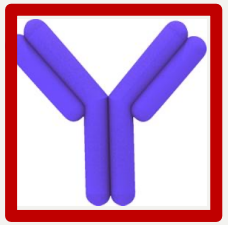
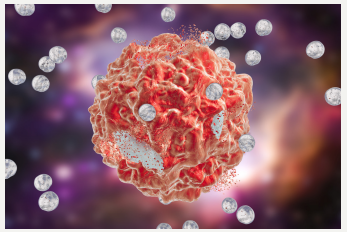
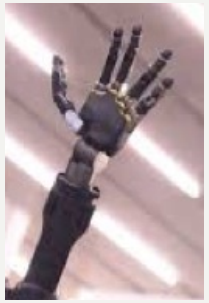
Academic-FDA Collaborations in Advancing Drug Development and Regulatory Sciences

Kathy Giacomini

UCSF

FDA Guidances and Policies Are Science-Based



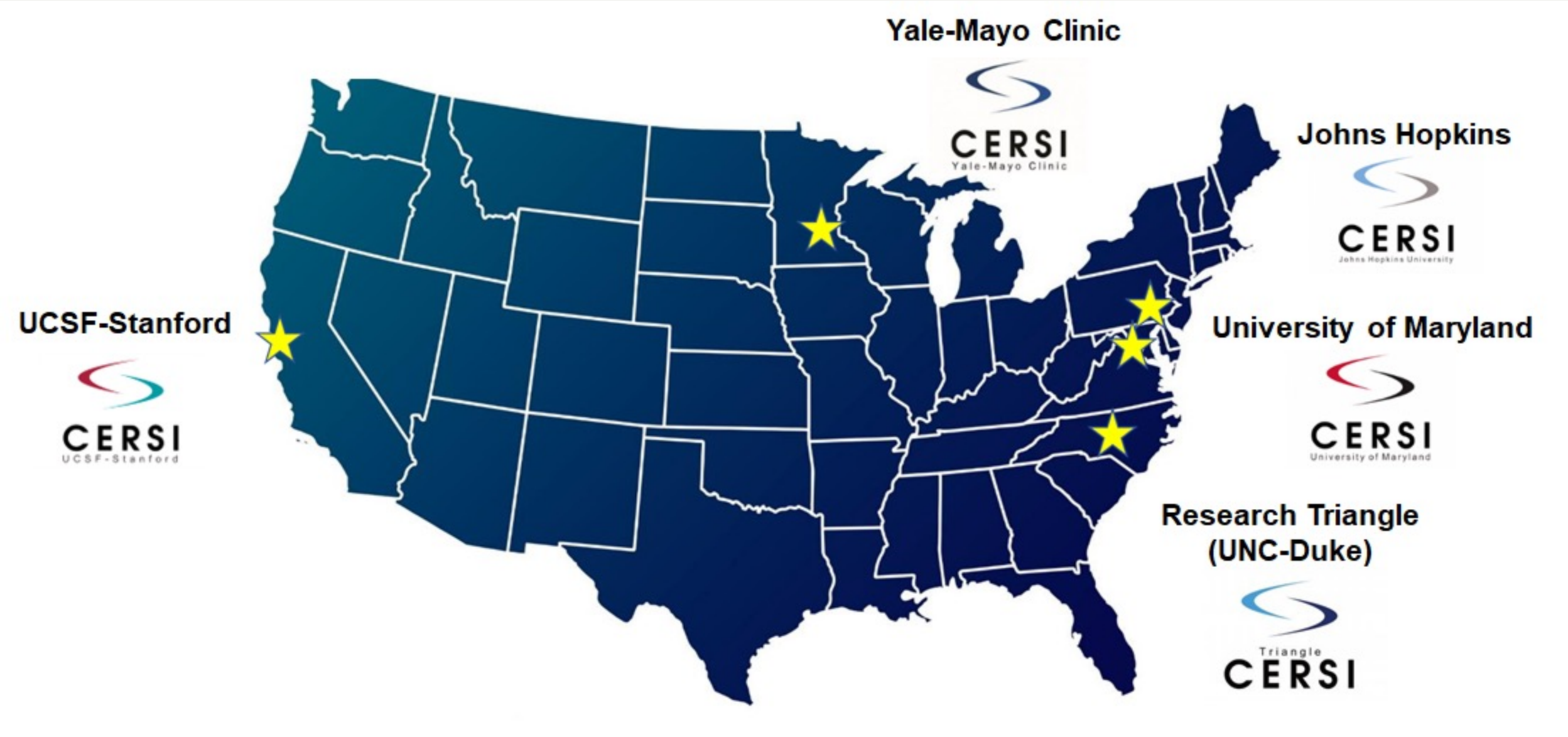
Research in Regulatory Science is Needed

Regulatory Science: Research that helps regulators make better decisions

Unmet Needs: Research Helps Regulators Do Their Jobs, Altman RB et al., Science Translational Medicine, 315:22, 2015

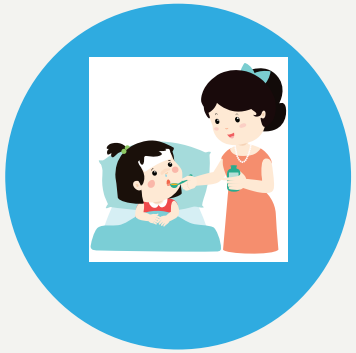
CERSI
UCSF-Stanford

FDA Established Centers of Excellence In Regulatory Science and Innovation (CERSIs)



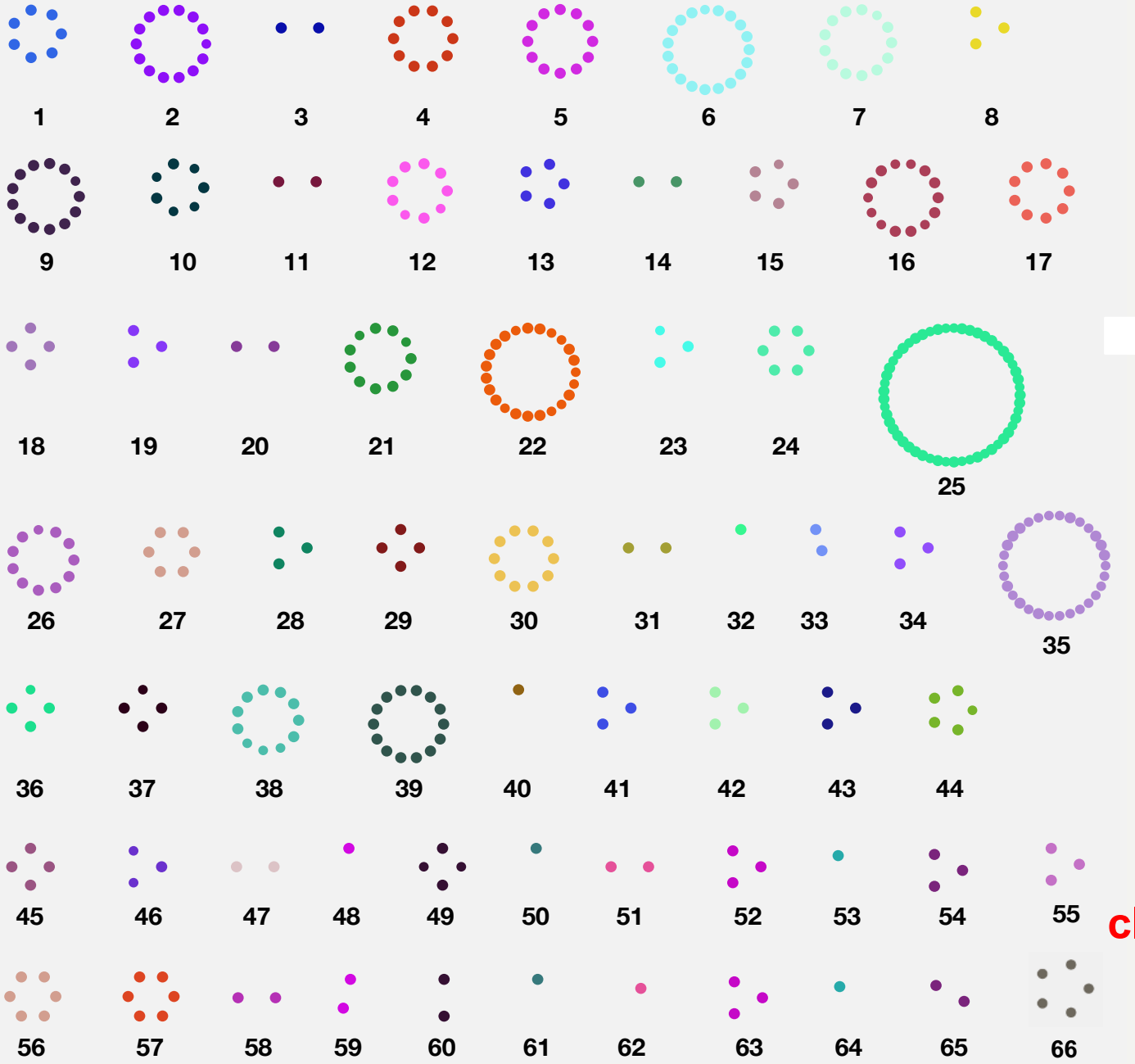
FDA Guidances Informing:

DRUG-DRUG INTERACTIONS



PEDIATRIC DOSING

OTHER



Solute Carrier Superfamily in the Human Genome

Which transporters are responsible for clinically important drug-drug interactions?

D. Drew et al., Chem Rev, 2021

Nature Reviews Drug Discovery 2010

ARTICLE

Membrane transporters in drug development

Giacomini, Kathleen M. ; Huang, Shiew-Mei ; Tweedie, Donald J. ; Benet, Leslie Z. ; Brouwer, Kim L. R. ; Chu, Xiaoyan ; Dahlin, Amber ; Evers, Raymond ; Fischer, Volker ; Hillgren, Kathleen M. ; Hoffmaster, Keith A. ; Ishikawa, Toshihisa ; Keppler, Dietrich ; Kim, Richard B. ; Lee, Caroline A. ; Niemi, Mikko ; Polli, Joseph W. ; Sugiyama, Yuicchi ; Swaan, Peter W. ; Ware, Joseph A. ; Wright, Stephen H. ; Yee, Sook Wah ; Zamek-Gliszczynski, Maciej J. ; Zhang, Lei

Nature reviews. Drug discovery, 2010-03, Vol.9 (3), p.215-236

❝ *Membrane transporters can be major determinants of the pharmacokinetic, safety and efficacy profiles of drugs...*❝

PEER REVIEWED OPEN ACCESS REVIEW ARTICLE

TOP

Nature Reviews Drug Discovery 2024

ARTICLE

Membrane transporters in drug development and as determinants of precision medicine

Galetin, Aleksandra ; Brouwer, Kim L. R. ; Tweedie, Donald ; Yoshida, Kenta ; Sjostedt, Noora ; Aleksunes, Lauren ; Chu, Xiaoyan ; Evers, Raymond ; Hafey, Michael J. ; Lai, Yurong ; Matsson, Par ; Riselli, Andrew ; Shen, Hong ; Sparreboom, Alex ; Varma, Manthena V. S. ; Yang, Jia ; Yang, Xinning ; Yee, Sook Wah ; Zamek-Gliszczynski, Maciej J. ; Zhang, Lei ; Giacomini, Kathleen M.

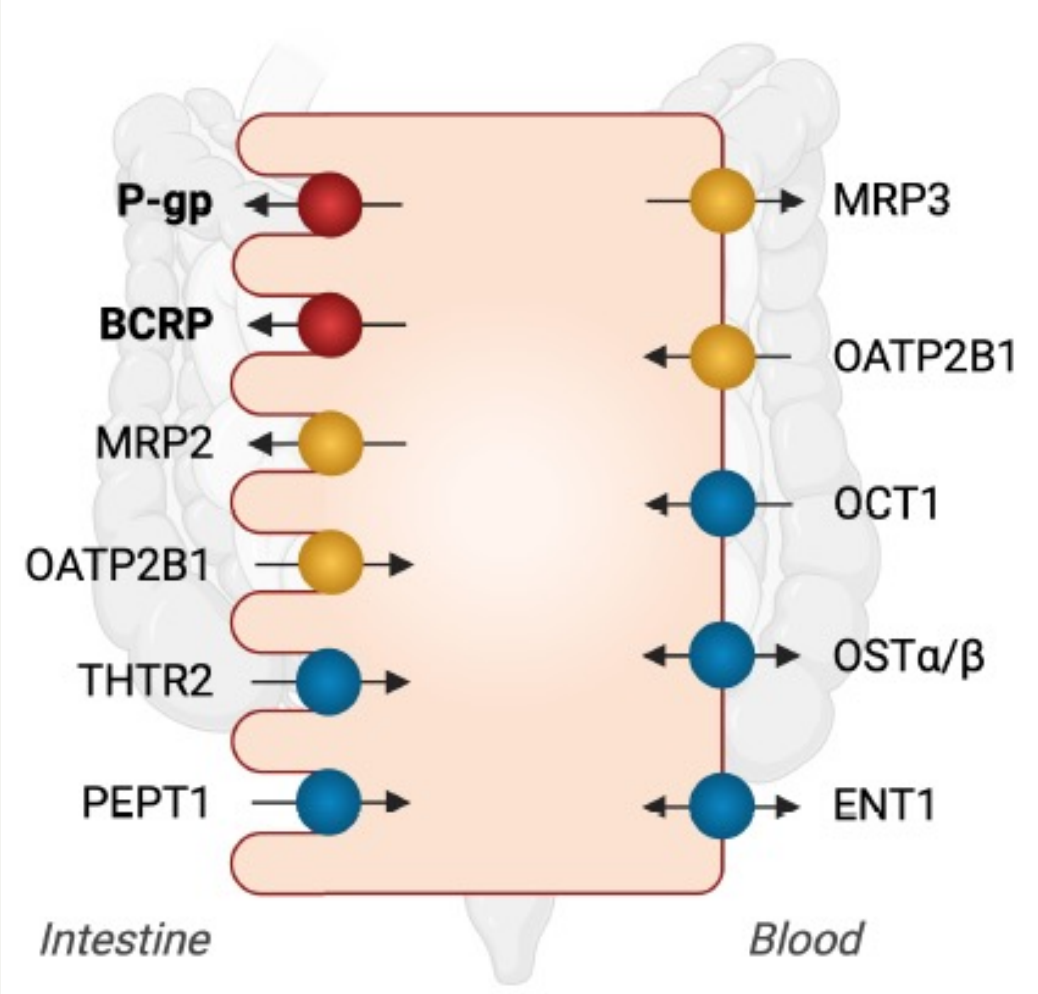
Nature reviews. Drug discovery, 2024-01

❝ *.... Since the initial publication from the International Transporter Consortium, significant progress has been made in understanding the roles and functions of transporters, as well as in the...*❝

PEER REVIEWED REVIEW ARTICLE

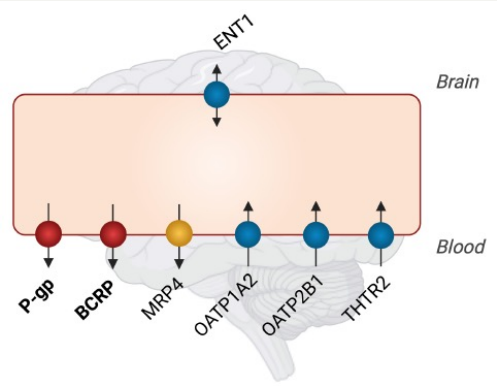
The International Transporter Consortium

Intestine

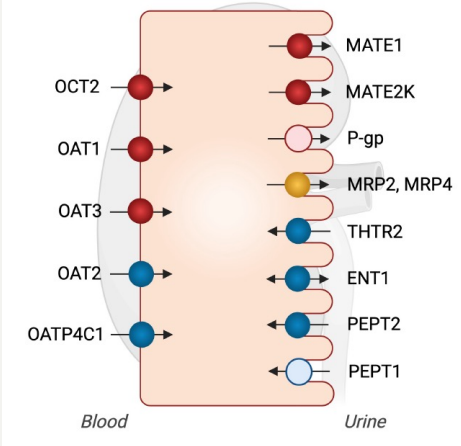


Transporters are Important Targets for Drug-Drug Interactions and Determinants of Pharmacokinetics

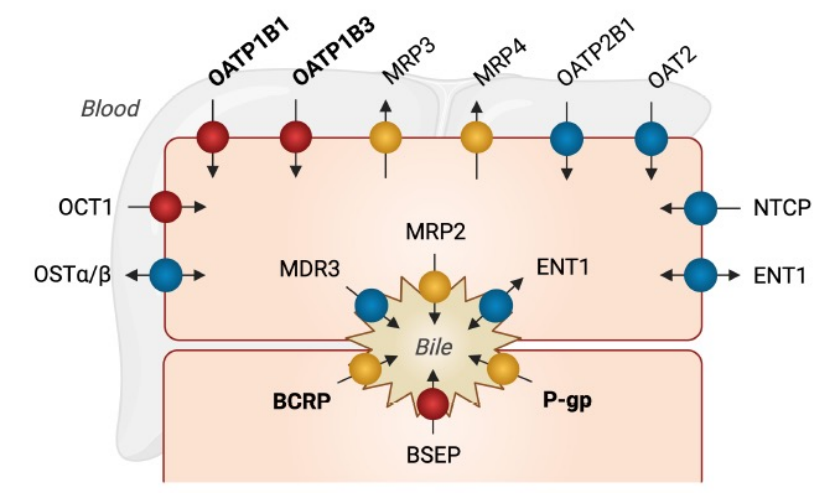
Blood-Brain Barrier



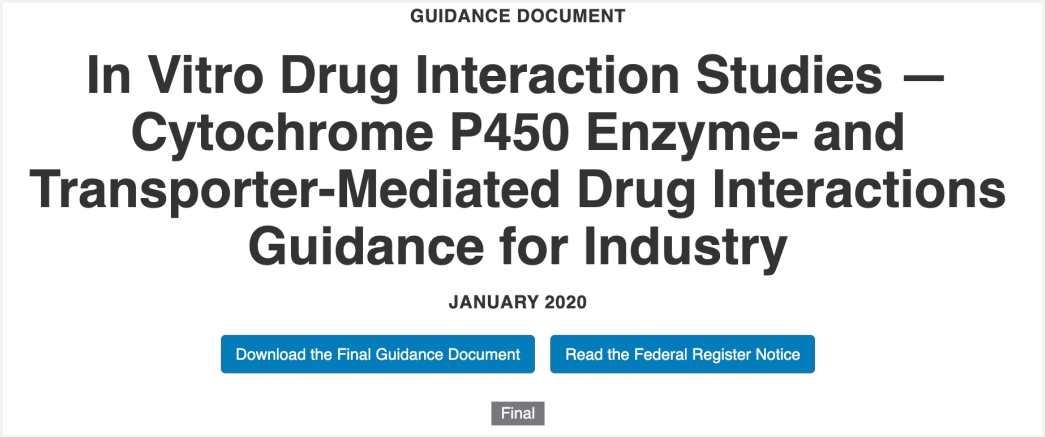
Kidney

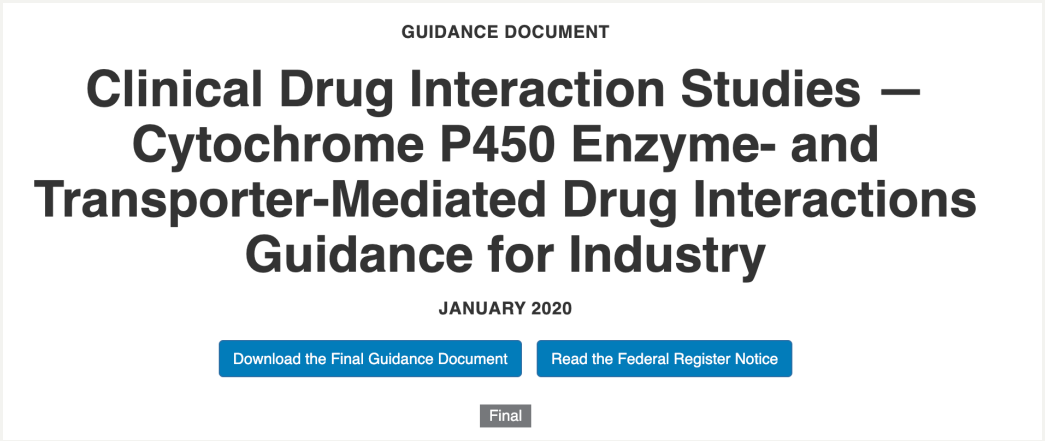


Liver



Transporters are Important Targets for Drug-Drug Interactions and Determinants of Pharmacokinetics





FDA Guidances from the Office of Clinical Pharmacology

FDA Guidances Informing:

DRUG-DRUG INTERACTIONS

PEDIATRIC DOSING

OTHER

50% of Drugs Are Not Approved for Pediatric Dosing

J Pediatr Pharmacol Ther. 2020; 25(3): 175–191.
doi: 10.5863/1551-6776-25.3.175
PMCID: PMC7134587
PMID: 32265601

*K*ey Potentially *I*nappropriate *D*rugs in Pediatrics: The KIDs List

Rachel S. Meyers, PharmD, Jennifer Thackray, PharmD, Kelly L. Matson, PharmD, Christopher McPherson, PharmD, Lisa Lubsch, PharmD, Robert C. Hellinga, PharmD, and David S. Hoff, PharmD

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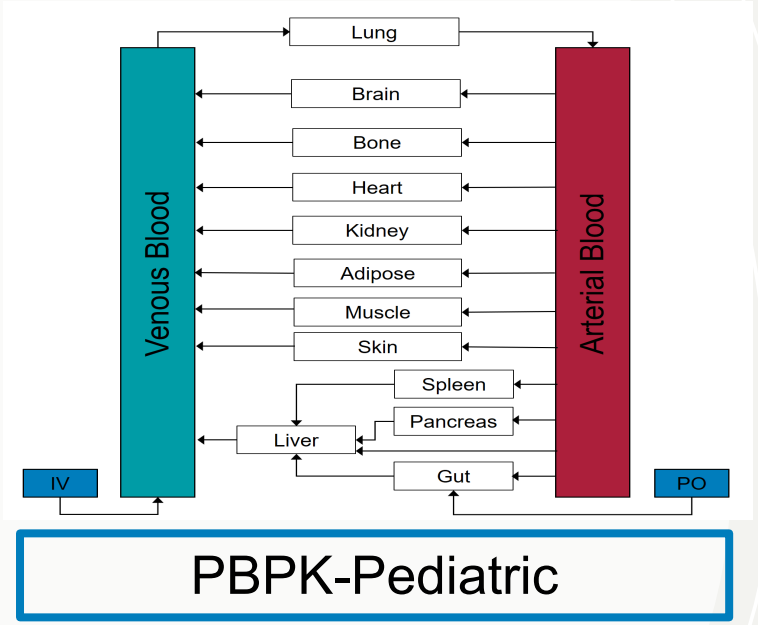
In fact, 50% of medications in the United States are still not labeled for use in children.[17]

General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

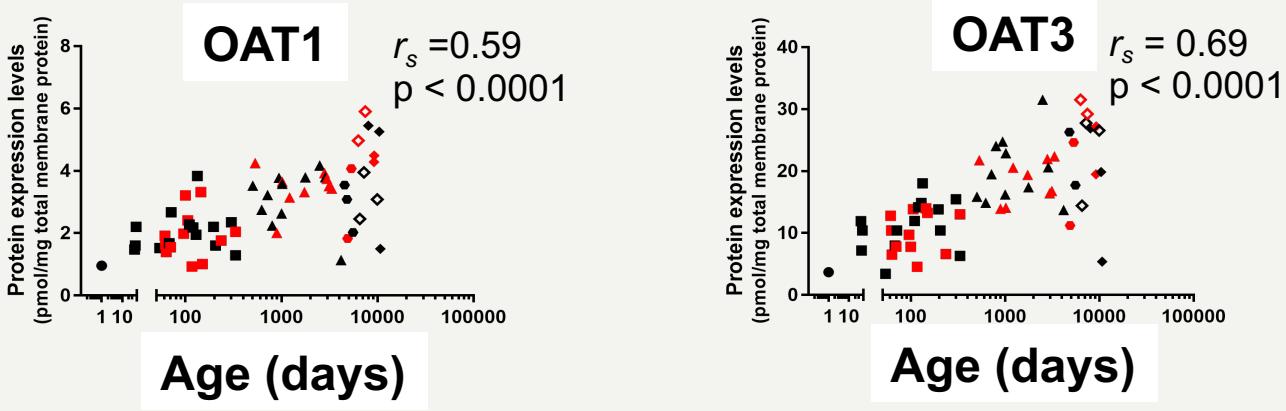
FDA Guidance 2020



"For example, the development of a PBPK (Physiologically Based Pharmacokinetic) ...model that integrates drug-dependent parameters (e.g., ... metabolic enzymes, transporters, and proteins) ..... is one possible approach."

Are there developmental changes in the expression level of drug transporters?

CERSI Collaboration: Renal Transporters Show Changes in Expression Levels with Age in Kidneys



Clinical Pharmacology & Therapeutics

Article | Open Access

A Comprehensive Analysis of Ontogeny of Renal Drug Transporters: mRNA Analyses, Quantitative Proteomics, and Localization

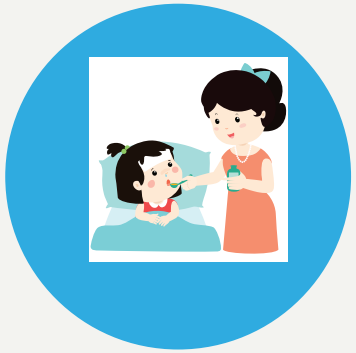
Kit Wun Kathy Cheung, Bianca D. van Groen, Edwin Spaans, Marjolein D. van Borselen, Adrianus C.J.M. de Bruijn, Ytje Simons-Oosterhuis, Dick Tibboel, Janneke N. Samsom, Robert M. Verdijk, Bart Smeets, Lei Zhang, Shiew-Mei Huang, Kathleen M. Giacomini, Saskia N. de Wildt

FDA and Academic Co-Authors

ORISE Fellow

FDA Guidances Informing:

DRUG-DRUG INTERACTIONS



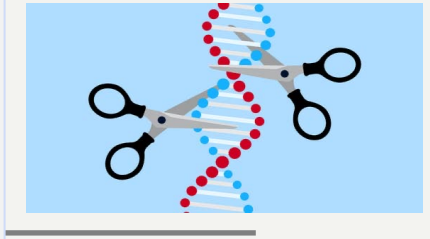
PEDIATRIC DOSING

OTHER

Examples of CERSI/FDA Research Projects and Goals

1. Projects: Genome Editing and Cell-Based Therapies

Goal: Provide unbiased comparison of two of the major methods (bioinformatics and in vitro methods) of identifying potential CRISPR/Cas9 off-target sites in human blood stem cells



2. Projects: OneSource & Defining Strength of Evidence in Therapeutic Development

Goal: Improve electronic health systems for clinical trials, and statistical framework and efficiency

3. Projects: Patient Preference and Patient Reported Outcomes

Goal: Include patient preference in regulatory decisions when weighing risks and benefits of new medical products

4. Projects: Safety and Effectiveness of COVID-19 Vaccines

Goal: Use real world data to ensure medical product safety and efficacy

Summary and Conclusions

1. Multi-sector consortia such as the International Transporter Consortium, which include subject matter experts from academia, industry and FDA are valuable in reviewing the evidence and making recommendations that inform regulatory guidances.

2. Several FDA supported research collaborations through the UCSF-Stanford CERSI were presented including pediatric dosing, and collaborations on CRISPR CAS9 products, simplifying clinical trials through harmonizing databases, incorporating patient preferences into regulatory decisions, and protecting public health through surveying new products such as COVID vaccines during the pandemic.

.





Acknowledgements: UCSF-Stanford CERSI Team

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Chair, Scientific Advisory Board

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Acknowledgements: FDA CERSI Team 2024

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CERSI Program Leader
Triangle CERSI Program Official

Special thanks to dozens of FDA scientists who serve as subject matter experts on our CERSI projects!


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