FDA/MCERSI Workshop

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 Brouwer[1], LM Aleksunes[2], B Brandys[3], GP Giacoia[4], G Knipp[5], V Lukacova[6], B Meibohm[7], SK Nigam[8], M Rieder[9], and SN de Wildt[10], 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

KLR Brouwer et al. Clin Pharmacol Ther 2015

Human Transporters

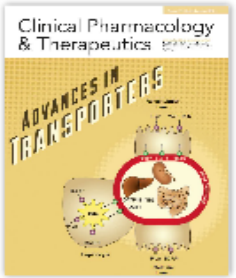
Clinical Pharmacology & Therapeutics

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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November 2018
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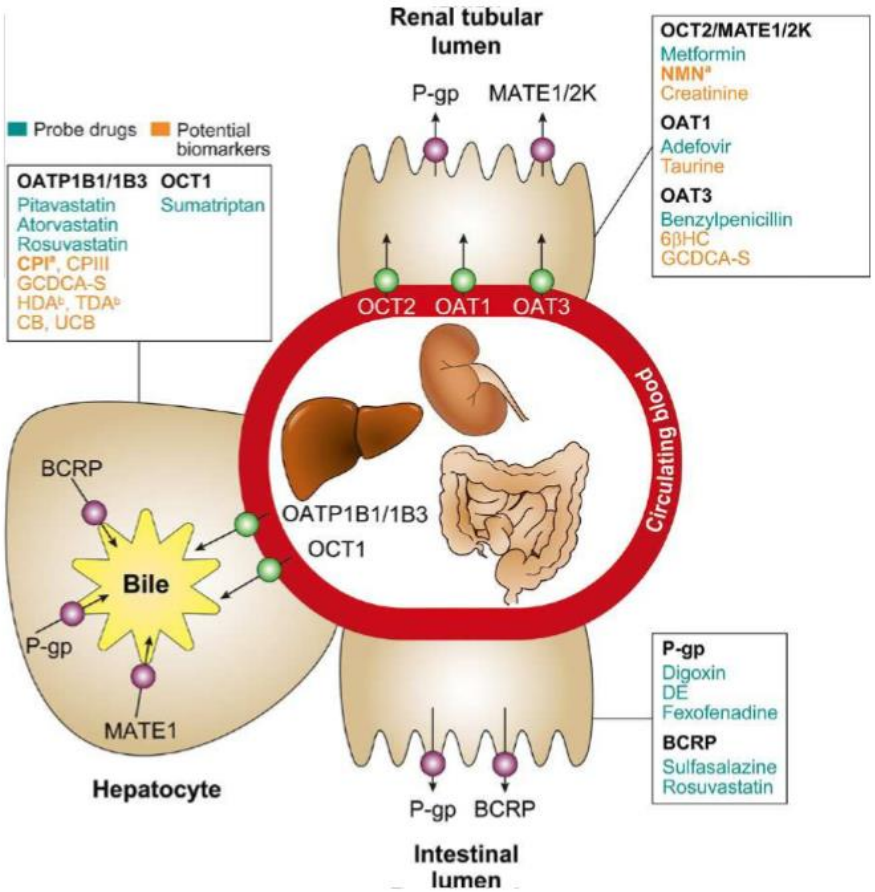


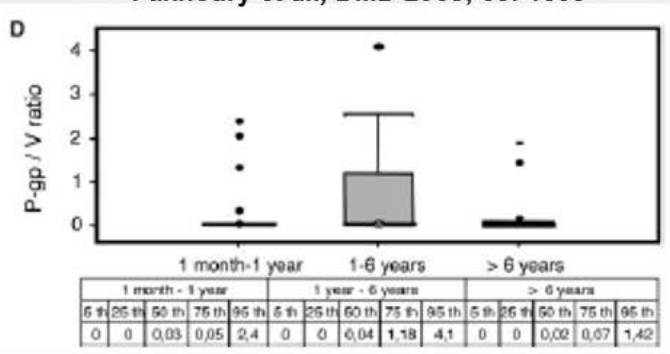
Chu X et al. ITC Consortium, Clin Pharmacol Ther 2018

Giacomini, Galetin, Huang, Editorial, Clin Pharmacol Ther 2018

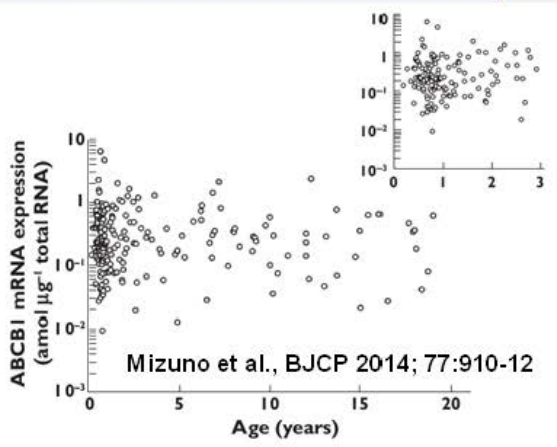
Ontogeny of Intestinal Transporters

P-gp mRNA data

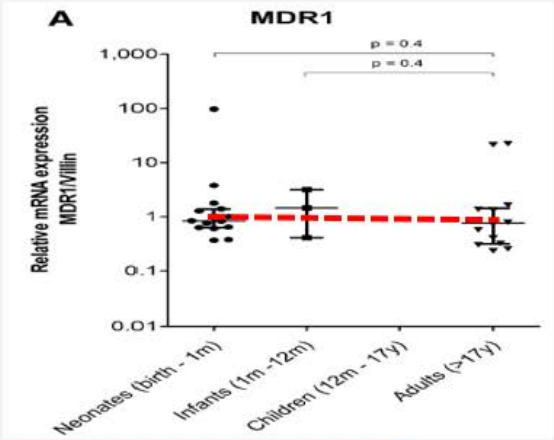
Fakhoury *et al.*, DMD 2005; 33: 1603



1 month - 1 year					1 year - 6 years					> 6 years				
5 th	25 th	50 th	75 th	95 th	5 th	25 th	50 th	75 th	95 th	5 th	25 th	50 th	75 th	95 th
0	0	0,03	0,05	2,4	0	0	0,04	1,18	4,1	0	0	0,02	0,07	1,42



Mooij *et al.*, DMD 2014; 42: 1268

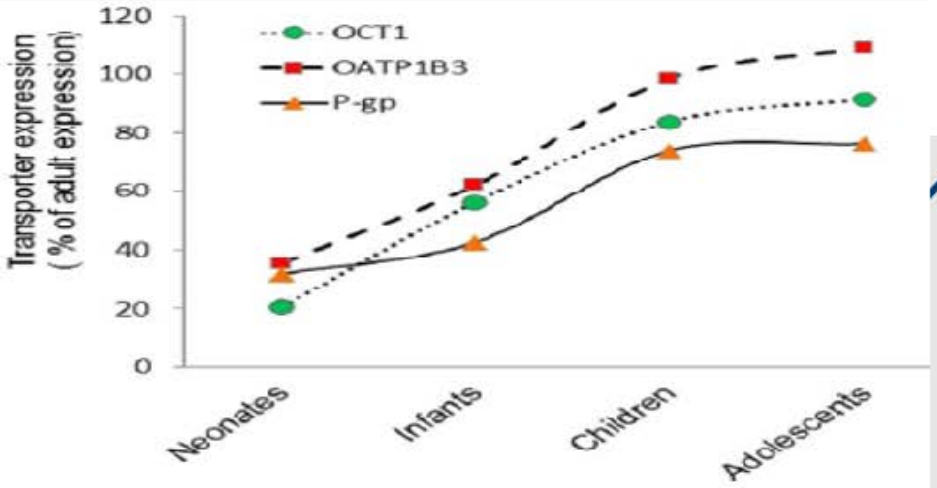


There appears to be no change with intestinal P-gp expression with age

Modified from Iain Gardner & Trevor Johnson, simcyp, CERTARA.

Ontogeny of Liver Transporters

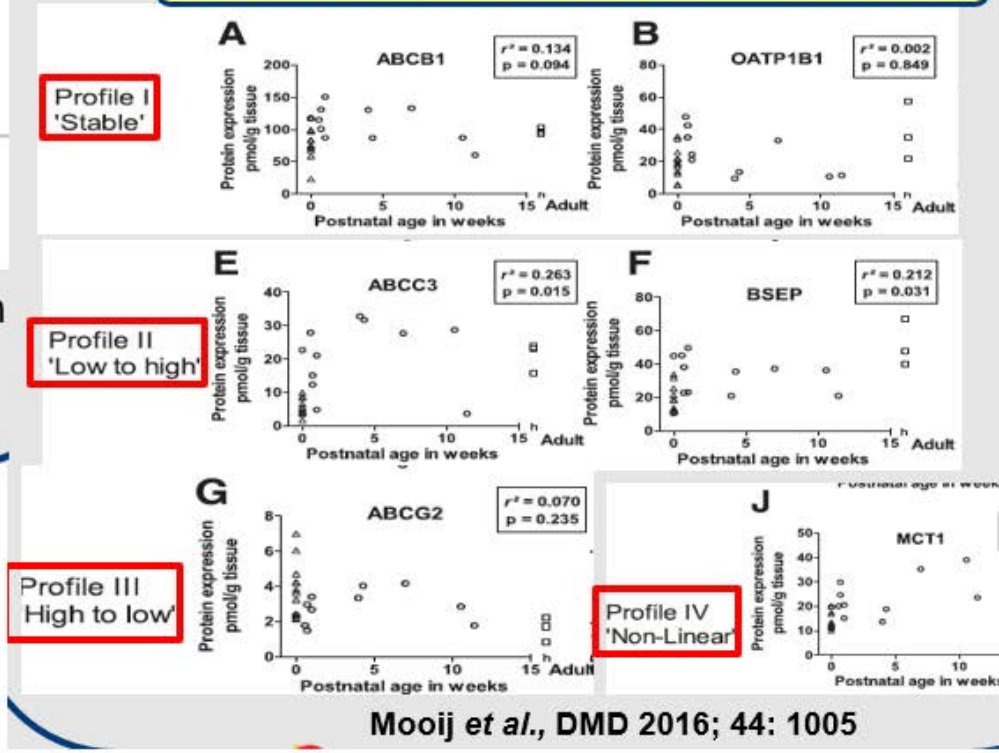
Protein abundance



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

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

Protein abundance <15 wks



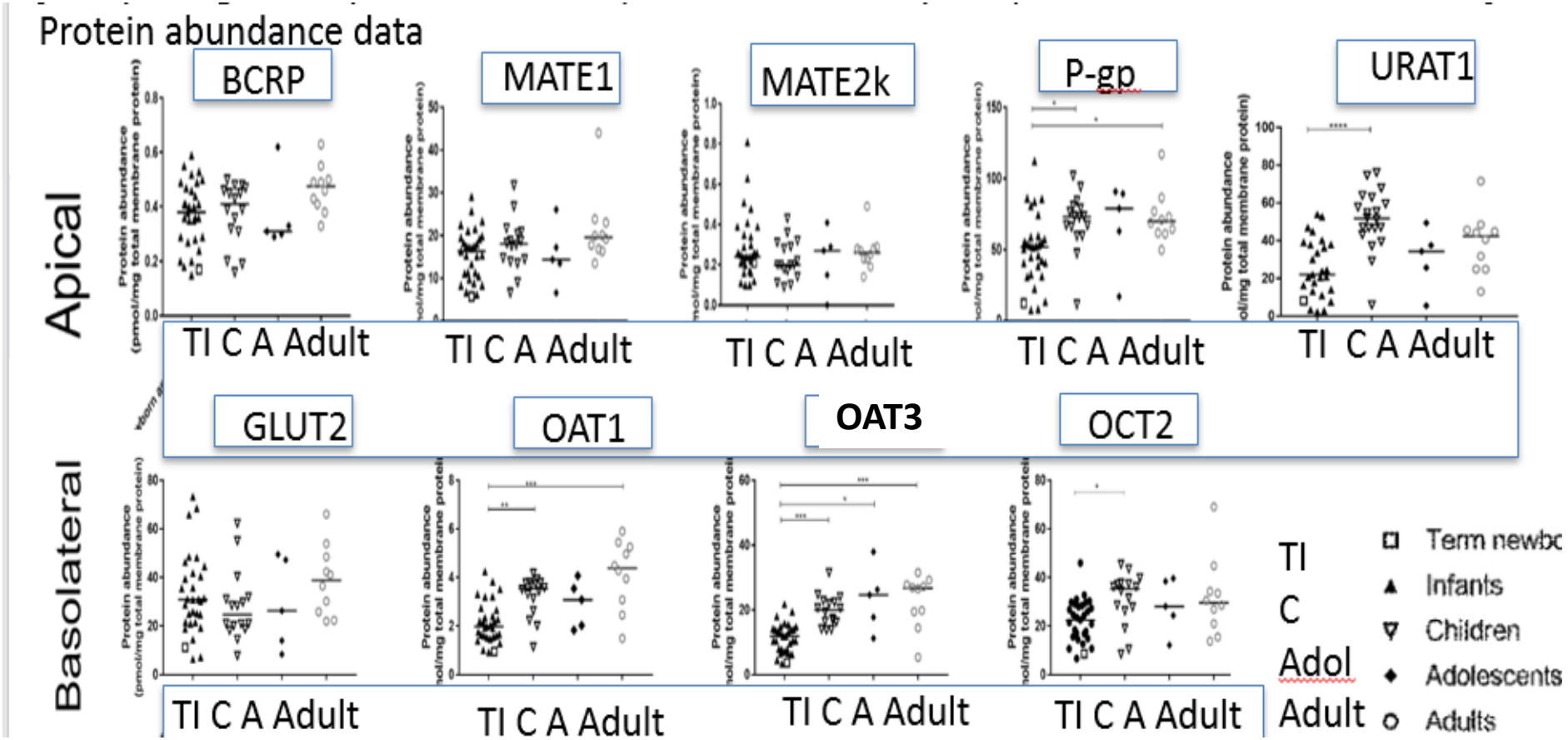
Mooij *et al.*, DMD 2016; 44: 1005

Modified from: Iain Gardner & Trevor Johnson, simcyp, CERTARA.

Ontogeny of Renal Transporters

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

[Study Design: Analyzed 184 human postmortem kidney samples from newborns to adults]

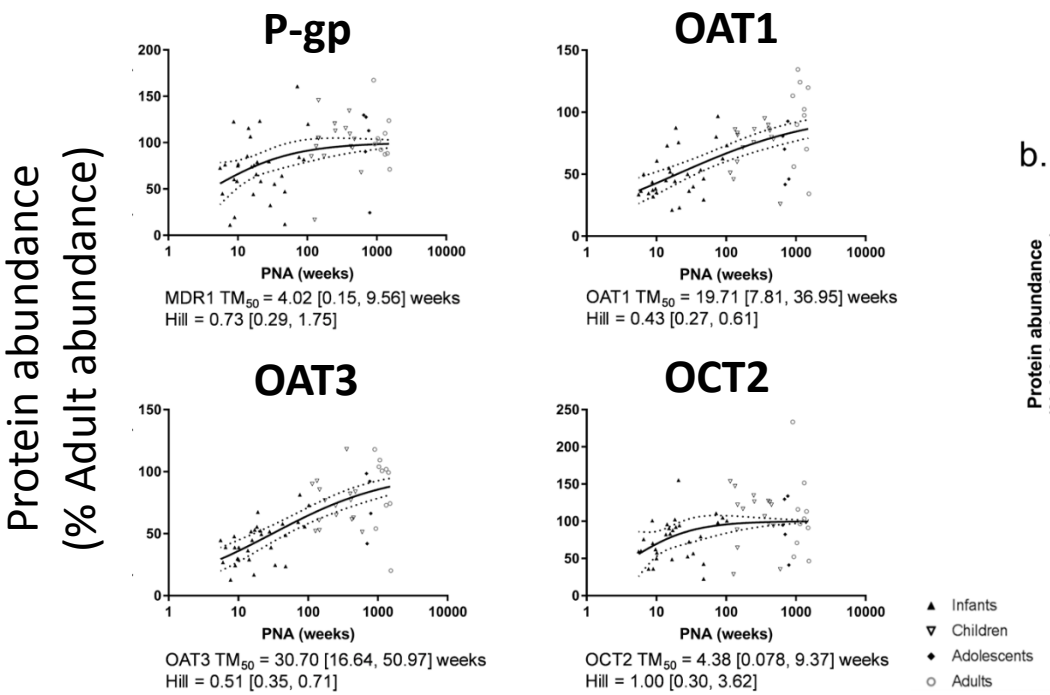


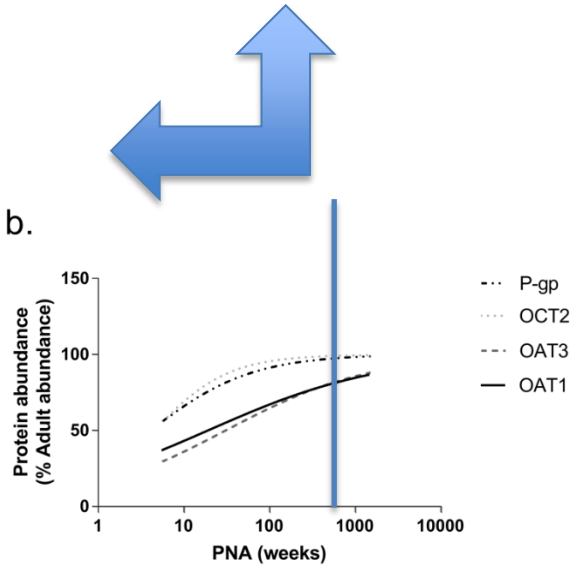
Kit Wun Kathy Cheung,*/ Bianca D. van Groen, * Edwin Spaans, Marjolein D. van Borselen, Adrianus C.J.M. de Bruijn, Ytje Simons-Oosterhuis, Dick Tibboel, Janneke N. Samsom, Robert M. Verdijk, Bart Smeets, Lei Zhang, Shiew-Mei Huang, Kathleen M. Giacomini,**/ Saskia N. de Wildt,** Clin Pharmacol Ther (2019; in press)

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



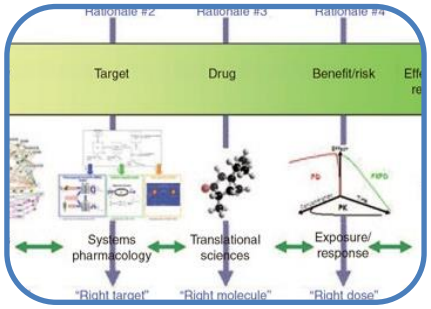


→ Ontogeny of certain renal membrane transporters displayed an age-dependent pattern, suggesting that the clearance of exogenous and endogenous substrates for these kidney transporters are subject to transporter-specific age-related changes

Kit Wun Kathy Cheung, Bianca D. van Groen, et al. Clin Pharmacol Ther (2019; in press)

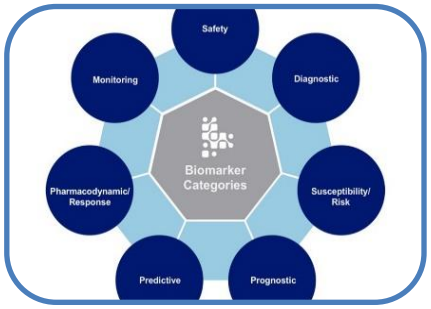
PDUFA 6: Regulatory Decision Tools

Complex Innovative Trial Designs



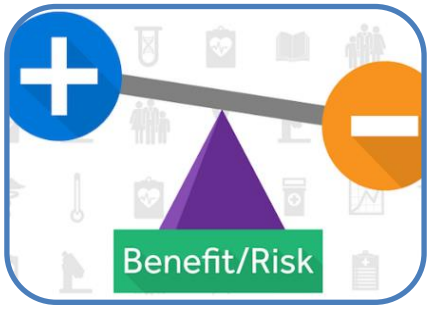
Model-informed Drug Development

MIDD



Biomarker Qualification

Real World Evidence



Benefit/Risk Assessment

Patient Voice

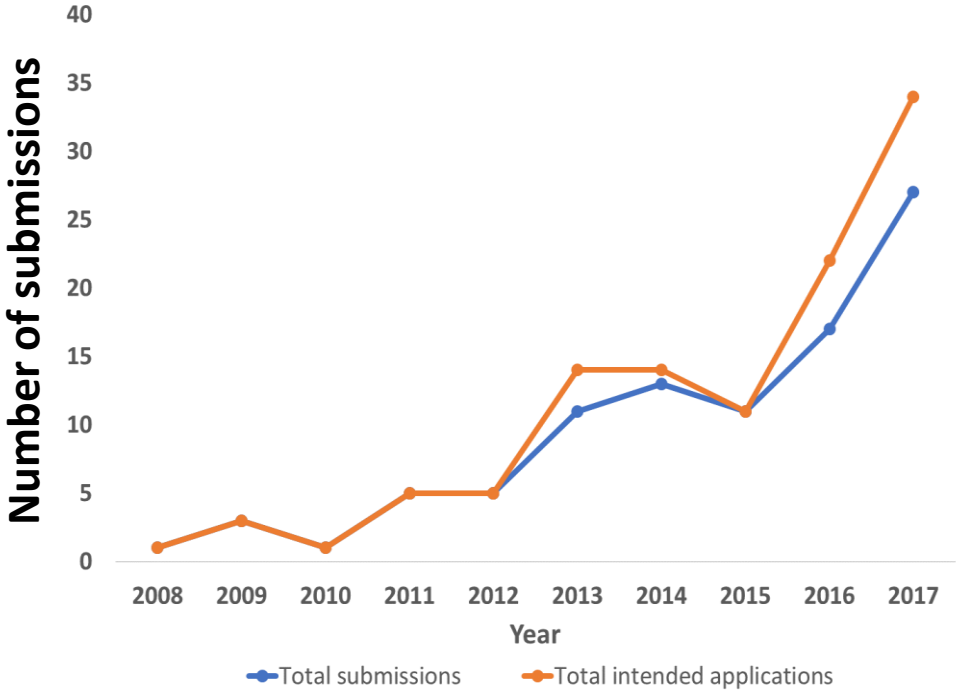
Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

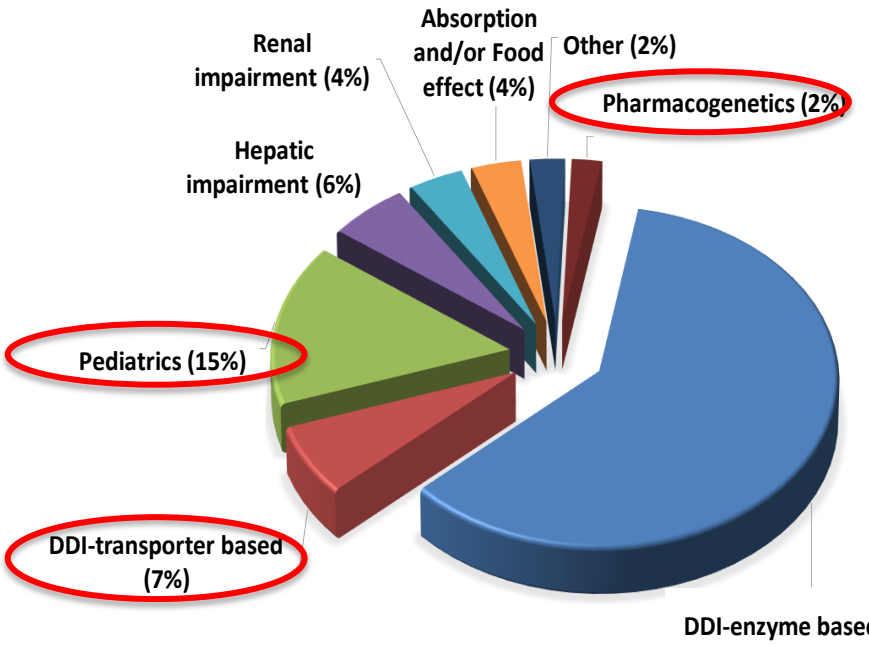
Yaning Wang[1]*, Hao Zhu[1], Rajanikanth Madabushi[1], Qi Liu[1], Shiew-Mei Huang[1] and Issam Zineh[1]

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

PBPK Submissions to FDA/OCP: 2008-2017

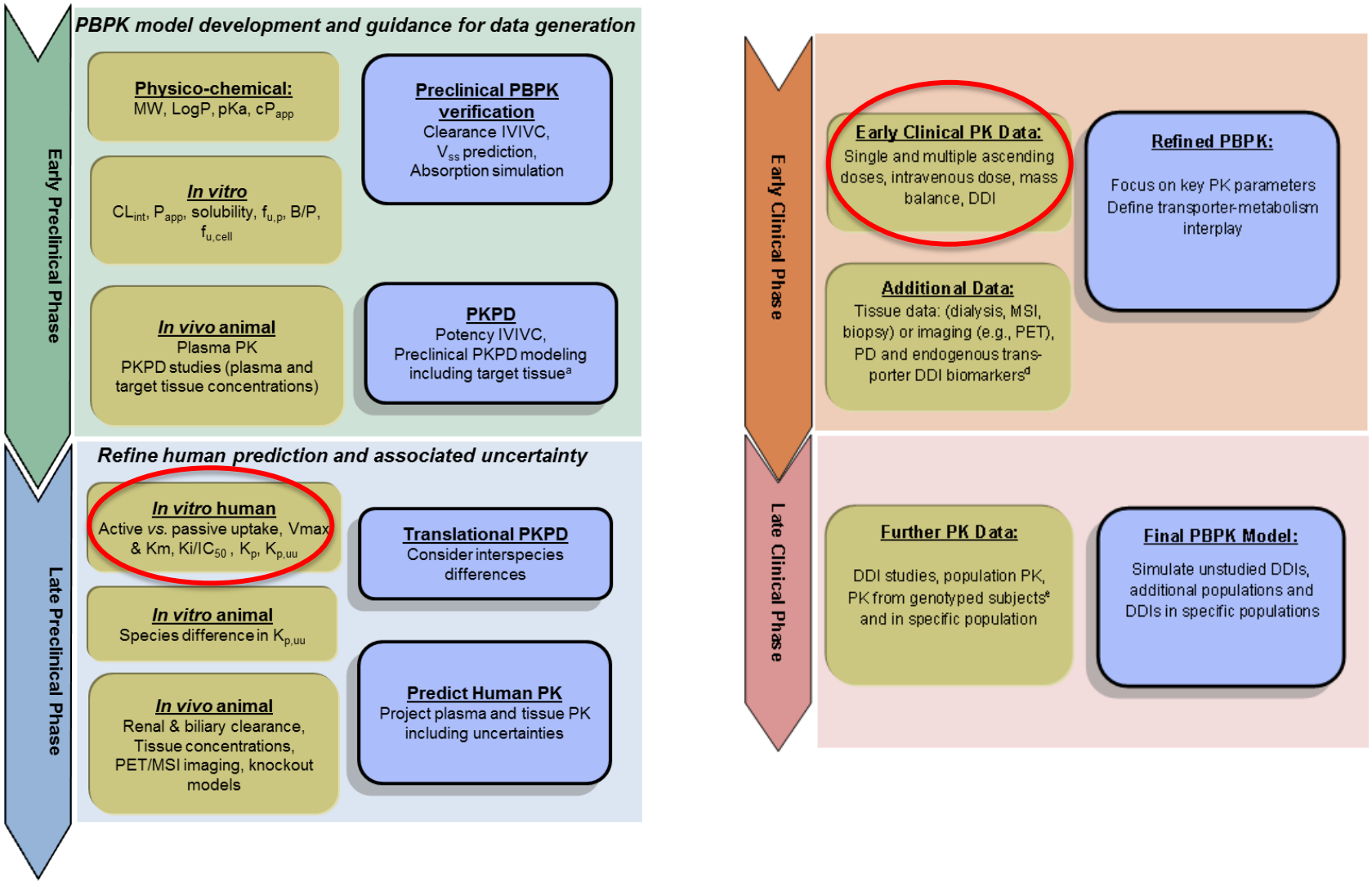




254 submissions were reviewed by OCP including 94 NDAs, from 2008-2017. Each submission might have more than one area of application. For example, one submission may include one or more PBPK models to be used to support enzyme-, transporter-mediated DDI, as well as food effect.

M Grimstein, Y Yang, X Zhang, J Grillo, S-M Huang, I Zineh, Y Wang. ***J Pharm Sci*** Jan 2019

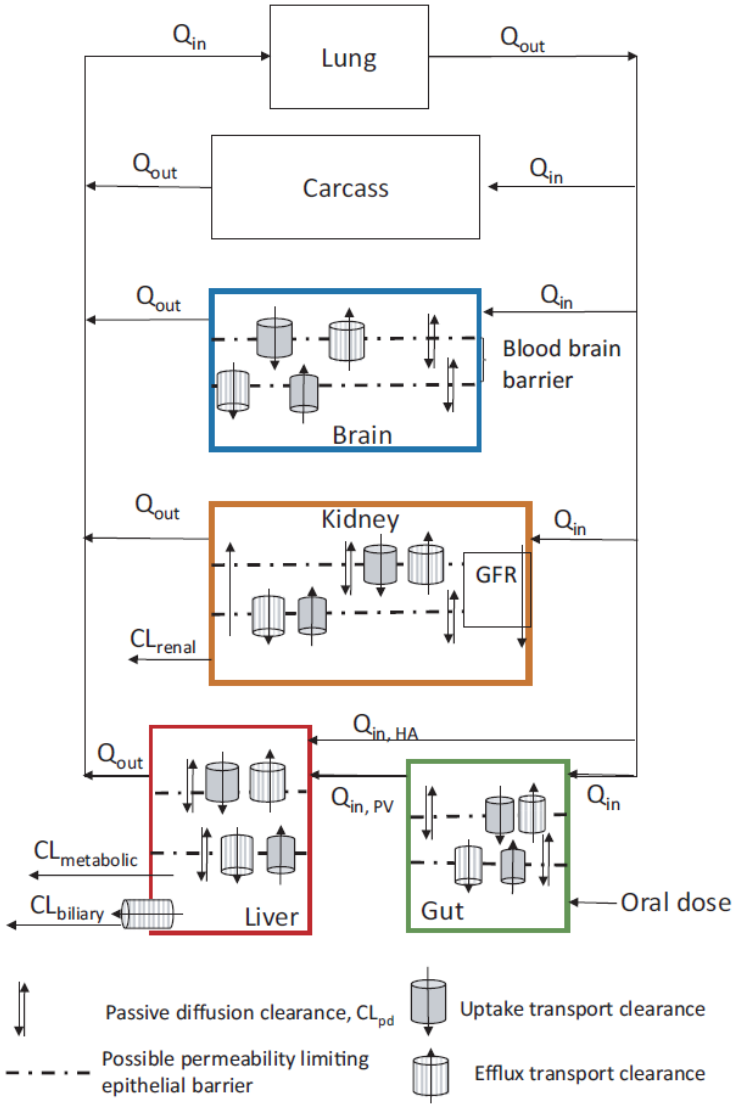
Integrated Workflow in PBPK Modeling Consideration



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, prefusion 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

N Isoherranen, R Madabushi, S-M Huang, *Clin Transl Sci* Jan 2019

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…..

FDA Advisory committee meeting: http://wayback.archive-it.org/7993/20170111202603/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm

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

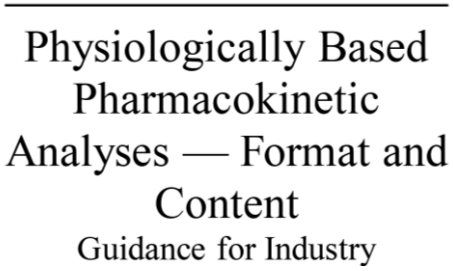
[Question 1]: What information should be included in a PBPK submission to the FDA to ensure adequacy of an analysis for its intended purpose? Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submissions will be used (e.g., 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

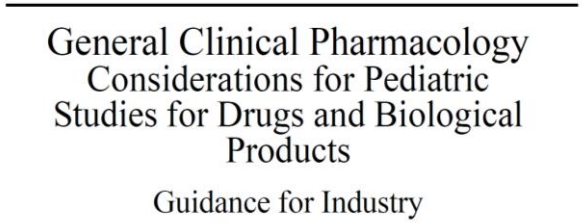
FDA, final, August 2018


EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

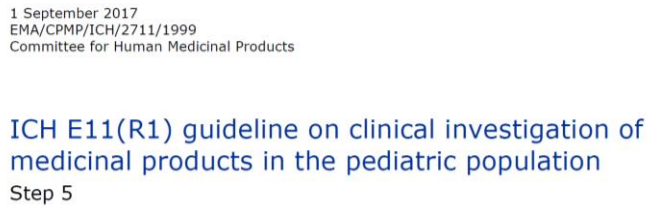
Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

EMA, final, December 2018


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

Guidance for Industry

FDA, draft, December 2014


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-pbpk-modelling-simulation_en.pdf

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

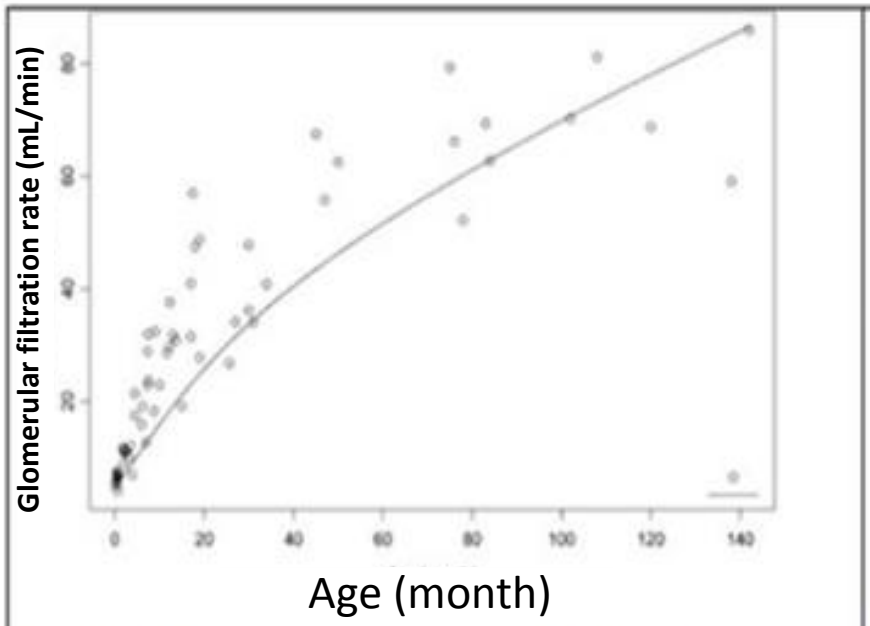


Figure 1 Developmental changes of renal glomerular filtration rate (GFR) measured by mannitol clearance. [6]

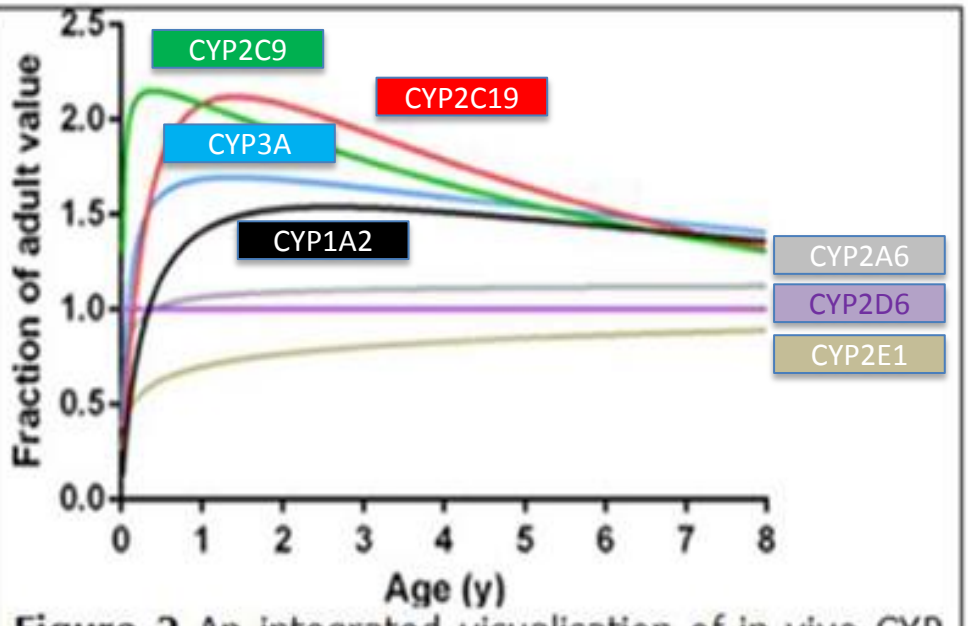
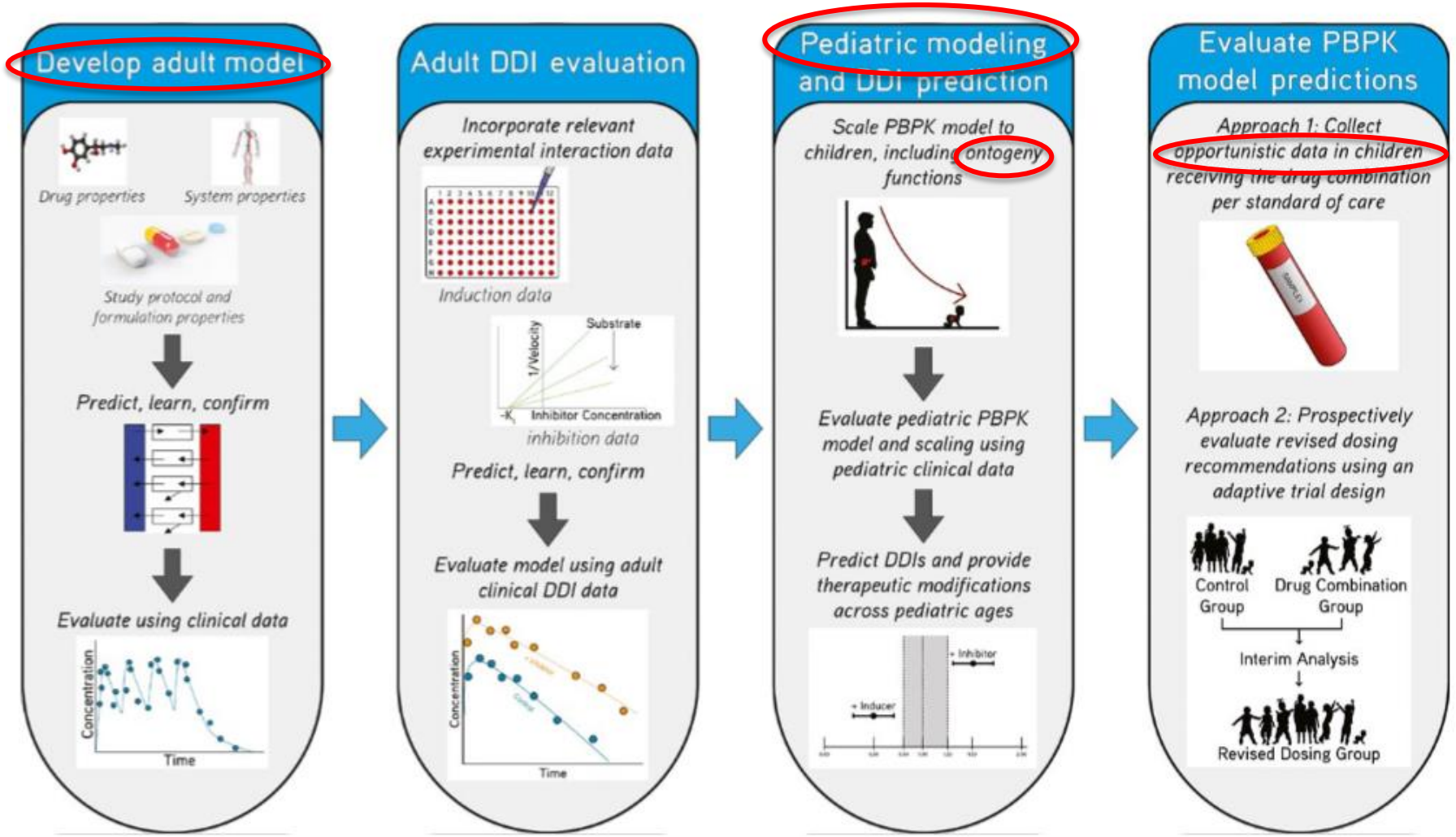


Figure 2 An integrated visualisation of in vivo CYP ontogeny for the major hepatic CYPs: CYP1A2 (black), CYP2A6 (gray), CYP2B6 and CYP2D6 (purple), CYP2C9 (green), CYP2C19 (red), CYP2E1 (gold), and CYP3A (blue). [2]

→… 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-



Salerno SN, Burckart GJ, Huang S-M, Gonzalez D, ***Clin Pharmacol Ther*** May 2019

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)

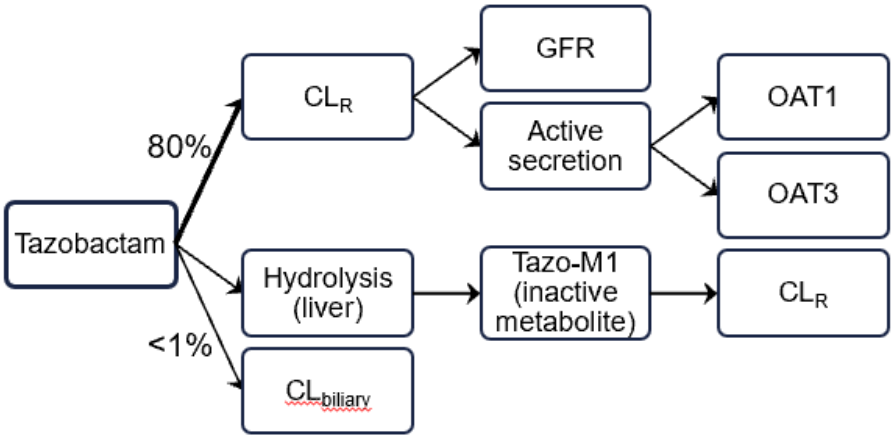


Fig 1. Elimination pathway of tazobactam

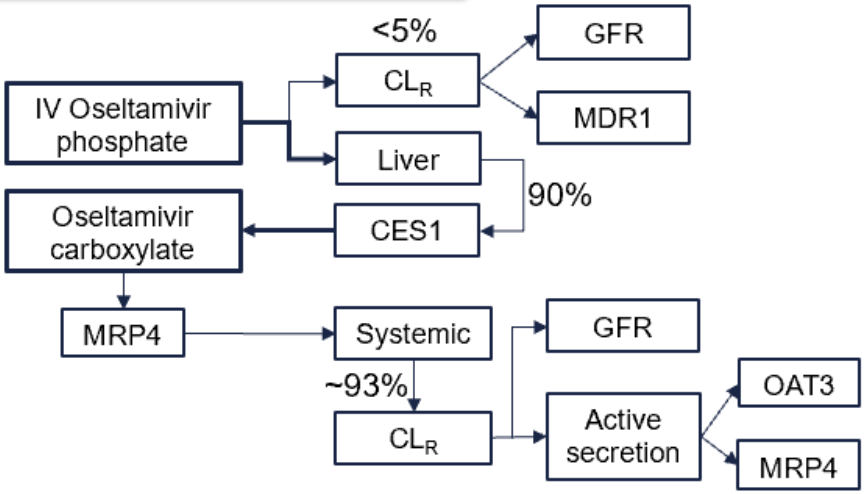


Fig 2. Elimination pathway of oseltamivir

CL_R = renal clearance; CLbiliary = biliary clearance; GFR = glomerular filtration rate; OAT = organic anion transporter; MRP4 = multidrug resistance protein 4; CES1 = carboxyesterase 1; MDR1=multidrug resistance protein 1

Kit Wun Kathy Cheung, Lei Zhang, Shiew-Mei Huang, Kathleen M Giacomini, ASCPT annual meeting, March 2019, Washington DC

Case Study (2)
-PBPK of Renally Cleared Drugs-

Methods

Adult PBPK model (PK-Sim® v7.3)[2]

Scaling + transporter ontogeny

Pediatric PBPK model (PK-Sim® v7.3)

Simulation: Adult population

Model verification

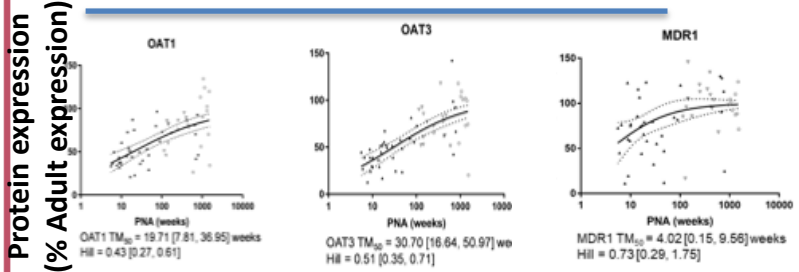
Simulation: Pediatric cohorts

vs

Allometric scaling

$$CL_{ped} = CLadult \times \left(\frac{Weight_{ped}}{Weight_{adult}}\right)^{0.75}$$

Ontogeny of OAT1/3, MDR1, CES1 and MRP4 integrated into pediatric PBPK model[1,3]



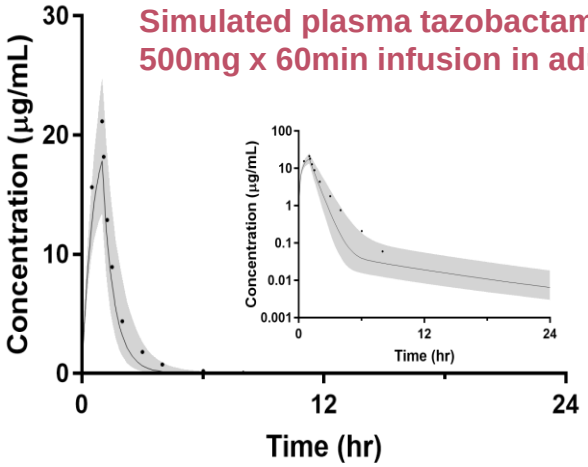
$$Fraction\ CES1\ adult\ expression^{3} = \left(\frac{1-0.2}{1.10^{0.56}+x^{0.56}}\right) \times x^{0.56} + 0.20$$

MRP4: no differences in the gene expression from neonates to adults[1]

Case Study (3)
-PBPK of Renally Cleared Drugs-

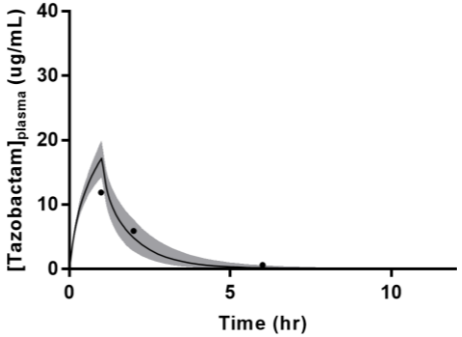
Tazobactam

Simulated plasma tazobactam concentrations following 500mg x 60min infusion in adults



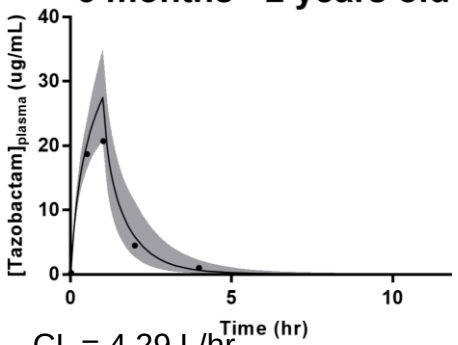
Pediatric PBPK model predicted tazobactam Cmax, AUC and CL adequately for 0-7 years old

0-3 month old



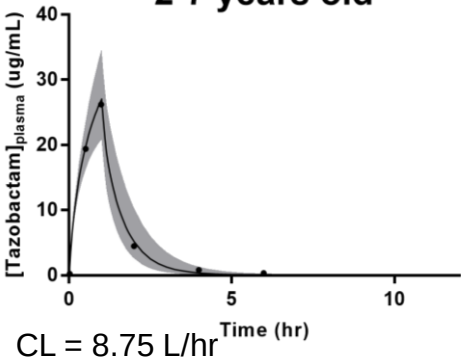
CL = 1.47 L/hr
Present study = 1.7 L/h (1.2-fold)
Allometry = 2.67 L/hr (1.8-fold)

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)

Kit Wun Kathy Cheung, et al, ASCPT presentation, March 2019, Washington DC

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

Kit Wun Kathy Cheung, et al, ASCPT presentation, March 2019, Washington DC

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

- Gilbert Burckart
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- Aleksandra Galetin
- Bianca D. van Groen*
- Kathy Giacomini
- Yaning Wang
- Saskia de Wildt
- Yuching Yang
- Lei Zhang
- Xinyuan (Susie) Zhang
- Issam Zineh
- Iain Gardner
- Trevor Johnson

*ORISE and MCMi


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U.S. FOOD & DRUG
ADMINISTRATION