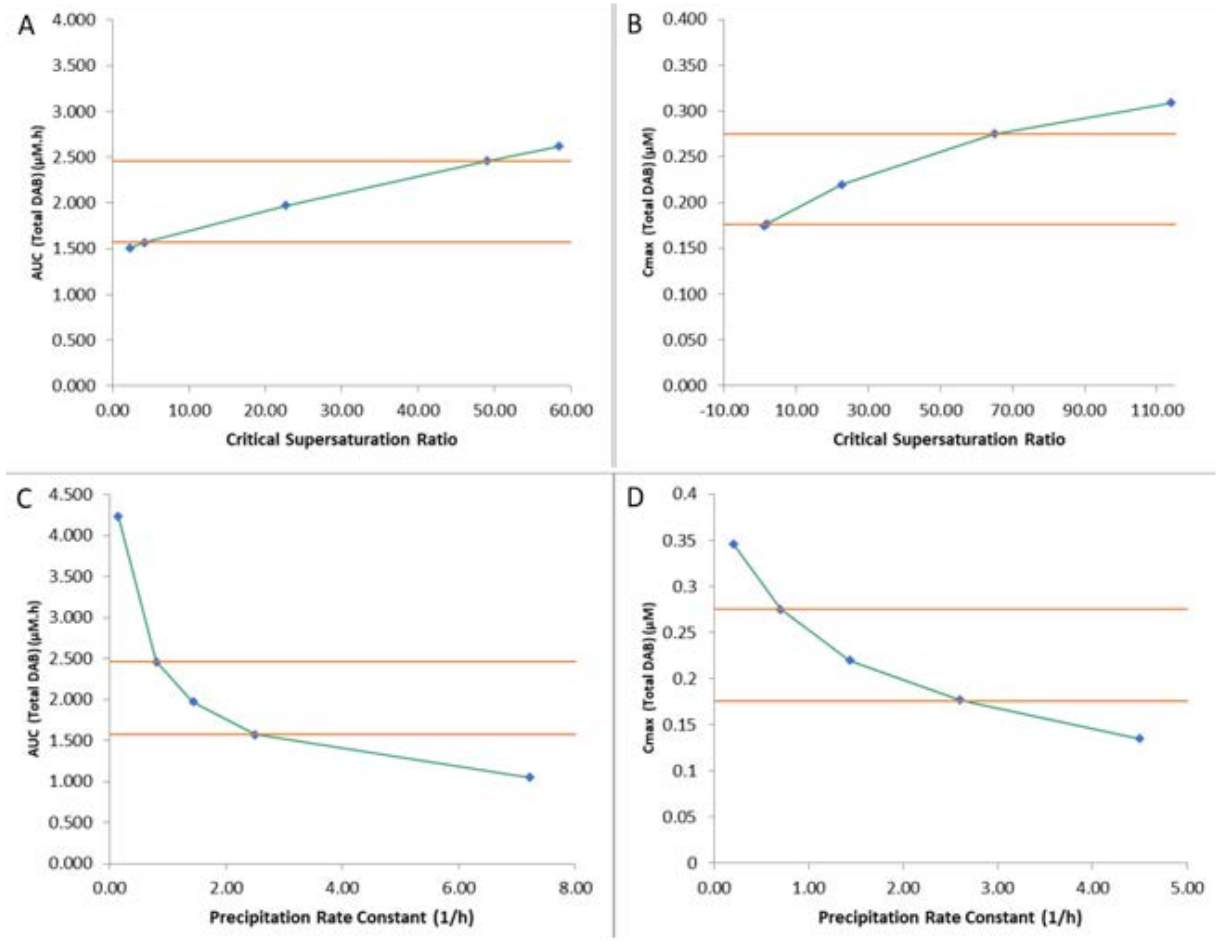
Evaluation of Formulation Properties

- Example: Dabigatran

✓ Dabigatran (Pradaxa®) is a prodrug with low oral bioavailability due to low solubility and P-gp mediated efflux in the gut

✓ Formulated as DABE coated pellets with acidified inner core to improve in vivo dissolution

✓ Generic formulations may contain different excipients compared to RLD



Modified from Presentation by Dr. Schmidt in May 4th 2020 Public Workshop

Opportunities in Regulatory Science (3)

- A model-informed approach where pharmacometric models are used to understand and optimize the operating characteristics of standard BE methods and designs
- The use of pharmacometric models was through the direct application of these models in the assessment of BE (model-integrated approaches)
  - The described model-integrated BE analysis method should have acceptable type I error and higher power to reach study goal
- A model and systems-based approach to address efficacy and safety questions related to generic substitution
  - The use of combined modeling and simulation approaches integrating drug-, formulation-, and patient-specific properties into an overarching framework provides a unique opportunity to leverage available information in a strictly quantitative fashion to assess formulation development strategy and regulatory standard

Summary

- Computational approaches represents a key component in the current landscape of regulatory science needs
- Conventional and novel PBPK/PKPD/E-R models will be critical toolsets in guiding computational pharmaceutics

Acknowledgement

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- Lei Zhang, PhD
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FDA
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ADMINISTRATION