Regulatory challenges and opportunities for model-based approaches for patient pharmacokinetic (PK) studies with sparse sampling design

ACoP10 workshops:

October 22, 2019, Orlando, FL

Session 4c: FDA Science Forum: Model-based Approaches for Patient Pharmacokinetic Studies with Sparse Sampling Design

Liang Zhao, PhD

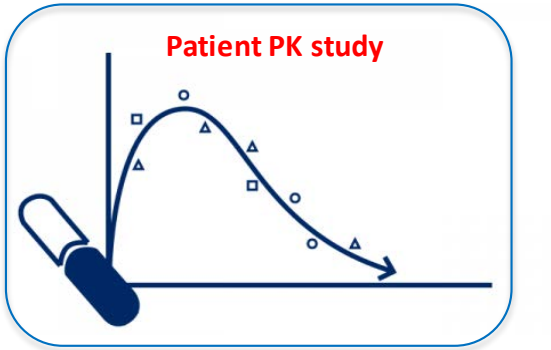
Division of Quantitative Methods & Modeling,

Office of Research and Standards, Office of Generic Drugs, CDER, FDA

Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Application of Patient PK studies in NDA and ANDA Drug Development Process

Patient PK studies assess bioavailability (BA) and bioequivalence (BE) in New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA)



NDA

- *Establish **safety and efficacy** of new drug by phase-I, phase-II and Phase-III clinical trials.*
  - *Phase-I : Safety, tolerability, PK, biomarkers, proof of principle*
  - *Phase-II: Efficacy, guidance of dose and dosing regimen*
  - *Phase-III : confirmation of efficacious dose, benefit/risk ratio, sub-group selection*

ANDA

- *Establish **bioequivalence (BE)** of generic test drug product to that of reference listed drug (RLD) by pharmacokinetic measure of –*
  - *Rate of absorption (peak exposure)*
  - *Extend of absorption (Total exposure)*
  - *Partial exposure*

Patient PK Studies and Sampling Design

Ideal PK study

Rich blood sampling

To capture Cmax, Kel

In some situations, it **may not** be feasible/practical to obtain rich samples

- **Special population**
  - Cancer patients
  - Pediatric patients
- **Biological matrix other than blood**
  - Middle ear fluid
  - Bronchoalveolar lavage
  - Aqueous humor
- **Other cases**
  - Late phase clinical study
  - Animal toxicity study
  - Cost reduction: Industry perspective

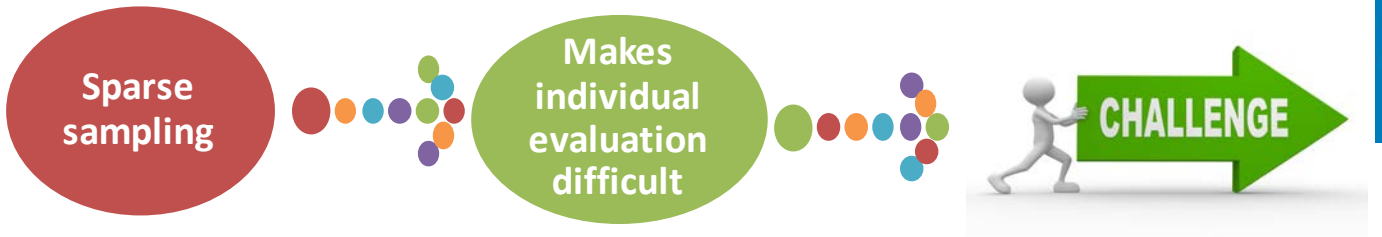
General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Guidance for Industry

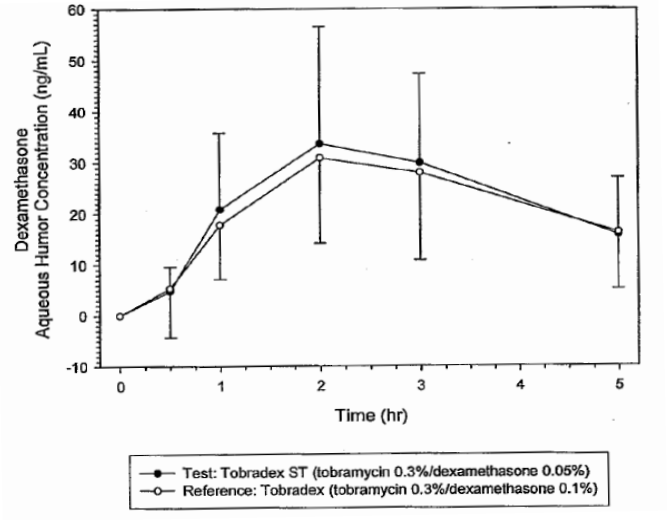
DRAFT GUIDANCE

"Sparse sampling of blood or plasma is considered more acceptable for pediatric studies, because the total volume of blood sampled can be minimized."

Challenges in Sparse Sampling:



- Sparse sample data are highly variable
- Required larger sample size (Total patients enrolled: 987)



NCA calculations for BE evaluations

- Exclusion of subject with missing data (crossover study)
- Sensitivity to missing data
- Interpolation problems from the last observation to ∞
- Equal weighting of observations

Exposure-Response analysis

- When individual data are sparse or uninformative, and parameter shrinkage is high, Empirical Bayes Estimates (EBEs) are considered less reliable
- The reliability of individual PK patient exposure metrics is dependent on –
  - The nature of the collected PK data
  - The validity of model assumptions (e.g., time-invariant pharmacokinetics, model structure, dose-proportional pharmacokinetics)

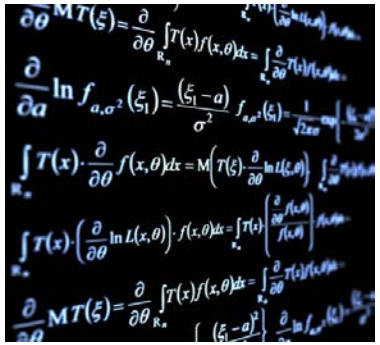
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/050818s000clinpharmr.pdf
Population Pharmacokinetics Guidance for Industry. https://www.fda.gov/media/128793/download

Model-integrated Drug Development Approach:

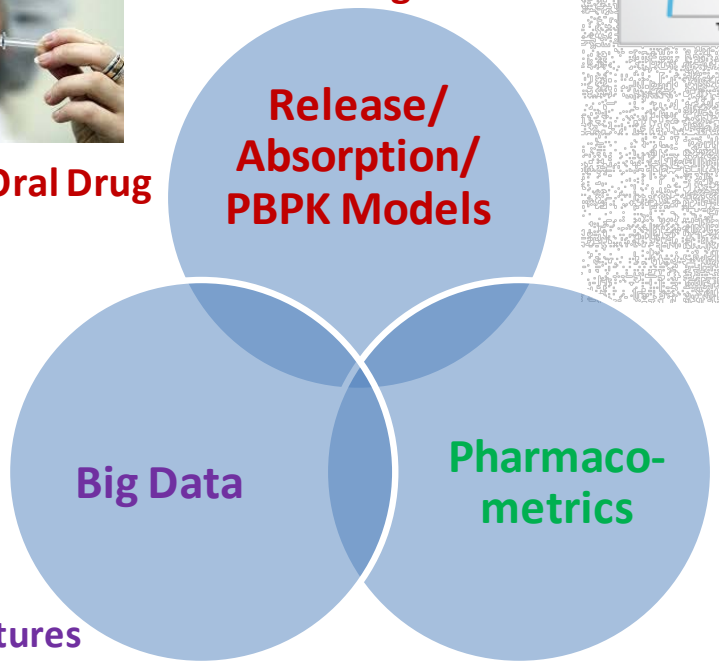
Core Tool Sets

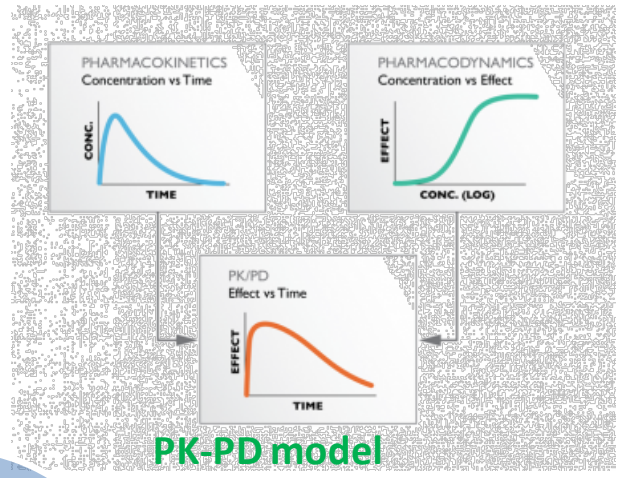
Non-Oral Drug

Oral Drug

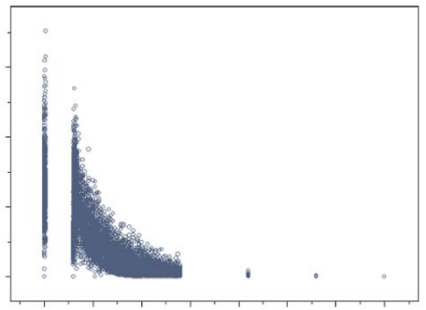


Machine learning toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models





PK-PD model



Population based model

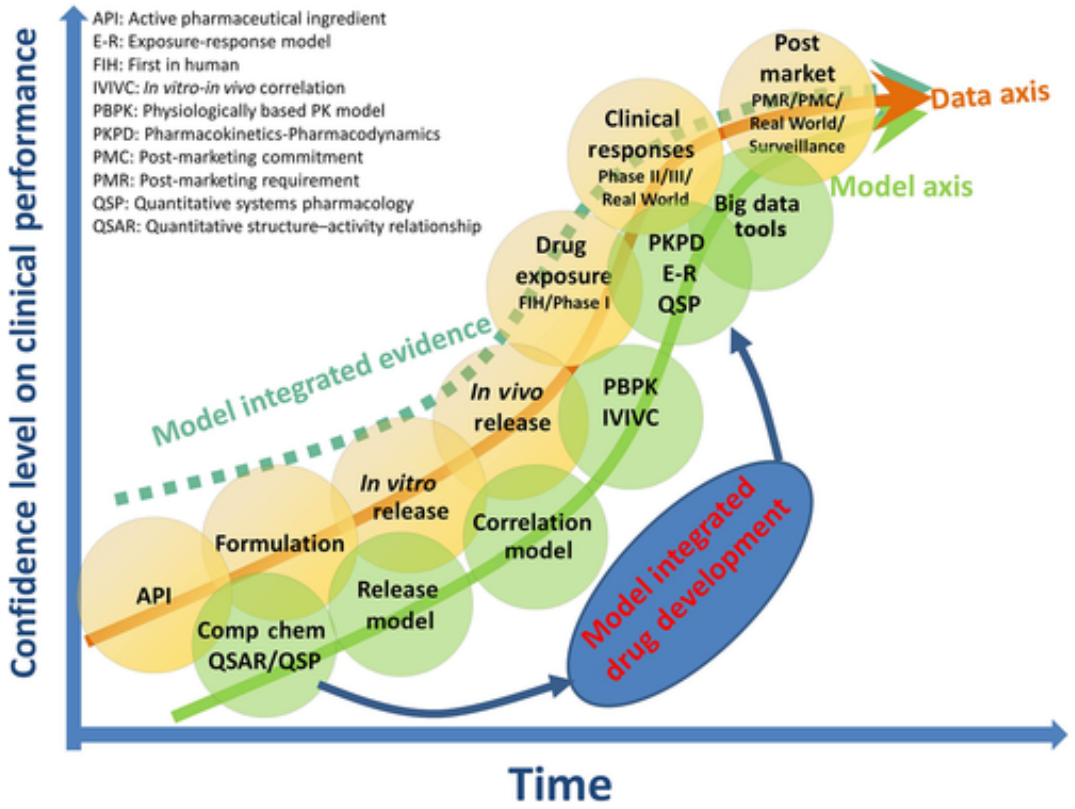
Application

- Generic drug development
- Modernizes review process
- Policy development
- Regulatory decisions

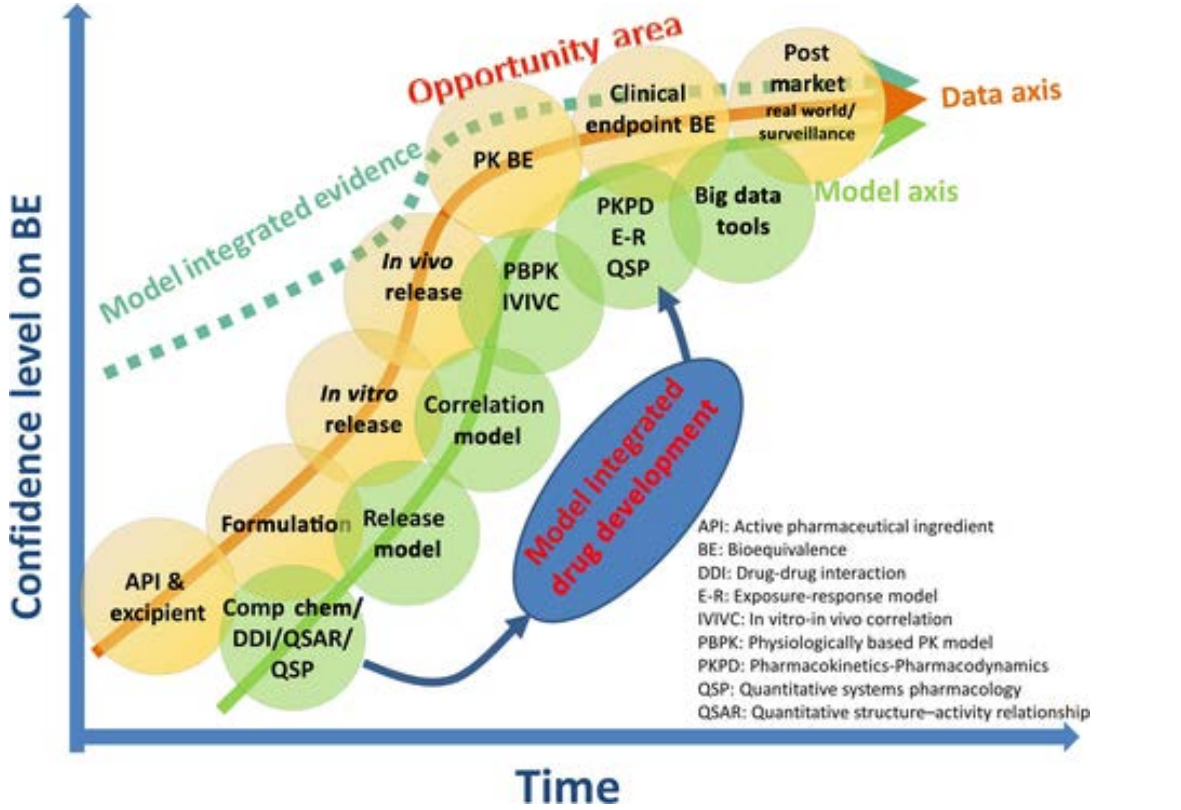
Application of Model-base Approaches in Drug Development

Application of quantitative methods and modeling is widespread in both new and generic drug development process

Model-integrated drug development for **new drugs**



Model-integrated drug development for **generic drugs**



Zhao et al. 2019. Generating Model Integrated Evidence for Generic Drug Development and Assessment. Clin Pharmacol Ther. 2019 Feb;105(2):338-349

Opportunities in Model Based Approach:

Example with Population PK modeling

Population (NLME) model based BE approaches

- Can naturally handle inherent problems with NCA calculations: unequal weighting of observations, missing data, data below the limit of quantification and interpolation from the last observation to ∞
- Simulations of expected PK profiles give an understanding of what features may be important to compare in a BE study
- PKPD models give an indication of the PK factors driving drug effect (clinical endpoint BE study)

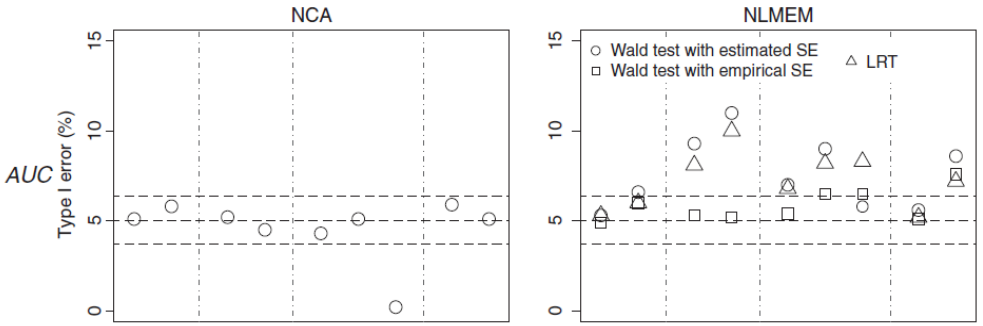
Bio-equivalence → Exposure-Response

Population PK modeling in Exposure-Response analysis

- Population PK models can predict individual patient exposures at specific time points regardless of the spread in sampling times (e.g., trough concentrations can be predicted for all subjects).
- When PK data are missing in a small number of subjects, population PK models can predict the most likely concentration-time profile based on the subject's individual covariates (e.g., body weight, genetic polymorphism, sex).

Overcoming Challenges in Model Based Approach

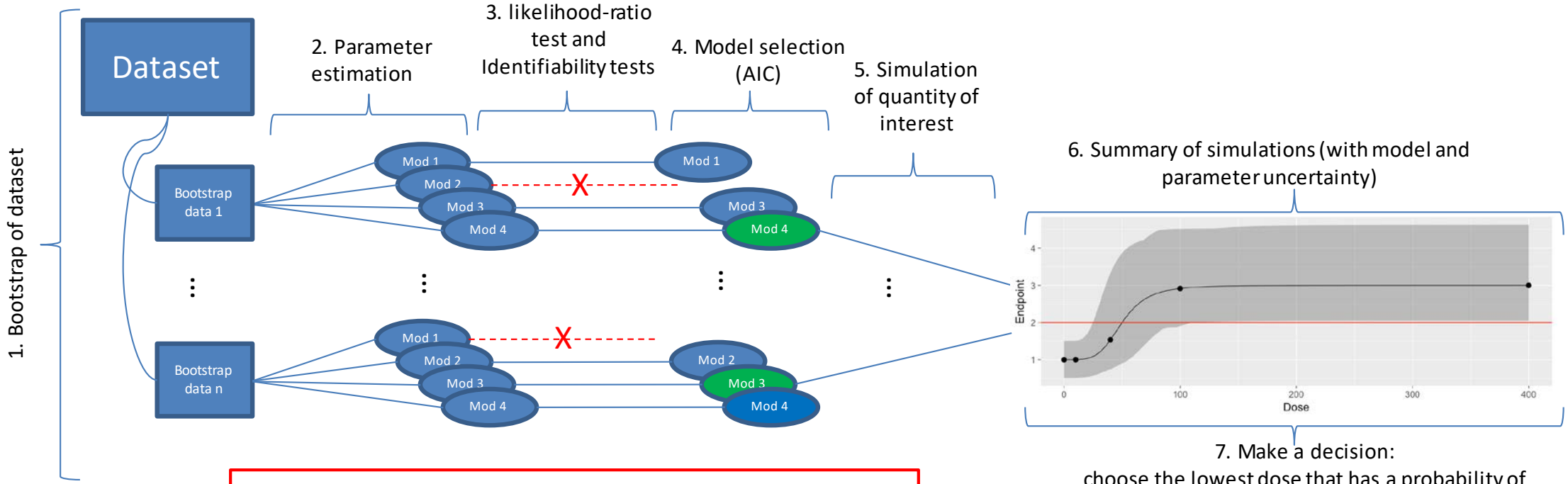
Published studies have shown that model-based approaches **may inflate type-I error**.



A. DUBOIS *ET AL 2011. Stat Med. 30(21):2582*

FDA Grant with University of Uppsala

Evaluation and development of model based bioequivalence analysis strategies



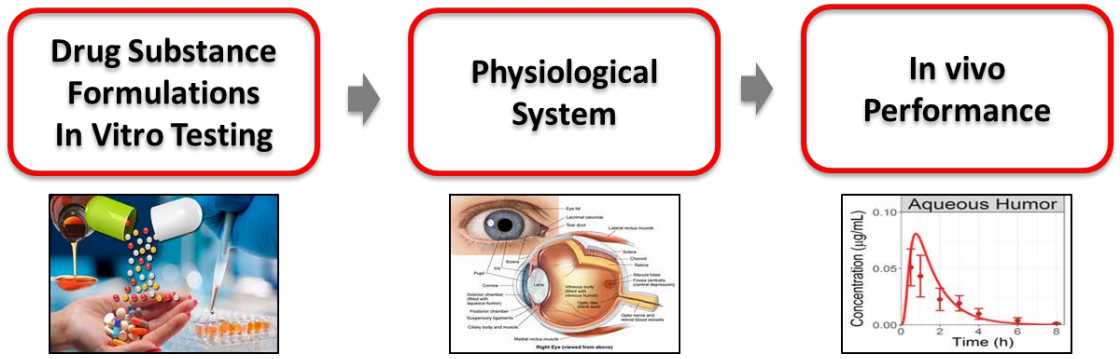
- *Incorporate model and parameter uncertainty*
- *Maintain type-I error*
- *Reduce model selection bias*

Courtesy to Andrew C. Hooker

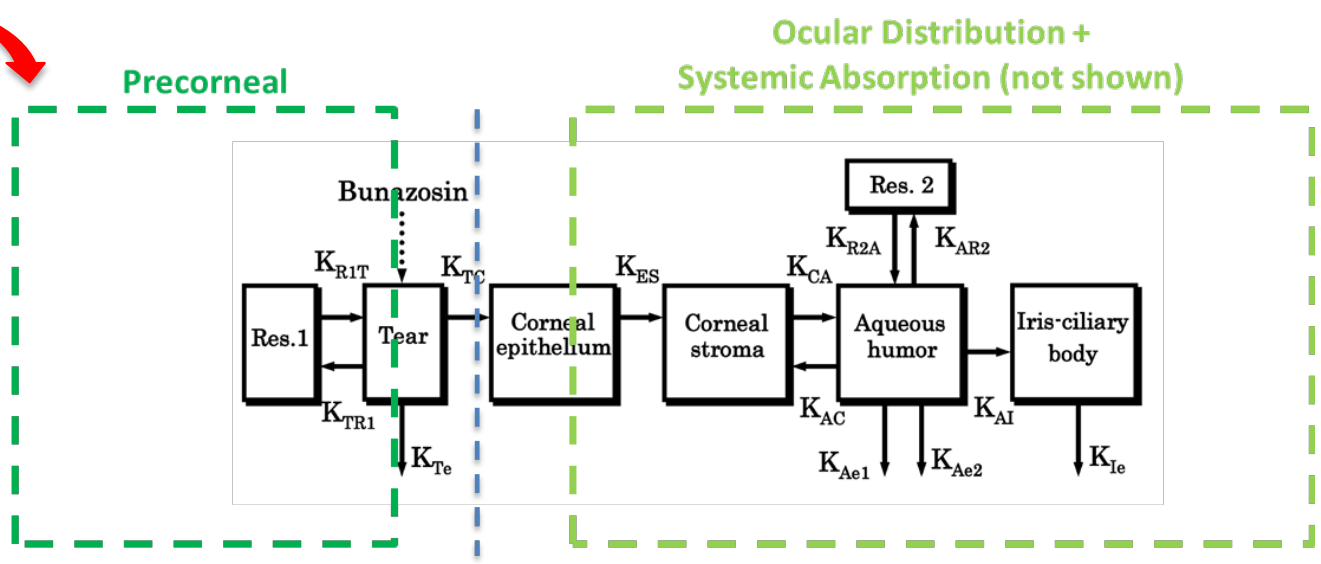
Model-Integrated Approaches:

Focus on Ophthalmic products

Ocular PBPK – Focus for BE Assessment of Bunazosin



- Modeling (i.e., mechanistic description) of the **formulation**
- Includes what happens to the product after topical application and interaction with tear film and eye blinking
- For **BE assessment**, here is where the difference between two products are inputted into the model



- Critical for accurate prediction of local concentrations -> protein (including enzymes) binding and effect modeling
- Critical for verification – confidence in local and systemic concentration predictions

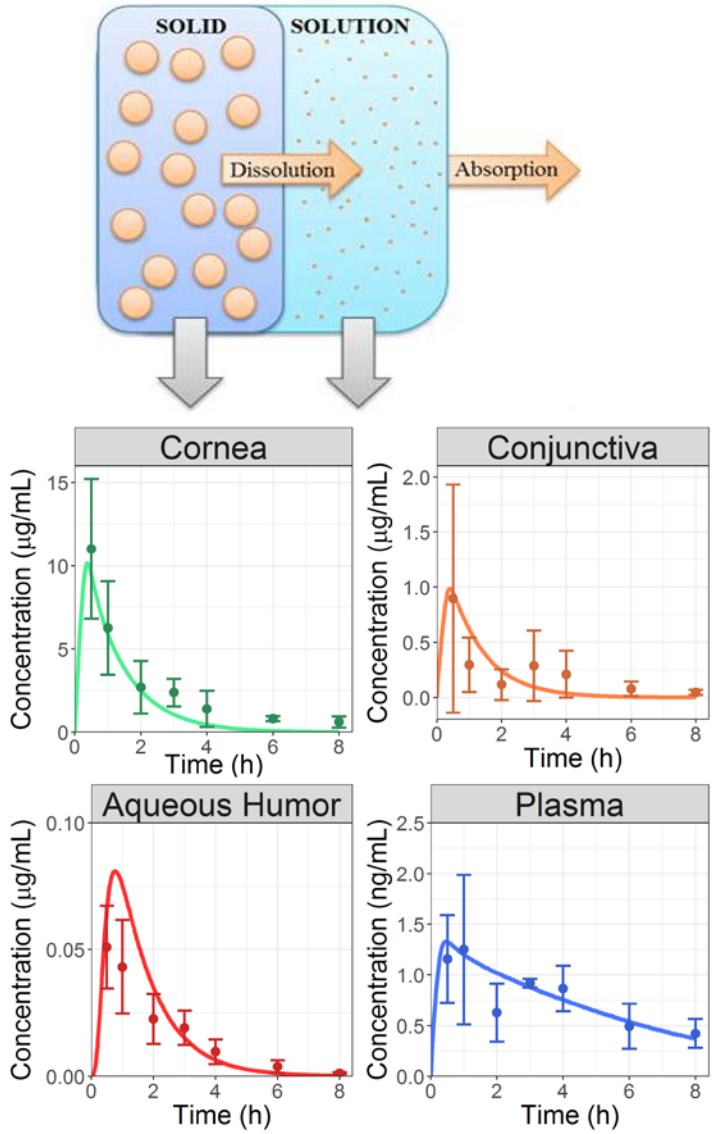
Courtesy to Andrew Babiskin

Ocular Compartmental Absorption and Transit (OCAT) Model to Identify Critical Quality Attribute of Dexamethasone Ophthalmic Suspension

- After instillation, several routes of API transport:
  - Dissolved API diffusing from tear film through cornea or conjunctiva
  - Solid particles and dissolved API cleared from eye surface through nasolacrimal drainage -> systemic circulation

- OCAT Model Development – internally conducted rabbit study with PK sampling from multiple ocular tissues and plasma

- Model Verification with multiple datasets showing:
  - Particle size impact on ocular absorption
  - Viscosity impact on ocular absorption
  - Non-linear dose-exposure relationship



Chockalingam, Ashok, et al. "Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model." Journal of pharmacological and toxicological methods 96 (2019): 9-14.
LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension." *AAPS J. 2019 May 20;21(4):65*

Courtesy to Andrew Babiskin

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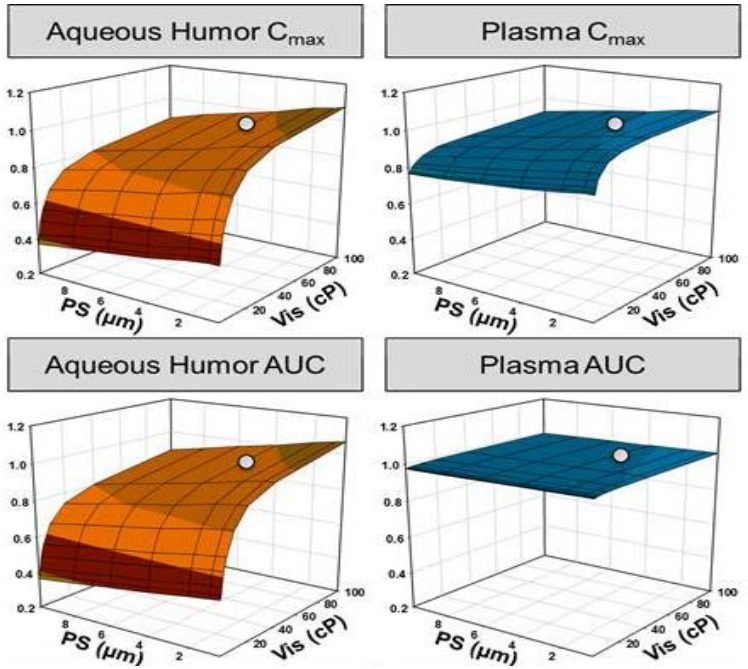
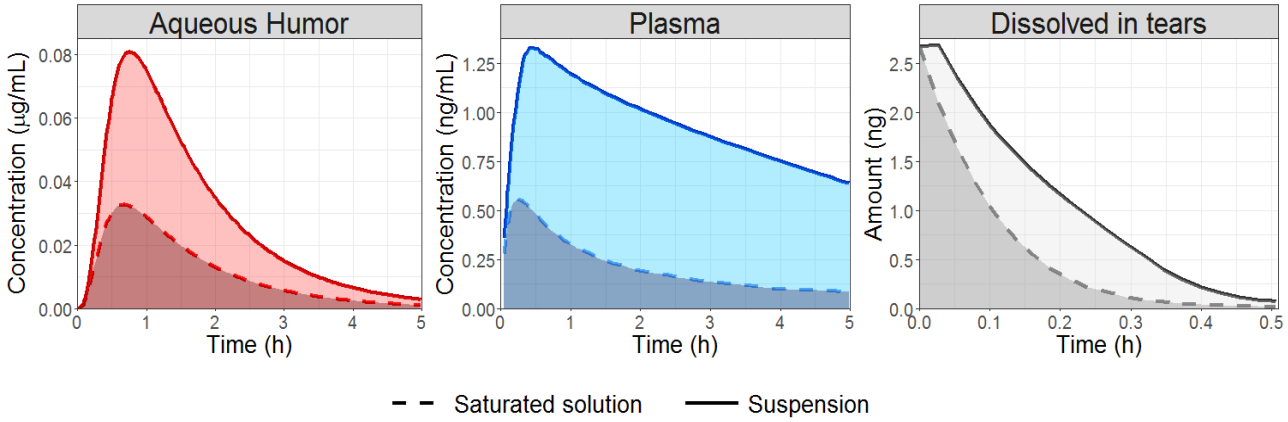


Parameter sensitivity analysis in rabbit on particle size (PS) and viscosity (Vis)

- Viscosity is a **critical attribute affecting BE**
- Plasma/systemic PK is not reflective of local concentrations



Saturated solution vs. suspension simulations

- Solid particles in formulation leads to higher aqueous humor concentrations, BUT …
- Also higher systemic exposure
- A tool for product development that can weigh benefits and risks

LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension." *AAPS J. 2019 May 20;21(4):65*

LeMerdy, Maxime, et al. "Physiologically-based Pharmacokinetic Model to Support Ophthalmic Suspensions Development." ASCPT AM 2019 poster.

Courtesy to Andrew Babiskin

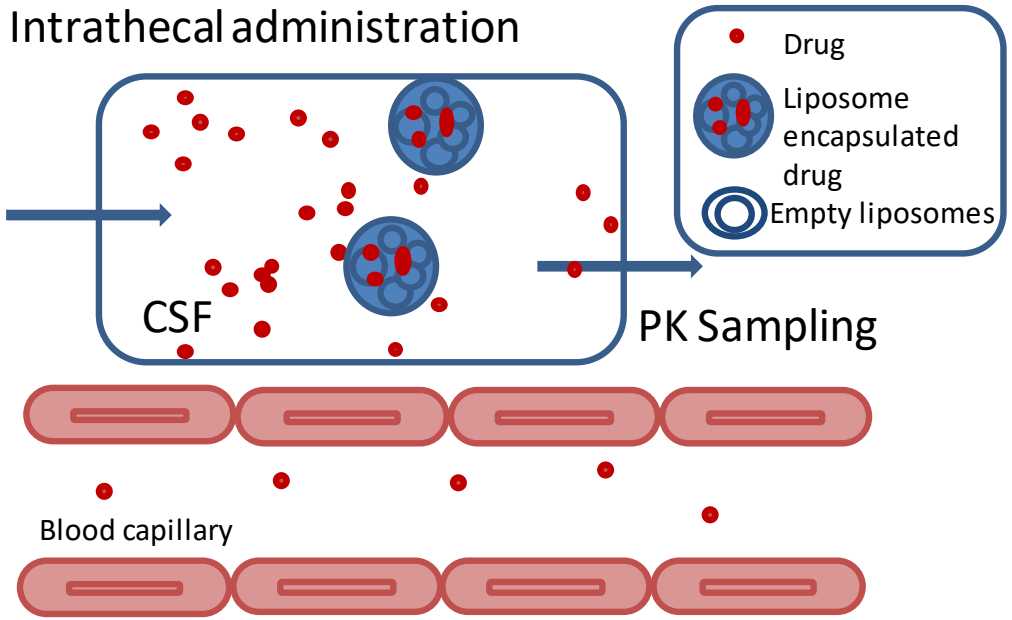
Model-Integrated Approaches:

Focus on Liposomal Injection (Cytarabine®)

In Vivo Process and Bioequivalence
Study Challenges: Liposomal Injection (Cytarabine®)

Indication and Regimen:
50 mg, administered intrathecally (intraventricular or lumbar puncture) every 14 days for treatment of lymphomatous meningitis

There is sustained release of cytarabine from the liposomes and the terminal half-life of free cytarabine was prolonged in cerebrospinal fluid (CSF) more than 40-fold when compared with conventional cytarabine injection (141 vs. 3.4 h)

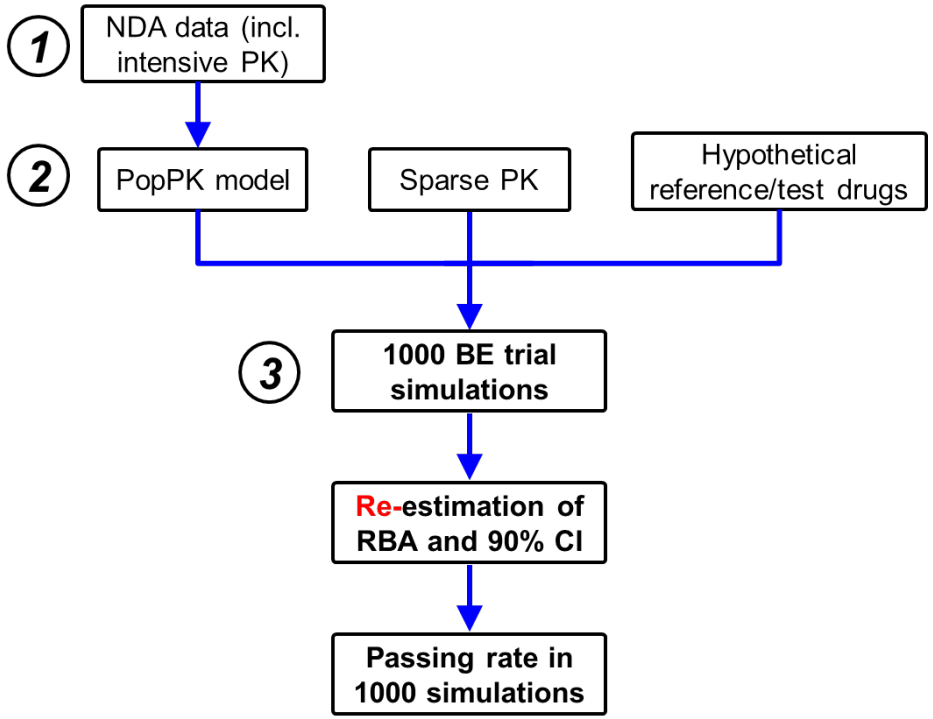


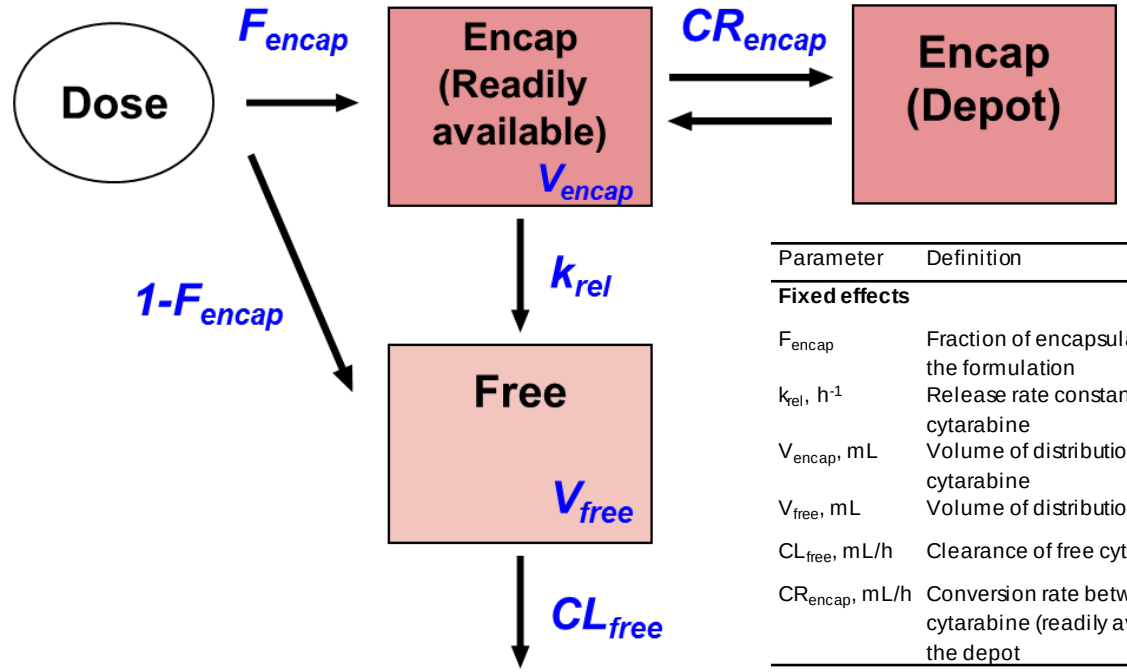
Challenges

- Difficult to enroll patients
- Intensive PK sampling is not feasible
- High inter- and intra-individual variability

Courtesy to Wenlei Jiang

Solutions: Model-Informed Bioequivalence Method





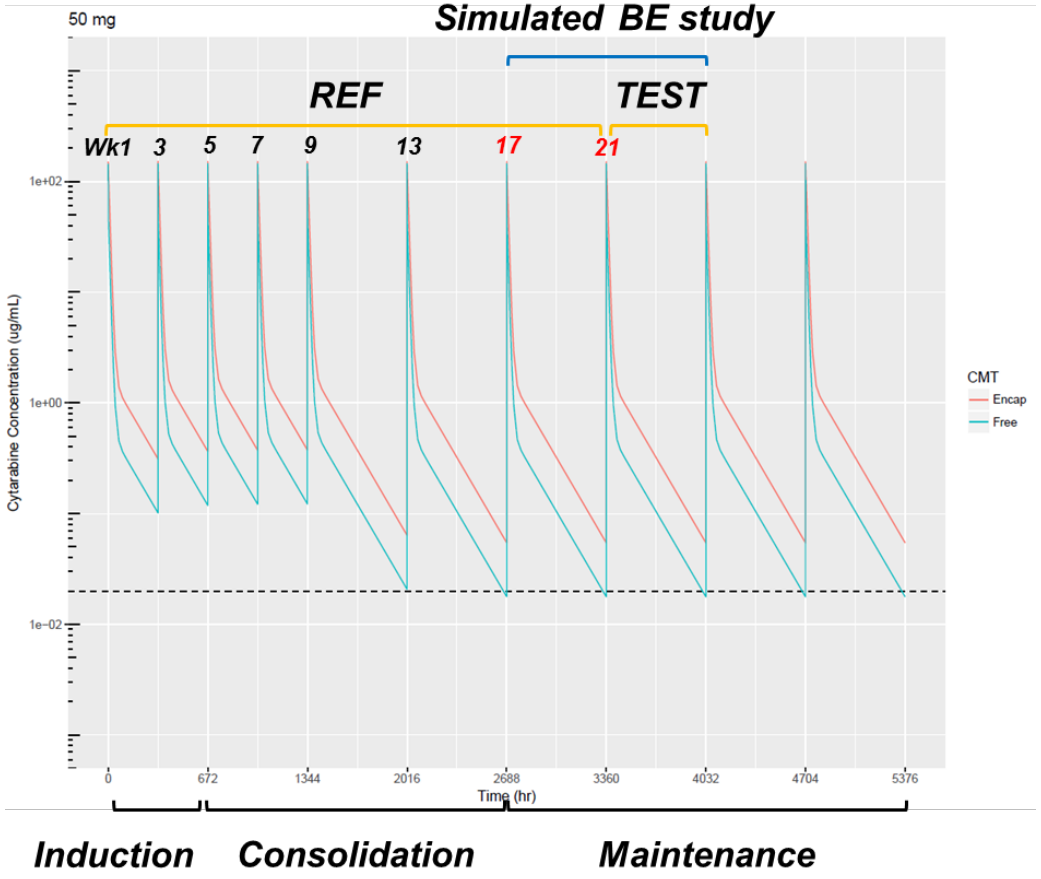
Parameter	Definition
Fixed effects	
F_{encap}	Fraction of encapsulated cytarabine in the formulation
k_{rel}, h^{-1}	Release rate constant from encapsulated cytarabine
V_{encap}, mL	Volume of distribution of encapsulated cytarabine
V_{free}, mL	Volume of distribution of free cytarabine
CL_{free}, mL/h	Clearance of free cytarabine
CR_{encap}, mL/h	Conversion rate between encapsulated cytarabine (readily available form) and the depot

Population PK Modeling of encapsulated and free cytarabine

Adapted from

Ken Ogasawara, Alejandro Pérez-Pitarch, Jia Chen, Myong-Jin Kim, Liang Zhao, Lanyan Fang. Bioequivalence Evaluation for a Complex Drug Product, Cytarabine Liposome Injection, Using Modeling and Simulation Approaches. American Conference of Pharmacometrics 2018, San Diego, CA

Population PK-Informed BE Limit



Limit	Minimal number of subjects
80.00 – 125.00%	68
70.00 – 142.86%	28
66.67 – 150.00%	24
60.00 – 166.67%	20
50.00 – 200.00%	8

RBA	20 patients with limit of 60 – 167%	8 patients with limit of 50 – 200%	
100% (= BE)	89.6	82.0	= estimate of power
167% (= BIE)	1.7	26.3	= estimate of type-I error

The model-based BE evaluation method with minimal 20 subjects and a widened BE limit of 60.00–166.67% provided reasonable statistical power and type-I error rate.

Adapted from

Ken Ogasawara, Alejandro Pérez-Pitarch, Jia Chen, Myong-Jin Kim, Liang Zhao, Lanyan Fang. Bioequivalence Evaluation for a Complex Drug Product, Cytarabine Liposome Injection, Using Modeling and Simulation Approaches. American Conference of Pharmacometrics 2018, San Diego, CA

Industry-Agency-Patient Ecology

Patients

Seek for affordable high quality generics

- No approved generic for cyclosporine ophthalmic solution (CEQUA®) and emulsion (RESTASIS®)
- Average supply costing patients ~$500 a month[1]

1. https://www.goodrx.com

Agency

Seeks confidence in the approval pathway

Model-integrated drug development

Industry

Seeks for clear, low risk-cost, ANDA submission path

- There are many challenges in generic drug development process
- Model-integrated drug development approach may help in generic drug development and review processes

Drug Approval

Win-Win Partnership

Excerpt of QMM-related grants/contracts under the GDUFA I regulatory science program

Variable	Grants/contracts	Institute	Start	End
New BE metrics	Pharmacometric modeling and simulation for evaluation of BE for leuprolide acetate injection	University of Utah	9/2015	Ongoing
	PK study of opioid drug product after insufflation of milled drug products	Vince & Associates Clinical Research	9/2015	9/2017
	PK–PD studies of methylphenidate extended-release products in pediatric attention-deficit/hyperactivity disorder	Massachusetts General Hospital	9/2014	Ongoing
	Pharmacometric modeling of immunosuppressant for evaluation of BE criteria	University of Utah	9/2014	2019
Physiologically based models for systemic and locally actin products	Design, development, implementation, and validation of a mechanistic PBPK framework for the prediction of the *in vivo* behavior of supersaturating drug products	Simcyp, Ltd.	9/2016	8/2018
	Development and validation of dermal PBPK modeling platform toward virtual BE assessment considering population variability	Simcyp, Ltd.	9/2014	8/2018
	Physiologically based biopharmaceutics and PK of drug products for dermal absorption in humans	University of South Australia	9/2014	8/2018
	Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling	Colorado State University	9/2016	8/2018
Physiologically based models for systemic and locally acting products	A cluster-based assessment of drug delivery in asthmatic small airways	University of Iowa	9/2016	9/2018
	Novel method to evaluate BE of nanomedicines	Nanotechnology characterization laboratory	5/2016	4/2018
	Investigate the sensitivity of PK in detecting differences in physicochemical properties of the active ingredient in suspension nasal products for local action	University of Florida	9/2013	11/2017
	An integrated multiscale–Multiphysics modeling and simulation of ocular drug delivery with whole-body PK response	CFD Corporation	9/2014	8/2017
	PBPK modeling and simulation for ocular dosage forms	Simulations Plus	9/2015	8/2017
Model-based BE assessment	Evaluation and development of model-based BE analysis strategies	Uppsala University	6/2017	6/2019
	Evaluation of model-based BE statistical approaches for sparse design PK studies	University of Paris	9/2016	9/2018
	Data-fusion based platform development of population PK–PD modeling and statistical analysis for BE assessment of long-acting injectable products	University of Massachusetts	9/2015	8/2018
	PK–PD studies of cardiovascular drugs	University of Florida	9/2014	8/2018
	Computational drug delivery: leveraging predictive models to develop bioequivalent generic long-acting injections	Qrono, Inc.	9/2015	9/2018
	IPD to advance oral product BE regulation	University of Michigan	9/2015	9/2018
	Correlation of mesalamine PK with local availability	University of Michigan	9/2013	9/2015

Take Home Messages

- Patient PK studies with sparse sampling are challenging in assessing relative BA and BE
- Innovative model-integrated drug development approaches can overcome challenges associated with sparse PK sampling
- Agency is open for alternative approaches to demonstrate BE
  - Identify CQAs for drug exposure and performance
  - Model-informed BE metrics and limit
  - Model-integrated BE assessment
- GDUFA regulatory science program is supporting technical enhancements in this area

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OGD/ORS/DTP

Darby Kozak & Team

OGD/ORS-IO

Wenlei Jiang
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Robert Lionberger

OB/DB-1

Li Yang

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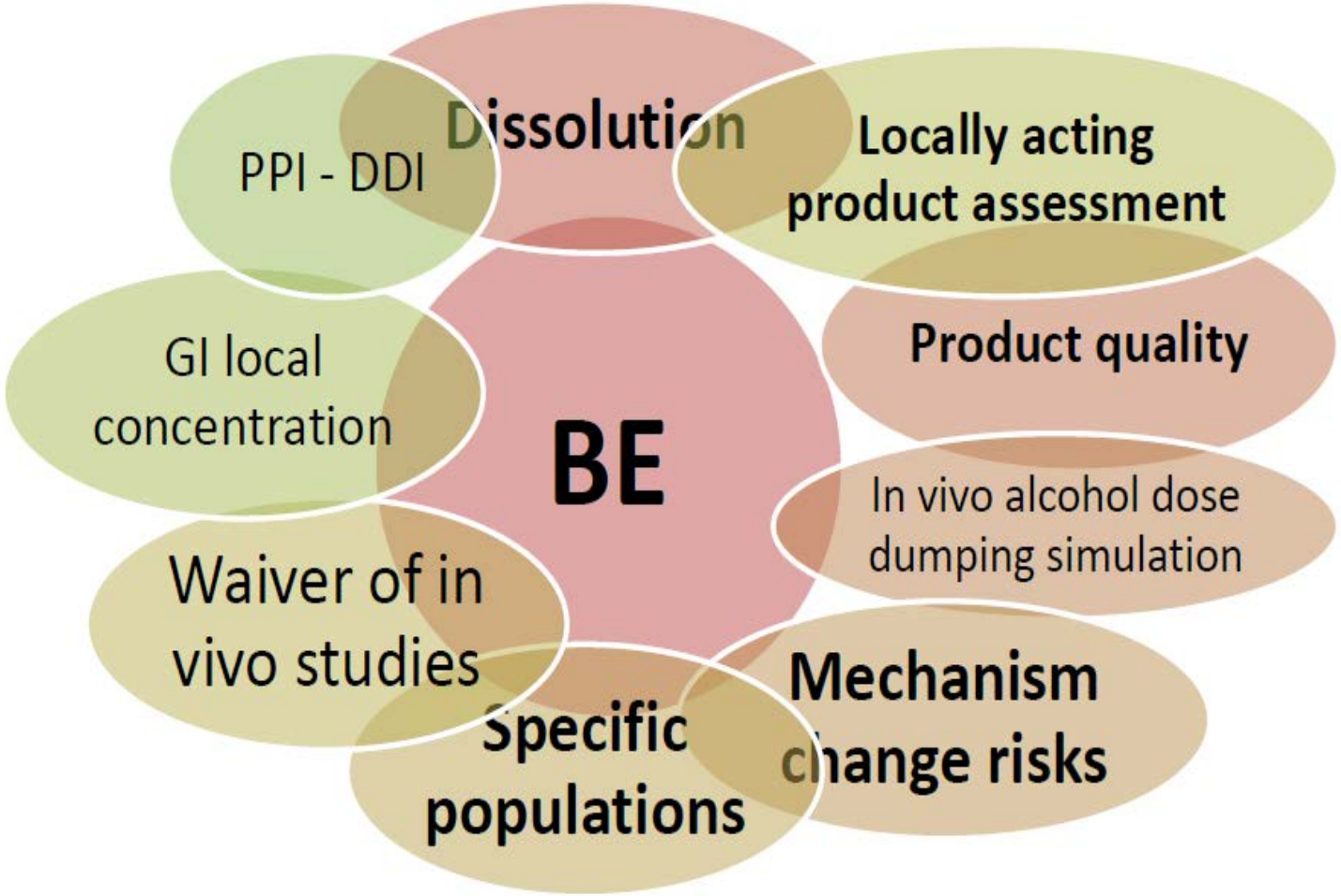
Simulations Plus, Inc., Contract #: HHSF223201810255P
CFD Research Corporation, Grant #: 1U01FD005249
CFD Research Corporation, Contract #: HHSF223201810151C

www.fda.gov/GDUFARegScience

Backups

Emerging Tool: PBPK Model Applications for Generic Products



- Agency is open to alternative BE approach with proper justifications
- PBPK modeling and simulation can address certain questions in generic drug development process