Physiologically-based pharmacokinetic modeling and simulation used in assessing bioequivalence for generic ophthalmic products

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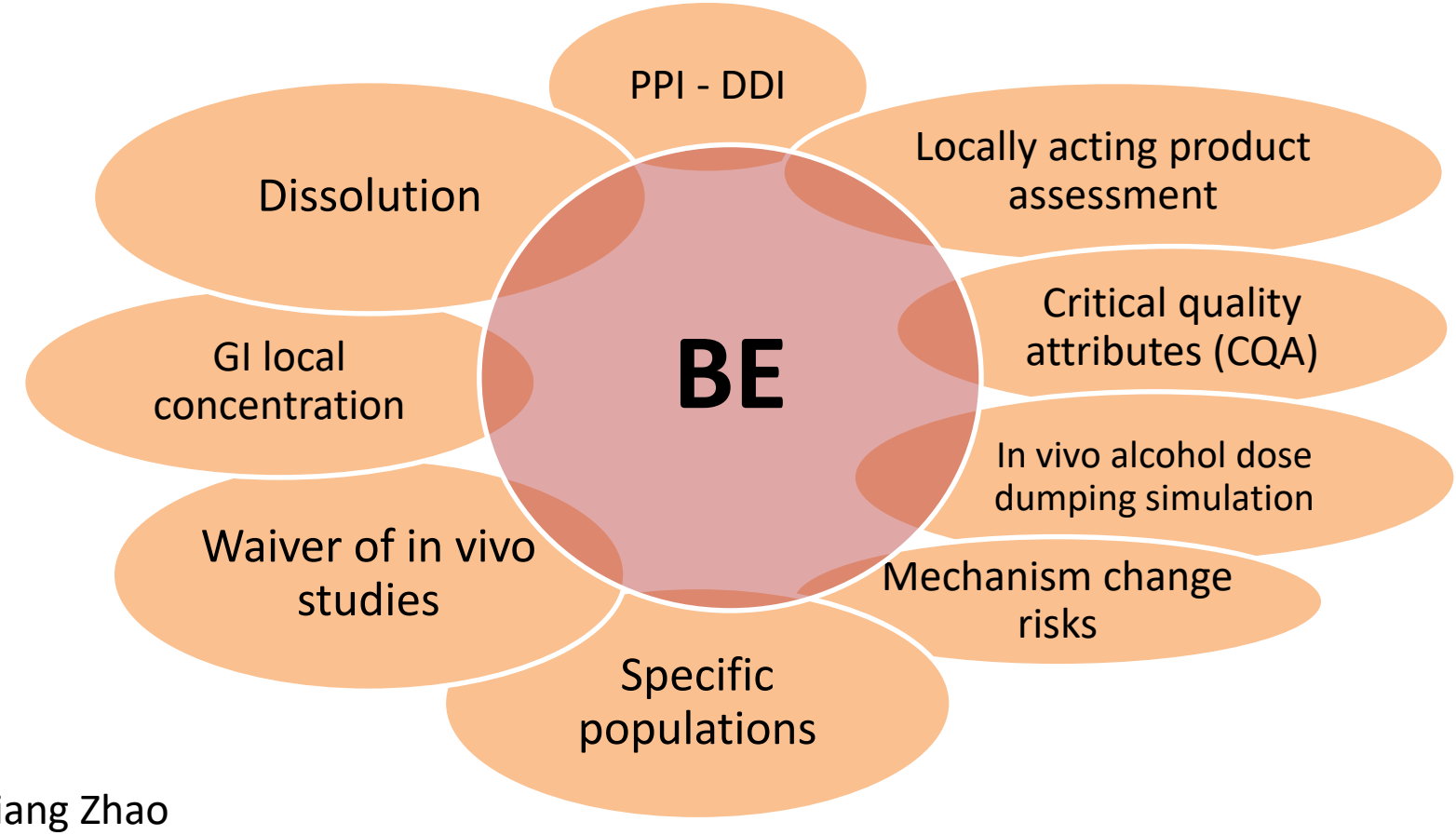
Overview

- Introduction to physiologically-based pharmacokinetic (PBPK) modeling
- PBPK Applications for Locally-Acting Products
- Ophthalmic PBPK modeling
  - External GDUFA-funded research
  - Internal case studies
- Future directions

PBPK Modeling

- Traditionally developed to describe:
  - Distribution of active moiety across different tissue once in systemic circulation
  - For orally-administered products, mechanistic absorption as the drug substance transits along the gastrointestinal tract
- The models integrate information on both “system” and “drug/drug product”:
  - Human (or other species) population or subpopulation physiology
  - Drug substance physicochemical properties
  - Drug in vivo interactions (e.g. transporters, metabolic enzymes)
  - Drug product characteristics (e.g., dissolution rate)

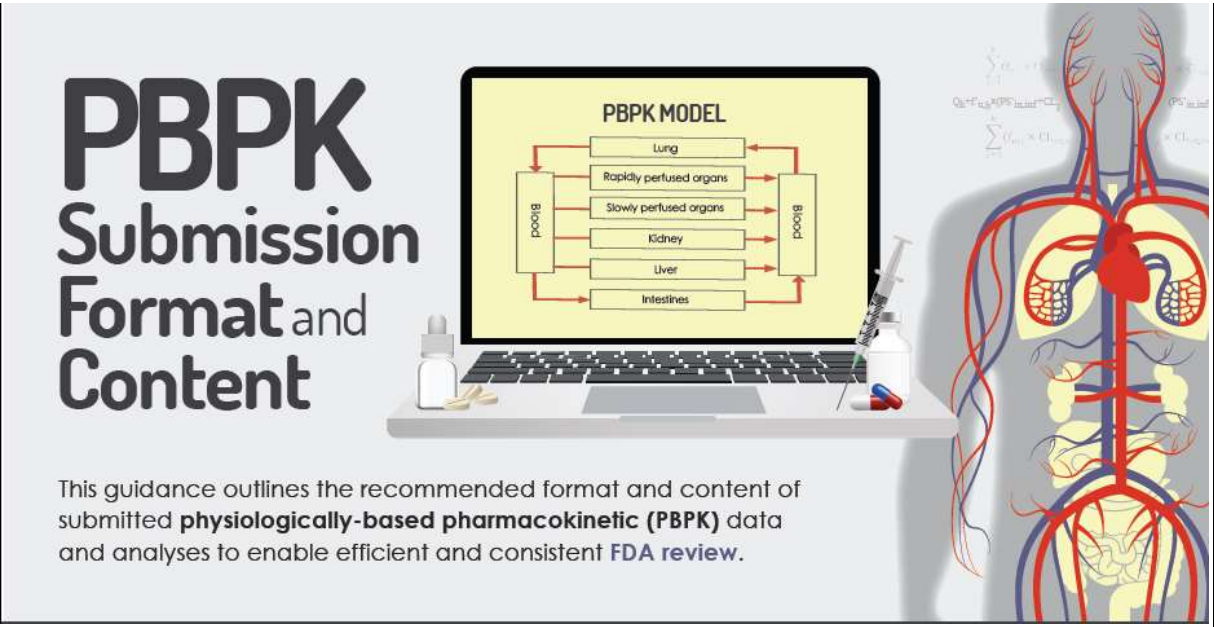
Regulatory Applications of PBPK Modeling



Source: Dr. Liang Zhao

BE: bioequivalence; PPI : proton pump inhibitor; DDI: drug-drug interaction

Guidance for Industry: PBPK Analyses – Format and Content



Executive Summary
- Objectives and rationale for the PBPK analyses
- Overview of the model
- Summary of key conclusions
- Discussion of the key scientific question the modeling is addressing

Introduction
- Synopsis and discussion of the drug's PK/ PD and exposure-response (E-R) information
- Brief PBPK related regulatory history to provide context for the PBPK analyses and cross-references to previous relevant PBPK submissions

Materials and Methods
- Overview of the modeling strategy
- Discussion of the modeling parameters and the simulation design
- Information on the modeling software used
- Electronic files related to modeling software and simulations

Results
- Discussion of model verification and any model refinement, including results of sensitivity analyses
- Presentation of the results of model application to address the key scientific question

Discussion
- Discussion of how the PBPK results adequately address the proposed scientific, regulatory, or clinical questions
- Discussion of the potential impact of limitations of the PBPK model

Appendices
- List of tables, list of figures, description of acronyms and abbreviations and references

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Finalized August 2018

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf

BE Challenges with Locally-Acting Products

- Direct quantification of active moiety concentrations at the site of action often not possible, not feasible and/or not ethical in humans
- If drug can be measured systemically, often there is no direct link between systemic and local drug exposure levels
- Pharmacodynamic (PD) and clinical endpoint (CE) BE studies are used to assess local concentrations indirectly, but these studies have their own challenges (e.g., time, operations, financial cost, lack of sensitivity)
- *In vitro* only BE methods may set a conservative design space for generic products

PBPK for Locally-Acting Products

Drug Substance
Formulation
CQAs

→

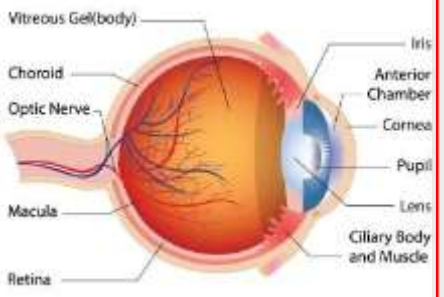
Physiological System

→

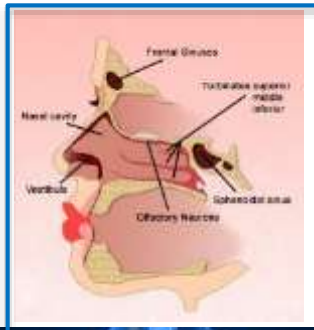
In vivo Performance

- Predict **systemic** AND **local** concentrations

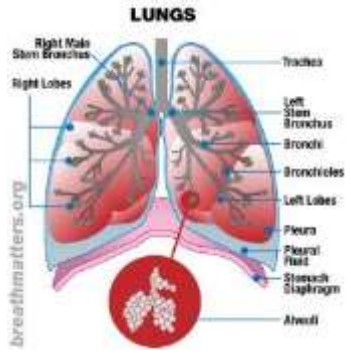
Ocular



Nasal



Pulmonary



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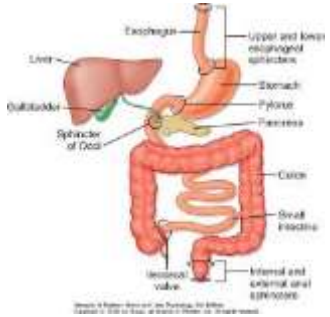
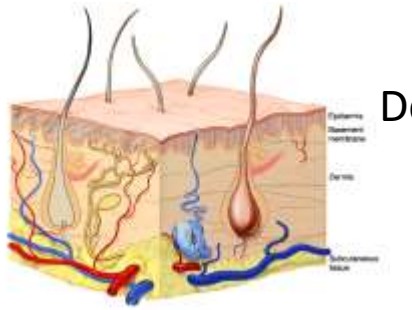
GI



Dermal



Dr. Eleftheria Tsakalozou

Adapted from Dr. Liang Zhao

Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

PBPK Applications for Locally-Acting Products

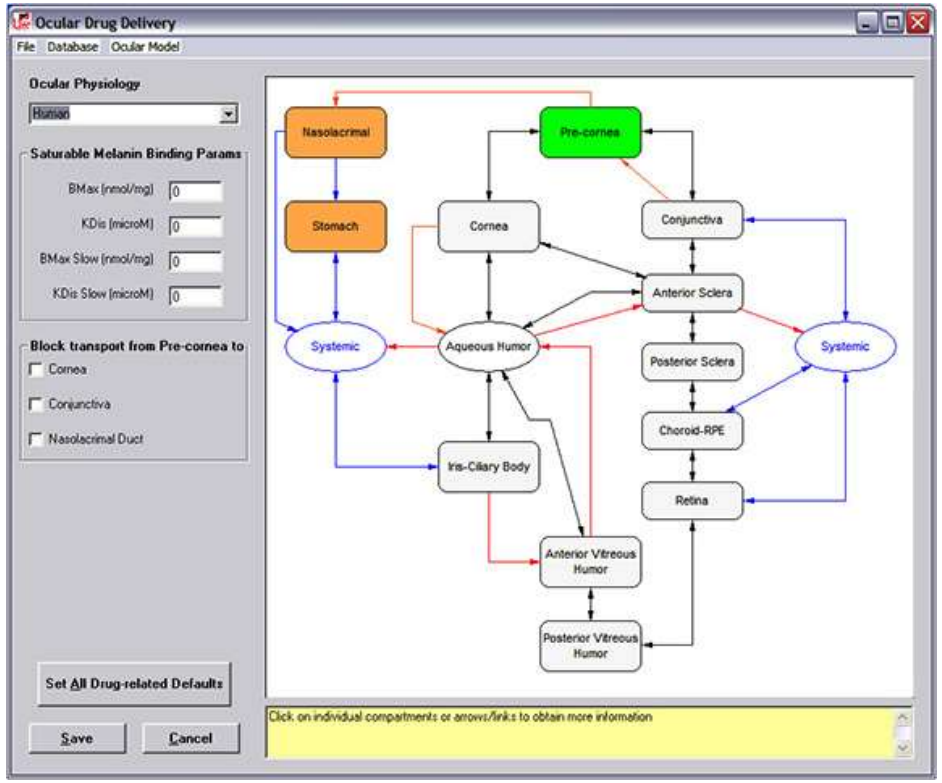
- Support product development -> gain confidence before conducting PD/CE BE study
- In lieu of conducting a PD/CE BE study,
  - Determine appropriate BE metrics on systemic PK to ensure local equivalence
    - establish a correlation between systemic PK and local PK
  - Simulate a virtual BE study on local (and systemic) PK based directly on formulation inputs
- CQAs:
  - Justify differences from the reference-listed drug (RLD)
  - Guide selection of clinically-relevant in vitro tests for BE

Ocular PBPK Modeling

- Models of eye anatomy and/or physiology that integrate:
  - Mechanisms of drug absorption from the ocular surface for topically-applied ophthalmic products
  - Mechanisms of drug distribution and clearance throughout different ocular tissues
- In 2014, based on locally-acting PBPK model limitations at the time, FDA issued RFA-FD-14-012 for developing PBPK models in humans for non-GI-absorbed products; 2 ocular PBPK grants awarded:
  - 1U01FD005211 to Simulations Plus, Inc.; PI: Michael Bolger
  - 1U01FD005219 to CFD Research Corporation; PI: Kay Sun
- On-going challenge: local PK data in humans are extremely limited; most data are pre-clinical (e.g., rabbits)

1U01FD005211: Simulations Plus, Inc.

- Title: ***PBPK Modeling and Simulation for Ocular Dosage Forms***
- Focus on Ocular Compartmental Absorption and Transit (OCAT™) model advancement for ophthalmic suspension formulation
- Work included:
  - OCAT model structure modification
  - Global parameter estimation module optimization
  - OCAT model validation on selected ophthalmic drugs (n>10)
  - OCAT model improvement for protein and melanin binding in ocular tissues
  - Derivation of new equations for objective functions and weighting
  - Cynomolgus monkey species incorporation in the GastroPlus OCAT models



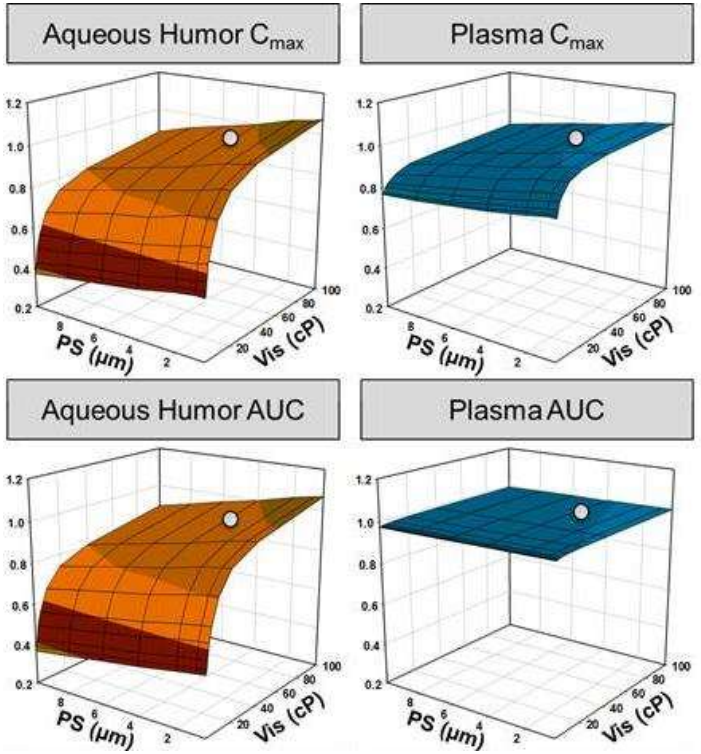
https://www.simulations-plus.com/assets/ocular-drug-delivery.jpg

1U01FD005219: CFD Research Corporation

- Title: ***An Integrated Multiscale-Multiphysics Modeling and Simulation of Ocular Drug Delivery with Whole-Body Pharmacokinetic Response***
- Goal was to develop an ocular model using a combined computational fluid dynamics (CFD) and PBPK approach in human and animal subjects
- Focus on solution and suspension dosage forms
- Work included:
  - Enhanced understanding of fluid transport between different regions of the eye
  - In vitro (ex vivo) cornea explant model validation on tracers and selected drugs
  - Aqueous humor dynamics model development with humor release (in ciliary processes) and reabsorption (in trabecular meshwork) linked to intraocular pressure (IOP) model - a foundation for the PD studies
  - Quantitative structure activity relationship (QSAR) models for drug permeability in rabbit ocular tissues

Internal Case Study: Dexamethasone suspension

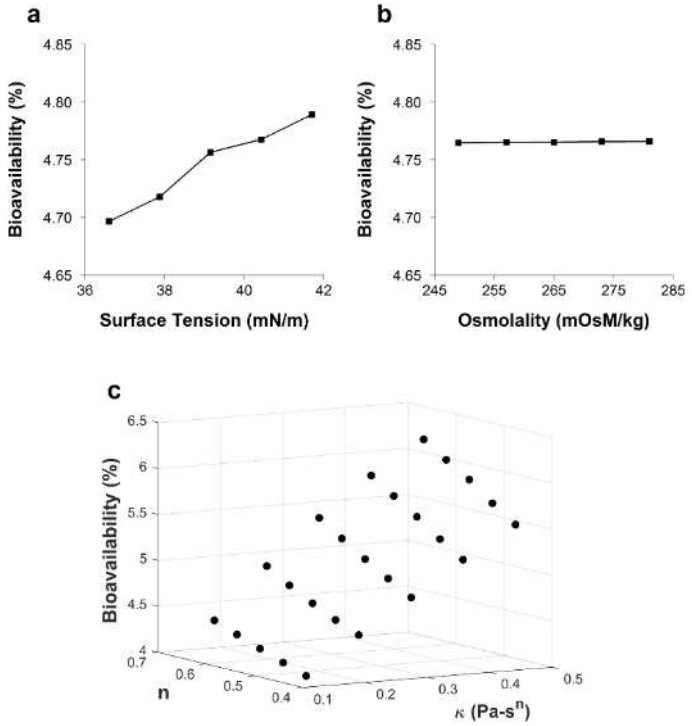
- Rabbit PBPK model developed in GastroPlus™ OCAT™ module
- Internally conducted rabbit study with dexamethasone suspension with PK sampling in multiple ocular tissues and plasma for model development
- Model verification with other published PK data:
  - Mean particle size (PS) and PS distribution on ocular absorption
  - Non-linear dose-exposure relationship
  - Formulation viscosity impact of ocular absorption
- Parameter sensitivity analysis in rabbit (figure at right) to assess impact of PS and viscosity on exposure
  - Viscosity is a critical attribute affecting BE
  - Plasma/systemic PK is not reflective of local concentrations



Adapted from Dr. Jianghong Fan and Dr. Maxime LeMerdy

Internal Case Study: Cyclosporine emulsion

- 2 internally-built models:
  - Physics/fluids-based approach to modeling tear firm breakup time (TBUT) – an endpoint affected by drug product application
  - Compartmental-based approach to predict bioavailability
- Studied impact of surface tension, osmolality, and power law viscosity on conjunctival bioavailability (figure at right) and TBUT
- Viscosity had the greatest influence on both outcomes



Adapted from Dr. Ross Walenga

Towards Verification ….

- Data availability?
  - Multiple formulations with PK/CE endpoints -> IVIVC
  - Unified model approach – test multiple products with a range of formulation characteristics and drug substance properties
- Species?
  - Rabbit modeling can inform formulation selection for eventual clinical study
  - Ability to extrapolate from rabbit to human – a challenge!
  - Human modeling can support bioequivalence and drug product specifications

Future Research Directions

- Goal: increase regulatory applicability of ocular PBPK models
- Ocular PBPK model improvements:
  - Enzyme and transporter incorporation
  - Protein content in ocular tissues
  - Tear pH dynamic
  - Impact of blinking rate
- Planned studies to aid model development work:
  - Tear film thickness and menisci measurements on rabbit ocular surface with cyclosporine emulsion
  - Tissue distribution, systemic PK, and IOP in rabbits with multiple formulations of brinzolamide suspension
  - In vitro permeability of drug substances through rabbit and human cornea and conjunctiva

Acknowledgments

FDA/OMPT/CDER

OGD/ORS/DQMM

Jianghong Fan
Maxime LeMerdy
Ross Walenga
Eleftheria Tsakalozou
Myong-Jin Kim
Liang Zhao

OGD/ORS/DTP

Darby Kozak & Team

OGD/ORS-IO

Lei K. Zhang
Robert Lionberger

OTS/OCP/DARS

Rodney Rouse & Team

OPQ/OTR/DPQR

Xiaoming Xu

Grantees

Simulations Plus, Inc.

PI: Michael Bolger, Grant #: 1U01FD005211

CFD Research Corporation

PI: Kay Sun, Grant #: 1U01FD005219

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