2021 FDA/CRCG Virtual Workshop
Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches
September 30, 2021

# Use of PBPK in New Drug Development and Regulatory Review
# - Clinical Pharmacology Perspective -

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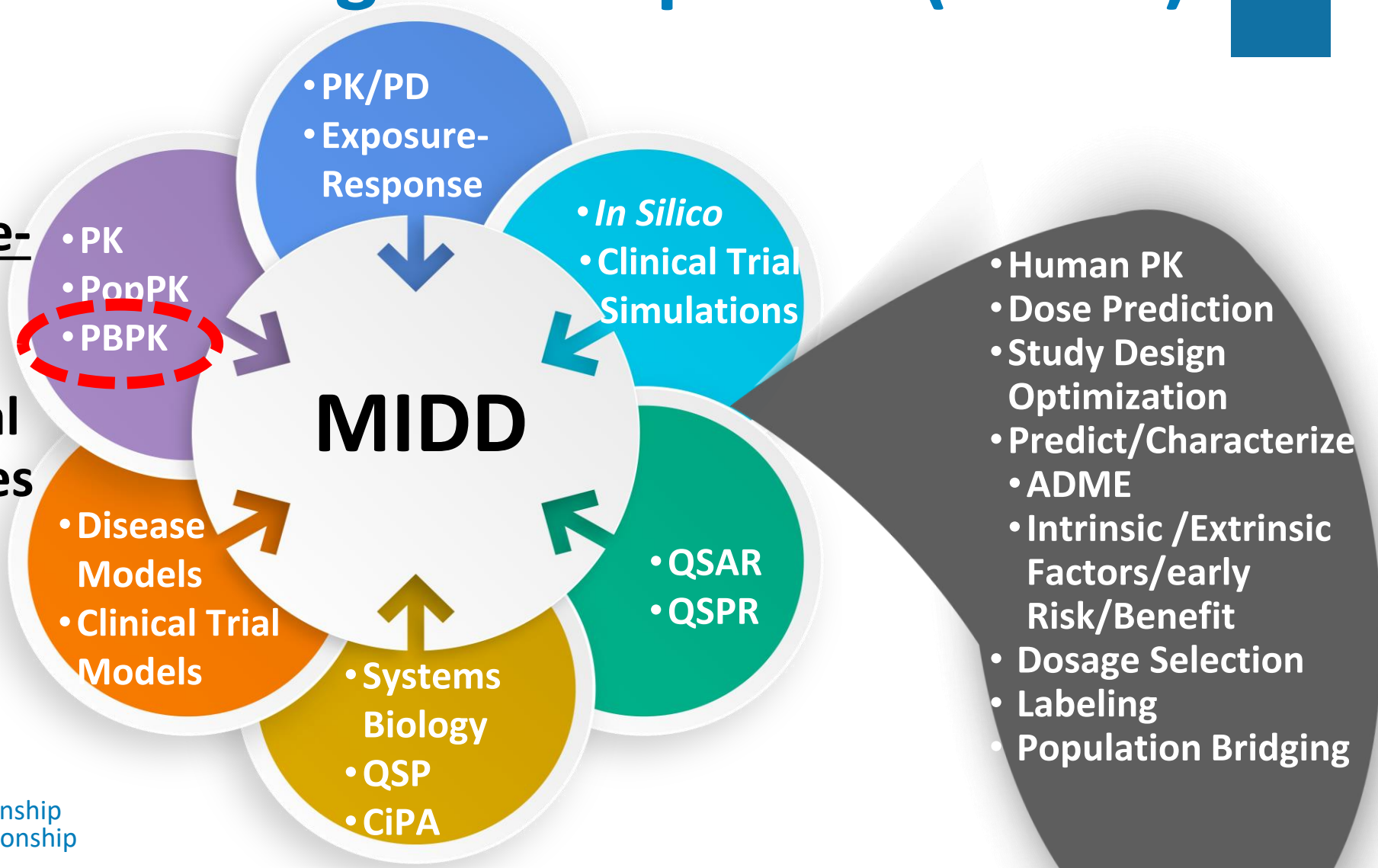
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

# Model-Informed Drug Development (MIDD)

**Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues***

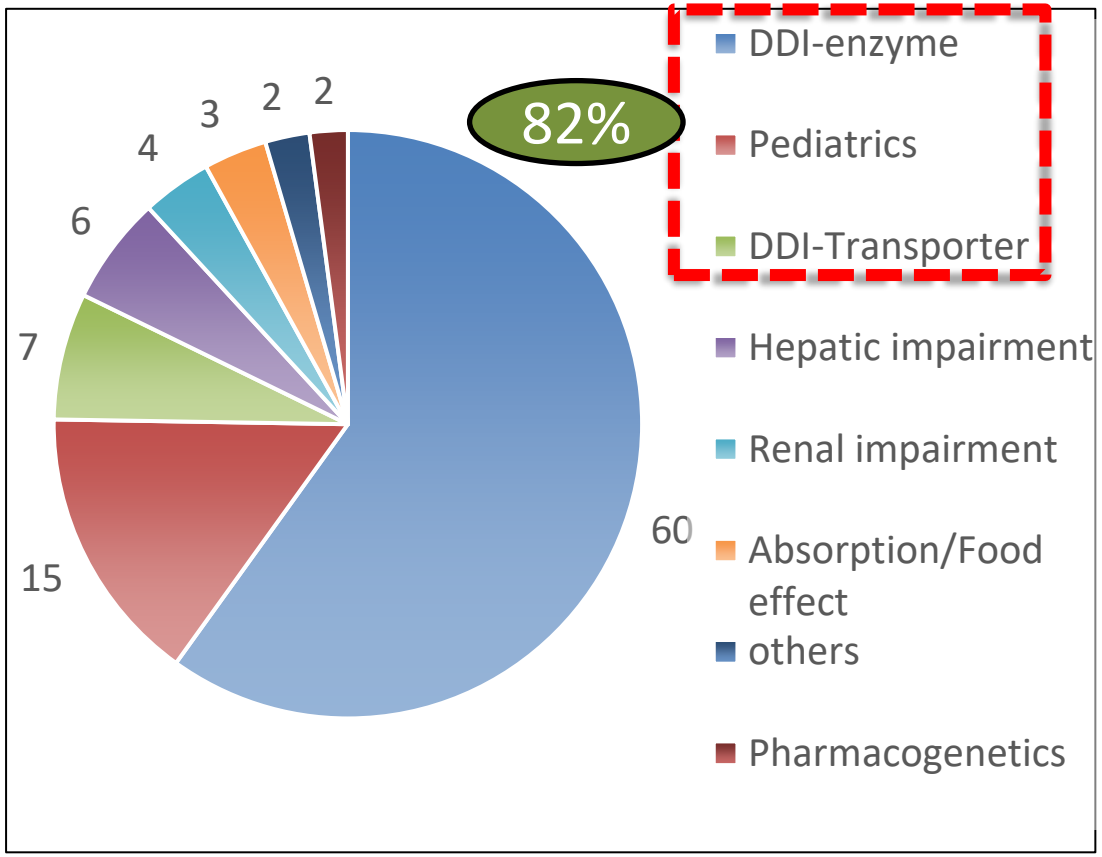



QSAR: Quantitative structure–activity relationship
QSPR: Quantitative structure–property relationship

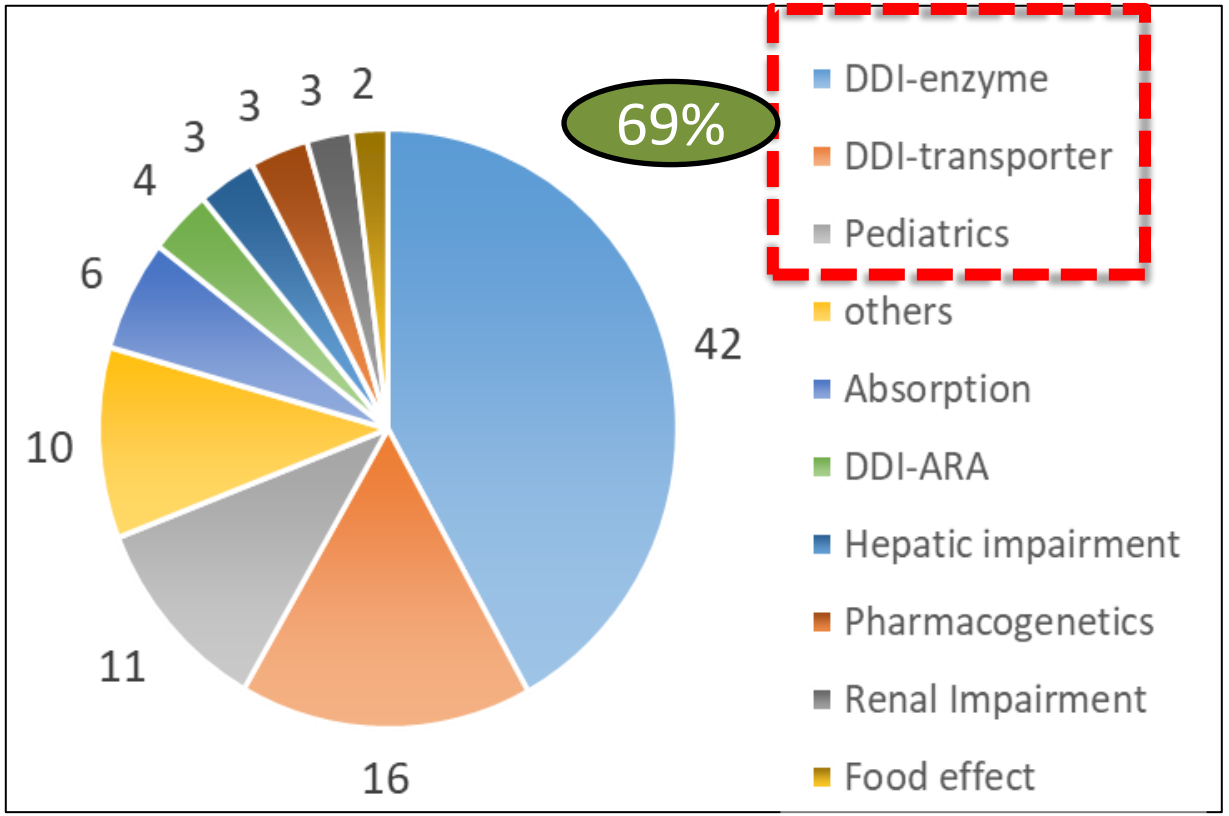
* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulat… the operating characteristics of a confirmatory clinical trial.

# PBPK Submissions to OCP (IND/NDA/BLA)

## 2008-2017 (N=254)




## 2018-AUG 2021 (N = 247)

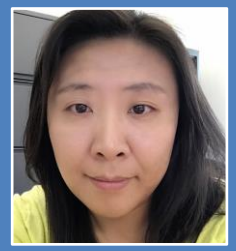



* One submission could include multiple applications

*Grimstein et al. J Pharm Sci. 2019 Jan;108(1):21-25; PBPK summary by X. Zhang*

# Office of Clinical Pharmacology (OCP)- PBPK Team in Division of Pharmacometrics

## Supporting All OCP Divisions



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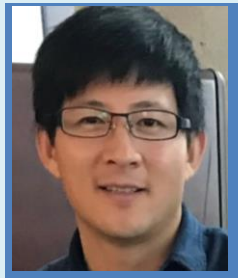


Guansheng Liu

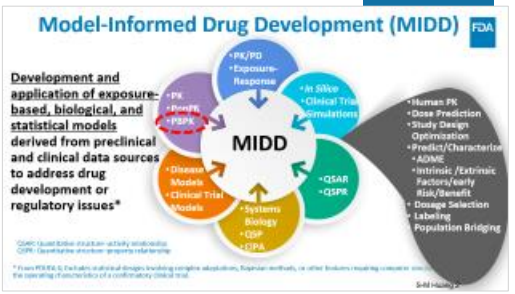
# OCP PBPK Team: Roles and Responsibilities

- **Policy**

  -Develop best practices/guidance on the use of PBPK

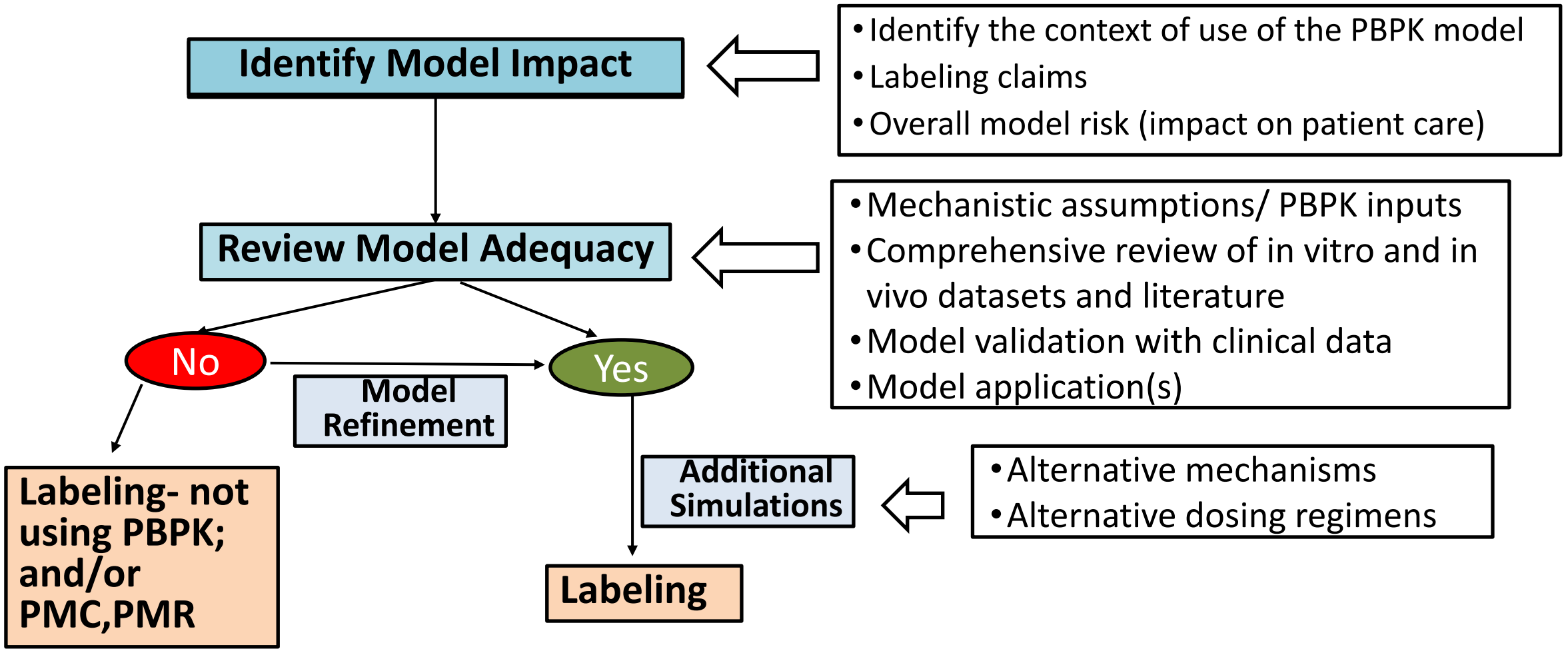
- **Review**
  - Coordinate and conduct PBPK reviews
  - Evaluate submitted PBPK models (and ask for refinement, if needed)
  - Maintain a PBPK knowledgebase
- **Research**
- **Outreach and Training**
  - Harmonize with other health regulatory agencies
  - Foster communications with thought leaders (scientific community)

# PBPK Review Focus at IND stage




- Application of PBPK analysis
  - To support DDI evaluation (to inform protocol design)
  - To support initial dose selection in clinical study in specific populations (e.g., pediatric; organ impairment); first-in-human study
    - To support dosing under Emergency Use Authorization (EUA)
- Discussion focus between the sponsor and the FDA (pIND/IND/MIDD meetings)
  - To discuss the acceptability of the proposed modeling approach

# PBPK Review Focus at NDA stage




→Challenges: uncertainty in system parameters; limited confidence in in vitro-in vivo extrapolation; appropriate model assumptions; short review timeline

# Regulatory Application & Predictive Performance

- Higher confidence, greater experience, fewer knowledge gaps, higher likelihood of acceptability to inform labeling and regulatory decisions
- Some experience, knowledge gaps identified, likelihood of acceptability to inform labeling and regulatory decisions case by case basis
- Limited experience, significant knowledge gaps, low likelihood of acceptability to inform labeling and regulatory decisions at this time

## Drug Interactions

- **CYP450 Drug as Substrate**
  - Inhibitor interaction prediction with higher potency clinical data verification
  - Concern with Rifampin under prediction
  - Dual enzyme time dependent inhibitor and inducer prediction not mature
- **CYP450 Drug as Perpetrator**
  - Negative interaction prediction
  - Some experience with positive interaction prediction, but knowledge gaps exist
- **Transporter**
  - Some experience with Pgp and combined Pgp/ CYP3A interaction prediction and negative interaction prediction for basolateral uptake transporters, but knowledge gaps exist
  - Intestinal BCRP, hepatic OATP1B1/3, NTCP, MRP2, OATPs, and renal OATs and OCT2 positive prediction not mature
  - in vitro/in vivo extrapolation for solute carriers complex
- **Phase II Metabolism**
  - Some experience with UGT's, but prediction not mature

## Specific Populations

- **Pediatrics**
  - Some experience, but knowledge gaps exist
    - Greater utility likely in age ≤ 2 years
- **Renal or Hepatic Impairment**
  - Some experience, but prediction not mature
- **Pregnancy, ethnicity, geriatrics, obesity, disease states**
  - Prediction not mature

## Other Areas

- **Food, formulation, & tissue concentration**
  - Prediction not mature
- **pH effect on Fa**
  - Some experience, but knowledge gaps exist
- **Absorption**
  - BCS Class I drugs
  - Some experience with BCS Class II, but knowledge gaps exist
  - BCS Class III and IV prediction not mature

*Adapted from Grimstein M. et al. J Pharm Sci. 2019; 108:21-25 and Wagner C. et al. CPT-PSP. 2015; 4:226-230; Slide courtesy of J. Grillo*

→ More on the progress at today's workshop

# Case 1- DDI (CYP3A + CYP2C9) & Genetics (Siponimod)

PBPK Model Development:
- CYP3A/2C9 substrates
- Absorption: first order, ka obtained by popPK
- Distribution: full body PBPK, Vss based on i.v. PK
- Elimination: $CL_{u,int}$ based on popPK analysis

PBPK Model Validation:
- SD, MD, and genotype PK (CYP2C9 *1/*1, *2/*3, and *3/*3)
- DDI with Rifampin, fluconazole in *1/*1, *1/*2, and *1/*3

PBPK Model Application:
- Evaluate the Combined Effects of CYP3A4/CYP2C9 modulation on PK in various CYP2C9 genotypes.**(*2/*2 & *2/*3)**

**Informed Labeling**

| CYP2C9 genotype | | + moderate CYP2C9 AND moderate or strong CYP3A4 inhibitor | + moderate CYP2C9 AND strong CYP3A4 inducer | |
|---|---|---|---|---|
| *1/*1 | 2 mg | Not recommended | Not recommended | |
| *1/*2 | 2 mg | | | |
| *2/*2 | 2 mg | | | |
| *1/*3 | 1 mg | | | |
| *2/*3 | 1 mg | | | |
| *3/*3 | contraindicated | | | |

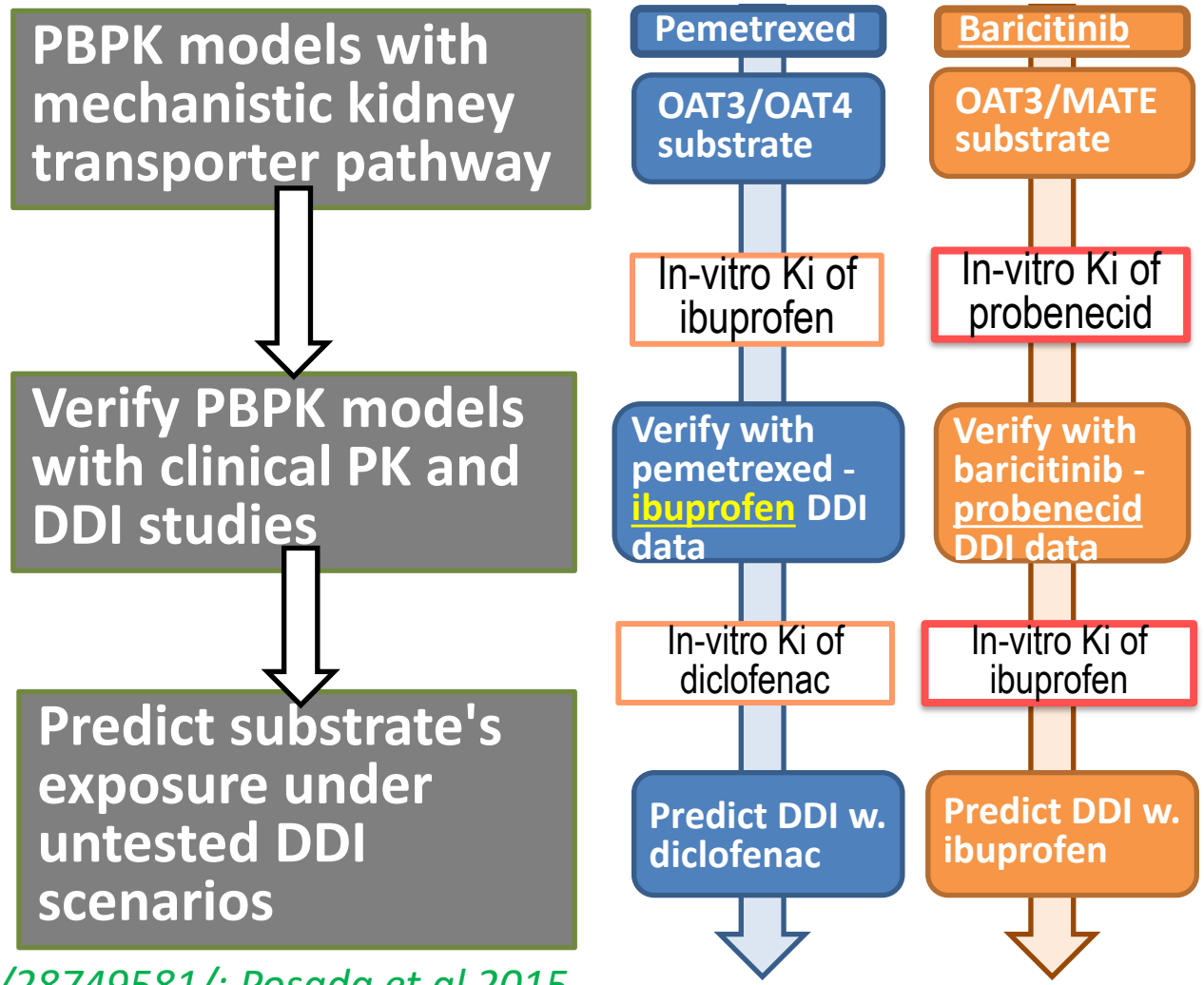
Extracted from MAYZENT labeling:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209884s003lbl.pdf

Clinical pharmacology review:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000ClinPharmR.pdf

# Case 2- OAT3-mediated DDI (Baricitinib)

**Indication:** JAK inhibitor
**PBPK context of use:** Clinical data showed that co-administrated with probenecid (OAT3 inhibitor) increased the exposure of baricitinib by 2-fold. What is the effect of ibuprofen (also an OAT3 inhibitor) on baricitinib PK

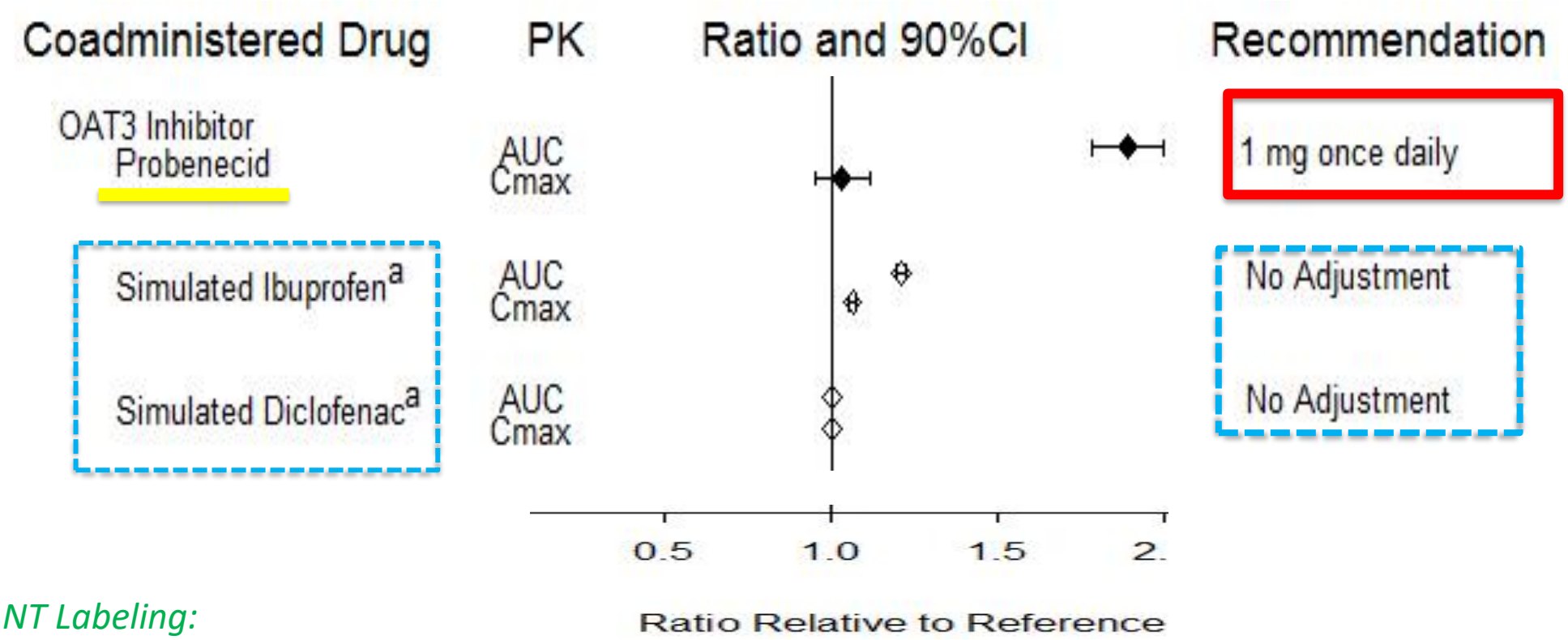
→ **Ability to predict the "Minimal" effect of ibuprofen (an OAT3 inhibitor) on baricitinib**




*Posada et al 2017 https://pubmed.ncbi.nlm.nih.gov/28749581/; Posada et al 2015 https://pubmed.ncbi.nlm.nih.gov/25504564/*
*NDA 207924 review and labeling: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000ClinPharmR.pdf*

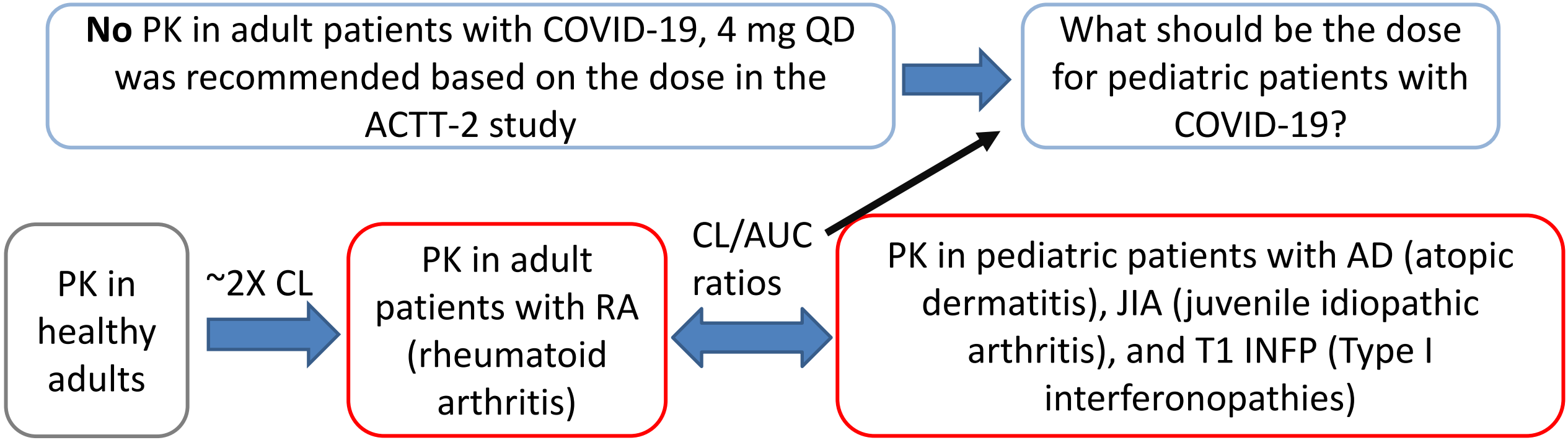
# Case 2- OAT3-mediated DDI (Baricitinib)- Labeling

- The recommended dose of OLUMIANT is **2 mg once daily** (2.1)
- OLUMIANT The recommended dose of OLUMIANT in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors, such as probenecid, is 1 mg once daily [see (7.1) and (12.3)].
- However, simulations with diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential) predicted minimal effect on the PK of baricitinib [12.3]




*OLUMINANT Labeling:*
*https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000Lbl.pdf*

# Case 3- Predicting PK in Pediatrics (Baricitinib)




Assumptions:

1. The effective exposure in pediatric patients (2-18 yrs) ~ adult patients with COVID-19.
2. The PK difference between adults and pediatrics is similar across different diseases.

***References-*** *EUA for Baricitinib CDER Review Document (fda.gov)*
*https://www.fda.gov/media/144473/download*

# Case 3- Predicting PK in Pediatrics (Baricitinib)- EUA for 2+ YO

**Emergency Use Authorization: Baricitinib for COVID-19 in hospitalized adults and pediatric patients 2+ YO requiring oxygen, mechanical ventilation or ECMO**

- The dose for adults was recommended based on the efficacy study ACTT-2
- The dose for pediatrics was based on the analyses of historic PK data and PBPK modeling

| Age (yrs) | eGFR (mL/min/1.73 $m^2$) | | |
|---|---|---|---|
| | ≥60 | 30 to < 60 | 15 to < 30 |
| Adult | 4 mg QD for max 14 days | 2 mg QD for max 14 days | 1 mg QD for max 14 days |
| 9-18 | 4 mg QD for max 14 days | 2 mg QD for max 14 days | 1 mg QD for max 14 days |
| 2-9 | 2 mg QD for max 14 days | 1 mg QD for max 14 days | Not recommended |

*Adapted from Fact sheet for EUA of baricitinib: https://www.fda.gov/media/143823/download November 19, 2020 (Baricitinib + remdesivir)*
*https://www.fda.gov/media/143822/download July 28, 2021 (Baricitinib only)*

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

# Application of PBPK Modeling and Simulation for Regulatory Decision Making and Its Impact on US Prescribing Information: An Update on the 2018-2019 Submissions to the US FDA's Office of Clinical Pharmacology

Xinyuan Zhang PhD, Yuching Yang PhD, Manuela Grimstein PhD, Jianghong Fan PhD, Joseph A. Grillo PharmD, Shiew-Mei Huang PhD, Hao Zhu PhD, Yaning Wang PhD

First published: 17 November 2020 | https://doi.org/10.1002/jcph.1767 | Citations: 9

# Example of PBPK in Recent Regulatory Review & Labeling

| | FDA Assessment | Labeling Section | Comments |
|---|---|---|---|
| larotrectinib | **PMR: use PBPK modeling to assess the effect of a moderate CYP3A inhibitor on the PK of larotrectinib** | **PMR** | **NA** | **DDI-enzyme** |
| | PMC: use PBPK modeling to assess the effect of a moderate CYP3A inducer on the PK of larotrectinib | PMC | NA | |
| entrectinib | To assess the effects of a strong (itraconazole) and moderate(erythromycin) CYP3A inhibitor on the PK of entrectinib and its active metabolite M5 | adequate | 7.1, 12.3 | DDI-enzyme, pediatrics |
| | To assess the effects of a strong (rifampin) and moderate (efavirenz) CYP3A inducer on the PK of entrectinib and its active metabolite M5 | adequate | 7.1, 12.3 | |
| | To predict the effect of entrectinib on CYP3A substrates (midazolam and ethinylestradiol) | inadequate | No | |
| | To predict the entrectinib PK in pediatric populations (4-20 years of age, and less than 4 years of age) following administration of F1, and F2A/F06 formulations | inadequate | No | |
| lemborexant | To assess the effect of a weak CYP3A inhibitor on the PK of lemborexant. | adequate | 2.2, 7.1, 12.3 | DDI-enzyme |

*Extracted from Zhang et al. JCP 2020: 60(S1)S160–S178*

# PBPK workshop November 2019

# Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making – A Workshop Summary

Daphney Jean,*,[1] Kunal Naik,*,[1] Lauren Milligan,[1] Stephen Hall,[2] Shiew Mei Huang,[1] Nina Isoherranen,[3] Colleen Kuemmel,[1] Paul Seo,[4] Million A. Tegenge,[5] Yaning Wang,[1] Yuching Yang,[1] Xinyuan Zhang,[1] Liang Zhao,[6] Ping Zhao,[7] Jessica Benjamin,[1] Kimberly Bergman,[1] Joseph Grillo,[1] Rajanikanth Madabushi,[1] Fang Wu,[6] Hao Zhu,[1] Issam Zineh‡,[1]

*Daphney Jean,* Kunal Naik,* Lauren Milligan, et al. CPT-PSP, in press*

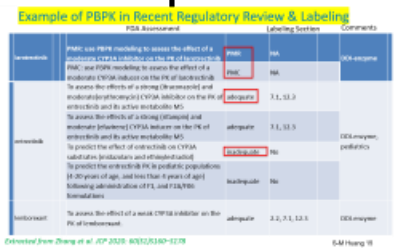
# To Address Challenges in the Applications of PBPK

- Increase effectiveness/efficiency of regulatory review
- Increase data acquisition, analysis, and transparency
- Harmonize PBPK credibility criteria in drug development and regulatory submission

*Daphney Jean,* Kunal Naik,* Lauren Milligan, et al. CPT-PSP, in press*

# Summary

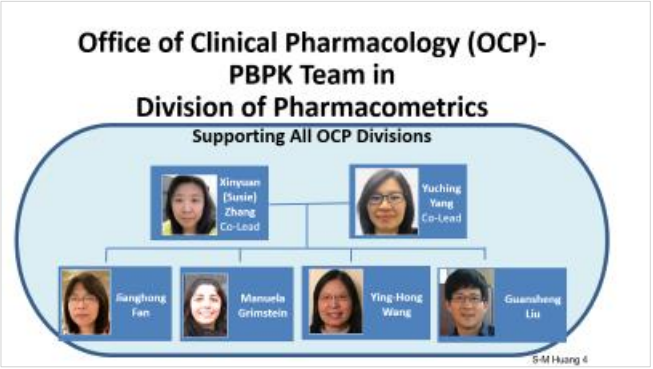
- PBPK is a critical component of MIDD with increasing frequency of use
- In new drug development, the applications have been in the DDI (metabolism; transport), pediatrics, and other patient factors (e.g., renal/hepatic impairment)
- Challenges need to continue to be addressed:
  - Uncertainty in system parameters (ontogeny, interleukin levels, specific popuations)
  - Limited confidence in in vitro- in vivo extrapolation; validity of model assumptions
  - Short review timeline (regulatory applications)
  - Others (see slide #15)




- It is critical to extend applications to integrate effects from multiple patient factors (pediatrics and DDI; older adults and DDI; renal impairment and DDI; genetics and DDI; food and pH effects, others)
- Need to continue to establish good practices in PBPK modeling of new drug & generic drug applications (slide #8, 16)

# Acknowledgements

- Office of Clinical Pharmacology (OCP) PBPK team



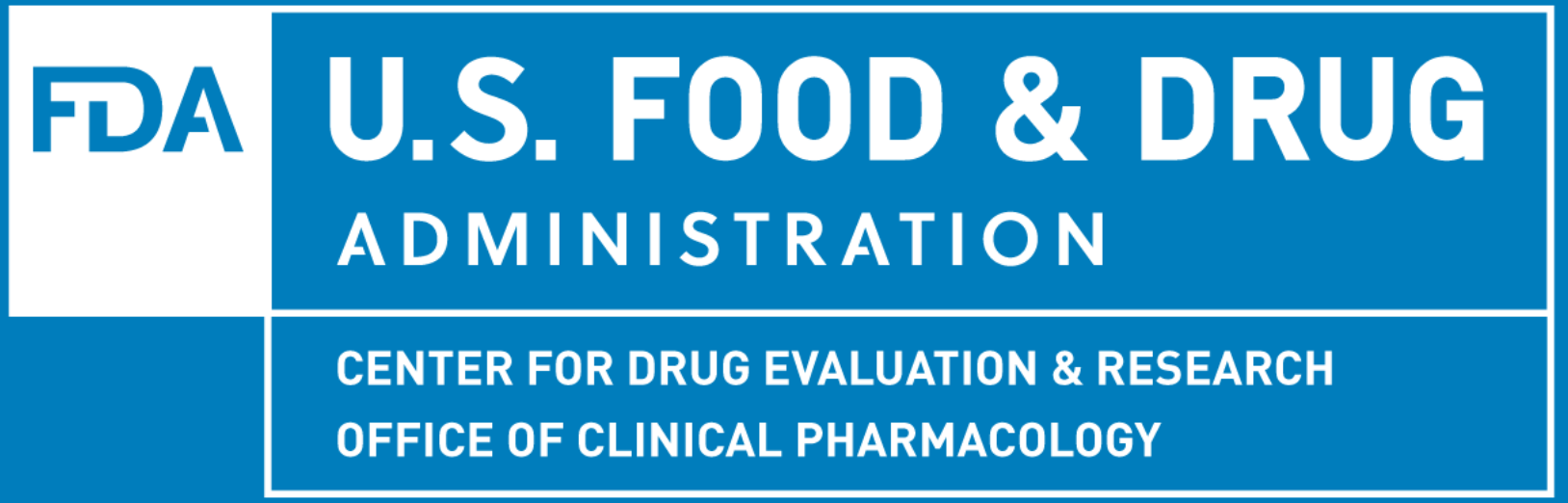

- OCP Review Staff

- Slide Preparation and Review:

  Xinyuan (Susie) Zhang, Yuching Yang, Jianghong Fan

  Kim Bergman, Qi Liu, Kellie Reynolds, Xinning Yang, Liang Zhao, Issam Zineh

- IND/NDA/BLA Applicants
- Academia Collaborators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