U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

PBPK Current Status and Challenges: A Regulatory Perspective

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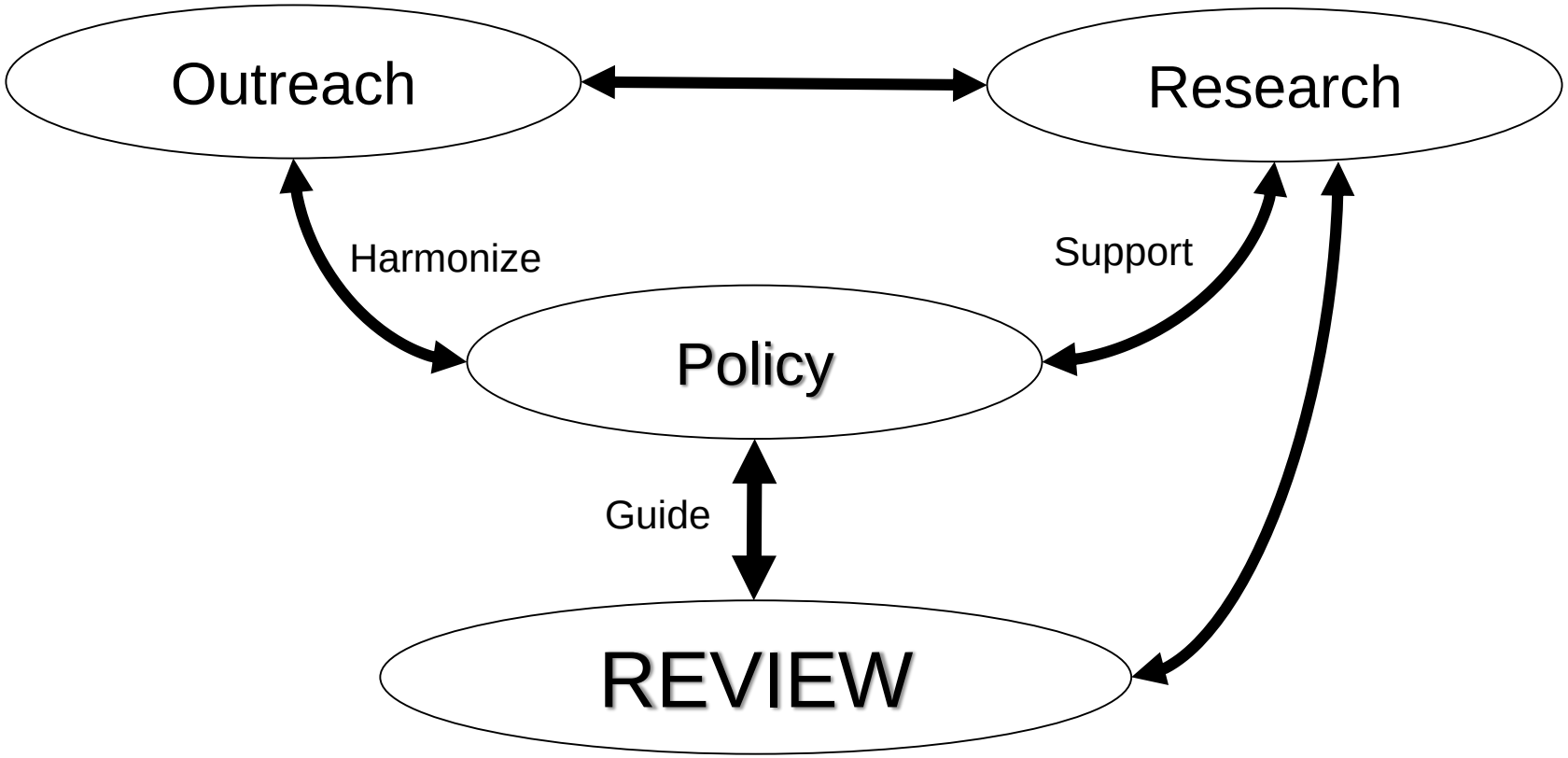
Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making

November 18, 2019
Silver Spring, MD

Outline

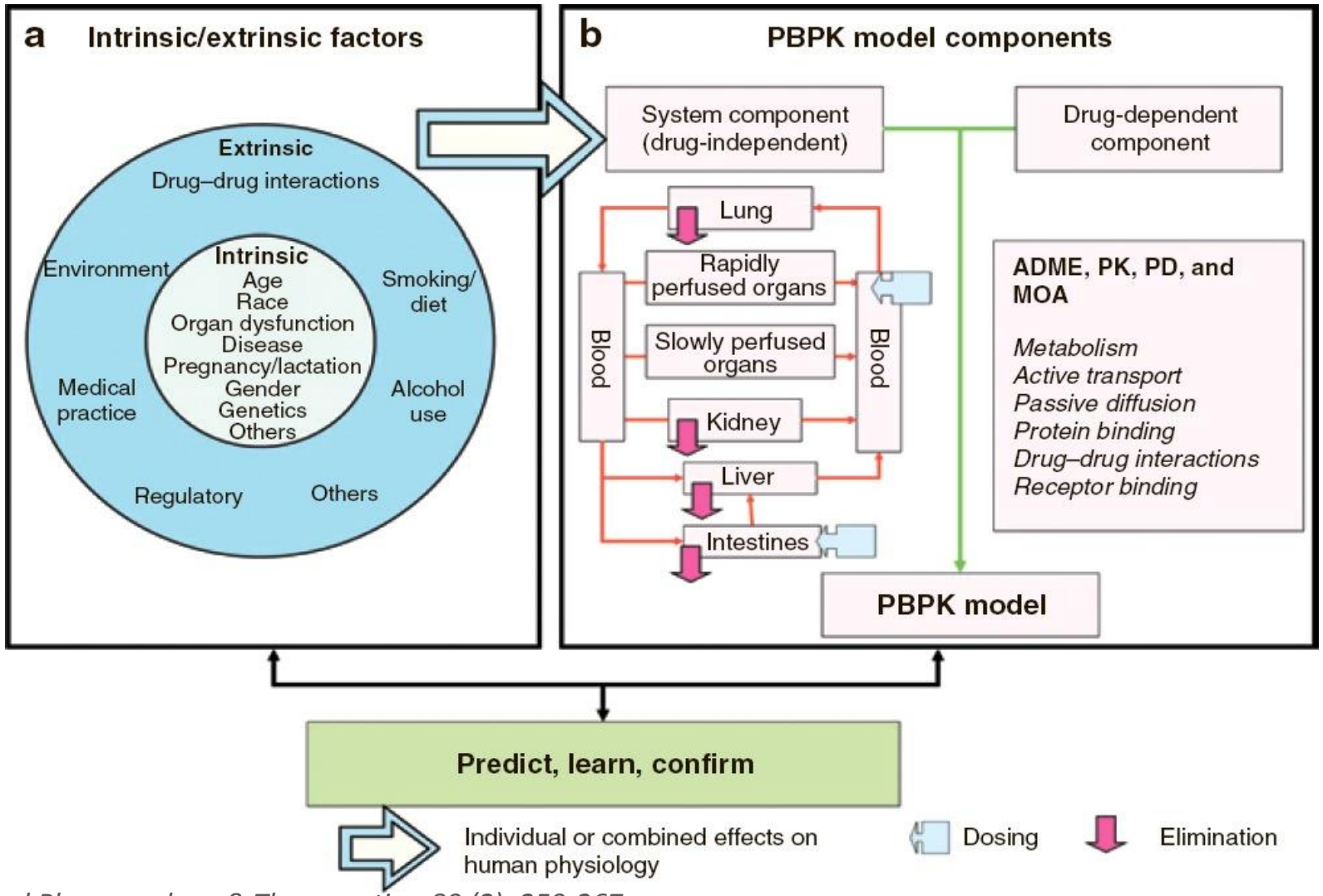
- Regulatory efforts in advancing PBPK M&S
  - Submission update
  - PBPK related guidances
  - Model informed drug development (MIDD) and PBPK
    - Workshops and Advisory Committee Meetings
- Challenges and proposals
- Summary

What do we do?



Modified from Zhao P. 2015 AAPS

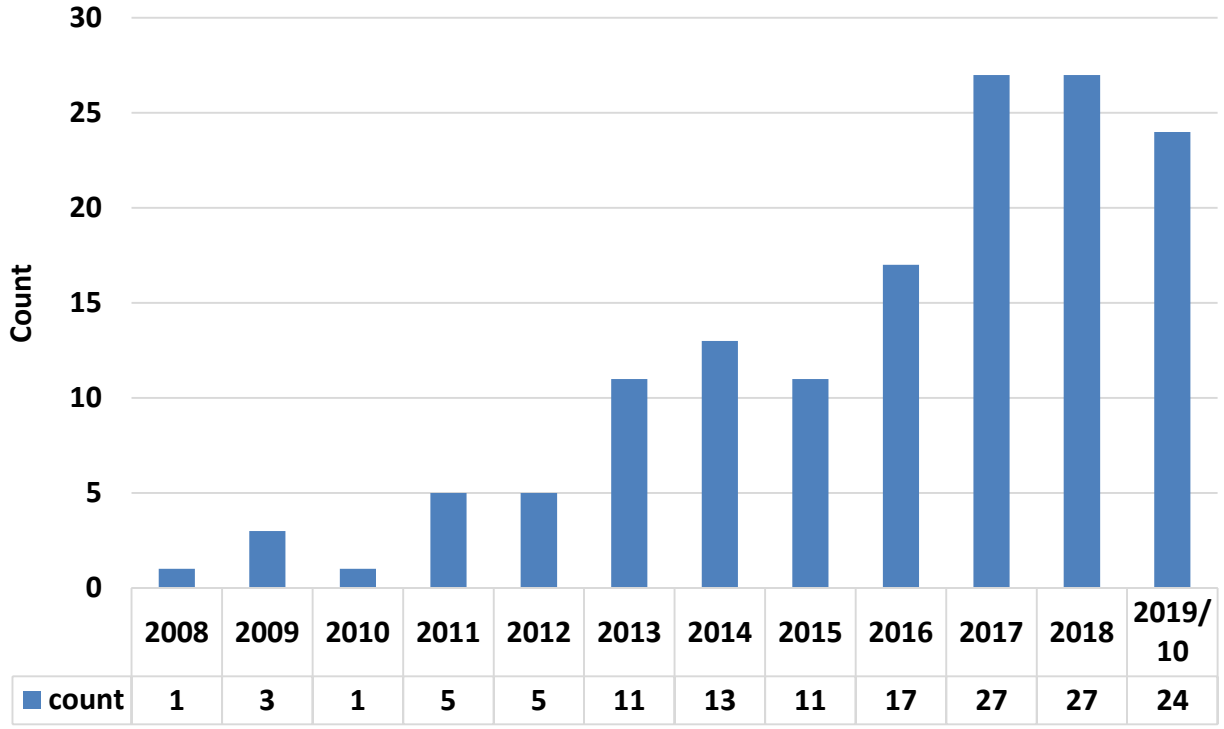
Utility of PBPK in Clinical Pharmacology Reviews



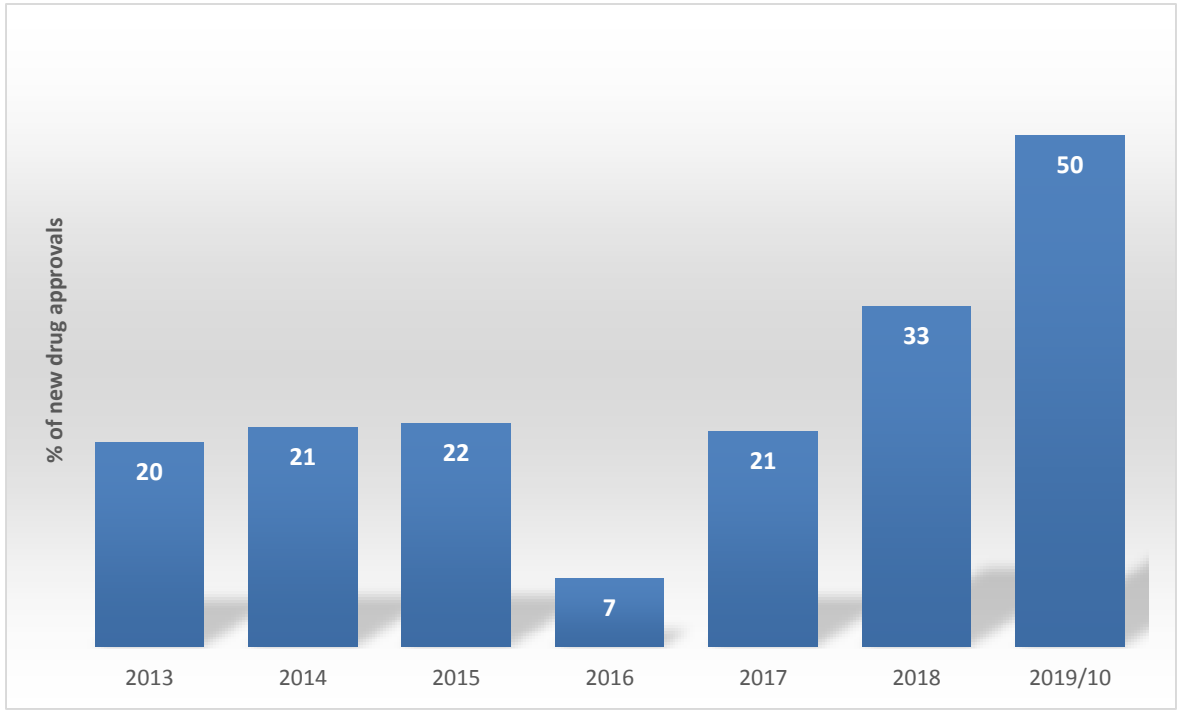
Zhao P., et al., 2011, Clinical Pharmacology & Therapeutics, 89 (2): 259-267.

Number of NDA/BLA Submissions to OCP Per Year Containing PBPK Analyses (updated 10/19/2019)

Number of NDA submissions containing PBPK analyses (2008-2019/10)

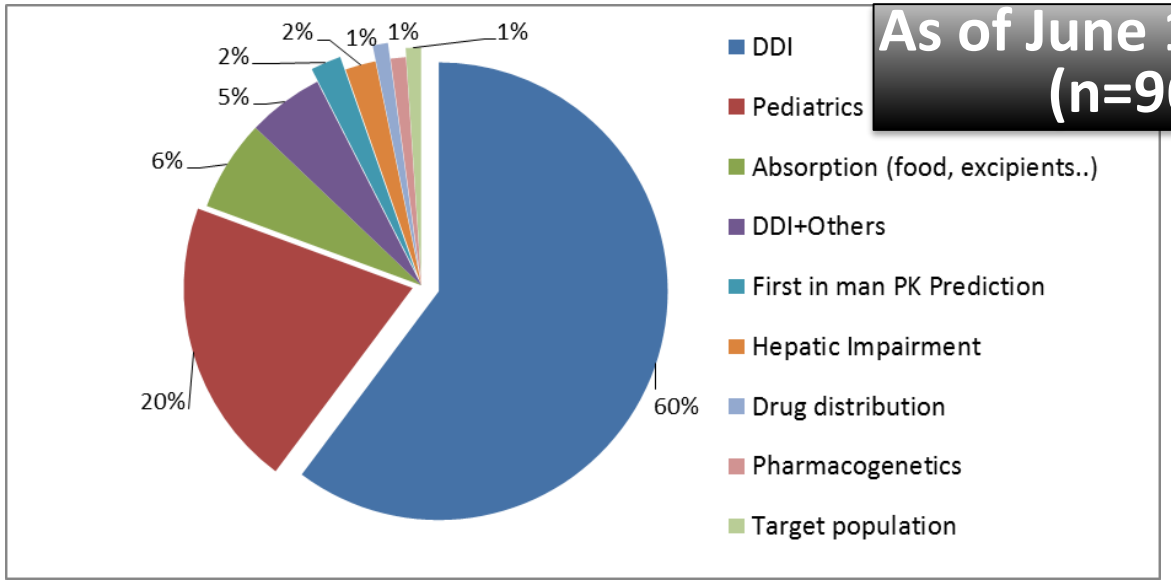


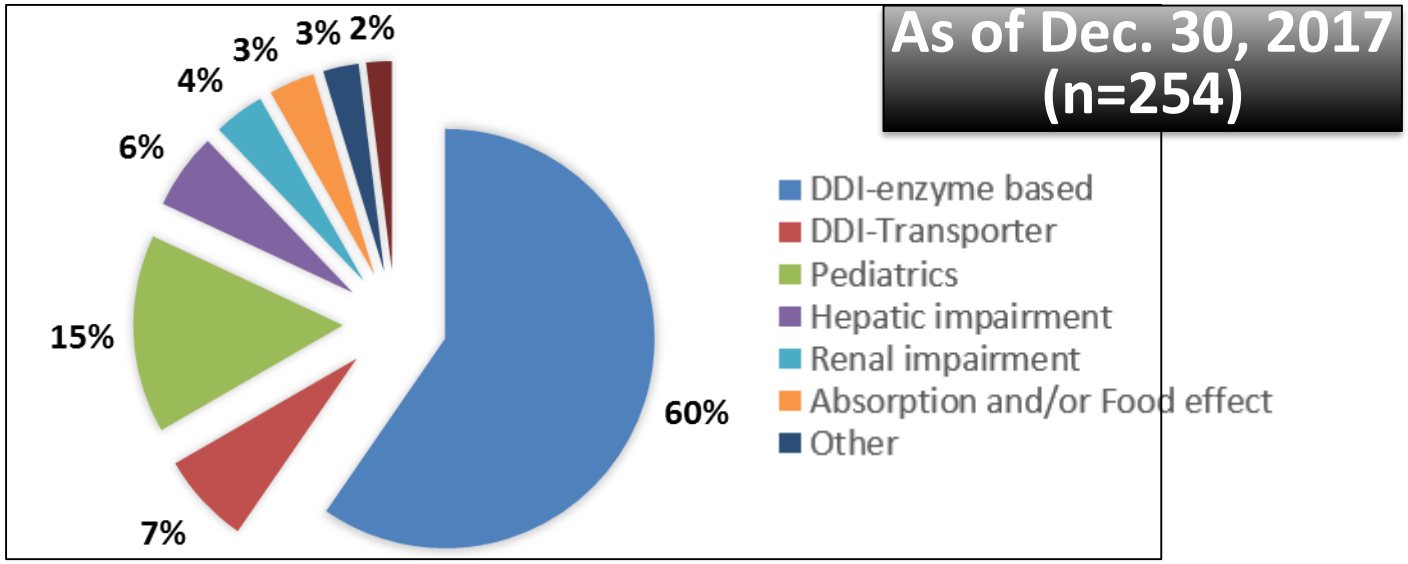
% of new drug approvals containing PBPK

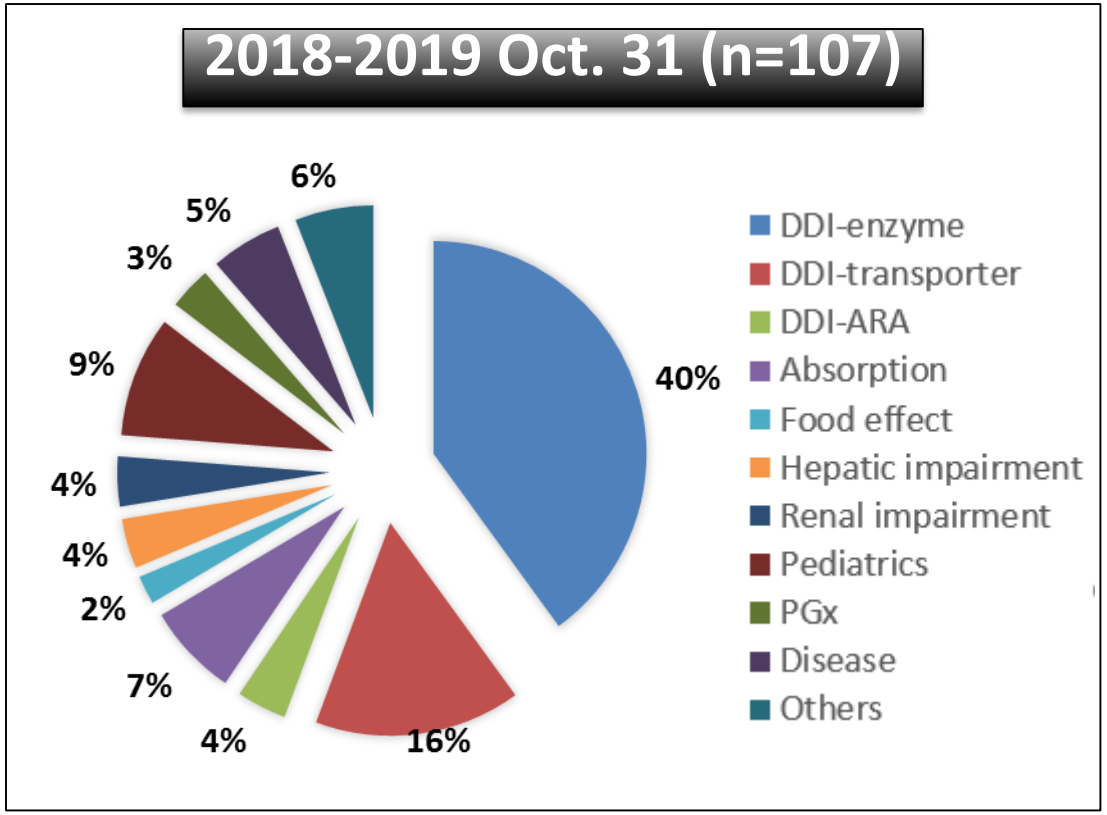


Grimstein et al. J Pharm Sci. 2019 Jan;108(1):21-25; Zhang X. 2019 PBSS workshop; Yang Y. 2019 AAPS

PBPK Submissions to OCP







Sinha, 2014 MHRA PBPK Workshop London, UK; Grimstein et al. J Pharm Sci. 2019 Jan;108(1):21-25;

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 Perpetrato

- Negative interaction prediction
- Some experience with positive interaction prediction, but knowledge gaps exist

Transporter Systems

- 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

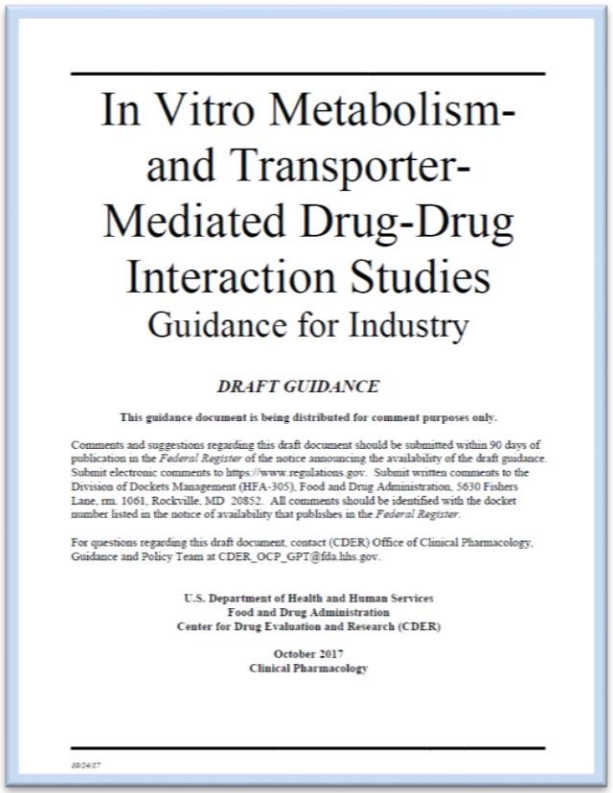
Absorption

- BCS Class I drugs
- Some experience with BCS Class II, but knowledge gaps exist
- BCS Class III and IV prediction not mature

Adapted from: Wagner, C. et al. CPT: pharmacometrics & systems pharmacology 2015; 4: 226-230; Grimstein, et al. J Pharm Sci. 2019 Jan;108(1):21-25

Slide courtesy of J. Grillo

PBPK Related Guidances



In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies

Guidance for Industry

DRAFT GUIDANCE

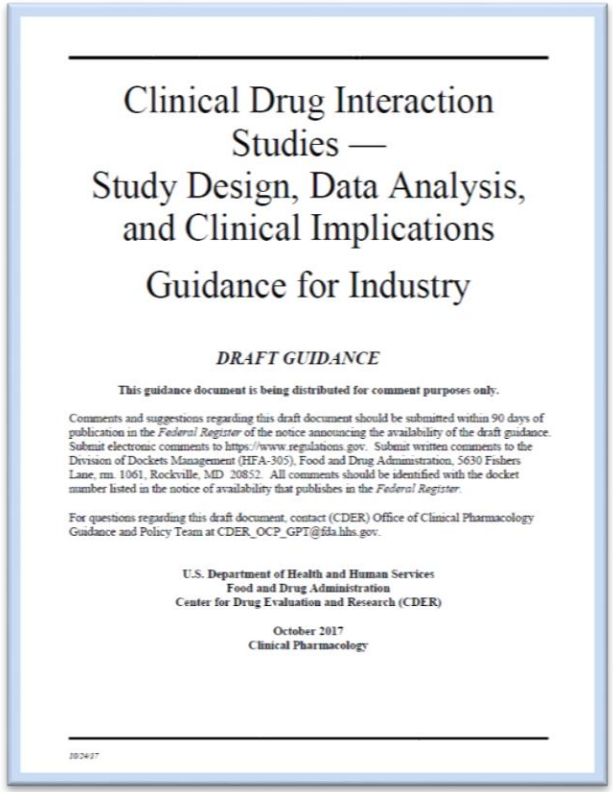
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology, Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2017
Clinical Pharmacology



Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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U.S. Department of Health and Human Services
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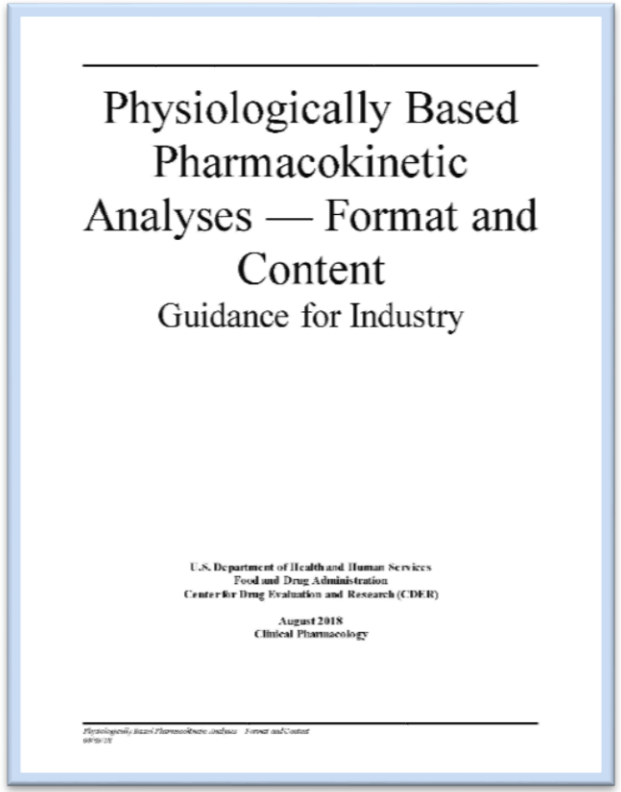
Clinical Pharmacology

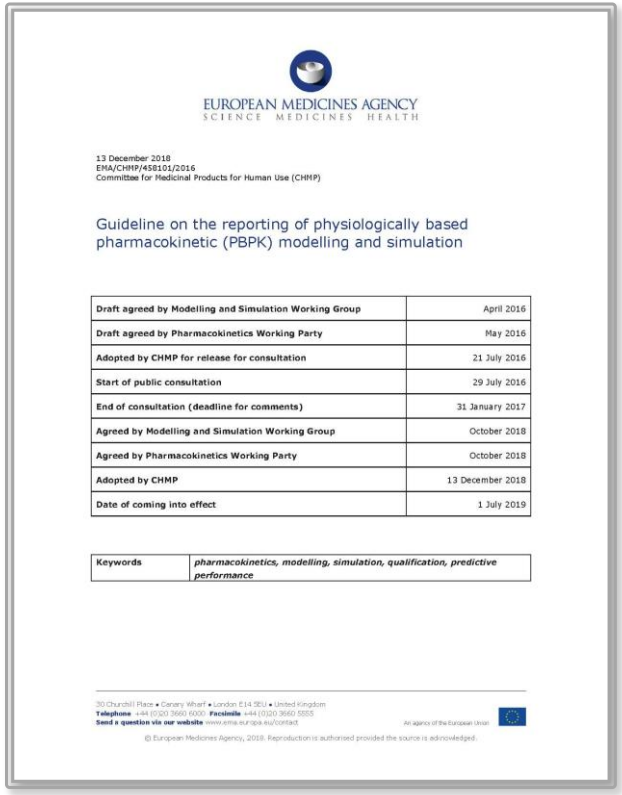


Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	*pharmacokinetics, modelling, simulation, qualification, predictive performance*

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Send a question via our website www.ema.europa.eu/contact

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https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf
https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

PBPK Analyses Report Content

Executive Summary	• Objectives (**intended uses**) • Overview of model development and simulations • Key conclusions
Introduction	• Brief and relevant drug's physicochemical, PK, PD, and E-R properties • PBPK related regulatory history including cross-referencing to PBPK study reports for different **intended uses**
Materials and Methods	• Details about model development, verification/modification (justification), and application • Details and sources of input parameters and key assumptions • Simulation design • Software (version)
Results	• Results from model verification/validation, and sensitivity analysis • Results from model application
Discussions	• Discuss the adequacy of PBPK analyses to support **intended uses** • Discuss any recommendation based on PBPK analyses and additional relevant evidence • Discuss model limitation
Appendices	• List of tables, figures, acronyms and abbreviations, references

https://www.fda.gov/media/101469/download

Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

Yaning Wang[1]*, Hao Zhu[1], Rajanikanth Madabushi[1], Qi Liu[1], Shiew-Mei Huang[1] and Issam Zineh[1]

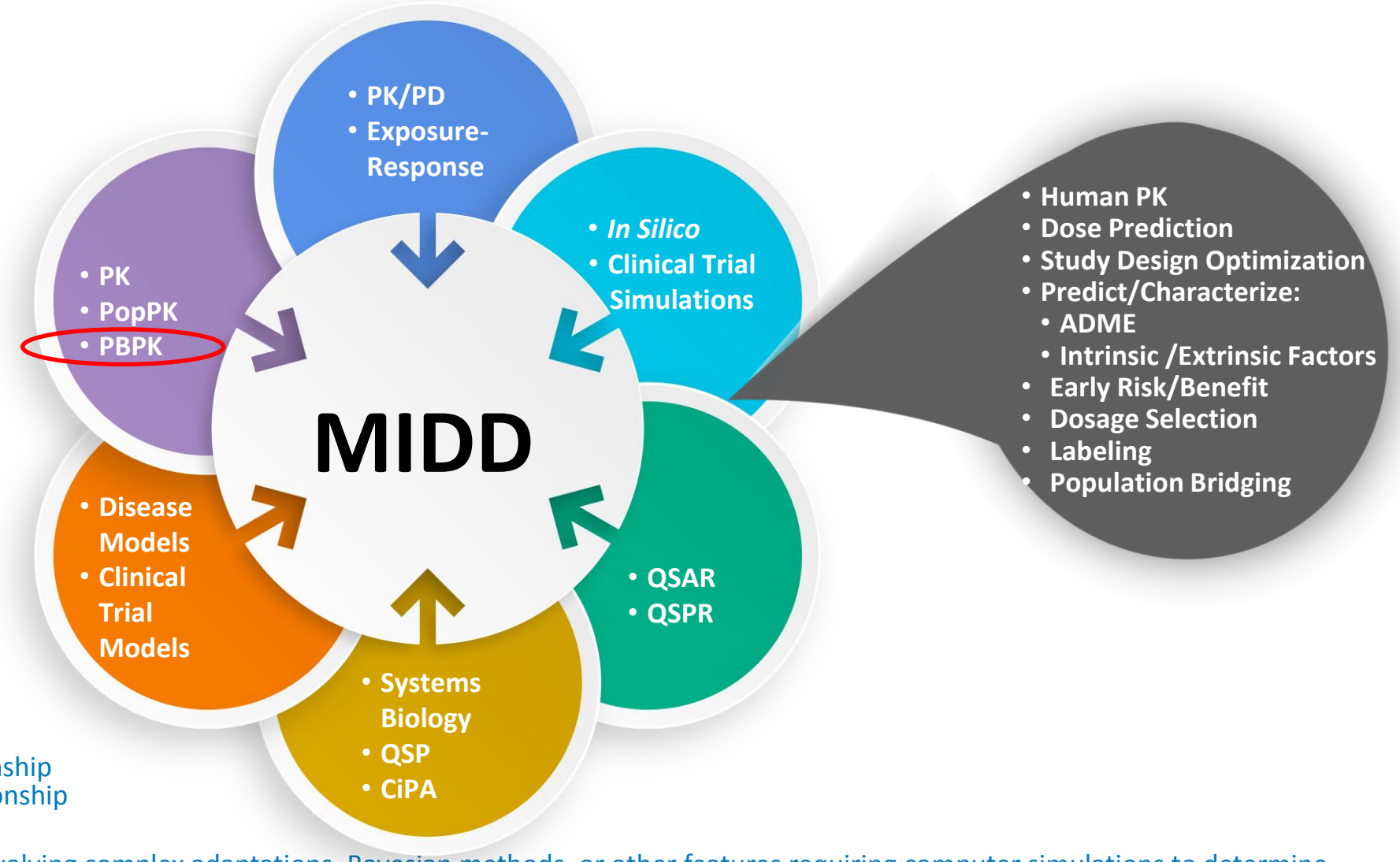
Model-informed drug development (MIDD) refers to the application of a wide range of quantitative models in drug development to facilitate the decision-making process. MIDD was formally recognized in Prescription Drug User Fee Act (PDUFA) VI. There have been many regulatory applications of MIDD to address a variety of drug development and regulatory questions. These applications can be broadly classified into four categories: dose optimization, supportive evidence for efficacy, clinical trial design, and informing policy. Case studies, literature papers, and published regulatory documents are reviewed in this article to highlight some common features of these applications in each category. In addition to the further development and investment in these established domains of application, new technology, and areas, such as more mechanistic models, neural network models, and real-world data/evidence are gaining attention, and more submissions and experiences are being accumulated to expand the application of model-based analysis to a wider scope.

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 105 NUMBER 4 | APRIL 2019

Huang SM 2019 AAPS

Model-Informed Drug Development

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 simulations to determine the operating characteristics of a confirmatory clinical trial.

Advisory Committee Meetings and Public Workshops on PBPK Modeling

- 2019: Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making
- 2019: Regulatory Education for Industry (REdI) and CERSI Workshop: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls
- 2017: Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Session I: Role for physiologically based pharmacokinetic (PBPK) modeling and simulation in drug development and regulation
- 2016: Public workshop: Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation Workshop

●●●●●●

- 2014: Public workshop: Application of Physiologically Based Pharmacokinetic Modeling to Support Dose Selection
- 2012: Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Topic 4: applications of PBPK modeling in pediatric studies

Needs for PBPK Modeling Best Practices

FDA perspective paper

- ***Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review*** (CPT 2011, PMID: 21191381)
- ***Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions*** (CPT 2012, PMID: 22713733)
- ***The Utility of Modeling and Simulation in Drug Development and Regulatory Review*** (JpharmSci 2013, PMID: 23712632)
- ***Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK*** (CPT-PSP 2015, PMID: 26225246)
- ***Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology*** (JpharmSci 2019, PMID: 30385284)
- ***Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation*** (CPT-PSP 2019, PMID: 31652029)

Industrys/academic comments

- ***Physiologically-Based Pharmacokinetics in Drug Development and Regulatory Science*** (Ann. Rev. Pharmacol. Toxicol 2011, PMID: 20854171)
- ***Physiologically based pharmacokinetic modeling in drug discovery and development: A pharmaceutical industry perspective*** (CPT 2015, PMID: 25670209)
- ***Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A Systematic Review of Published Models, Applications, and Model Verification*** (DMD 2015, PMID: 26296709)
- ***Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation***(CPT-PSP 2015, PMID: 27069774)
- ***Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective*** (CPT 2018, PMID: 29315504)
- ***Model-Informed Drug Discovery and Development: Current Industry Good Practice and Regulatory Expectations and Future Perspectives*** (CPT-PSP 2019, PMID: 30411538)

Selected examples only

Challenges and Proposals

Challenges	Proposals
System parameters: • Lack of understanding in transporter expression/activity • Lack of understanding in ontogeny	Methodology development
Drug parameters: • Limited confidence in IVIVE in certain scenarios • Lack of characterization of drug disposition	Methodology development
Limited review timelines for complex models	Process: early communication with relevant review divisions Resource: knowledge management

Collaboration Opportunities

- **Academic Institutions**
  - Collaborative Agreements (e.g., MOU, CRADA)
  - CDER Network of Experts (NoE) Program
- **Academic Faculty**
  - Faculty Sabbatical/Scientific Visit Program
  - Advisory Committees (AC)/Special Government Employee (SGE)
- **Professional & Graduate Students**
  - Doctor of Pharmacy APPE Rotations
    - Clinical Pharmacology
    - Drug Labeling
  - Student Summer Internships (Salaried)
    - Professional and Graduate Students
  - ORISE Fellows
- **Industry**
  - IQ consortium
- **Platform developers**

MOU: https://go.usa.gov/xQxVa; **NoE:** https://go.usa.gov/xQxyu; **AC:** https://go.usa.gov/xQxVk; **APPE:** https://go.usa.gov/xQxV5; **ORISE:** https://go.usa.gov/xQxVN

Summary

- **PBPK submission becomes routine at FDA**
- **Accumulating experience in non-DDI scenarios**
- **Active research is ongoing to support future guidance development and review activity**

Acknowledgements

- FDA fellows:
  - Yu Jiang
  - Hechuan Wang
  - Shaun S. Kumar
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- FDA OCP/DPM
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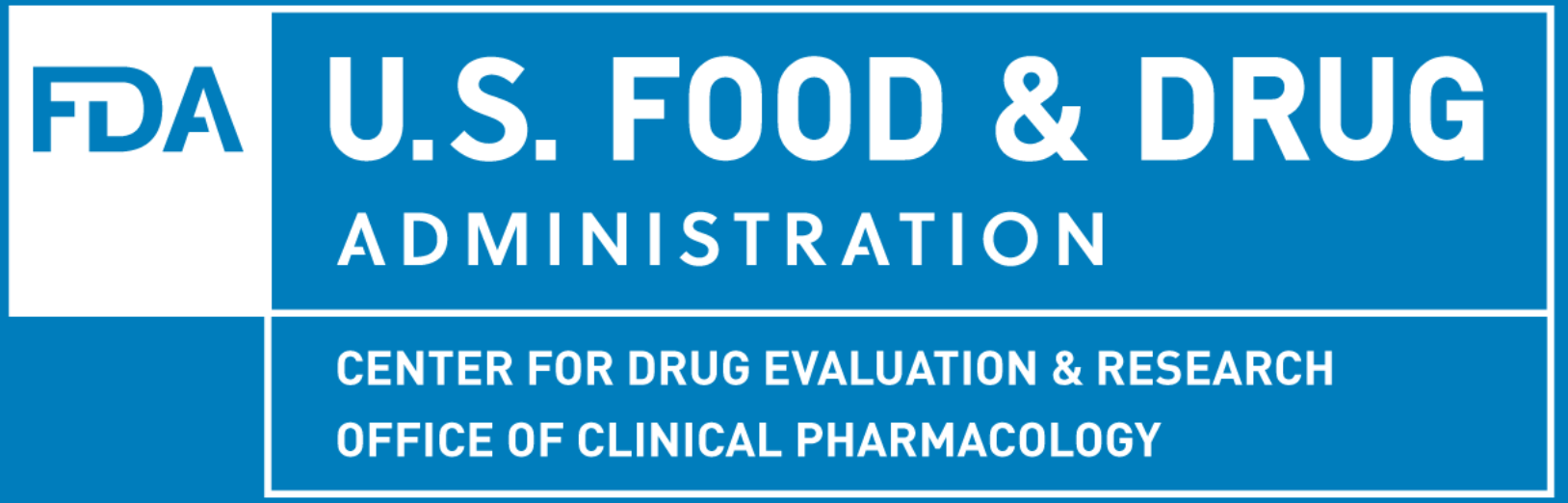
  - Jianghong Fan
  - Manuela Grimstein
  - Xinyuan Zhang
  - Yuching Yang
- FDA OCP IO
  - Joe Grillo
  - Shiew-Mei Huang
  - Issam Zineh
  - EPPM staff

THANK YOU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