Reflections on the Practice of R&D:

Balancing Academic Curiosity Analyzing Observations for a Lifetime with Patient-centricity and Market-driven Necessities to Move Fast

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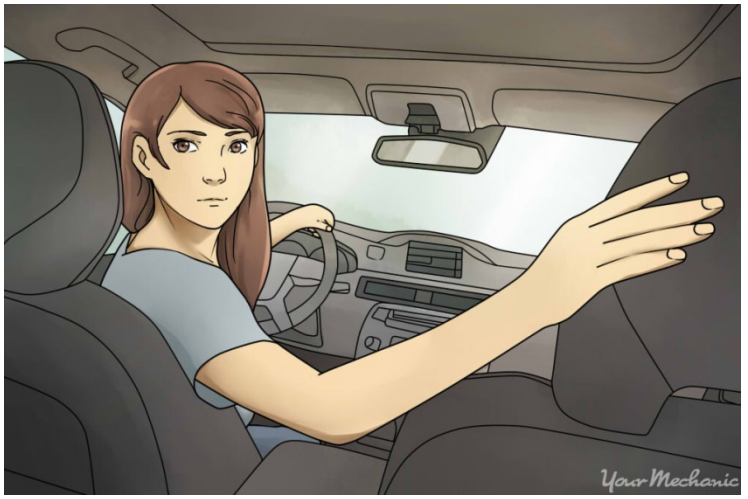
What does this mean?

Reverse

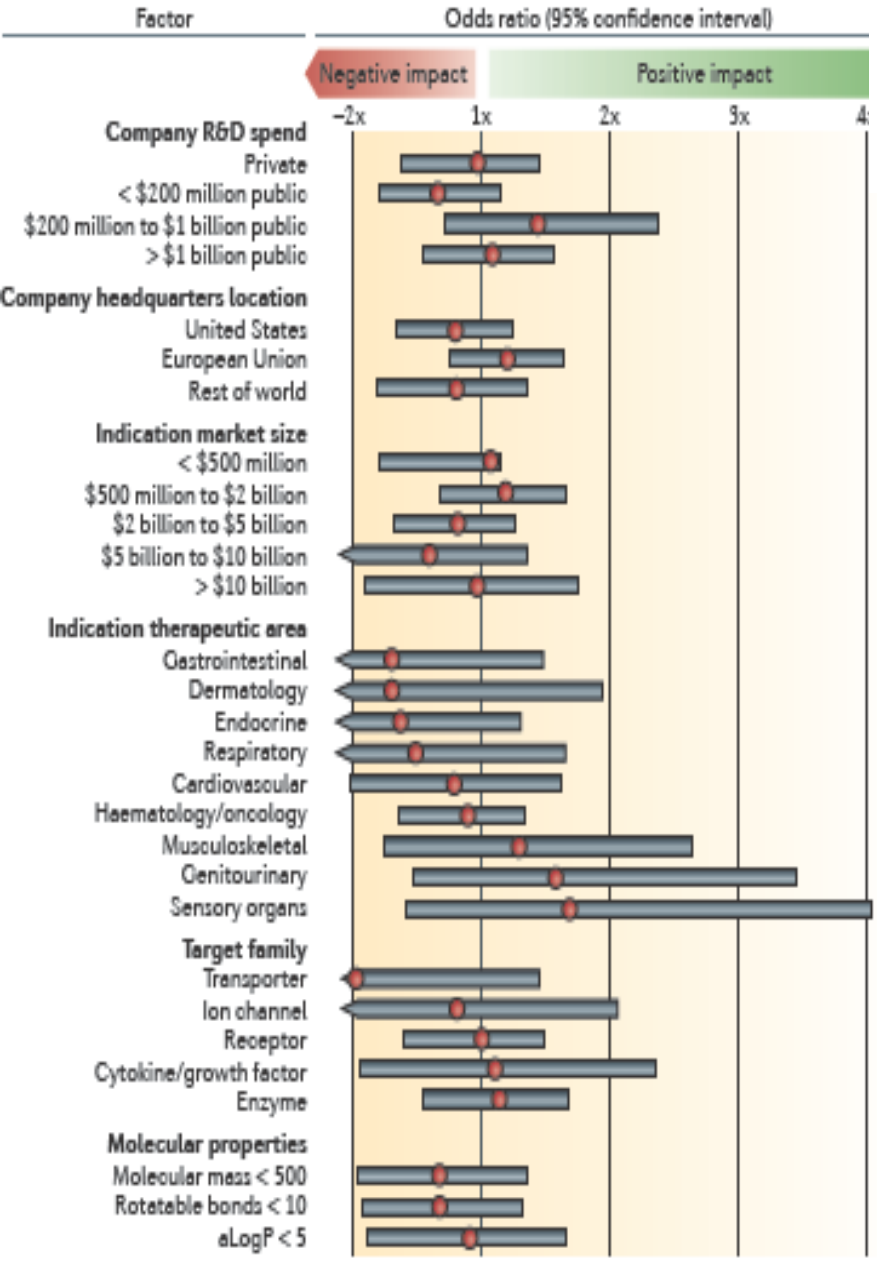


Google Translate

Break through language barriers

Translation

Determinants of Success

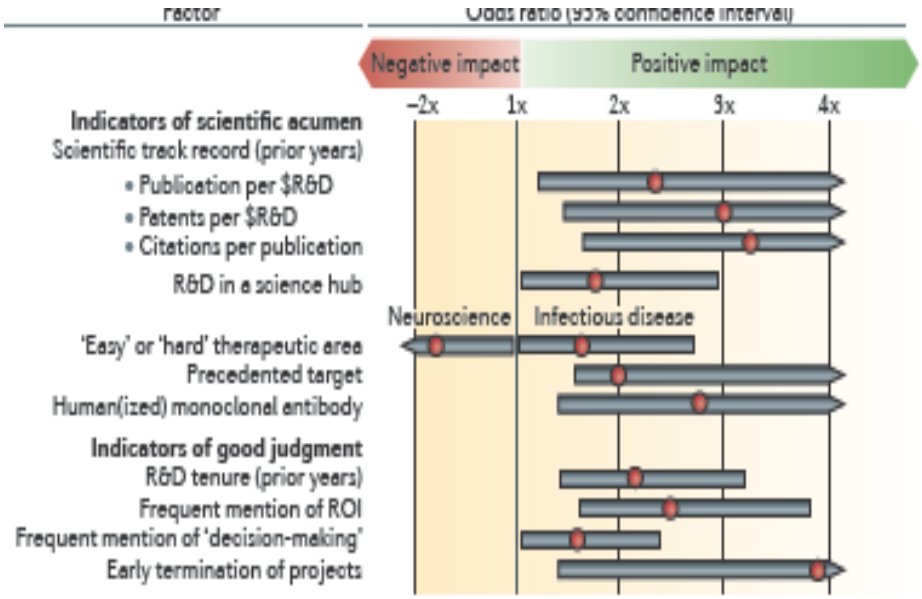


FROM THE ANALYST'S COUCH

Does size matter in R&D productivity? If not, what does?

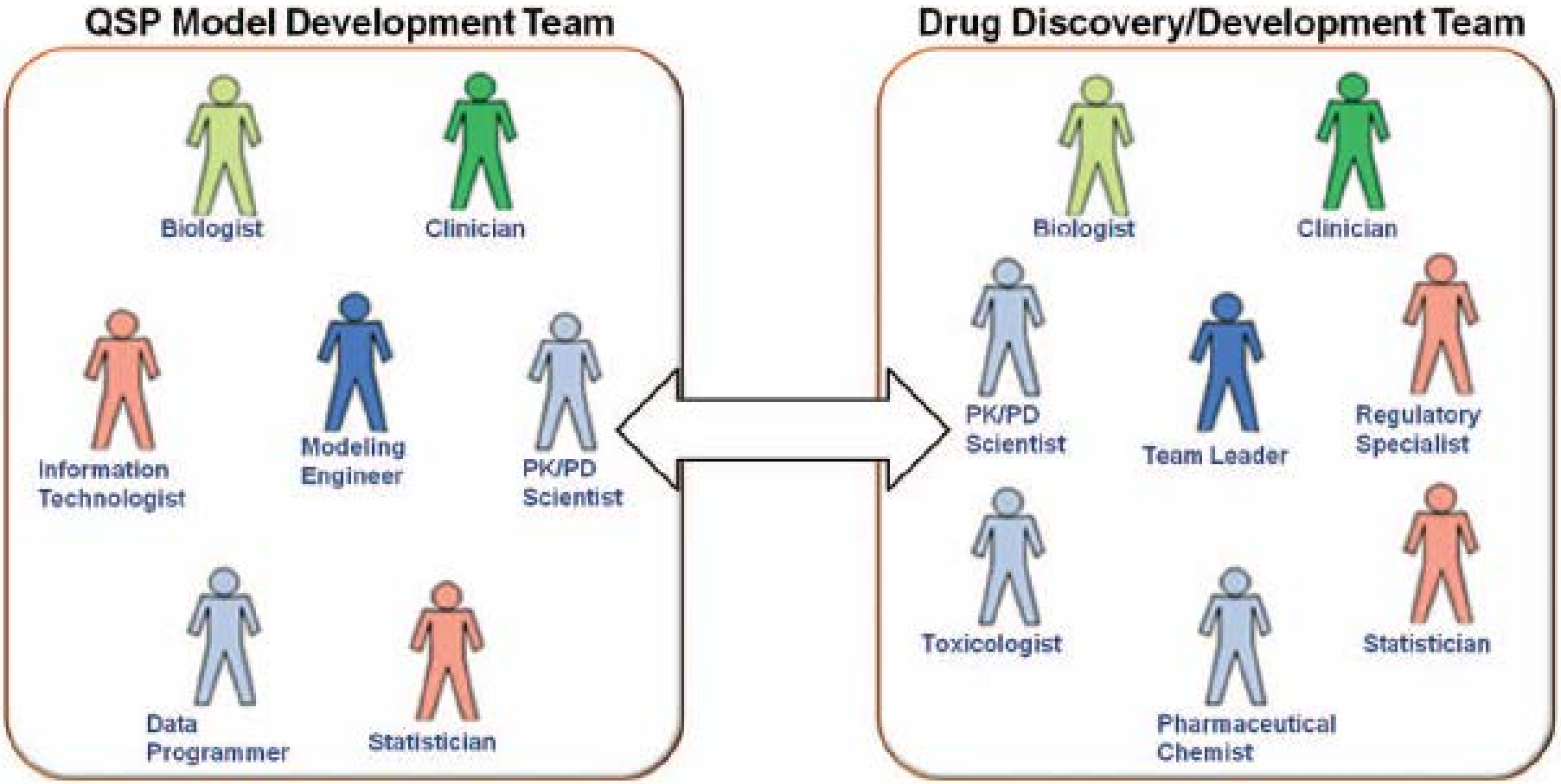
Michael Ringel, Peter Tollman, Greg Hersch and Ulrik Schulze

NATURE REVIEWS | DRUG DISCOVERY V12, DEC 2013, 901



Integration of Various Scientific Pieces is NOT AN EASY TASK!

The Challenge of Multi-Disciplinary Work-Flow

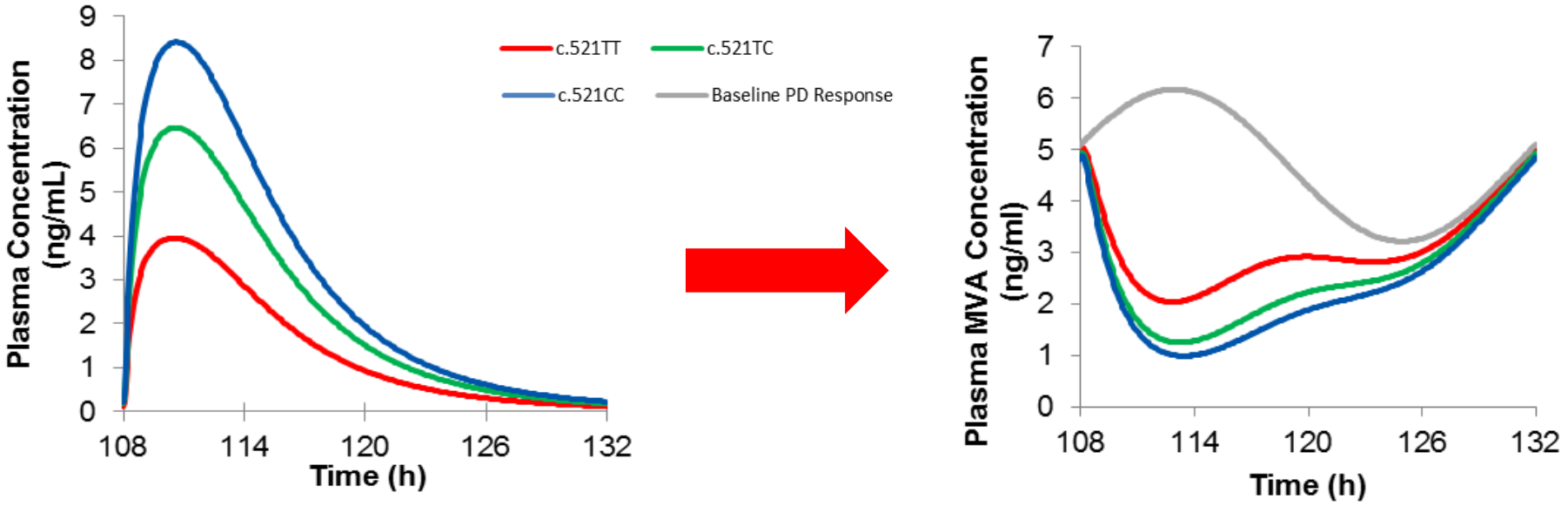


Implementation of QSP is a long and complex process.

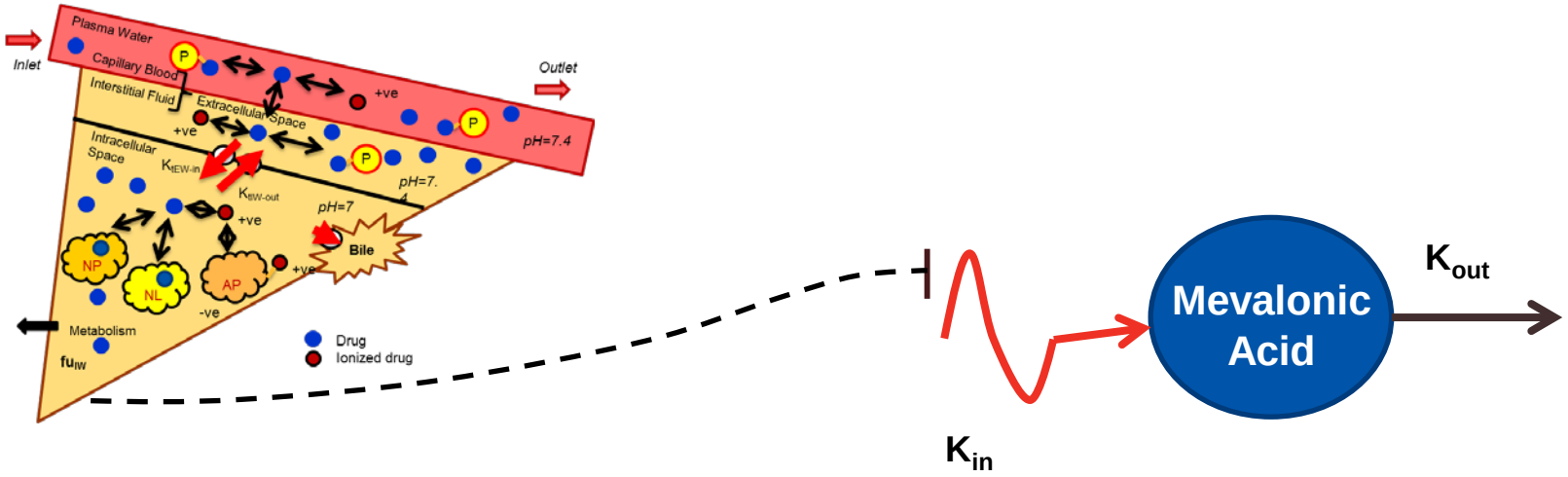
QSP cycles are defined by integration of experimental data and biological *knowledge, generation of hypotheses* & testing of those hypotheses with experiments.

Leil & Bertz 2015

Modelling Based on Simulated Concentrations in Liver

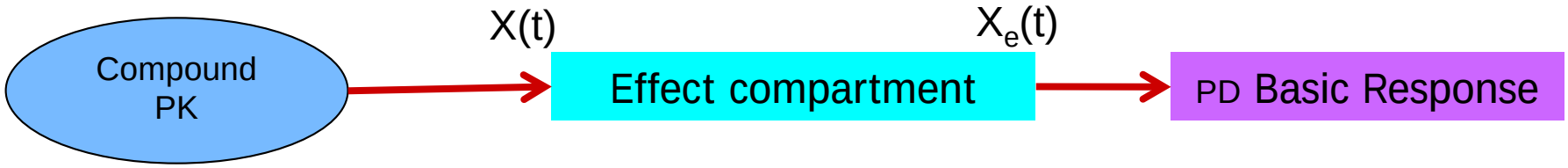


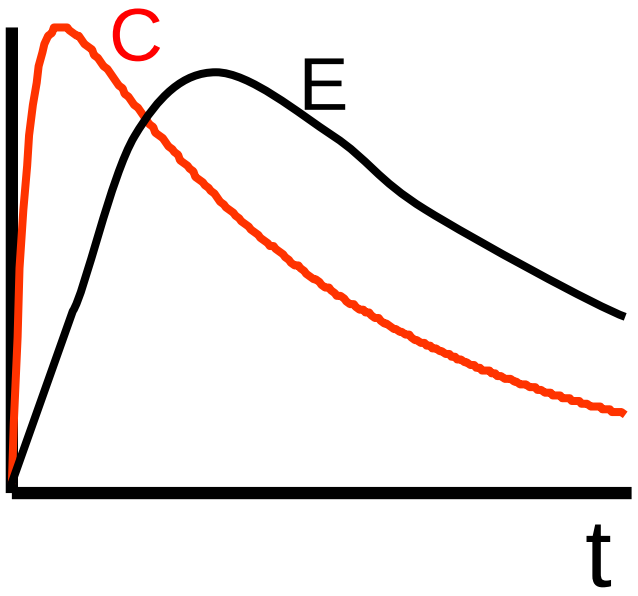
OATP1B1 c.521T>C associated with a 2.6% lower fractional LDL-C reduction per allele in <3000 patients treated with rosuvastatin daily (Chasman *et al.*, 2012)!

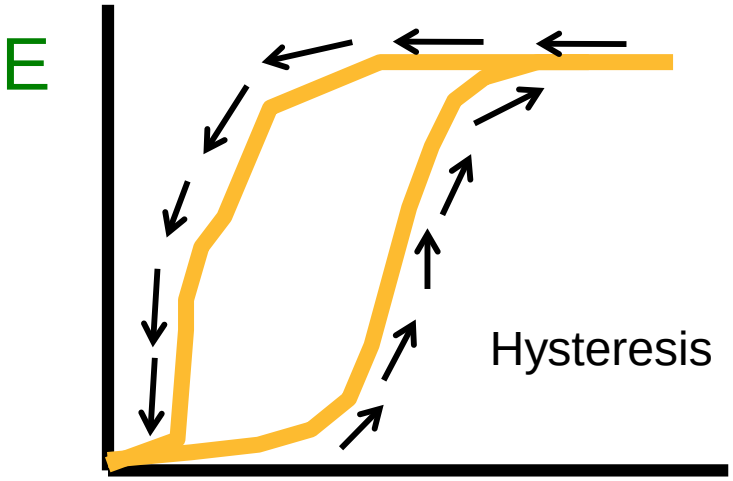


Rose *et al.*, PSP 2014

The Challenges: Reference Point (systemic vs organ)







$$\uparrow\leftrightarrow AUC_{tissue} = \frac{\uparrow AUC_{sys} \cdot CL_{in}\downarrow}{CL_{out}\downarrow}$$

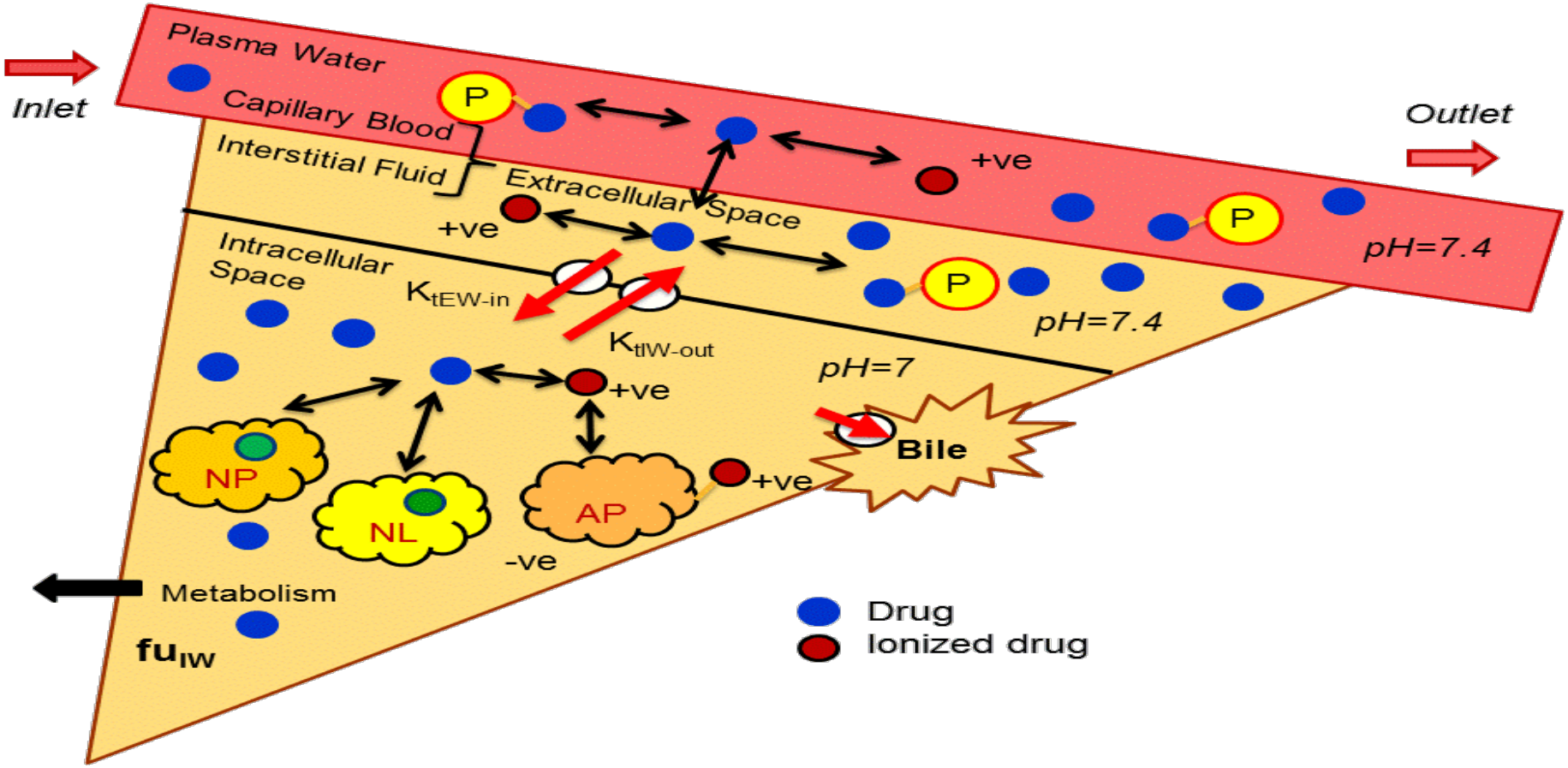
C

Clin Pharmacokinet
DOI 10.1007/s40262-013-0097-y

ORIGINAL RESEARCH ARTICLE

A Mechanistic Framework for In Vitro–In Vivo Extrapolation of Liver Membrane Transporters: Prediction of Drug–Drug Interaction Between Rosuvastatin and Cyclosporine

M. Jamei · F. Bajot · S. Neuhoff · Z. Barter · J. Yang · A. Rostami-Hodjegan · K. Rowland-Yeo



Gaps: Current Status: Information on Specific Drug

Commentary

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology

The Journal of Clinical Pharmacology
2015, XX(XX) 1–6

DOI: 10.1002/jcph.579

A Proposal for Scientific Framework Enabling Specific Population Drug Dosing Recommendations

Pravin R. Jadhav, PhD, MPH[1], Jack Cook, PhD[2], Vikram Sinha, PhD[3], Ping Zhao, PhD[3], Amin Rostami-Hodjegan, PharmD, PhD[4], Vaishali Sahasrabudhe, PhD[2], Norman Stockbridge, MD, PhD[5], and J. Robert Powell, PharmD[6]

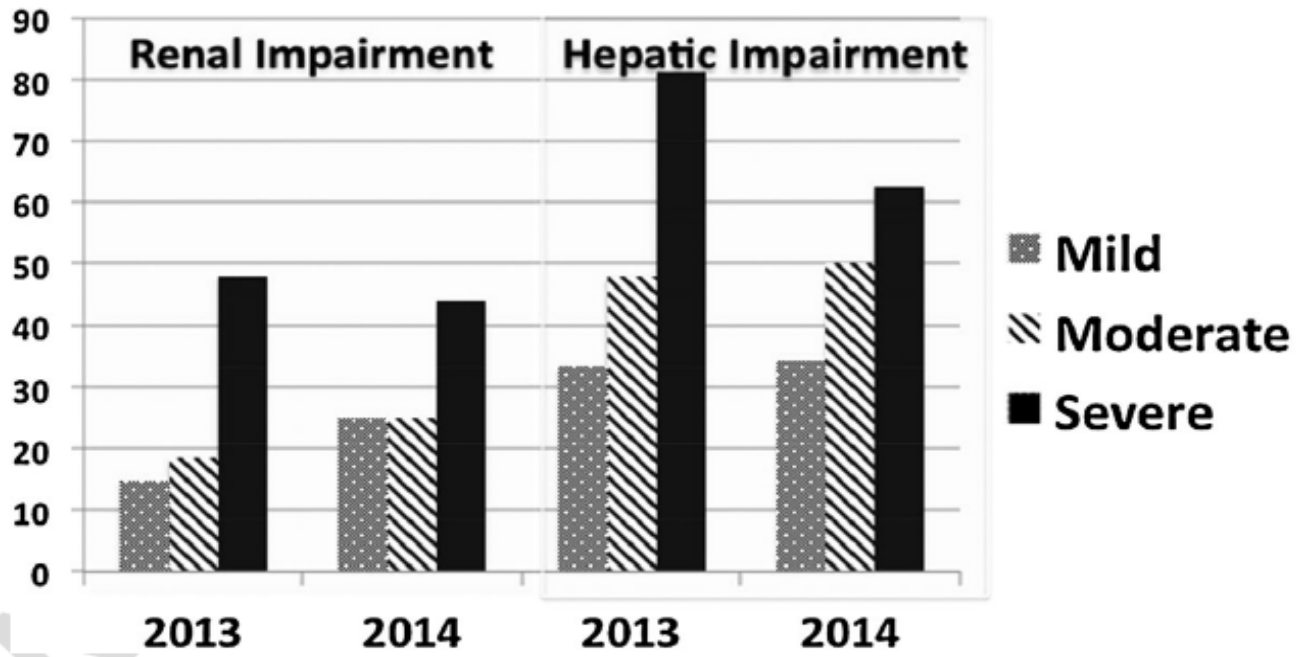
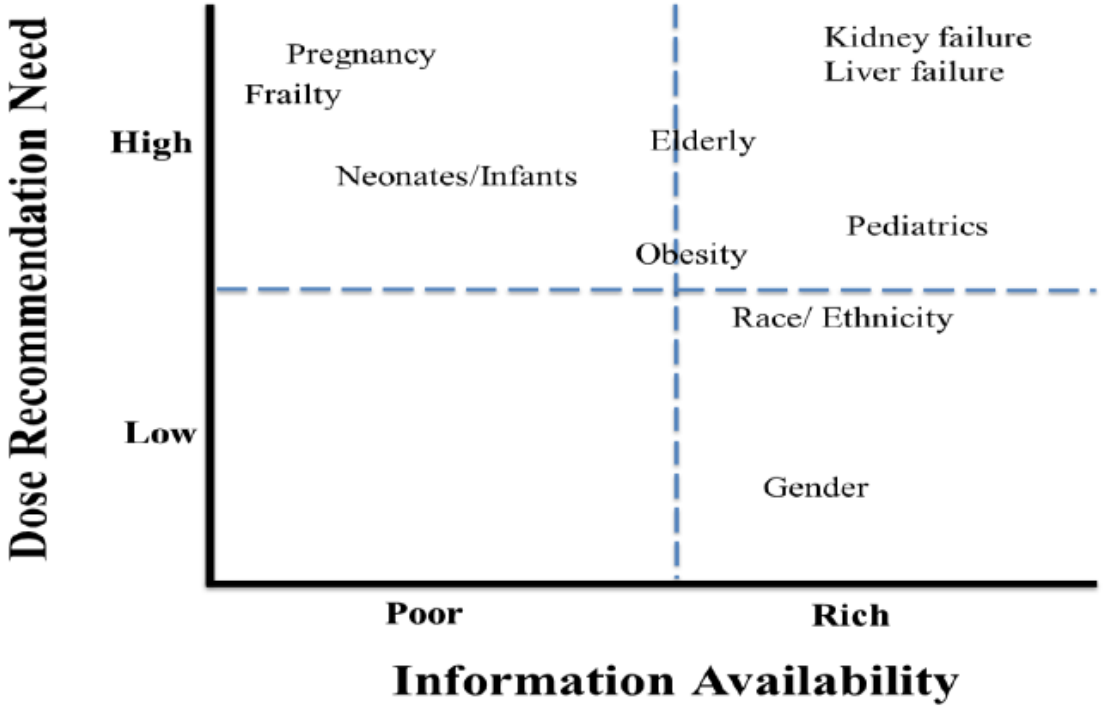


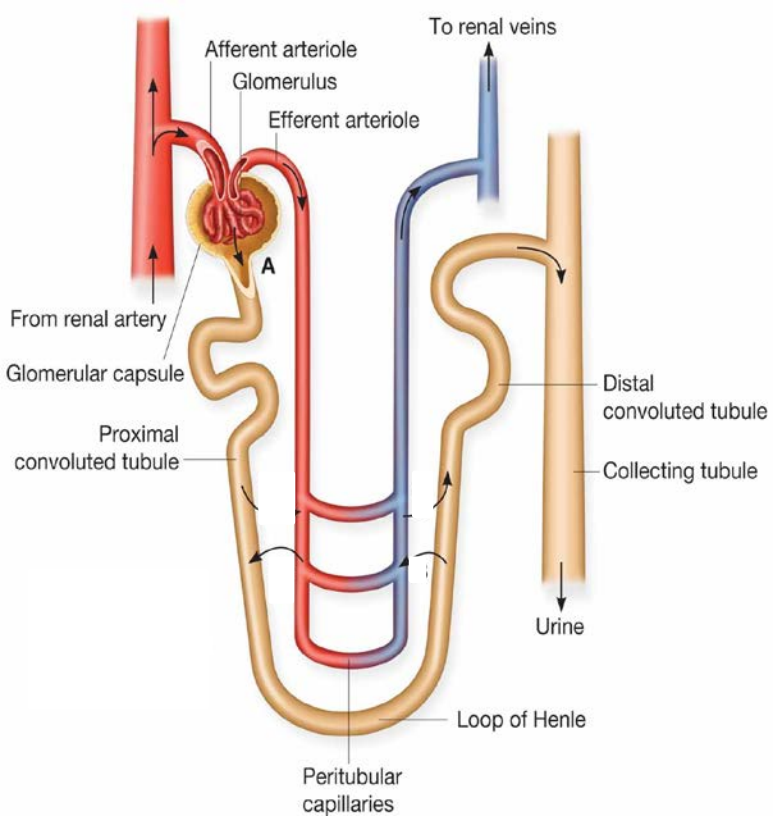
Figure 1. Proportion of 2013 and 2014 approvals without explicit dosing recommendations at the initial approval.

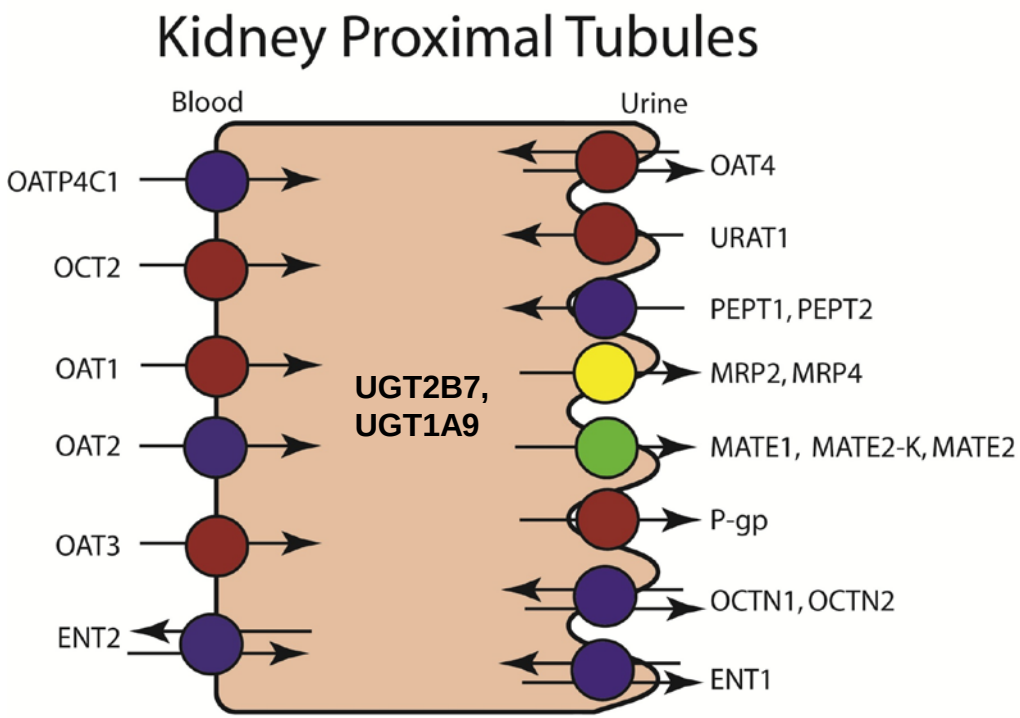
Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons From the Past and a Roadmap for the Future

AS Darwich[1], K Ogungbenro[1], AA Vinks[2,3], JR Powell[4], J-L Reny[5,6], N Marsousi[7], Y Daali[5,7], D Fairman[8], J Cook[9], LJ Lesko[10], JS McCune[11], CAJ Knibbe[12], SN de Wildt[13,14], JS Leeder[15,16], M Neely[17], AF Zuppa[18], P Vicini[19], L Aarons[1], TN Johnson[20], J Boiani[21] and A Rostami-Hodjegan[1,21]



Renal elimination of drugs





- **Active uptake via OAT1/3, OCT2 paired with efflux transporters MRP2/4, MATEs**
- **Proximal tubule cells also express drug metabolising enzymes**
- **Reabsorption - generally passive, active reabsorption via OAT4, PEPT1/2**

Bottom-Up and Top-Down Mechanistic CL_R

Prediction

Clinical data

In vivo input

Learn & Confirm

Physiologically- based models

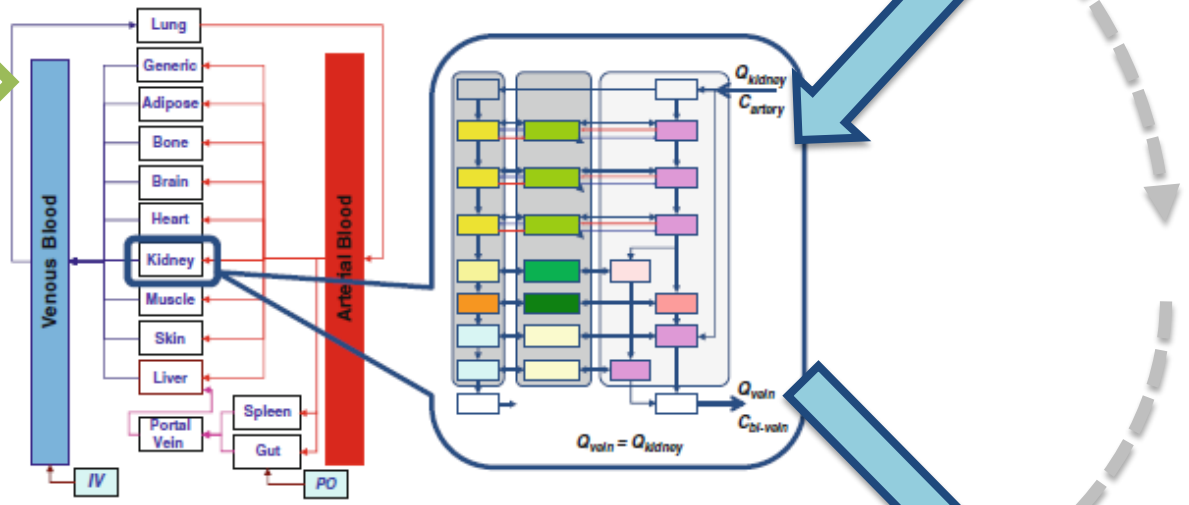


Fig. 7.3 Mech KiM nested in a whole body-PBPK model

In vitro input
System parameters

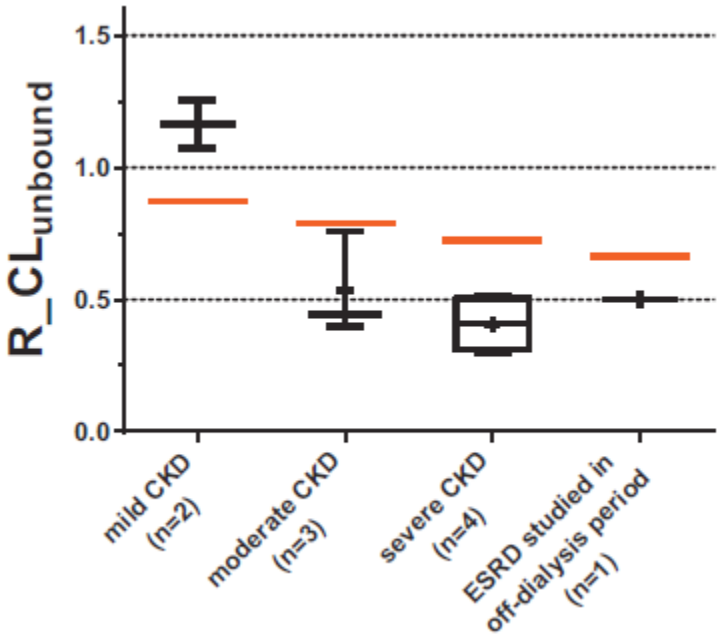
Model Parameters

Estimation

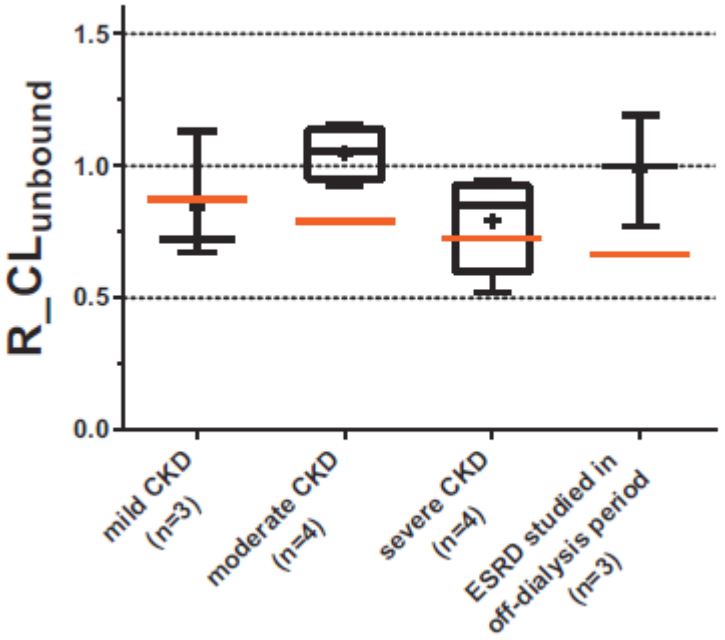
Neuhoff S, Gaohua L, Burt H, Jamei M, Li L, Tucker G, et al. Accounting for Transporters in Renal Clearance: Towards a Mechanistic Kidney Model (Mech KiM). In: Sugiyama Y, Steffansen B, editors. Transporters in Drug Development: Springer New York; 2013. p. 155-77.

Systematic evaluation of the CKD effect on CYPs

CYP2D6



CYP3A4/3A5

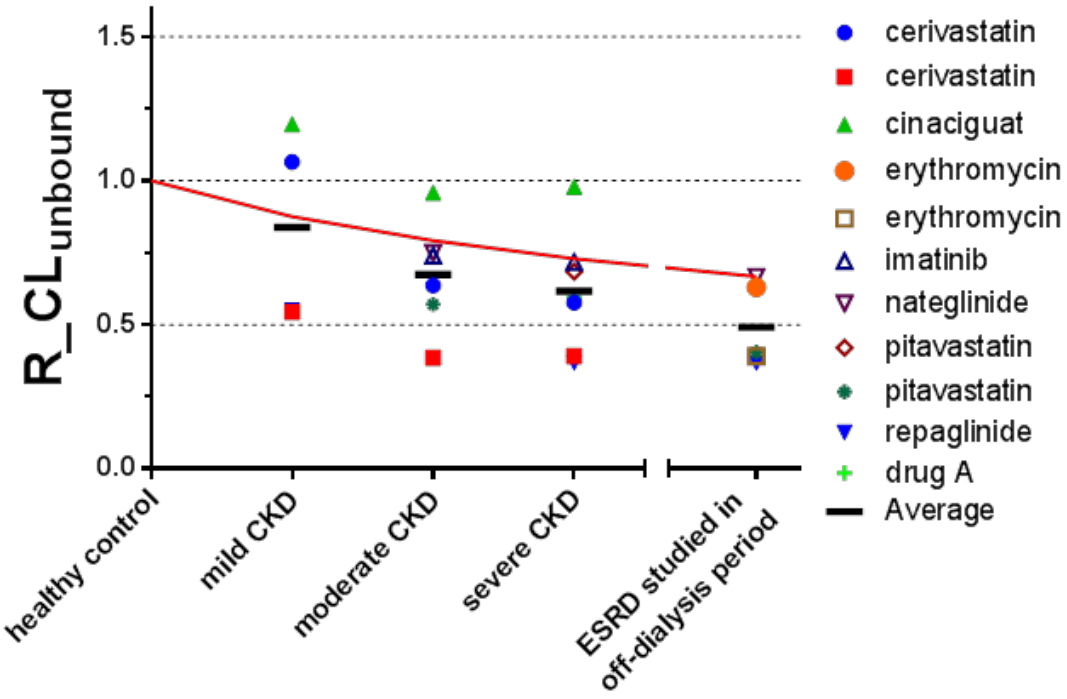


- **CYP2D6-mediated clearance decreased in parallel with the severity of CKD**
- **No apparent relationship between the severity of CKD and CYP3A4/5-clearance**

Effect of CYP1A2, CYP2C8, CYP2C9 and CYP2C19 – Poster Tan et al.

Yoshida Clin Pharmacol Ther 2016

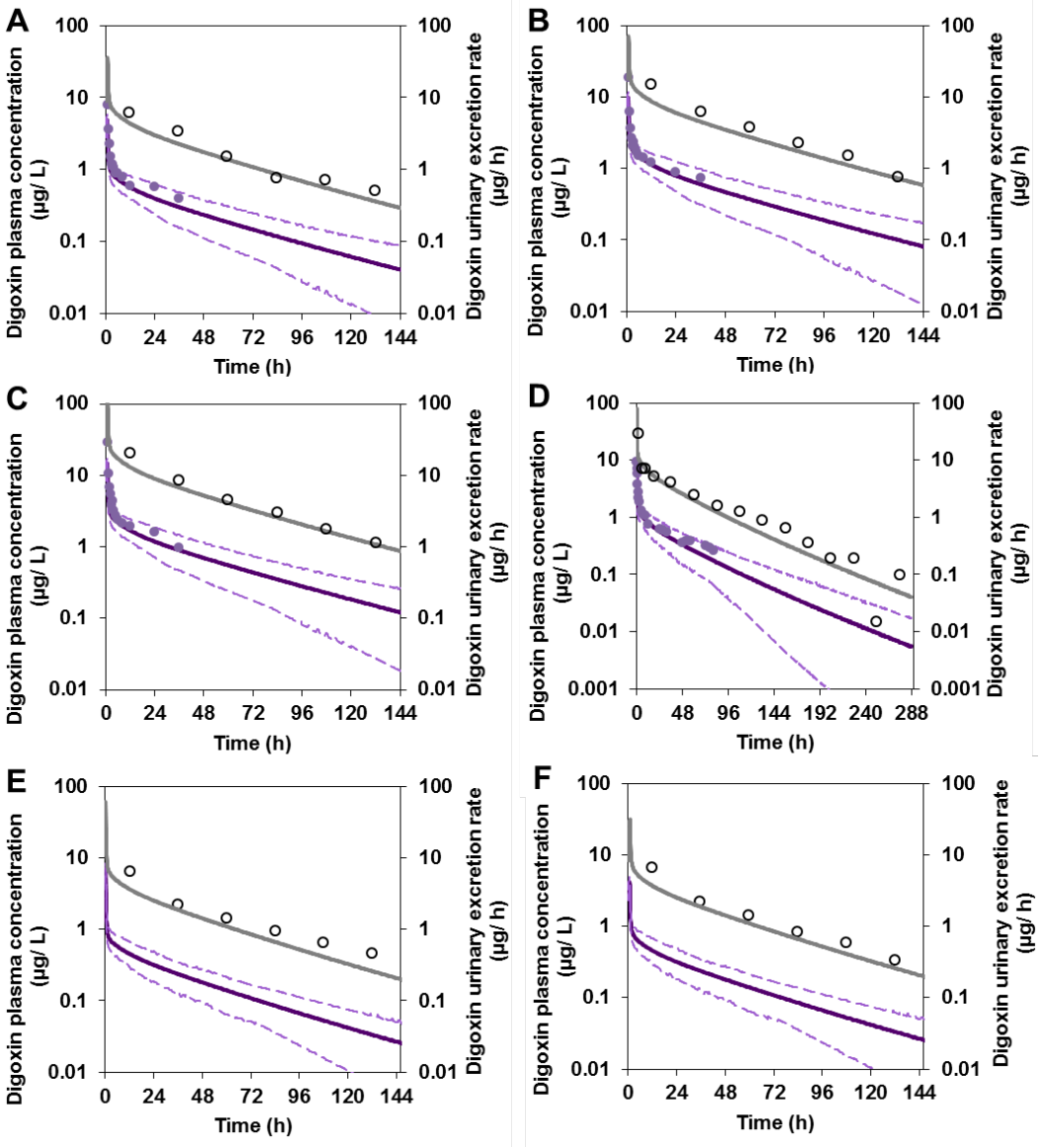
Effect of CKD on OATP1B1



- Decrease in clearance in parallel with CKD severity
- Challenges:
  - Lack of binding data in RI subjects
  - Overlap between CYP2C8 and OATP1B1 model drugs

Poster Tan et al. - ITCW and ASCPT PT-020

Digoxin mechanistic kidney model verification

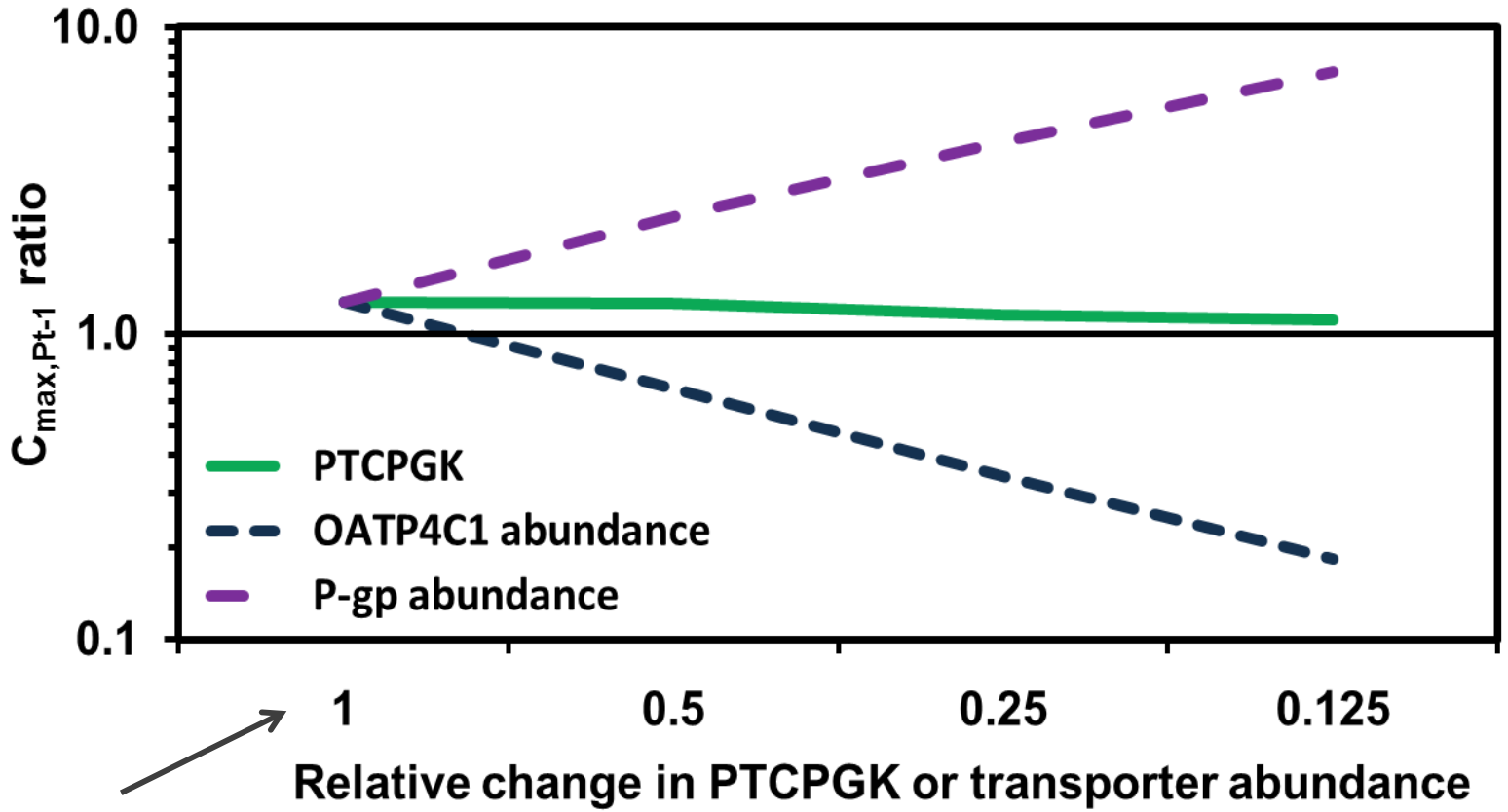


Plasma concentration

Urinary excretion rate

Mechanistic digoxin kidney model: prediction of CL_R in severe renal impairment

Additional mechanisms considered: i) ↓ transporter expression or ii) ↓ number of tubular cells



Change in GFR only
(severe renal impairment;
GFR = 15 – 30 mL/ min)

$$\text{CL}_\text{R}\ \text{ratio} = \frac{\text{CL}_\text{R}\ (\text{renal impairment})}{\text{CL}_\text{R}\ (\text{healthy subjects})}$$

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 2016

1 April 2016
EMA/199678/2016

Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

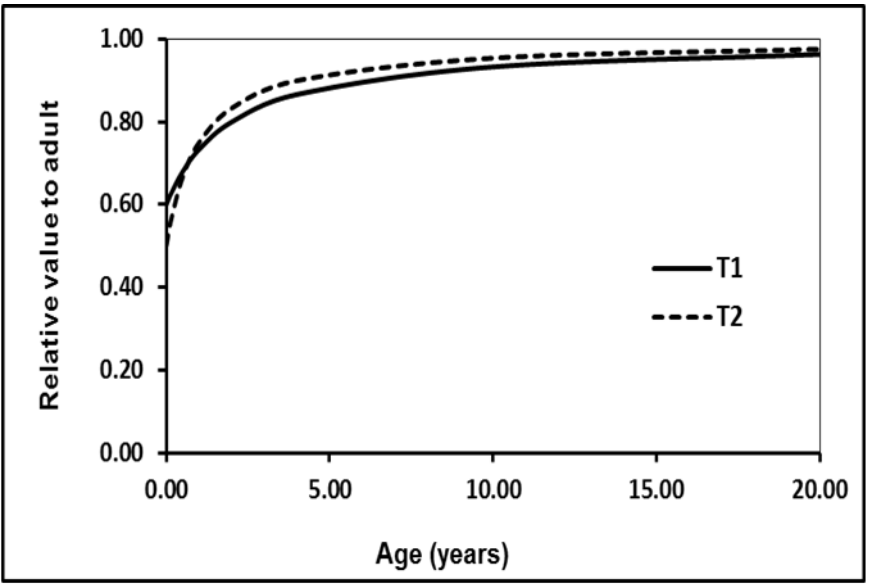
Draft

May 2016

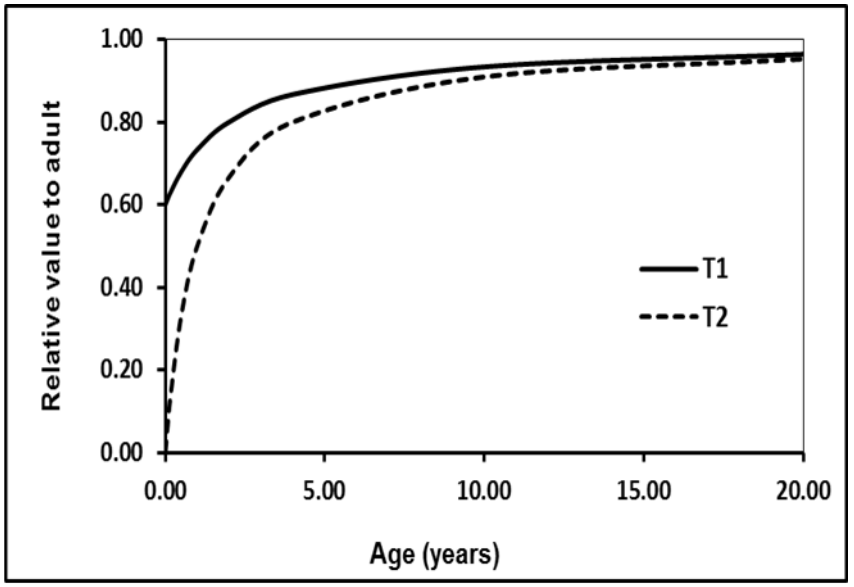
Objectives and Points to consider– EMA Workshop on extrapolation of efficacy and safety in medicine development across age groups

17 – 18 May 2016, European Medicines Agency, London

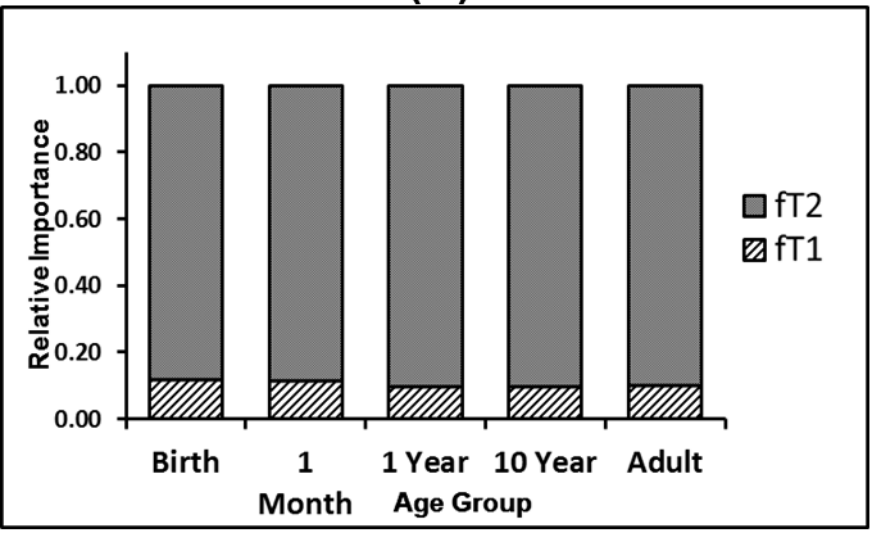
What are the challenges? Variable ontogeny (enzymes/transporters)



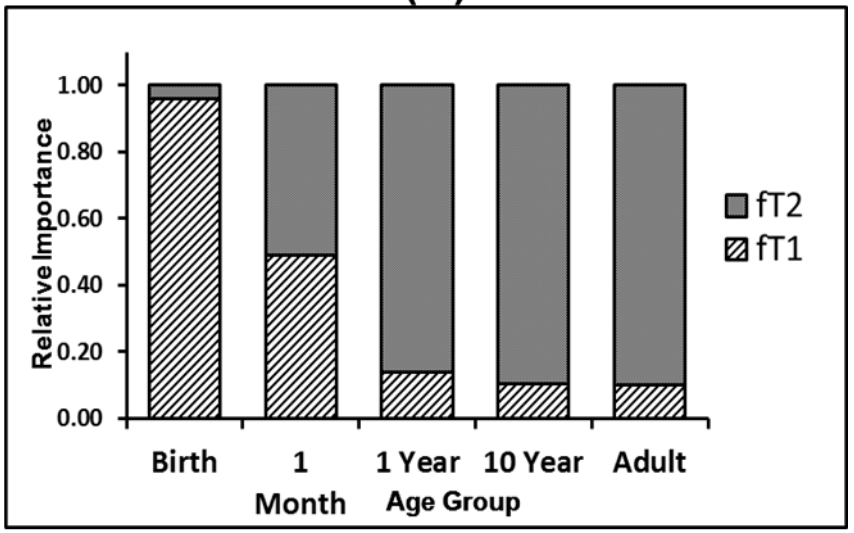
(A)



(B)



(C)



(D)

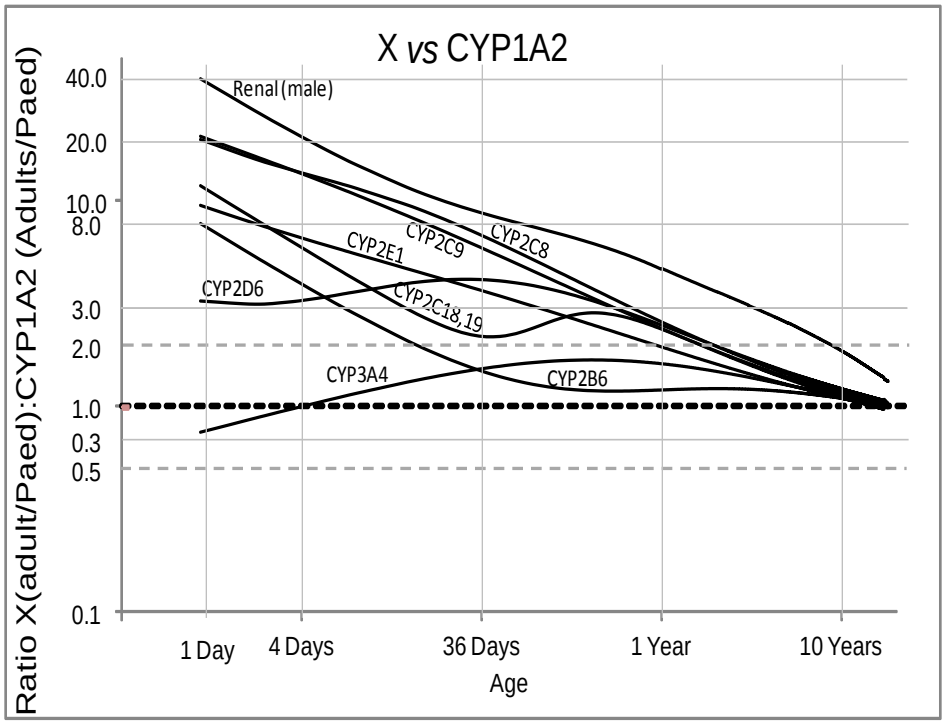
Relative Importance of Pathways: “Ratio of Ratios”!

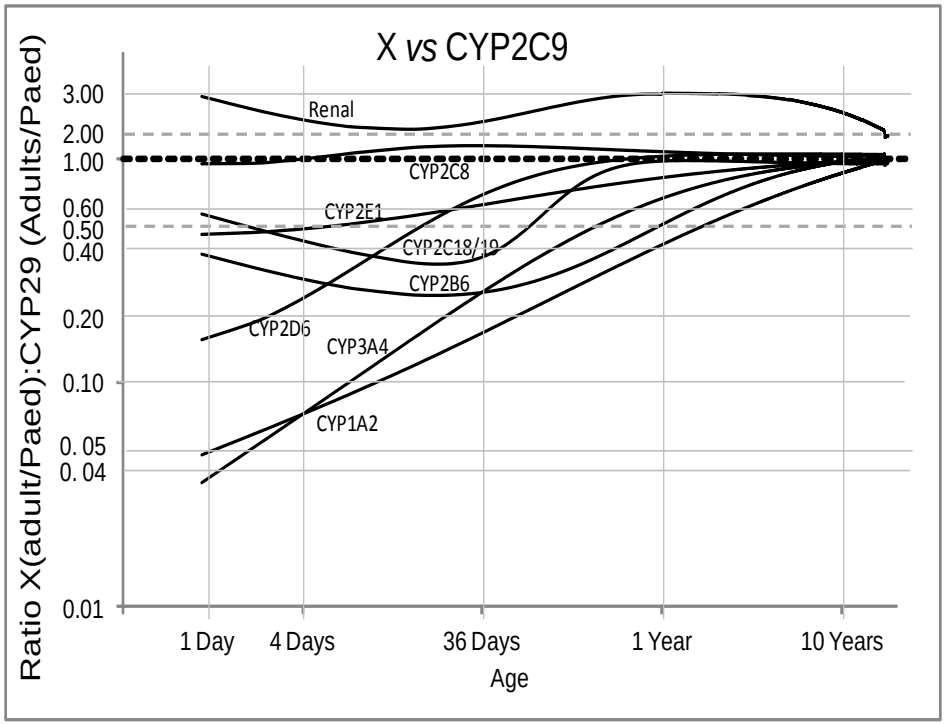
Age Related Changes in Fractional Elimination Pathways for Drugs: Assessing the Impact of Variable Ontogeny on Metabolic Drug–Drug Interactions

J Clin Pharmacol
2013; 53: 857–865

Farzaneh Salem, PharmD[1], Trevor N. Johnson, PhD[2], Zoe E. Barter, PhD[2], J. Steven Leeder, PharmD, PhD[3,4,5], and Amin Rostami-Hodjegan, PharmD, PhD, FCP[1,2]

$$\text{Relative Ontogeny} = \frac{\dfrac{\text{Pathway A in Paediatrics}}{\text{Pathway A in Adults}}}{\dfrac{\text{Pathway B in Paediatrics}}{\text{Pathway B in Adults}}}$$





Absence of info on free local concentrations: Sensitivity???

Ontogeny of Plasma Proteins, Albumin and Binding of Diazepam, Cyclosporine and Deltamethrin

Sethi; et al

Pediatric Research accepted article preview online 16 November 2015;

Fig. 1

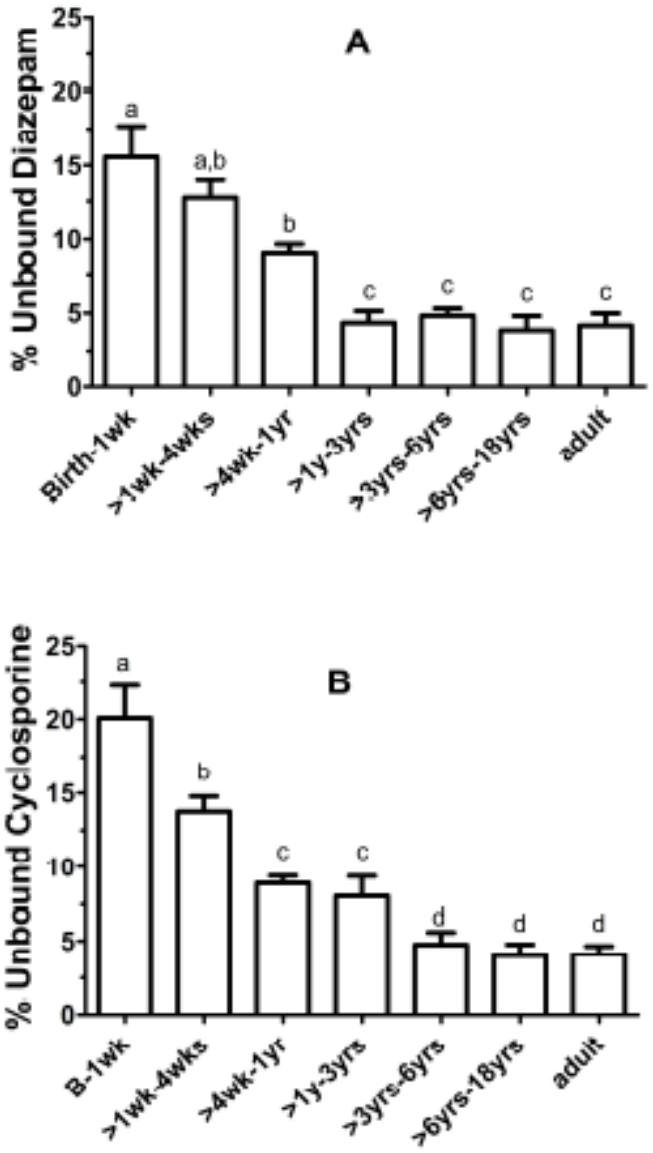
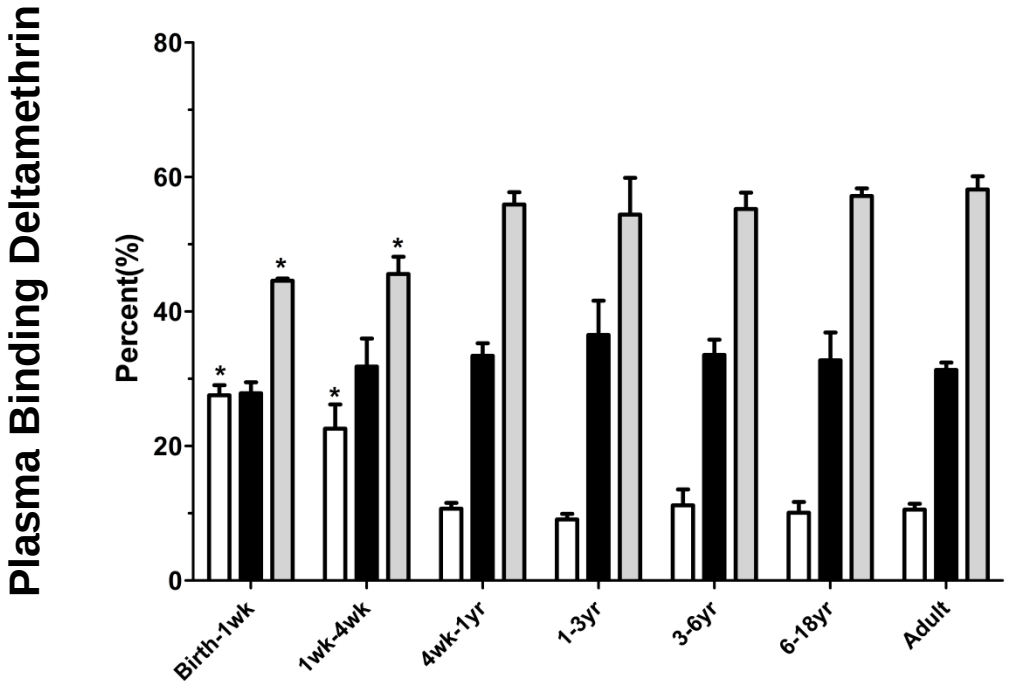


Fig. 2

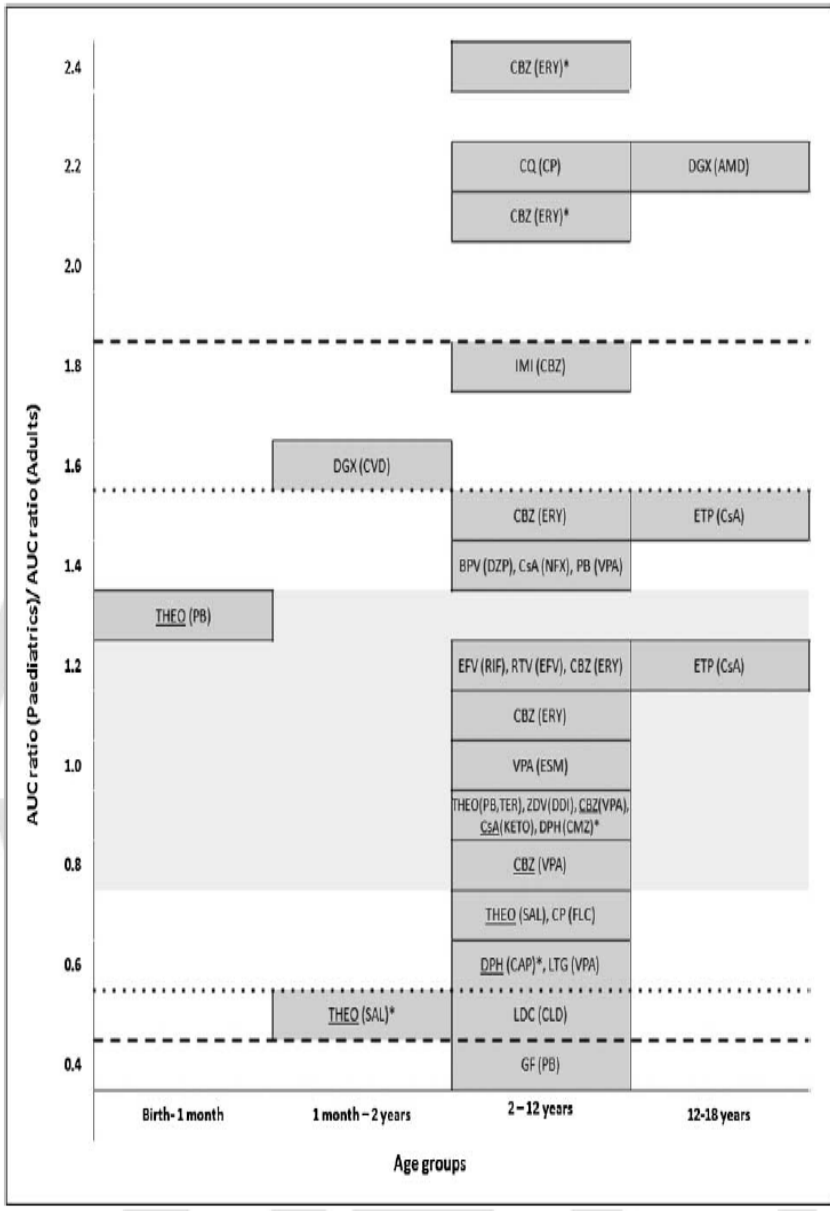


Reasoning?

Do Children Have the Same Vulnerability to Metabolic Drug–Drug Interactions as Adults? A Critical Analysis of the Literature

Farzaneh Salem, PharmD[1], Amin Rostami-Hodjegan, PharmD, PhD and Trevor N. Johnson, PhD[2]

An age-related trend in the magnitude of DDIs could not be established. However, the study highlighted the clear paucity of the data in children younger than 2 years. Care should be exercised when applying the knowledge of DDIs from adults to children younger than 2 years of age.



Regulatory View on Application of IVIVE/PBPK/Paediatrics

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

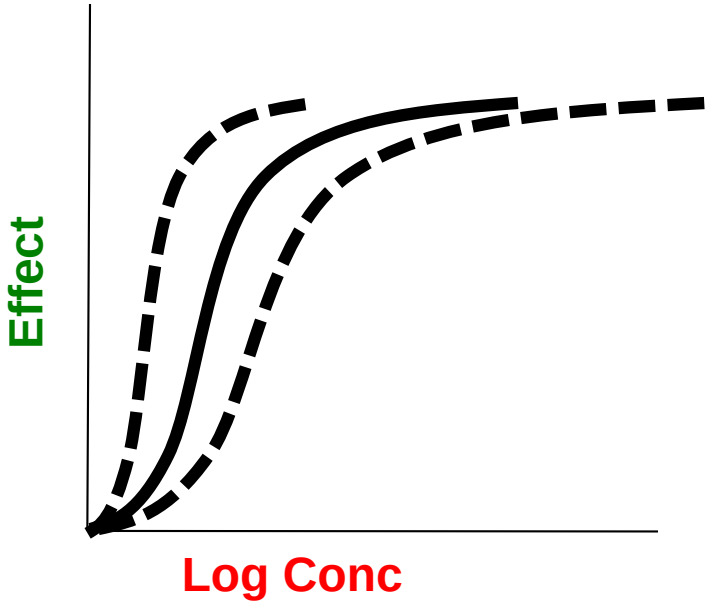
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

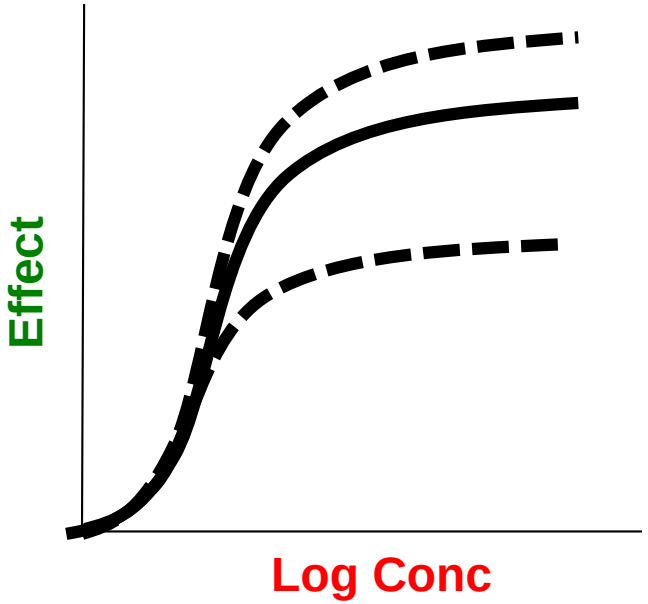
5.2.5. Special Populations

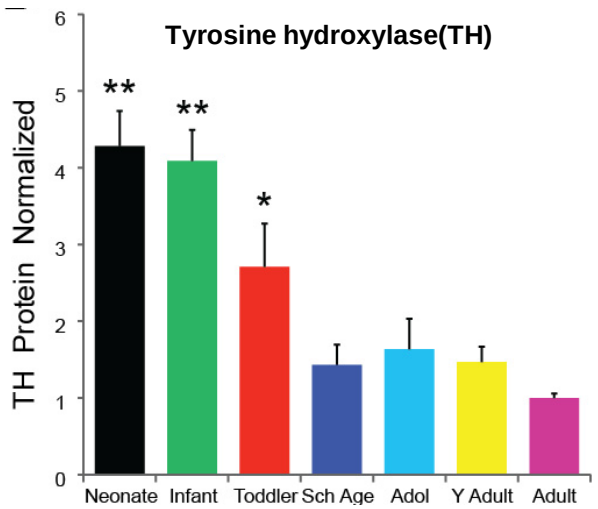
An interaction effect **may not be directly extrapolated** to specific subpopulations that have a markedly different contribution of the affected enzyme and/or transporter to the clearance of the investigational drug. Such subpopulations may include carriers of certain alleles…impaired renal function…and young paediatric patients (< 2 years)

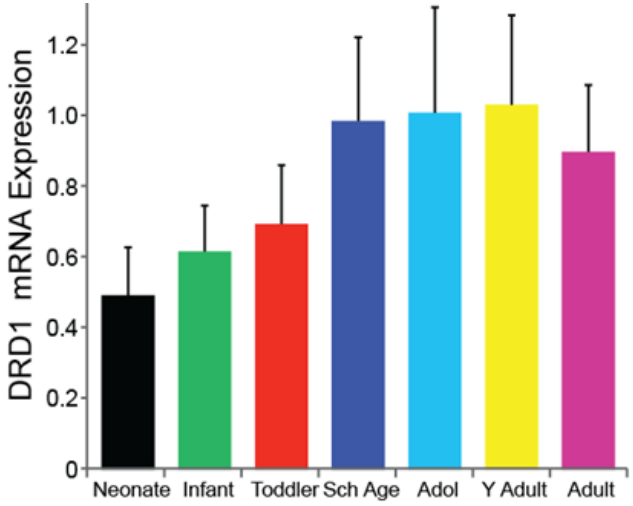
……**It may also be acceptable to use PBPK simulations** to predict the interaction effect in the subpopulation if the simulation is qualified for this purpose. This includes an adequate prediction of the relative contribution of enzymes to *in vivo* clearance. Thus, the results of potent inhibition (or polymorphism) of the separate enzymes *in vivo* should be well predicted. ……**PBPK simulations may serve as a basis for treatment recommendations.** However, specific dose recommendations may need support by *in vivo* interaction data in the subpopulation.

True vs Apparent PD Differences in Paediatrics









Rothmond et al., 2012

Combining Top-Down and Bottom-Up Modelling

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12234

Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data

Nikolaos Tsamandouras,[1] Amin Rostami-Hodjegan[1,2] & Leon Aarons[1]

[1]Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, University of Manchester, Manchester and [2]Simcyp Limited, Blades Enterprise Centre, Sheffield, UK

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Professor Leon Aarons, Manchester Pharmacy School, The University of Manchester, Stopford Building, Room 3.35, Oxford Road, Manchester M13 9PT, UK.
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E-mail: leon.aarons@manchester.ac.uk

Keywords
Bayesian analysis, identifiability, middle-out approach, parameter estimation , PBPK, population variability

Received
8 July 2013
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Accepted Article Published Online
3 September 2013

Take Home Message From over half a a century ago

We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been.

George Wilhelm Merck

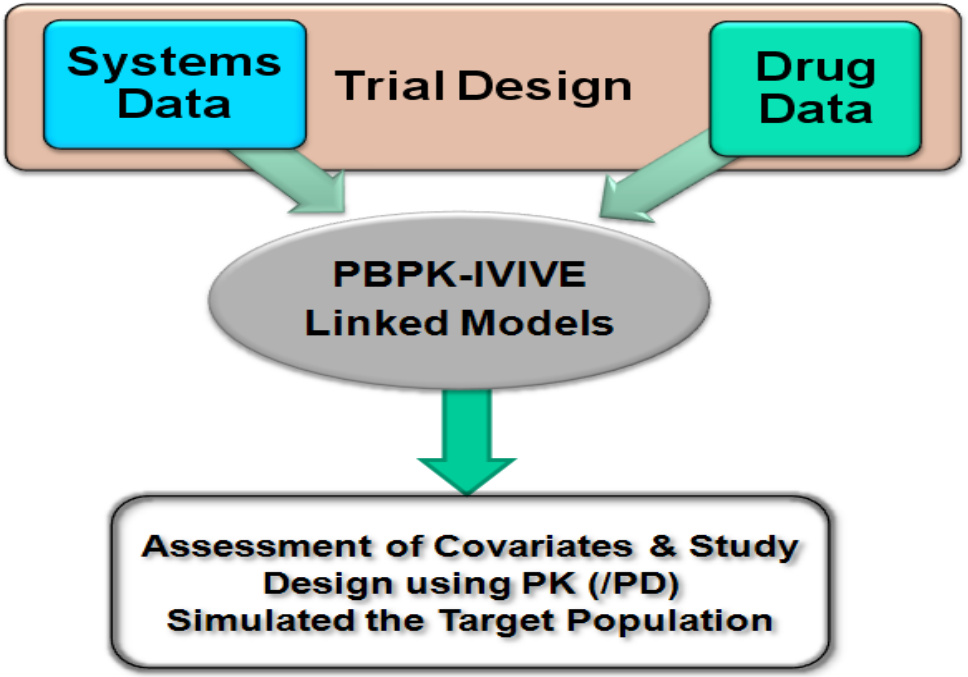
Drug-Focused vs System-Focused Research & Development

STATE OF THE ART nature publishing group

Physiologically Based Pharmacokinetics Joined With *In Vitro–In Vivo* Extrapolation of ADME: A Marriage Under the Arch of Systems Pharmacology

A Rostami-Hodjegan[1,2]

Schematic Representation of Workflow



Associated IT Elements

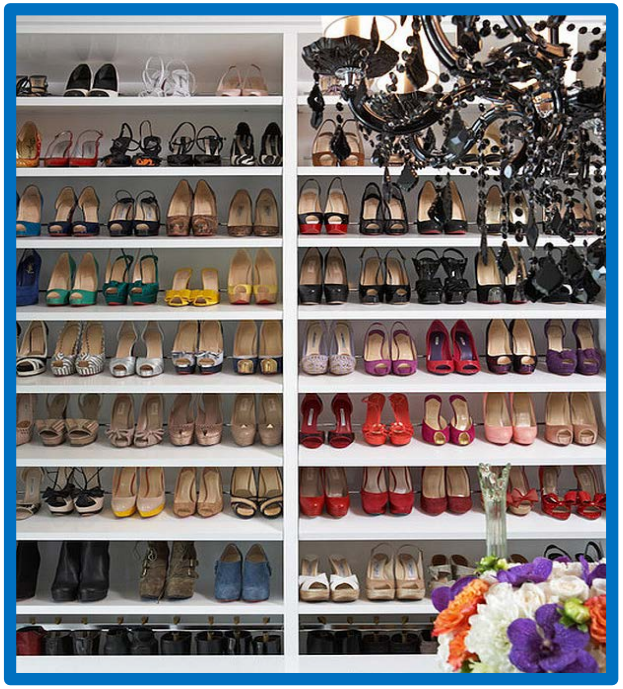
Input Data:
- Population Library
- Compound File
- Project (Workspace)

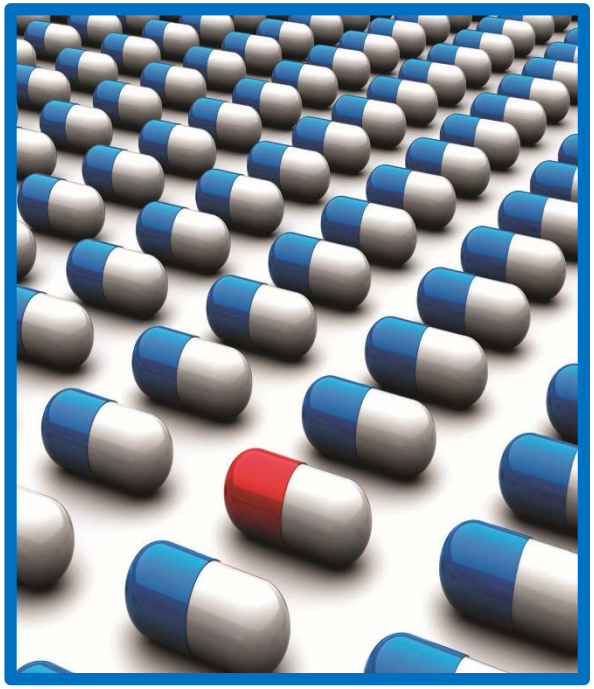
Integrated Models
- Simulation Tool
- Simulation Environment

Output
- Raw Output Data
- Output Environment
- Data Analysis

One Size Fit All Mentality

Defining the ROADMAP for SOLVING A PROBLEM
(by the Key Opinion Leaders from the Health Care, Academia and Industry)





"Your shoe fits the size of your foot, so why is your drug dose not tailored to your own personal characteristics in the same way? Why do drugs all come in one size fits all? OK may be only two sizes!"

Medication Use in Pregnancy and the Pregnancy and Lactation Labeling Rule

L Sahin[1], SC Nallani[2] and MS Tassinari[1]

CLINICAL PHARMACOL THERAP
100(1): 23-25 (2016)

8. USE IN SPECIAL POPULATIONS

8.1 Pregnancy	8.2 Lactation	8.3 Females and Males of Reproductive Potential
Pregnancy Registry Risk Summary Clinical Considerations (Includes *"Dose adjustments during pregnancy and the postpartum period"*) Data	Risk Summary Clinical Considerations Data	Pregnancy Testing Contraception Infertility

A brief outline of the re-formatted labeling: In each subsection, clinical pharmacology data can be included.

See draft guidance: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

Figure 1 The pregnancy and lactation labeling final rule and changes to the prescription drug labeling.

Connectivity of Various Efforts

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

SECTION I - ENSURING THE FFECTIVENESS OF THE HUMAN DRUG REVIEW PROGRAM

PART J . Enhancing Regulatory Decision Tools To Support Drug Development And Review

3. Advancing Model-Informed Drug Development

To facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, herein referred to as "model-informed drug development" (MIDD) approaches, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop its regulatory science and review expertise and capacity in MIDD approaches. This staff will support the highly-specialized evaluation of model-based strategies and development efforts.

b. FDA will convene a series of workshops to identify best practices for MIDD. Topics will include: (1) physiologically-based pharmacokinetic modeling; (2) design analysis and inferences from dose-exposure-response studies; (3) disease progression model development, including natural history and trial simulation; and (4) immunogenicity and correlates of protection for evaluating