# Physiologically-based pharmacokinetic modeling and simulation approaches: Best practices for regulatory applications related to locally-acting generic drugs

**Eleftheria Tsakalozou, Ph.D.**
Division of Quantitative Methods and Modeling
Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

# Overview

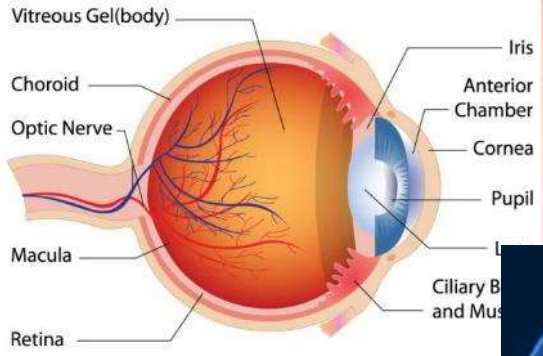
- Bioequivalence (BE) of locally-acting drug products
- Physiologically-based pharmacokinetic (PBPK) modeling

  Best practices on:

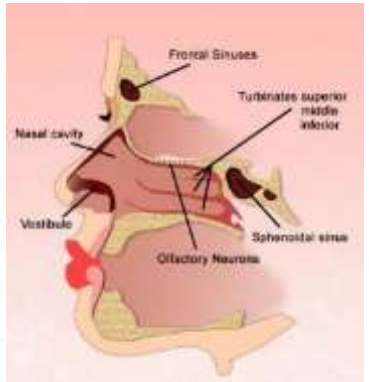
  - Model development
  - Model performance assessment
  - Virtual bioequivalence (VBE) studies
  - Reporting and documentation
- Case example: approved Abbreviated New Drug Application (ANDA) for a complex topical drug product

# Locally-acting drug products

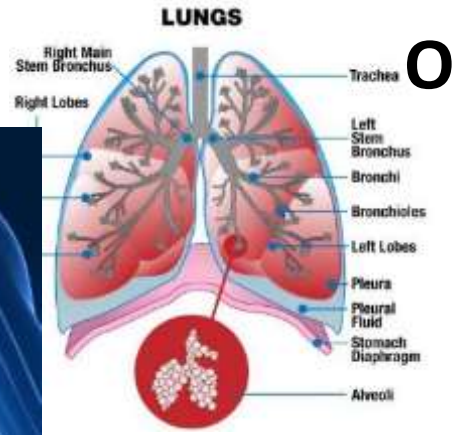
**Ophthalmic**



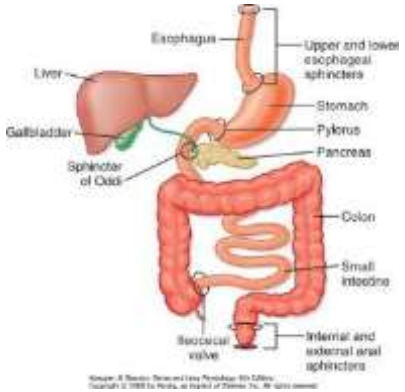

**Nasal**



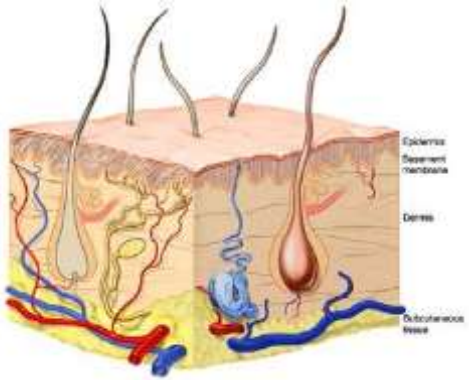

**Orally inhaled**




**Gut**




**Topical**
**Transdermal**





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.

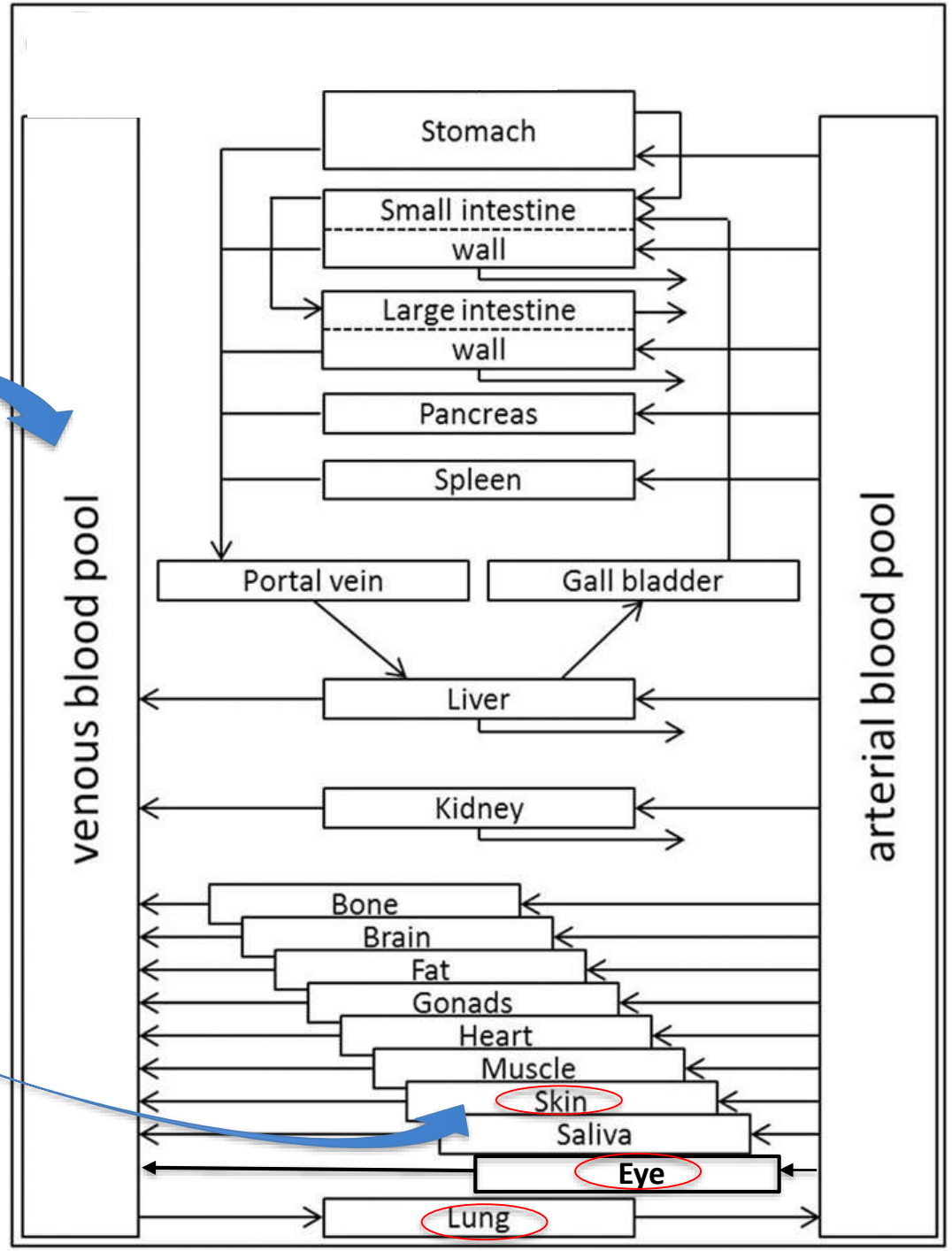
# PBPK modeling for locally-acting drug products

What we can measure:

- Formulation in vitro performance
  - Systemic drug exposure

What we would like to know:

- Local drug concentrations




Modified from Front Pharmacol. 2012 May 21;3:92

# Applications of PBPK modeling

New investigational agents:

- Candidate selection in preclinical phase
- Animal-to-human extrapolation studies
- Drug-drug interaction studies
- Early formulation selection studies
- Assess disease impact
- Dose adjustment for specific populations (organ impairment, pediatric population, etc.)

Generic drug products:

- Product-specific guidance (PSG) development
  - Alcohol dose dumping
  - Risk assessment for change in drug release mechanism
- Alternative approaches for demonstrating bioequivalence (BE)
  - In vitro testing in lieu of in vivo BE studies
  - Locally-acting drug products
- Extrapolate BE assessments in subpopulations
  - Disease
  - Age
- Drug product development
  - “Safe space” for critical attributes of drug products (dissolution specifications)

# PSGs for complex locally-acting drug products

Option 1: R and T are Q1/Q2

- In vitro characterization (Q3 similarity)
- (+ In vivo BE study with PK endpoints)
- (+ In vivo comparative clinical endpoint BE study)

PBPK modeling to support drug product development

PBPK modeling to support alternative BE approaches

**Using modeling and simulation for non-Q1/Q2 products is a work in progress**

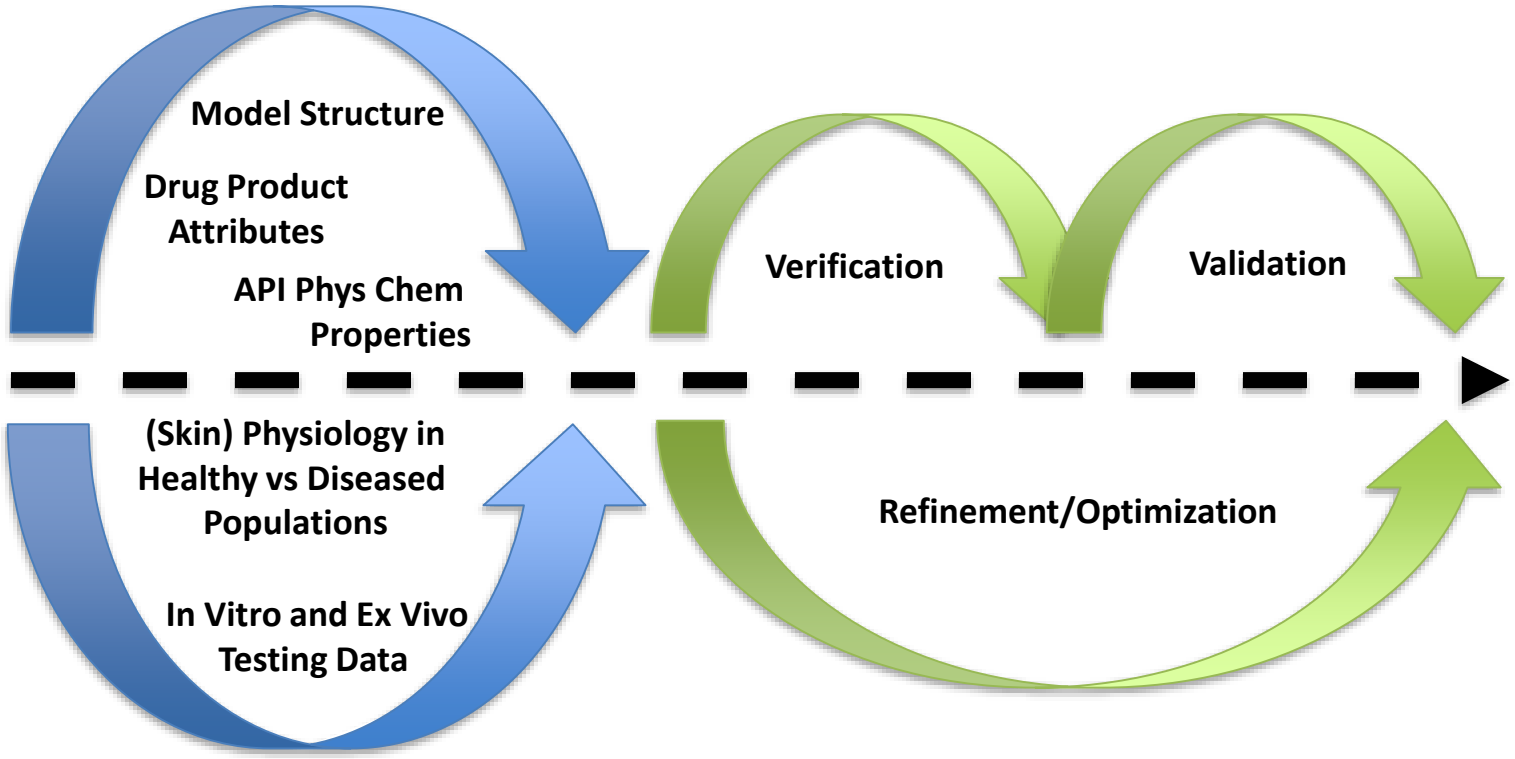
Option 2: R and T are <u>not</u> Q1/Q2

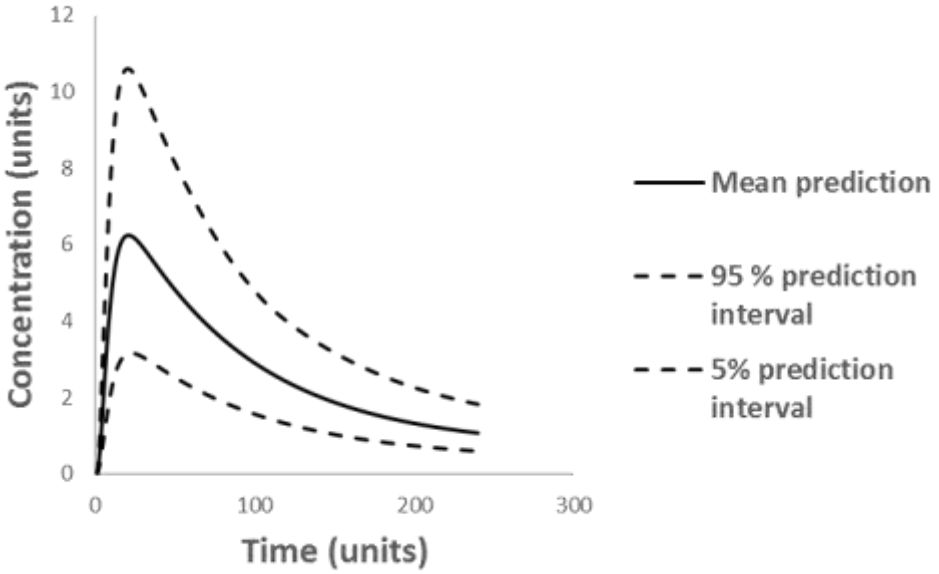
- In vivo comparative clinical endpoint BE study



R: Reference, T: Test
Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product

# PBPK modeling for locally-acting drug products



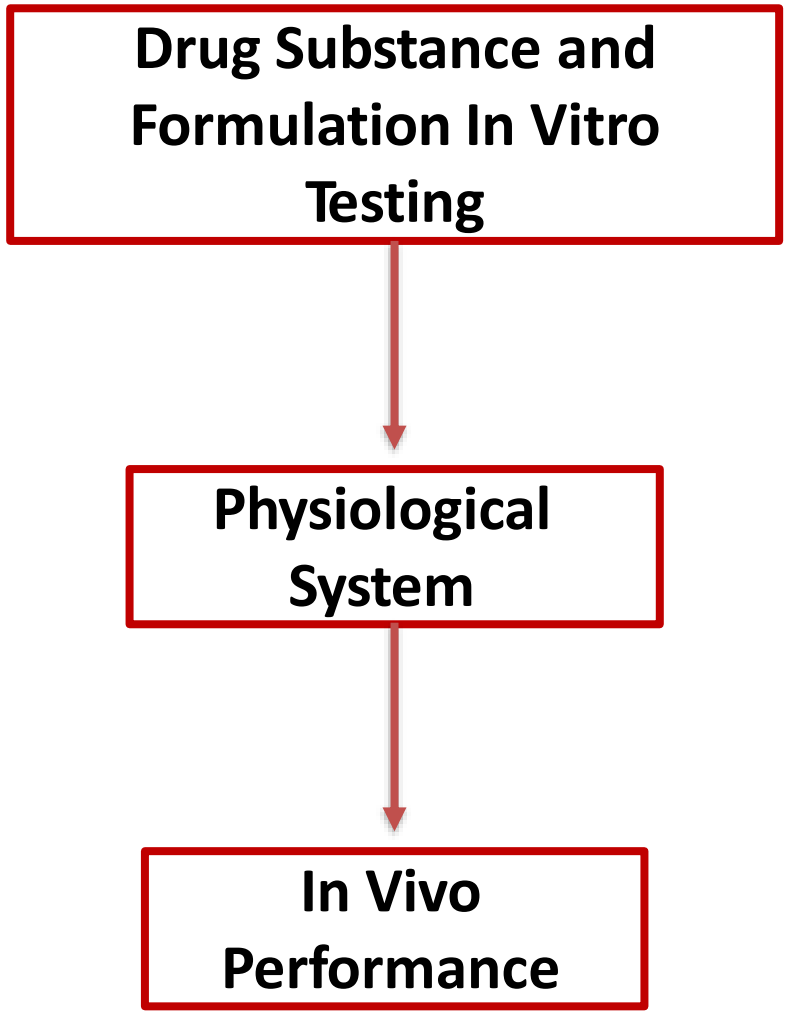



# Best practices: internal reporting and documentation

- Modeling analysis plan:
  - Objectives, model input (assumptions) and reference sources for in vivo/in vitro data used
  - “living document”

- Modeling analysis report:
  - Technical aspects of the modeling task
  - Conclusions that may inform decisions should be clearly presented and discussed

# Best practices: model development




- Model input (data)
  - Good quality
  - Low uncertainty
  - Experimentally derived
  - Biologically plausible
- Model structure justified and supported by data or sensitivity analysis
- Parameter/population variability
- Parameter correlations
- Disease state impacting BE assessment outcome

# Best practices: model development

*Model verification*

- Model components:
  - Differential equations
  - Code
  - Engine for executing applications
- Biological plausibility:
  - Physiology (route of administration and site of action)
  - Drug substance ADME properties
  - Drug product attributes



ADME: Absorption, Disposition, Metabolism, Elimination

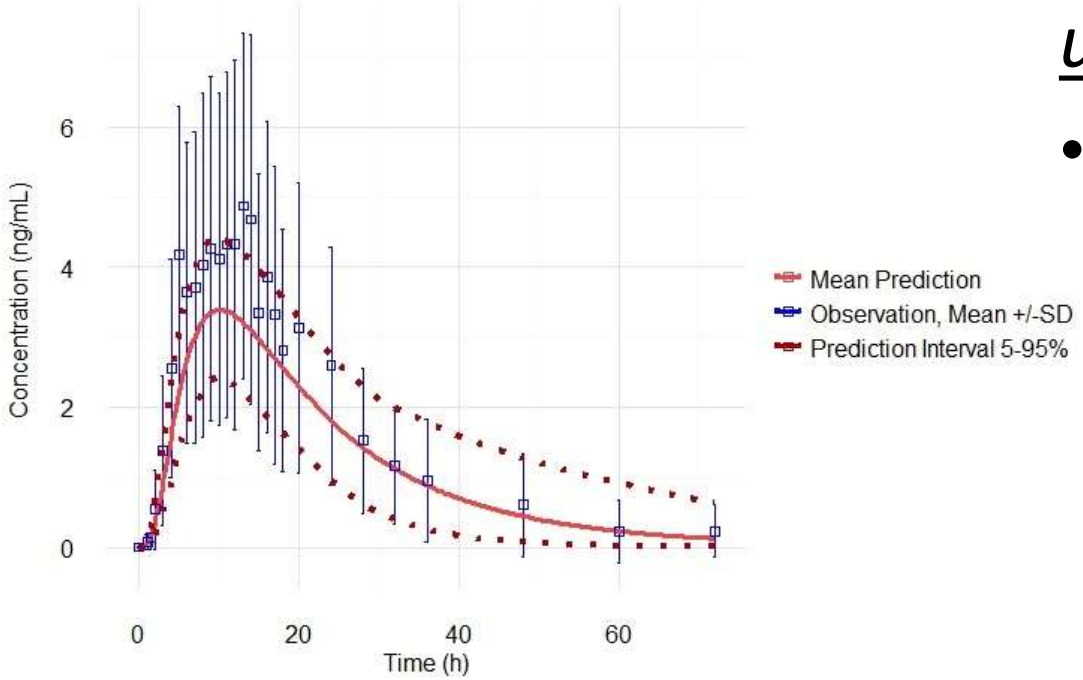
# Best practices: model performance assessment

"Model verification should provide sufficient information to clearly demonstrate that the proposed PBPK model is appropriate for the modeling purpose or question asked for the particular drug product and study population and is robust enough to respond to perturbations in uncertain parameters"*



*Zhao et al., 2019. CPT:PSP 8, 347-351

# Best practices: model performance assessment




Oxybutynin chloride extended release tablet (DITROPAN XL®), 15 mg given orally at fasting state*

* Tsakalozou et al. AAPS, November 2016, Denver CO.

*Model validation for purpose (intended use) for drug product of interest*

- Observed data on systemic and local exposure:
  - Good quality
  - Clinically relevant scenarios
  - Drug product-specific
  - Variability
- Acceptance criteria:
  - Regulatory impact of the decision
  - Established a priori and used consistently

# Best practices: model performance assessment

*Platform performance assessment:*

- Models developed under the same principles as the drug product of interest
  - APIs of similar physicochemical properties and ADME characteristics
  - Dosage forms of variable compositional complexity for the same route of administration
  - Not used for model development
- Models developed to capture physiology variables and their interplay with product attributes:
  - Disease
  - Patient population



API: Active Pharmaceutical Ingredient

# Best practices: model performance assessment

*Platform performance assessment*

- Ocular PBPK:
  - Validate model in animal species - interspecies extrapolation
  - In vitro or ex vivo data (site of action)
  - In vivo systemic and local exposure data in humans
- Inhalation/nasal PBPK:
  - In vitro or ex vivo data (site of action)
  - In vivo systemic and local exposure data in humans
- Dermal PBPK:
  - In vitro or ex vivo data (site of action)
  - In vivo systemic and local exposure data in humans

# Best practices: model performance assessment

*Considerations and challenges:*

- Data availability for model validation, for establishing in vivo-in vitro relationships, for describing drug product-physiology interplay
- Systemic exposure does not reflect local concentrations
- Model validated only for the range of conditions of the dataset used

# Best practices: model refinement

*“middle-out” modeling approach involving  parameter optimization*

Knowledge gaps?

- Fit-for-purpose model
- Model structural and numerical identifiability
- Parameter collinearity
- Additional model verification necessary

# Best practices: model application

*Virtual bioequivalence assessments*

- Leverage models developed for R and T product to generate population predictions

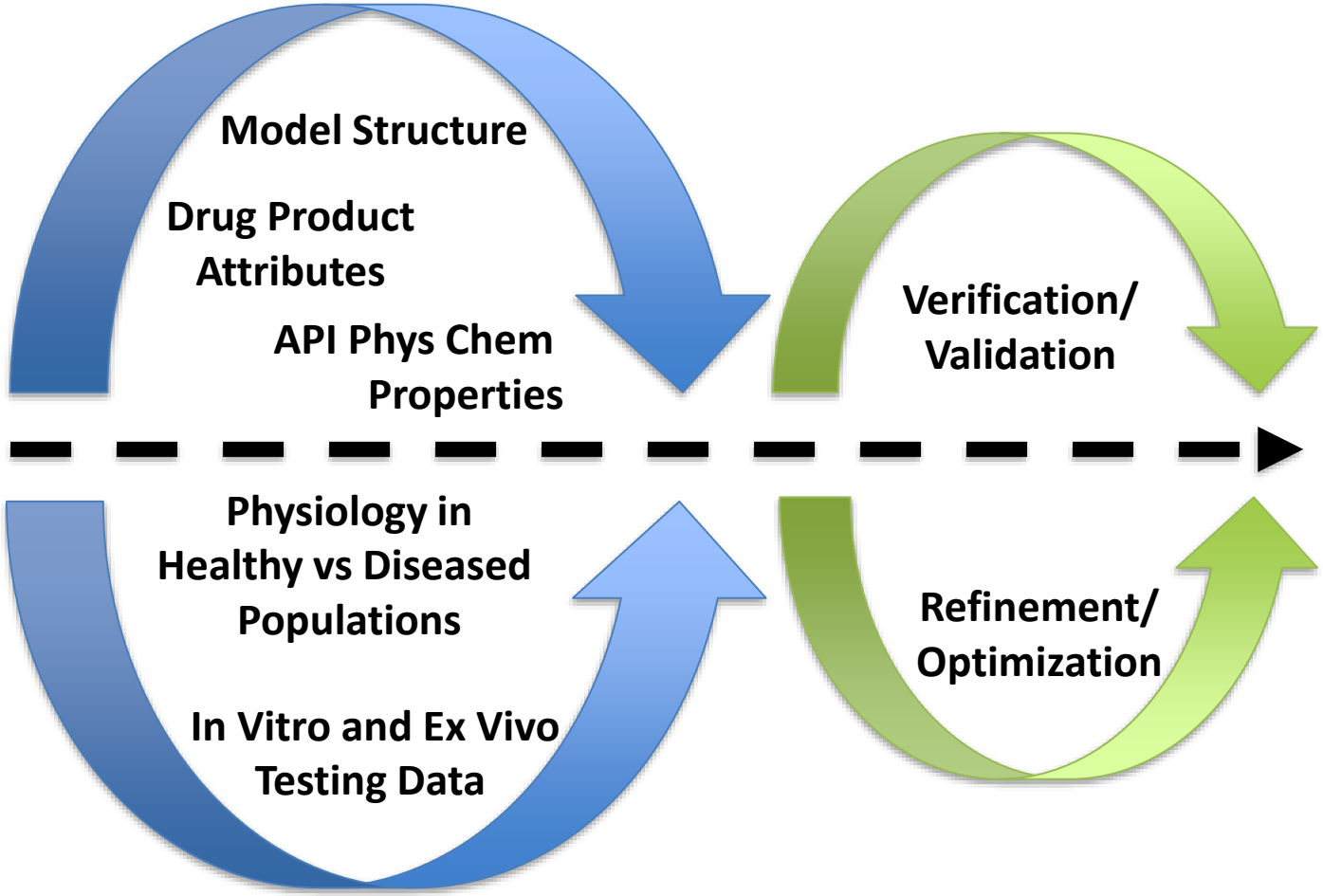
*Identification of clinically relevant drug product attributes (sensitivity analysis)*

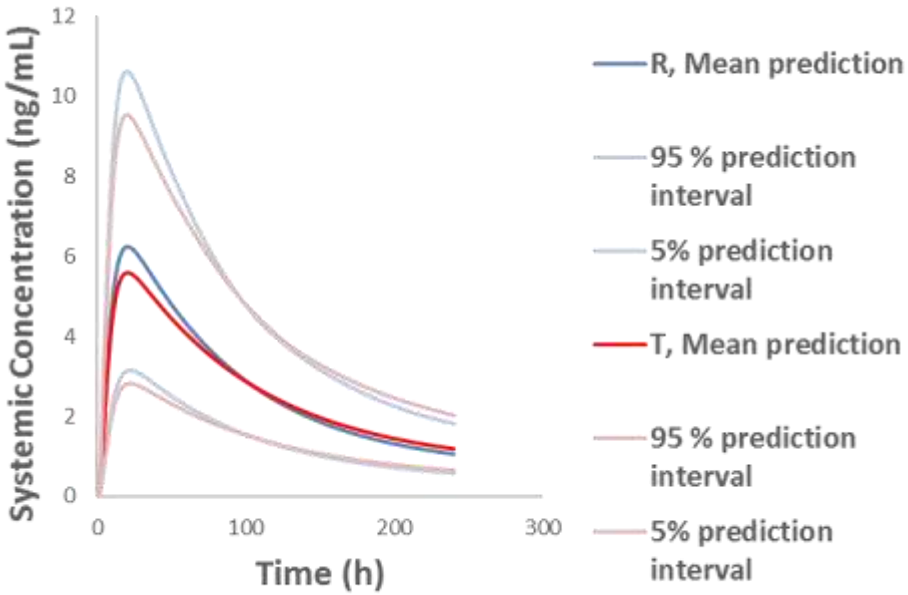
- Considerations:
  - Sources of variability incorporated into the model  realistic population predictions
  - Sample size impacted by highly variable pharmacokinetic behavior



R: Reference, T: Test

# PBPK modeling for generic locally-acting drug products to support a regulatory decision




**Are R and T bioequivalent?**

R: Reference, T: Test

# Best practices: regulatory submission

## Physiologically Based Pharmacokinetic Analyses — Format and Content

### Guidance for Industry

August 2018
Clinical Pharmacology



13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

## Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

# Best practices: regulatory submission

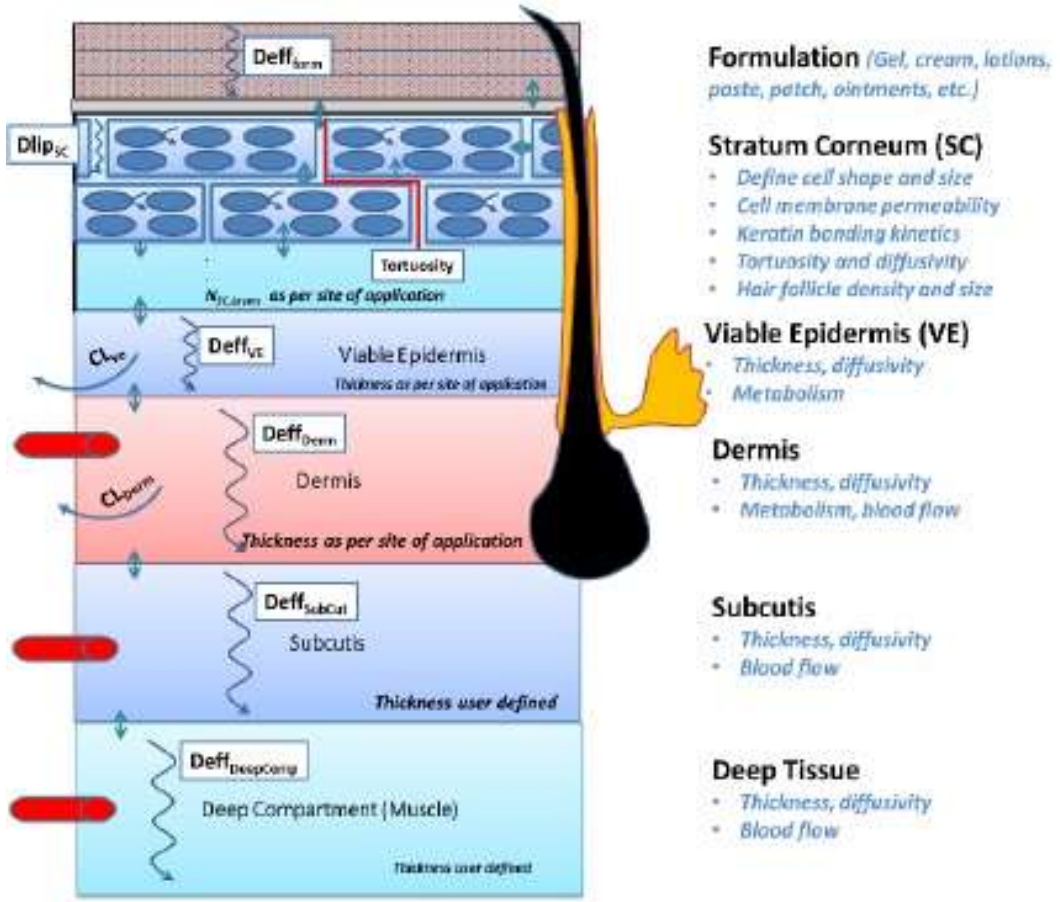
*Highlights:*

- Modeling and Simulation report:
  - Model development and performance assessment are documented in detail
  - Model assumptions and conclusions are data- and science-supported
  - Model limitations are clearly stated and considered for simulations and outcome reporting
- Executable final model files, model input and output files and their description
- Submitted material updated as a result of interactions with the Agency

# Take home messages

- PBPK models for locally-acting products can be used to support:
  - Development of a drug product prior approval
  - Alternative BE approaches
- Model development is an intense and resource-demanding process due to:
  - Complexity of the models and the drug products (remote target site)
  - Limitations in data availability in model development and validation
- PBPK modeling supporting an ANDA: early interaction between industry and regulatory agency should be initiated - pre-ANDA meeting request program, GDUFA II

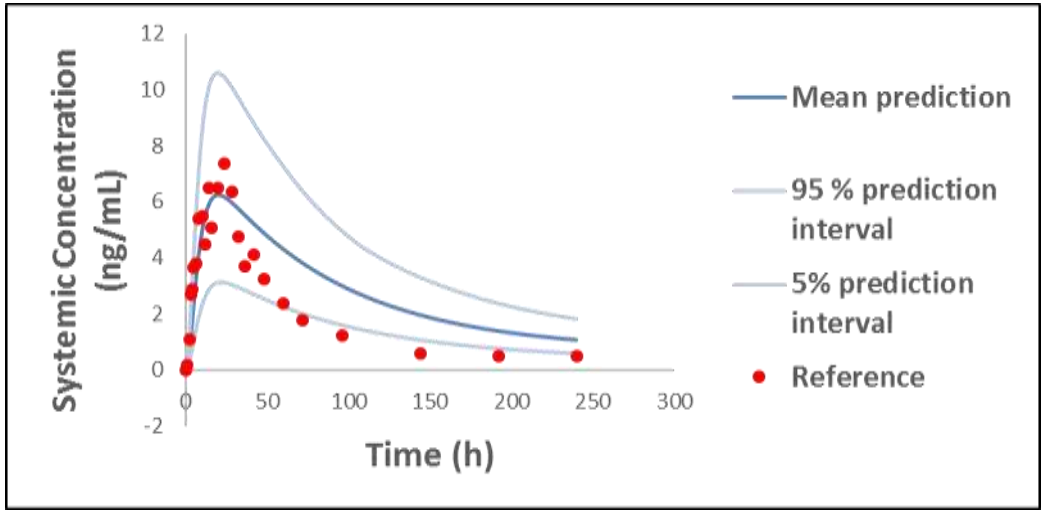
# Dermal PBPK model supporting ANDA 211253 approval

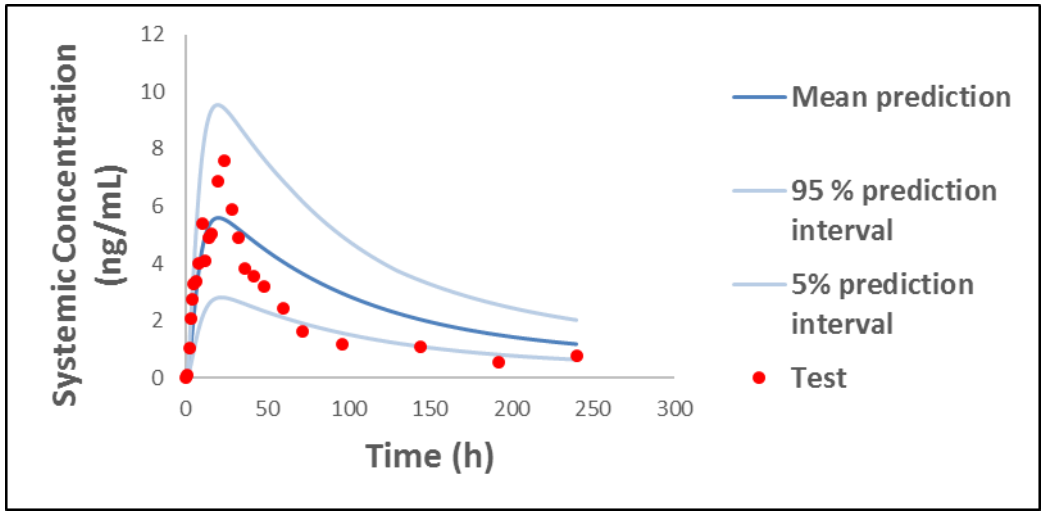



- Diclofenac sodium topical gel, 1%
- Alternative BE approach for a Q1/Q2/Q3 formulation: dermal PBPK model in lieu of an in vivo comparative clinical endpoint BE study
- Model development:
  - API physicochemical properties
  - API ADME properties
  - Formulation attributes for R and T drug products (viscosity, globule size, pH)

R: Reference, T: Test

# Dermal PBPK model supporting ANDA approval

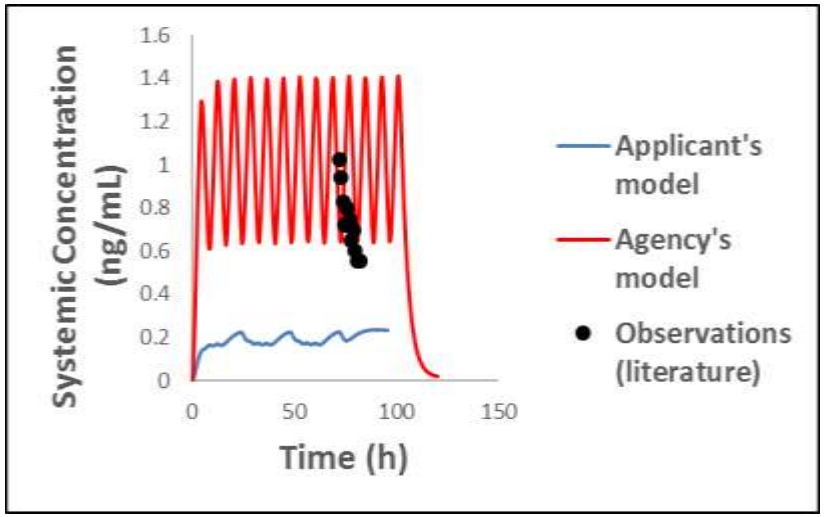


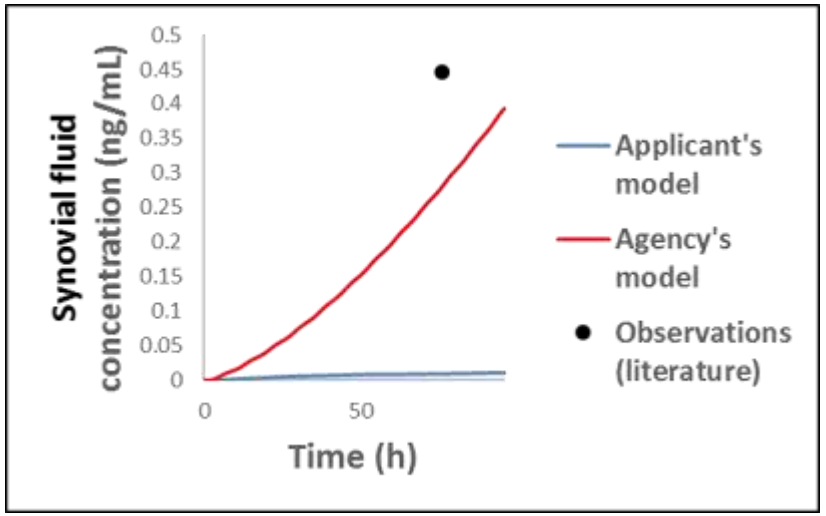




- Platform performance assessment:
  - >10 PBPK models for TDS and topical products
  - Multiple doses/product strengths and dosing regiments
  - Satisfactory model performance
- Model performance assessment for diclofenac sodium topical gel, 1%:
  - Literature and application data on doses, product strengths, dosing regiments, routes of administration and local/systemic exposure data
  - Formulation attributes for R and T
  - Good predictions of systemic exposure

R: Reference, T: Test, TDS: Transdermal Delivery System

# Dermal PBPK model supporting ANDA approval

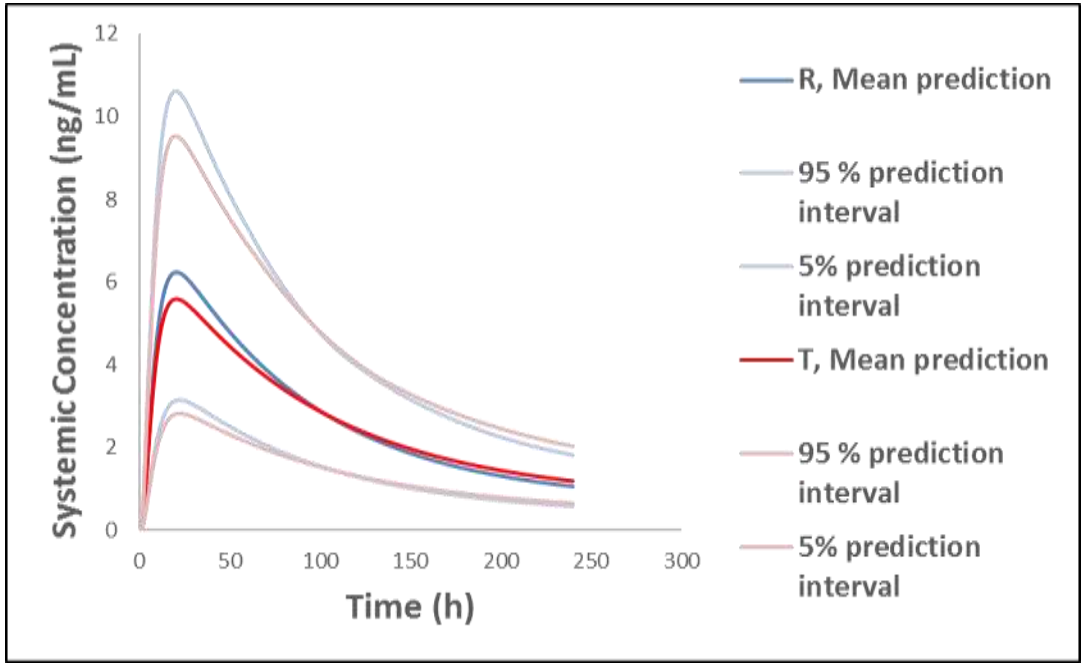


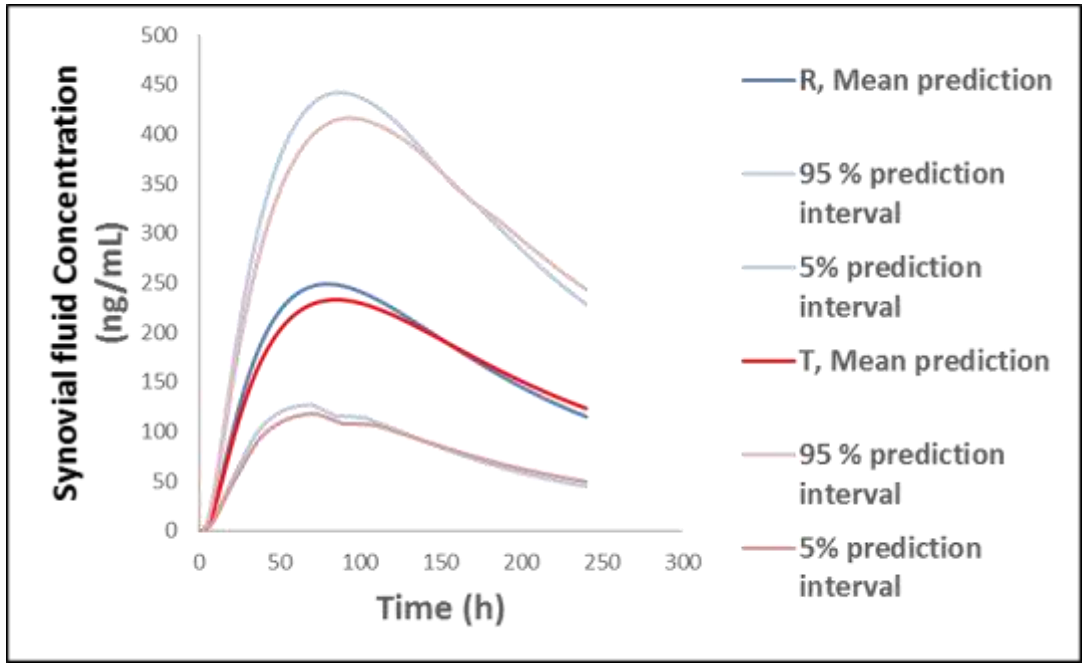




- Refined model to improve synovial fluid exposure predictions (by the Agency)
  - Protein binding in all skin layers
  - Drug product attributes updated
  - Partition coefficients modified leveraging observed local drug amounts

# Dermal PBPK model supporting ANDA approval

- Conducted virtual BE assessments on predicted systemic and local exposure data
  - ✓**R and T drug products were found bioequivalent**




R: Reference, T: Test

# Conclusions

- PBPK models can be used to inform product development decisions and support alternative BE approaches for generic locally-acting drug products.
- Applicants are encouraged to follow best practices when developing PBPK models for generic locally-acting drug products as these are communicated by the Agency in guidances and other public forums.
- Applicants are encouraged to engage with the Agency early in their product development program by making use of the pre-ANDA meeting request program (GDUFA II) – case example of the approved ANDA for a complex topical drug product.

# Acknowledgments

**FDA/OMPT/CDER**

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Darby Kozak & Team
Sam Raney & Team
Kimberly Witzmann & Team

*OGD/ORS-IO*

Lei K. Zhang
Robert Lionberger

www.fda.gov/GDUFARegScience

# Generic Drug User Fee Amendments: Regulatory Science/Research

| Grant/Contract | Institute | Grant or Contract No. |
|---|---|---|
| An integrated multiscale-multiphysics modeling framework for evaluation of generic ophthalmic drug products | CFD Research Corporation | HHSF223201810151C |
| GastroPlus OCAT model extension and validation | SimulationsPlus, Inc | HHSF223201810255P |
| A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs | CFD Research Corporation | HHS223201810182C |
| Characterization of key system parameters of mechanistic dermal PBPK models in various skin diseases and performance verification of the model using observed local and systemic concentrations | Simcyp, Ltd | 1U01FD006521 |
| Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations | SimulationsPlus, Inc | 1U01FD006526 |
| Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems | University of Queensland | 1U01FD006522 |
| PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform | Children's Hospital of Los Angeles | 1U01FD006549 |


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References:


- Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. Zhao P, Rowland M, Huang SM. Clin Pharmacol Ther. 2012 Jul;92(1):17-20.
- Establishing best practices and guidance in population modeling: an experience with an internal population pharmacokinetic analysis guidance. Byon W, Smith MK, Chan P, Tortorici MA, Riley S, Dai H, Dong J, Ruiz-Garcia A, Sweeney K, Cronenberger C. CPT Pharmacometrics Syst Pharmacol. 2013 Jul 3;2.
- Generating Model Integrated Evidence for Generic Drug Development and Assessment. Zhao L, Kim MJ, Zhang L, Lionberger R. Clin Pharmacol Ther. 2019 Feb;105(2):338-349.
- Current scientific consideration to verify physiologically-based pharmacokinetic models and their implications for locally acting products. Zhao L, Seo P, Lionberger R. CPT Pharmacometrics Syst Pharmacol. (2019) 8, 347-351.
- Evaluating systems pharmacology models is different from evaluating standard pharmacokinetic-pharmacodynamic models. Agoram B. CPT Pharmacometrics Syst Pharmacol. 2014 Feb 19;3.
- Requirements to Establishing Confidence in Physiologically Based Pharmacokinetic (PBPK) Models and Overcoming Some of the Challenges to Meeting Them. Peters SA, Dolgos H. Clin Pharmacokinet. 2019 Jun 25.
- Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective. Shebley M, Sandhu P, Emami Riedmaier A, Jamei M, Narayanan R, Patel A, Peters SA, Reddy VP, Zheng M, de Zwart L, Beneton M, Bouzom F, Chen J, Chen Y, Cleary Y, Collins C, Dickinson GL, Djebli N, Einolf HJ, Gardner I, Huth F, Kazmi F, Khalil F, Lin J, Odinecs A, Patel C, Rong H, Schuck E, Sharma P, Wu SP, Xu Y, Yamazaki S, Yoshida K, Rowland M. Clin Pharmacol Ther. 2018 Jul;104(1):88-110.
- Commentary on Fit-For-Purpose Models for Regulatory Applications. Wang Y, Huang SM. Pharm Sci. 2019 Jan;108(1):18-20.
- C Wagner, P Zhao, Y Pan, V Hsu, J Grillo, SM Huang and V Sinha, Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK, *CPT: Pharmacometrics & Systems Pharmacology*, 4, 4, (226-230), (2015).
- Shiew-Mei Huang, Darrell R. Abernethy, Yaning Wang, Ping Zhao and Issam Zineh, The utility of modeling and simulation in drug development and regulatory review, *Journal of Pharmaceutical Sciences*, 102, 9, (2912-2923), (2013).
- European Medicines Agency. Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation https://www.ema.europa.eu/documents/scientific-guideline/guideline-qualification-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf
- US Food and Drug Administration. Physiologically based pharmacokinetic analyses—format and content guidance for industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf
- http://www.who.int/ipcs/methods/harmonization/areas/pbpk_models.pdf
- Reverse Translation in PBPK and QSP: Going Backwards in Order to Go Forward With Confidence. Rostami-Hodjegan A. Clin Pharmacol Ther. 2018 Feb;103(2):224-232.