

FDA/MCERSI Workshop



U.S. FOOD & DRUG
ADMINISTRATION

**Pediatric Ontogeny: Ready for Incorporation into Modeling
in Pediatric Drug Development?**

May 16, 2019, Natcher Conference Center, Bethesda, MD

Ontogeny of Transporter Function

Shiew-Mei Huang

Office of Clinical Pharmacology

Office of Translational Sciences

CDER/FDA

Prior Recommendations of a Pediatric Transporter Working Group



Human Ontogeny of Drug Transporters: Review and Recommendations of the Pediatric Transporter Working Group

KLR Brouwer¹, LM Aleksunes², B Brandys³, GP Giacoia⁴, G Knipp⁵, V Lukacova⁶, B Meibohm⁷, SK Nigam⁸, M Rieder⁹, and SN de Wildt¹⁰, on behalf of the Pediatric Transporter Working Group

Table 4 Recommendations

- Build multidisciplinary, international collaborative networks to facilitate collection and sharing of data on pediatric transporters, including expertise in preclinical studies (e.g., knockout and *in vitro* models), pediatrics, clinical pharmacology, pharmacogenomics, pharmacometrics, and pharmacovigilance
- Establish central (perhaps regional) tissue repositories where surgical and postmortem samples can be stored with clear guidelines for tissue collection and handling to preserve sample integrity
- Continue to support the training of scientists in pediatric clinical pharmacology with expertise in transporters, pharmacogenomics, pharmacometrics, and pharmacovigilance
- Increase the awareness of clinicians regarding the importance of transporters in pediatric drug disposition
- Identify examples relevant to pediatric pharmacotherapy where developmental differences in transporter expression or activity could translate into clinically relevant effects
- Work with professional groups to develop guidelines on how drug therapy may be altered due to variations in transporter expression or activity
- Identify selective and specific biomarkers for transporter activity in pediatric patients
- Investigate basic developmental mechanisms regulating transporter expression and activity in the different organs in pediatric health and disease
- Develop pediatric-relevant *in vitro/in silico* and systems biology models to predict transporter function in the context of overall drug disposition

Human Transporters



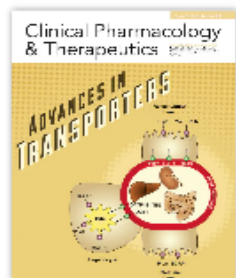
Clinical Pharmacology
& Therapeutics

November 2018

The International Transporter Consortium: Summarizing Advances in the Role of Transporters in Drug Development

Kathleen M. Giacomini, Aleksandra Galetin, Shiew Mei Huang

- Transporter of emerging clinical importance
- Clinical evaluation of transporter-mediated drug-drug interactions
- Disease associated changes in transporter expression and/or activity
- Novel methods and best practices (in vitro, in vivo, in silico and their integrated application) have been presented
- Knowledge gaps need to be addressed via collaborative efforts, such as ITC

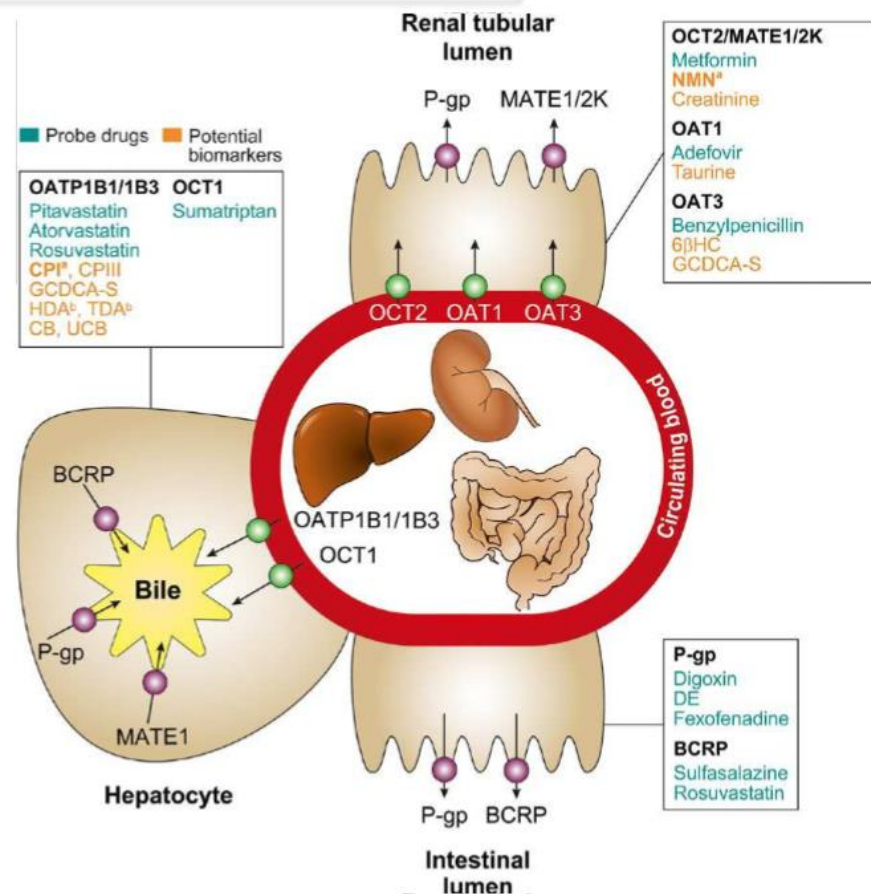


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Advances in Transporters

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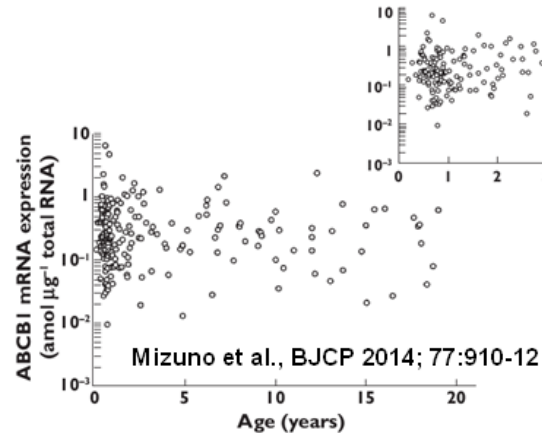
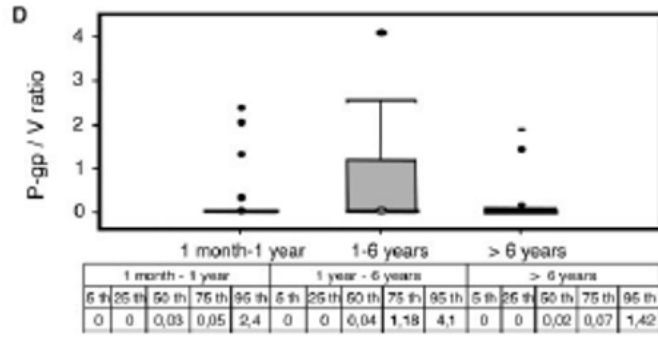
Chu X et al. ITC Consortium, Clin Pharmacol Ther 2018

S-M Huang 3

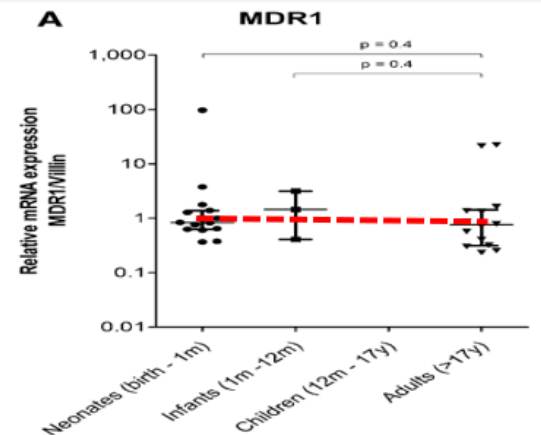
Ontogeny of Intestinal Transporters

P-gp mRNA data

Fakhoury et al., DMD 2005; 33: 1603



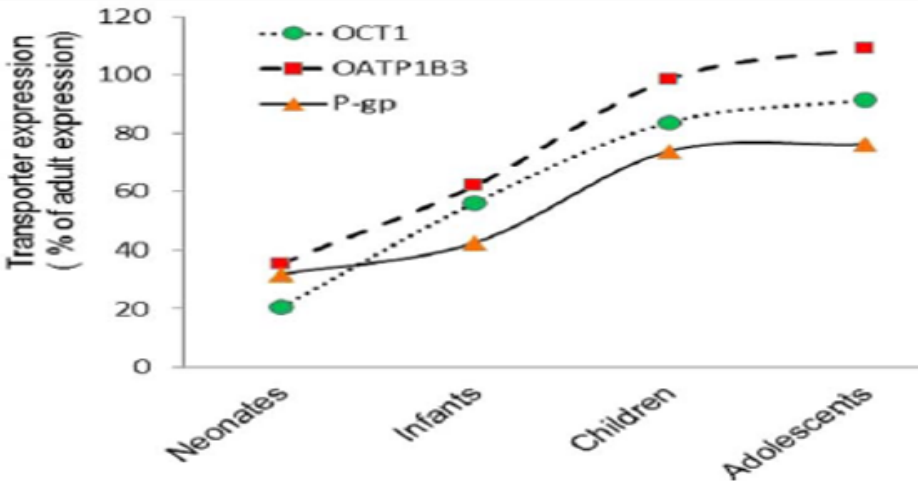
Mooij et al., DMD 2014; 42: 1268



There appears to be no change with intestinal P-gp expression with age

Ontogeny of Liver Transporters

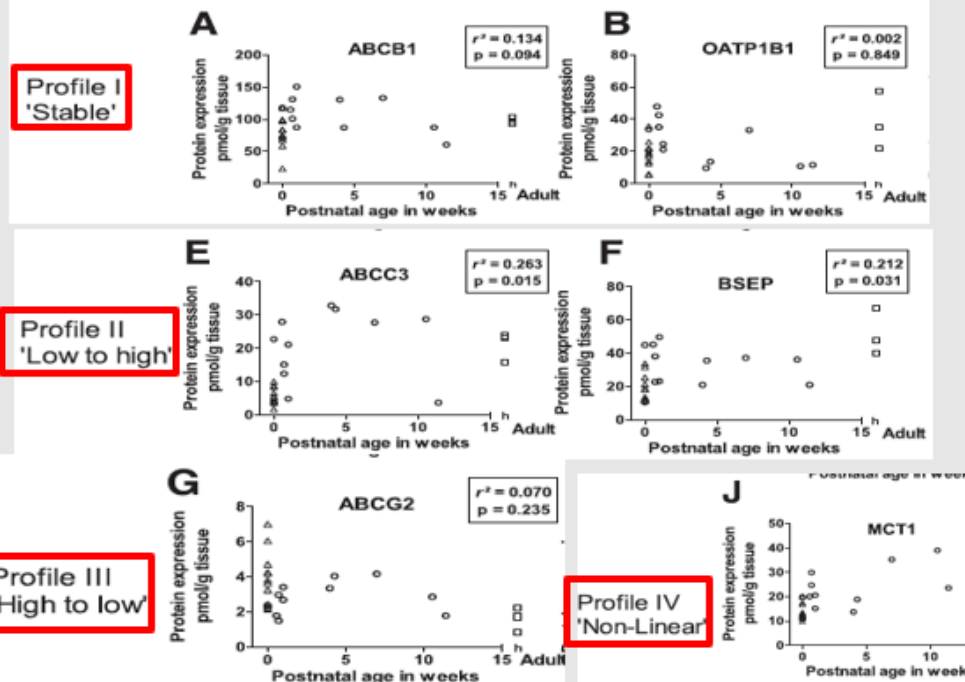
Protein abundance



OCT1, OATP1B3 & P-gp - significantly lower in neonates & infants than adolescents & adults

Prasad *et al.*, CPT 2016; 100: 362

Protein abundance <15 wks



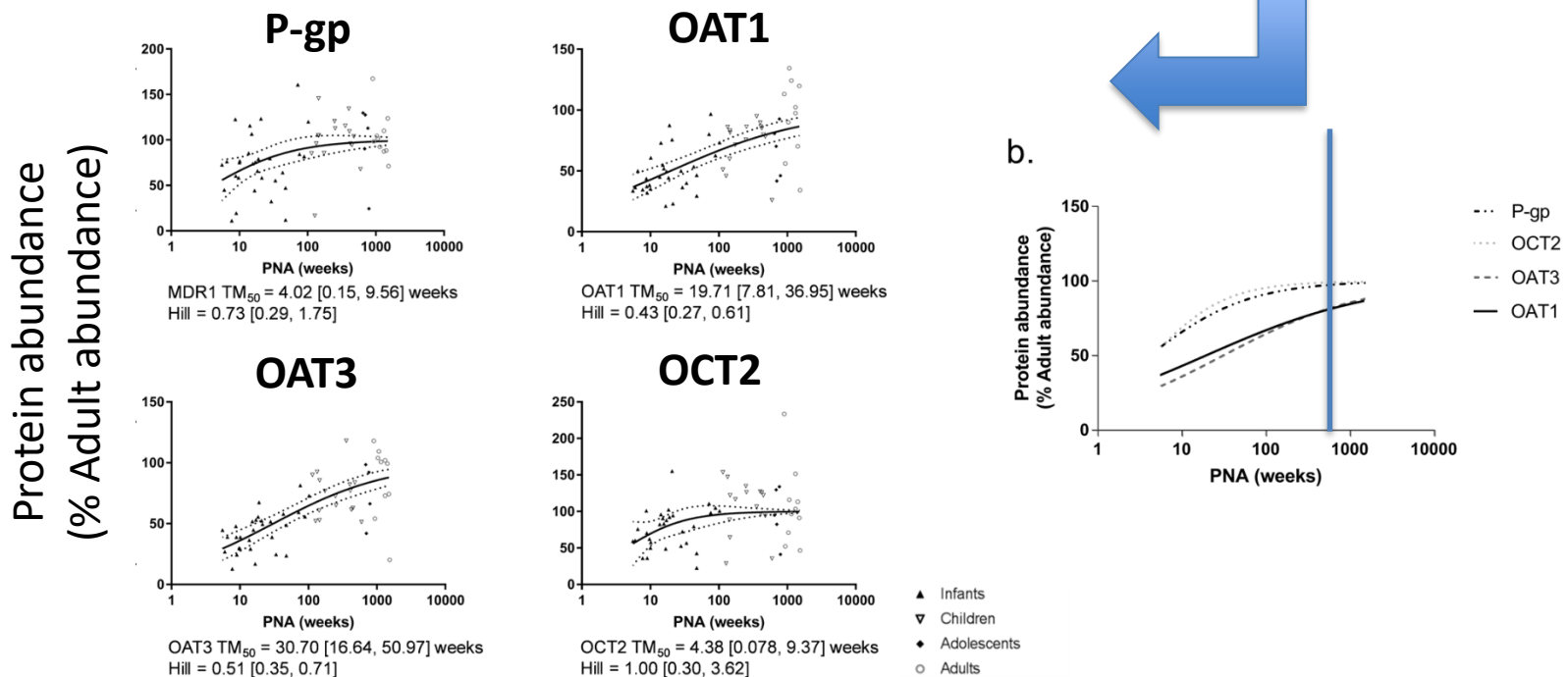
Mooij *et al.*, DMD 2016; 44: 1005

Ontogeny of Renal Transporters



A comprehensive analysis of ontogeny of renal drug transporters: mRNA analyses, quantitative proteomics and localization

- The expression of most of 11 renal transporters characterized in this study increased with age during the earliest developmental periods (< 2years old)
- Maturation patterns was transporter-dependent

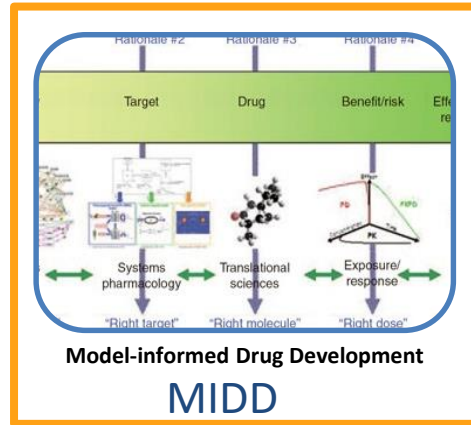


→ Ontogeny of certain renal membrane transporters displayed an age-dependent pattern, suggesting that the clearance of exogenous and endogenous substrates for these kidney transporters are subject to transporter-specific age-related changes

PDUFA 6: Regulatory Decision Tools

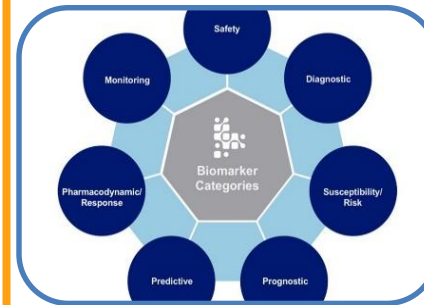


Complex Innovative Trial Designs



Model-informed Drug Development

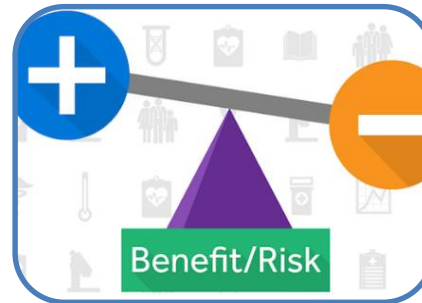
MIDD



Biomarker Qualification



Real World Evidence



Benefit/Risk Assessment



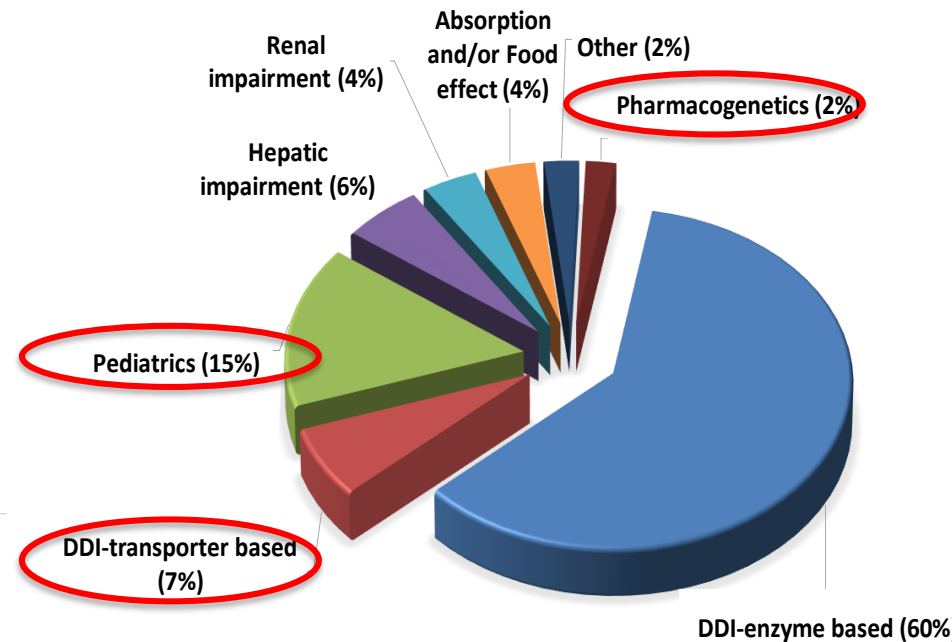
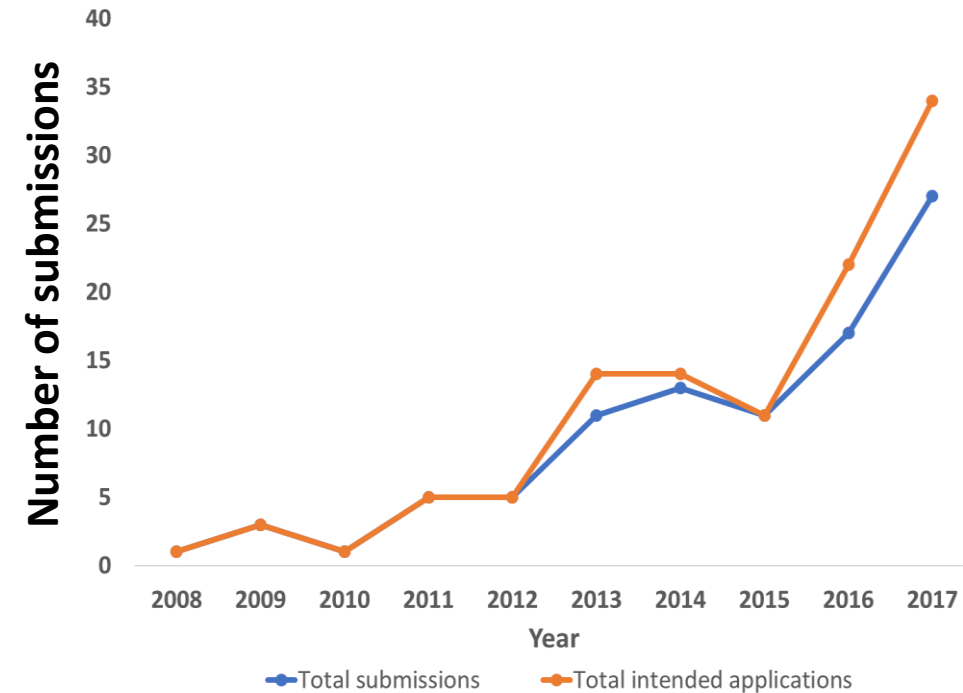
Patient Voice

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

Yaning Wang^{1*}, Hao Zhu¹, Rajanikanth Madabushi¹, Qi Liu¹, Shiew-Mei Huang¹ and Issam Zineh¹

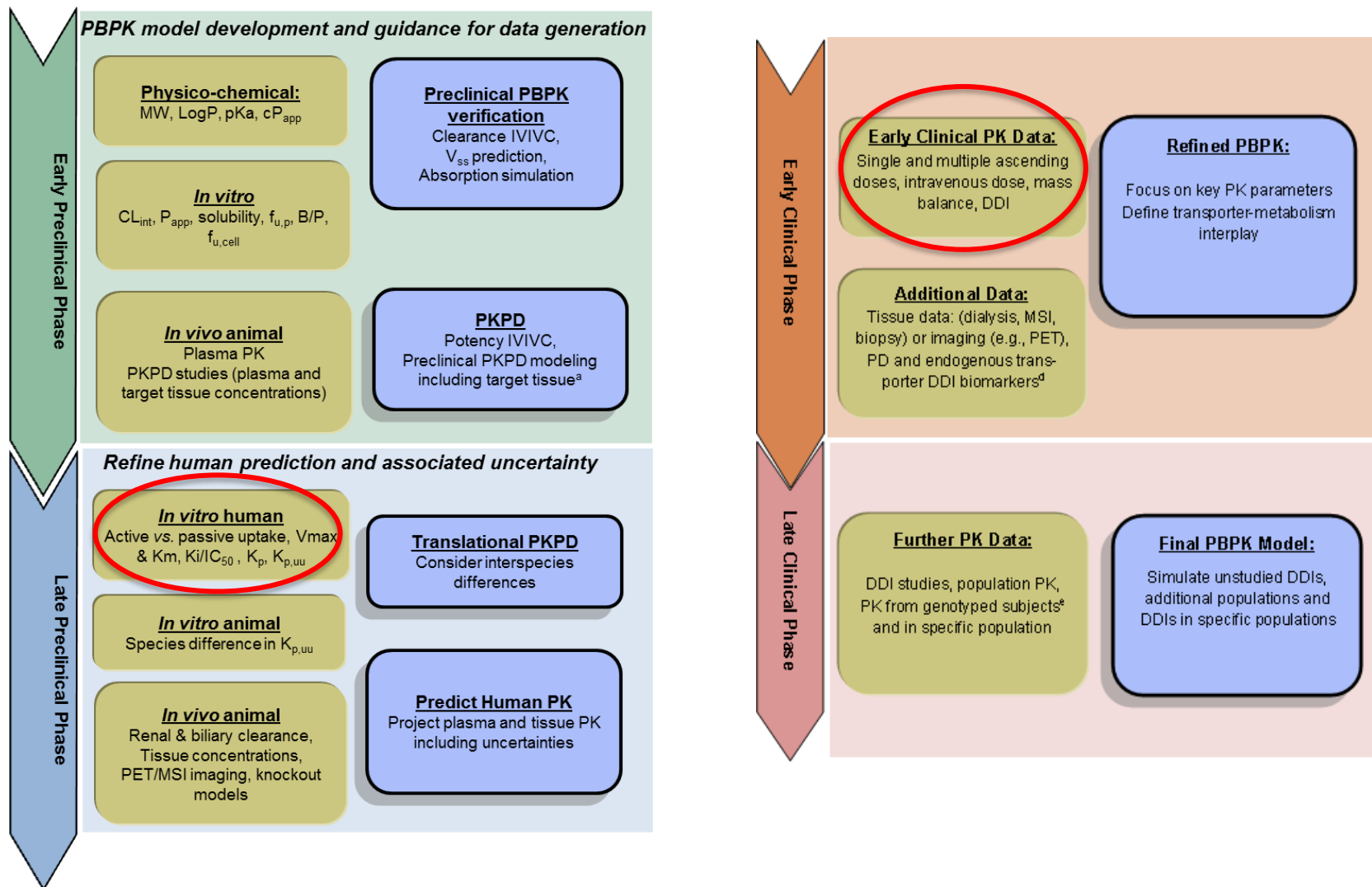
Model-informed drug development (MIDD) refers to the application of a wide range of quantitative models in drug development to facilitate the decision-making process. MIDD was formally recognized in Prescription Drug User Fee Act (PDUFA) VI. There have been many regulatory applications of MIDD to address 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.

PBPK Submissions to FDA/OCP: 2008-2017



254 submissions were reviewed by OCP including 94 NDAs, from 2008-2017. Each submission might have more than one area of application. For example, one submission may include one or more PBPK models to be used to support enzyme-, transporter-mediated DDI, as well as food effect.

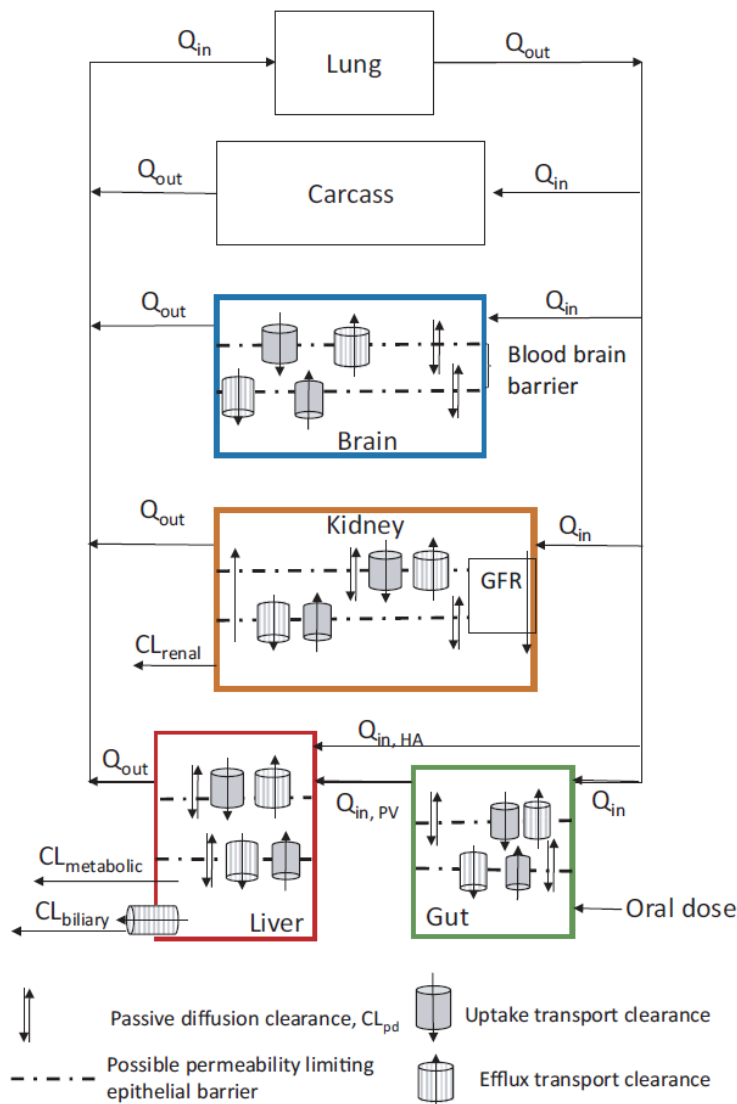
Integrated Workflow in PBPK Modeling Consideration



Giacomini, Galetin, Huang, Clin Pharmacol ther November 2018

Adapted from Guo et al, Clin Pharmacol ther November 2018

PBPK Model



Key parameters required to build a reliable PBPK model:

- Good system model
 - Well characterized ADME of the drug
- absorption kinetics (rate & extent)
 - distribution parameters (organ partitioning, perfusion vs. permeability limitations)
 - metabolism (in drug eliminating organs, such as the liver)
 - excretion (by the kidney & into the bile)

→ Microphysiological systems may help in obtaining quality key parameters; although quantitative translation is still sparse

March 14, 2012 Meeting for the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology



[Question 1]: Should modeling and simulation methods be considered in all pediatric drug development programs?

[13 Yes]. The committee unanimously agreed that modeling and simulation methods should be considered in all pediatric drug development programs. However, the committee acknowledged that there are knowledge gaps and limitations regarding the application.....

[Question 4]: Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time?

[7 Yes]. agreed that routine use of PBPK in pediatric drug development, when possible, should be recommended at the present time...would be beneficial in better anticipating and understanding the PK variability in the pediatric populations.....

[6 No]. Pediatric PBPK models still have significant knowledge gaps,...pharmacogenetic effects on drug metabolism/transport, ontogeny of transporters, etc.....

March 15, 2017 Meeting for the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology



[Question 1]: What information should be included in a PBPK submission to the FDA to ensure adequacy of an analysis for its intended purpose? Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submissions will be used (e.g., to inform clinical study planning vs. labeling or regulatory decision making). What are the principles or criteria that should be considered?

[Committee Discussion]: Many committee members discussed that flexibility was very important when considering the type of information that should be included in a PBPK submission and that it may be useful to present the timeline of the evolution of the model (data, assumptions, etc) with appropriate annotations to support the modeling and conclusions from the modeling...that special populations (e.g., pediatrics, elderly, patients with various organ dysfunction) should be considered and that the guiding principles should be the interpretation of the applications and the modeling should be in the context of the population being considered for the intended use.

[Committee Discussion]: ..Harmonization of the processes with regulatory bodies worldwide will be helpful

FDA Advisory committee meeting:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm535520.htm>

Regulatory Guidance Documents

- PBPK & Pediatrics -



Physiologically Based
Pharmacokinetic
Analyses — Format and
Content
Guidance for Industry

FDA, final, August 2018

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

FDA, draft, December 2014



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

EMA, final, December 2018

1 September 2017
EMA/CPMP/ICH/2711/1999
Committee for Human Medicinal Products

ICH E11(R1) guideline on clinical investigation of
medicinal products in the pediatric population
Step 5

ICH, final, September 2017

FDA: <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>

EMA: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpbk-modelling-simulation_en.pdf

EMA (Q/A): How should Ontogeny/Organ Maturation.. Be implemented into Models

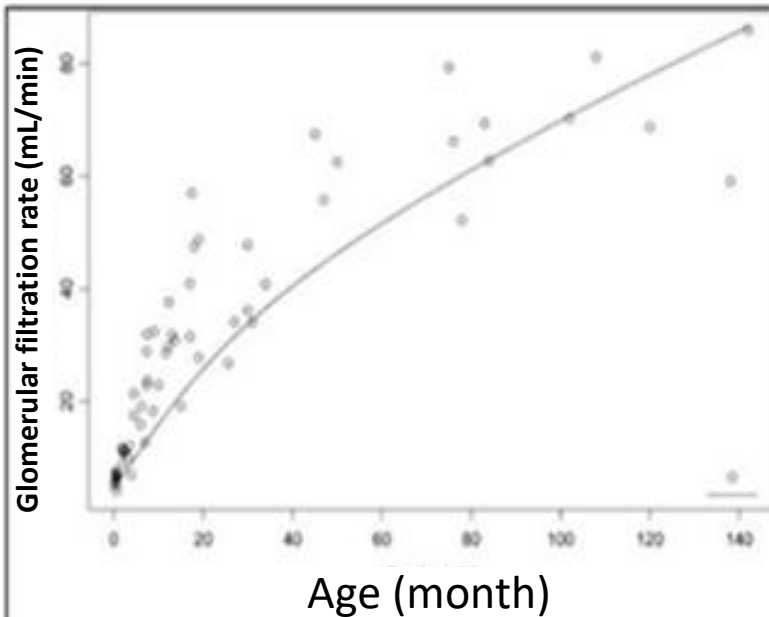


Figure 1 Developmental changes of renal glomerular filtration rate (GFR) measured by mannitol clearance. [6]

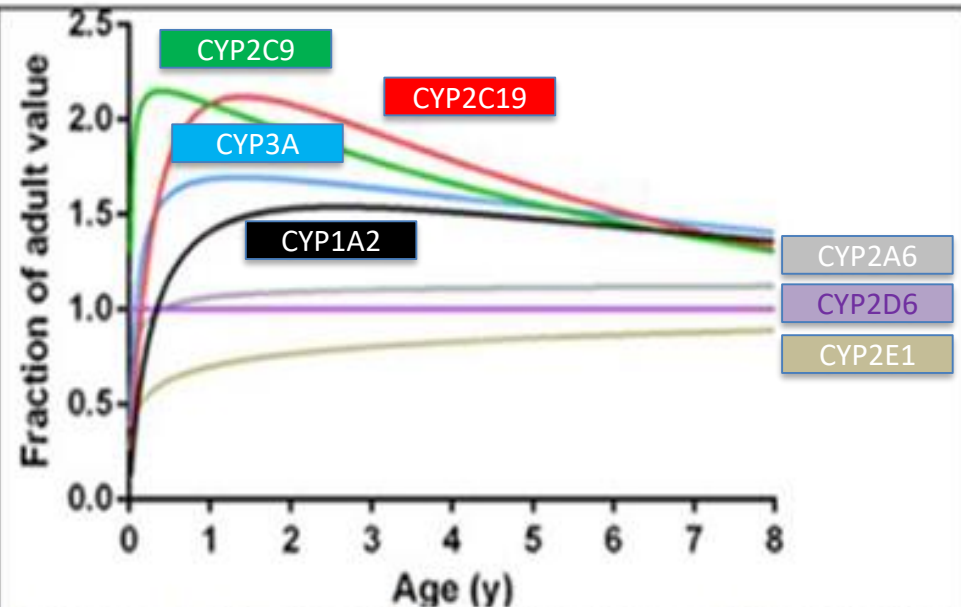
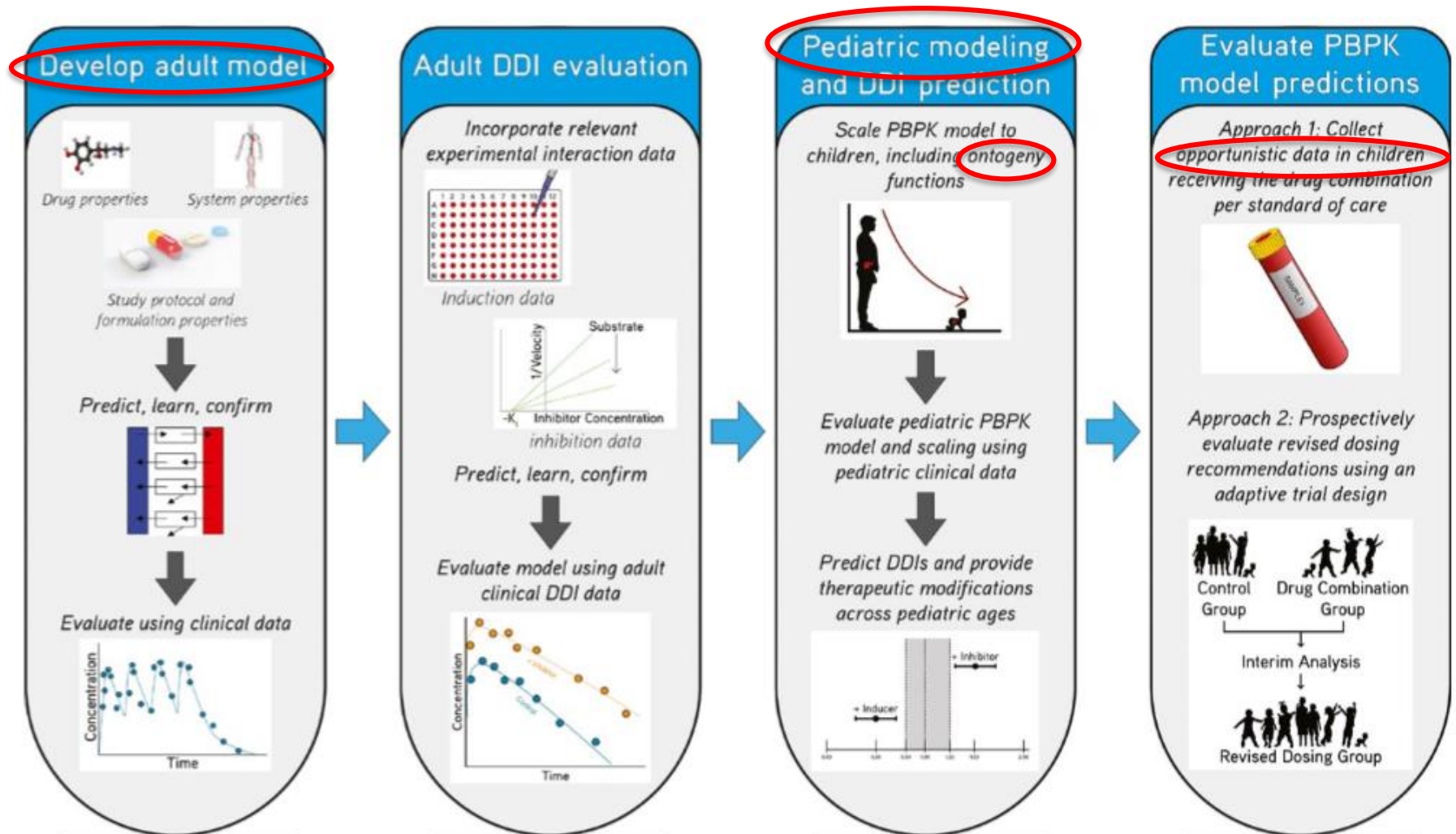


Figure 2 An integrated visualisation of in vivo CYP ontogeny for the major hepatic CYPs: CYP1A2 (black), CYP2A6 (gray), CYP2B6 and CYP2D6 (purple), CYP2C9 (green), CYP2C19 (red), CYP2E1 (gold), and CYP3A (blue). [2]

→... It is important to include maturation function(s) to describe paediatric pharmacokinetics....(November 2018)

Modified from EMA: <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers>

Pediatric Drug-Drug Interactions -Barriers & Opportunities-



Case Study

-PBPK of Renally Cleared Drugs-



Physiologically-based pharmacokinetic (PBPK) modeling with integrated renal transporter ontogeny to simulate the systemic exposure of intravenously (IV) administered tazobactam, IV oseltamivir and oseltamivir carboxylate (OC) in children (0-18 years old)

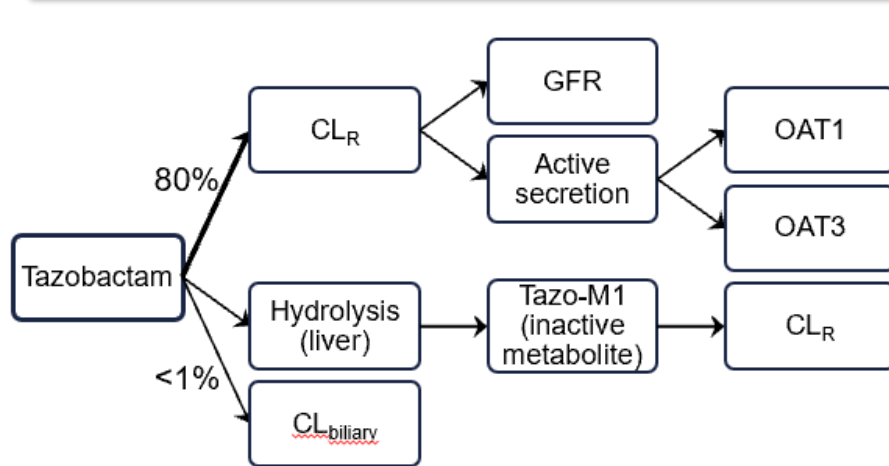


Fig 1. Elimination pathway of tazobactam

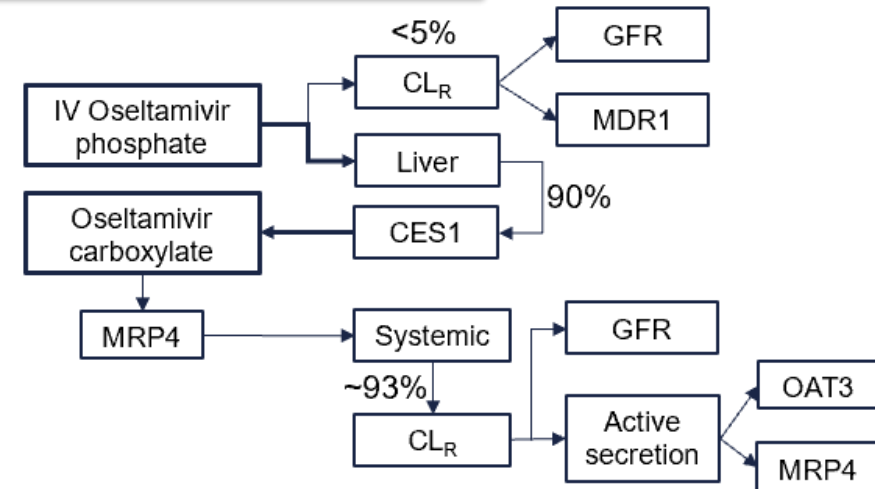


Fig 2. Elimination pathway of oseltamivir

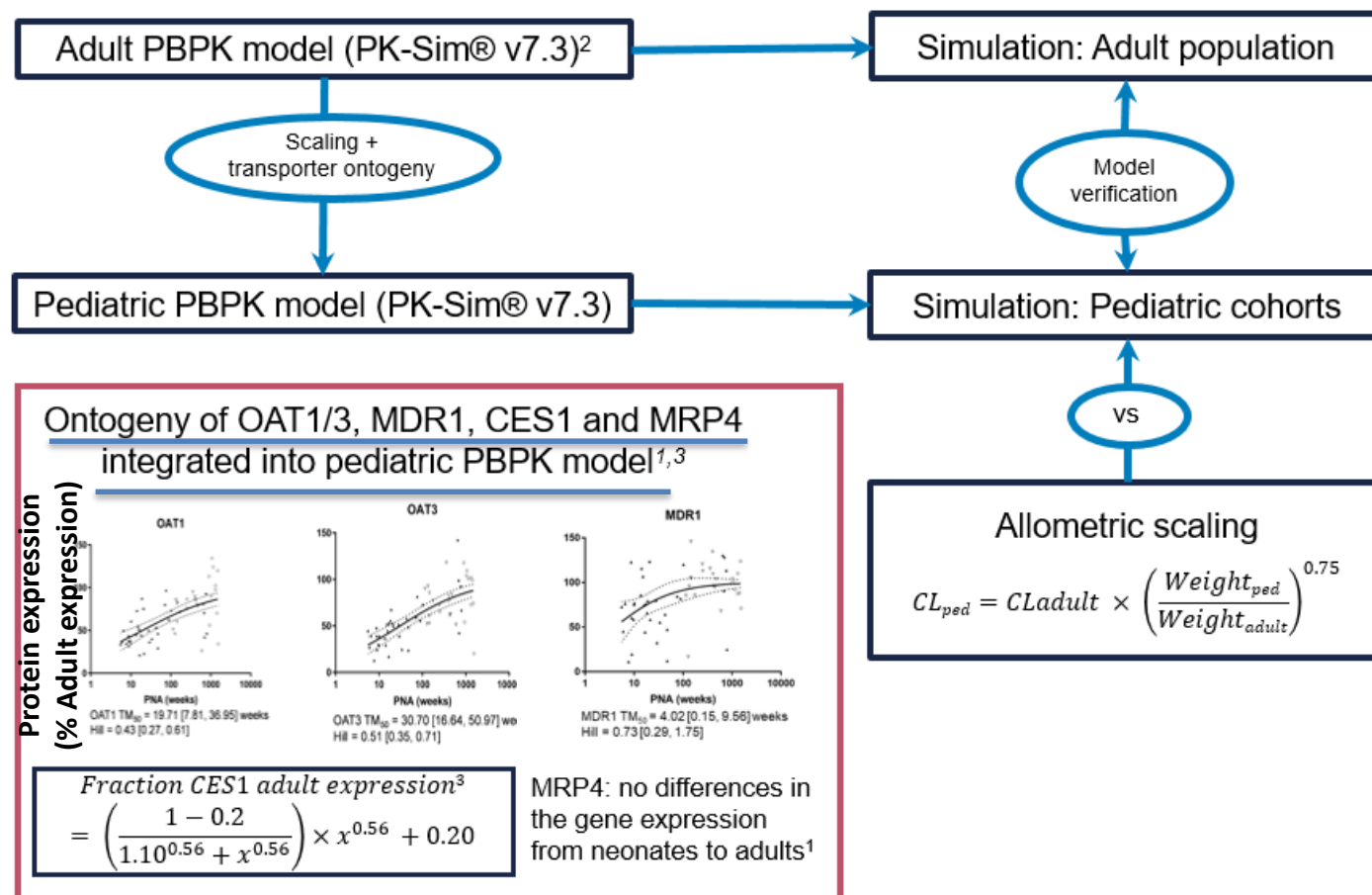
CL_R = renal clearance; CL_{biliary} = biliary clearance; GFR = glomerular filtration rate; OAT = organic anion transporter; MRP4 = multidrug resistance protein 4; CES1 = carboxylesterase 1; MDR1 = multidrug resistance protein 1

Case Study (2)

-PBPK of Renally Cleared Drugs-



Methods

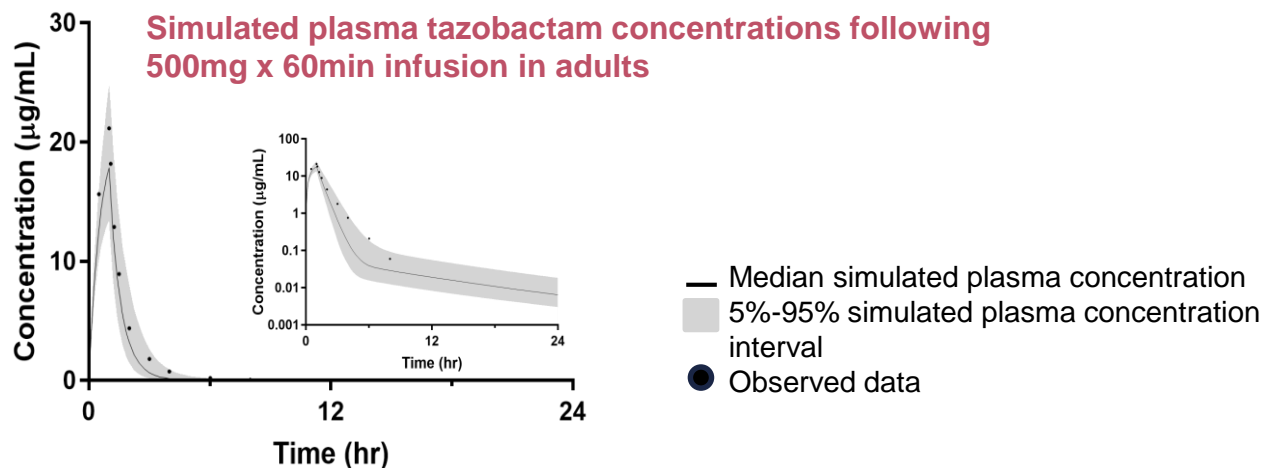


Case Study (3)

-PBPK of Renally Cleared Drugs-

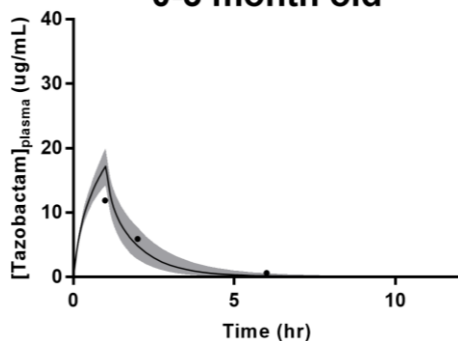


Tazobactam



Pediatric PBPK model predicted tazobactam C_{max}, AUC and CL adequately for 0-7 years old

0-3 month old

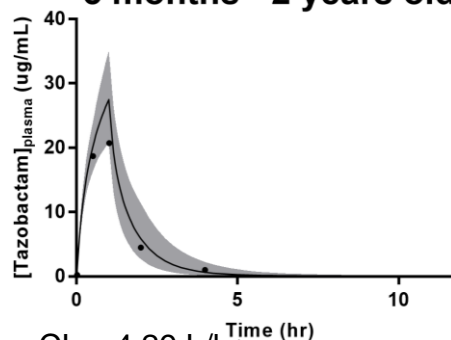


CL = 1.47 L/hr

Present study = 1.7 L/h (1.2-fold)

Allometry = 2.67 L/hr (1.8-fold)

3 months - 2 years old

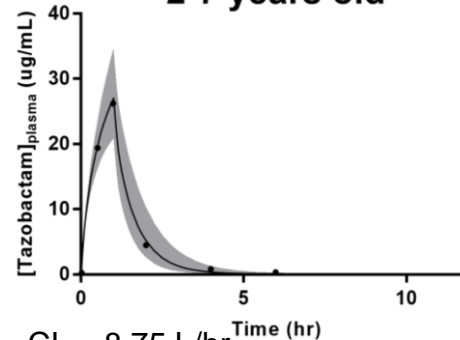


CL = 4.29 L/hr

Present study = 4.0 L/h (1.1-fold)

Allometry = 4.89 L/hr (1.1-fold)

2-7 years old



CL = 8.75 L/hr

Present study = 6.9 L/h (1.3-fold)

Allometry = 6.92 L/hr (1.3-fold)

Case Study (4)

-PBPK of Renally Cleared Drugs-



- This study illustrates the utility of pediatric PBPK in simulating exposure of drugs that are actively renally secreted in pediatric patients
- Pediatric PBPK models complemented allometry by predicting the whole PK profile, rather than just the clearance
- Pediatric PBPK models incorporating transporter ontogeny data could enhance drug dosing in pediatric patients and decision-making in pediatric drug development

Summary



- International collaborative efforts have improved the understanding of the role of transporter in drug PK, PD, and response and should continue
- Modeling and simulation is critical and should be used in pediatric drug development; harmonization of regulatory processes is critical in the successful application
- Understanding of drug disposition and drug metabolism/transport and their interplay continue to be critical in the application of PBPK
- Knowledge gaps remain (e.g., system parameters in PBPK) and will continue to require collaborative work

Acknowledgement

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- *ORISE and MCMi

