Workflow for PBPK Modeling to Support Pediatric Research and Development

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Industrial Strength PBPK

Outline

- Industrial Application of PBPK for Pediatrics
- PBPK Practices – Non-pediatric workflow
  - **Relevance for transition**
- Concerns Pediatric Applications
  - **In the absence of precedence . . .**
- Pediatric Workflows
  - **Fit-for-purpose vs Best Practice → there is a difference here!**
- Request for clarification ☺

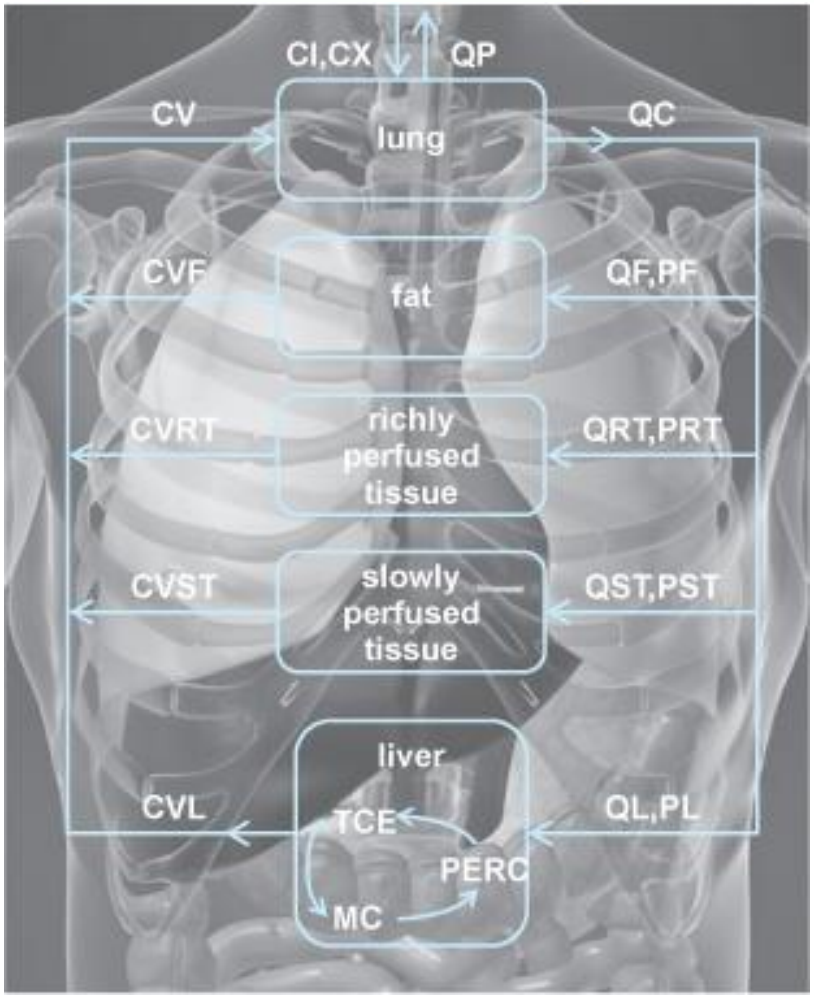
Drug Development Expectations for PBPK when Guiding Pediatric R&D

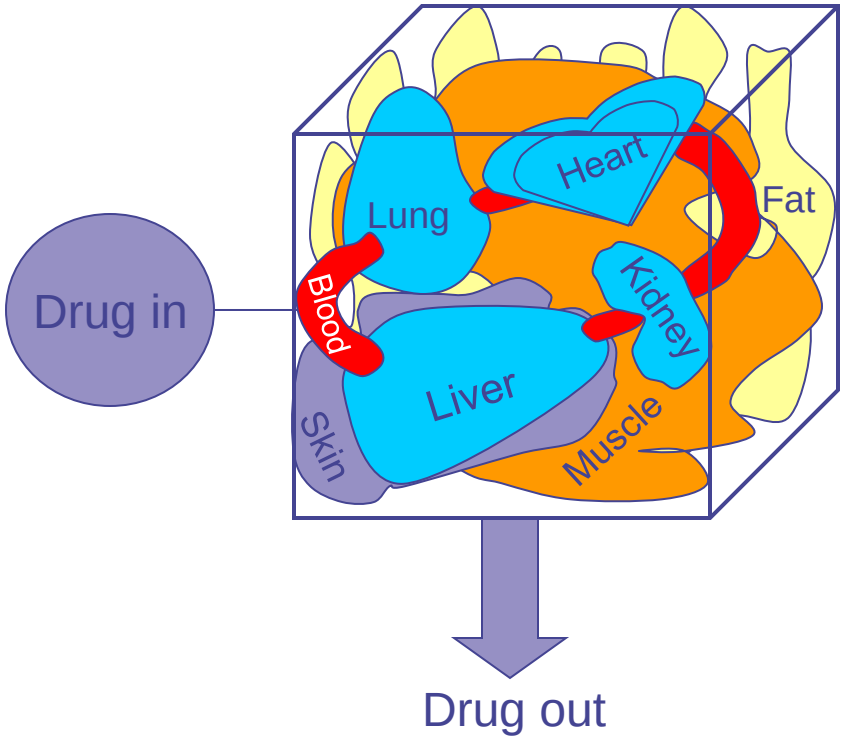
- Guide initial dosing rationale
- Evaluate DDI potential in pediatric subpopulations (across age strata)
- Examine developmental / maturational concerns
- Guide pediatric formulation development
- Examine non-systemic exposure requirements
- Support* dosing recommendations

PBPK Added-value for Pediatric R&D

- Consideration of non-traditional drug administration (route, formulation, etc)
- Physiologic–mechanistic explanation for PD effects
- Correlation of non-systemic exposures with toxicity
- Dose-exposure evaluation of non-systemic target exposures
- Definition of pediatric sub-populations based on physiologic characteristics (that differ from otherwise healthy pediatric populations)

Comfort with Predictions?





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PBPK Practices – Non-pediatric workflow

- The majority of PBPK experience in the pharmaceutical industry is driven by DDI concerns.
- The pediatric experience has been driven (in the past) by regulatory query.
- Many companies have PBPK groups, dedicated personnel or working groups
  - **Several research efforts (e.g., post doctoral projects) are exploring the ROI for peds.**

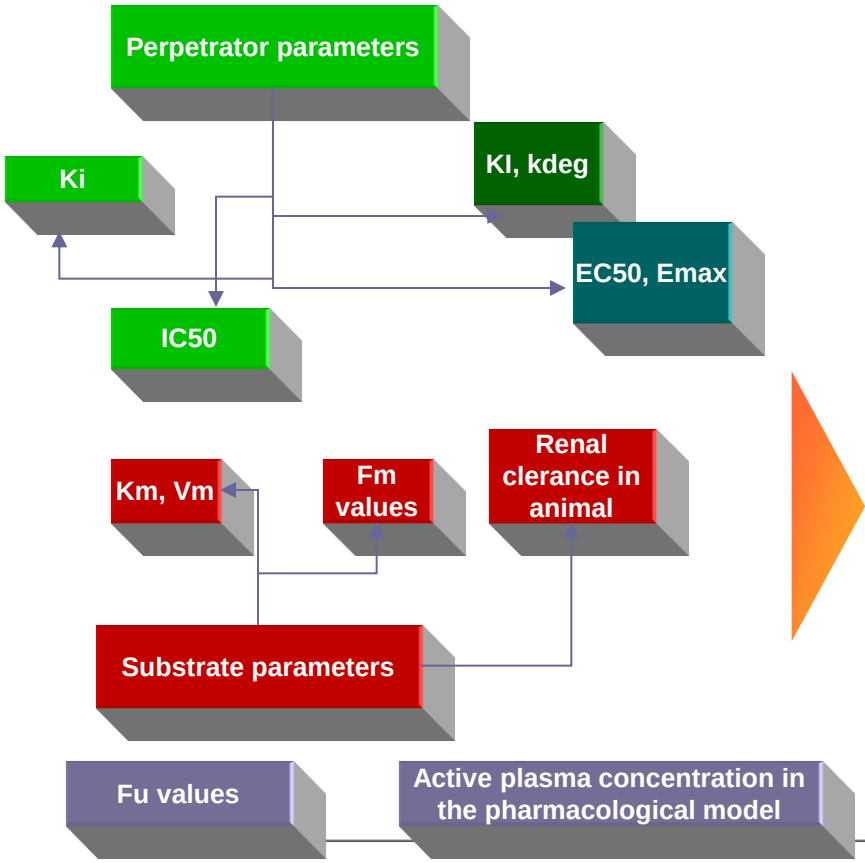
By Phase PBPK Workflow / Practice

- Experience of the Sanofi PBPK Working Group

Discovery / Preclinical Phase

Dynamic (MDM) and static (MSM) approaches

Available data



Addressed questions

MSM approaches

Overall rough DDI risk assessment for selecting candidates

- DDI risk assessment toward representatives of therapeutic class,
- To be put in perspective with the intended indication.
- Therapeutic class ranking according to the risk assessment.

MDM approaches

Preparing for the future

Start building up PBPK model, rough model, not used for decision making in most of cases

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Phase I: FIH; Single and repeat dose

Dynamic (MDM) and static (MSM) approaches

Available data

PK profile with Cmax, t1/2,…

Total clearance of the compound; linearity, renal clearance

Possible insight of genetic polymorphic enzyme involvement

Addressed questions

MSM approaches

Rough DDI risk assessment toward potential co-med

Use of clinical concentrations for risk assessment refinement, done at different dosages for DDI anticipation with co-med in phase II if any. Identification of possible substitution inside each class.

MDM approaches

PBPK for internal purpose

Refinement of the PBPK model.
Clinical interaction simulation with probe compounds, at different dosage.

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Phase II / III

Dynamic (MDM) and static (MSM) approaches

Available data

Addressed questions

Dose selection and corresponding exposure in patients.

PK in special population. Knowledge of elimination pathways of the drug (C14 study)

Outputs of clinical interaction conducted in healthy volunteers, with probe compounds*.

Validation of the DDI PBPK model for waiver, authorities experience

MSM approaches

Rough DDI risk assessment toward potential co-med

Refinement of the predictions through comparison with clinical data obtained with probe compounds.

DDI risk assessment towards all the compounds likely to be co-administered in phase III trials, in the target patient population.
→ Inclusion criteria.

MDM approaches

PBPK for internal and regulatory purpose

Refinement (validation?) of the PBPK model, with observed interaction outputs from clinical studies .

Predicted PK used for PK/PD simulations.

Simulations mixing covariates: interaction in special populations What if ? e.g.Impact of formulation

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Submission phase

Dynamic (MDM) and static (MSM) approaches

Available data

Identification of covariates in POPPK approach,' 'top-down"

To be put in perspective with PBPK mode ''bottom-up"

Addressed questions

MSM approaches

Rough DDI risk assessment toward potential co-med

Upon request, DDI risk assessment toward additional therapeutic class.

MDM approaches

PBPK for regulatory purpose

- Use of simulation in order to avoid conducting interaction studies. Validated model.
- Simulations of clinical situations unlikely to be evaluated experimentally.
- Predicted PK used for PK/PD simulations

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Transition to Pediatrics?

- Benefits
  - Well-defined adult model inherited
  - Mature appreciation for metabolic clearance mechanisms
  - Implicit valuation of *in vitro* inputs via sensitivity analyses
- Additional considerations for pediatrics
  - Non-metabolic clearance mechanisms and volume of distribution considerations (potentially)
  - Developmental / maturational considerations
  - Pediatric populations not described by existing physiologic databases

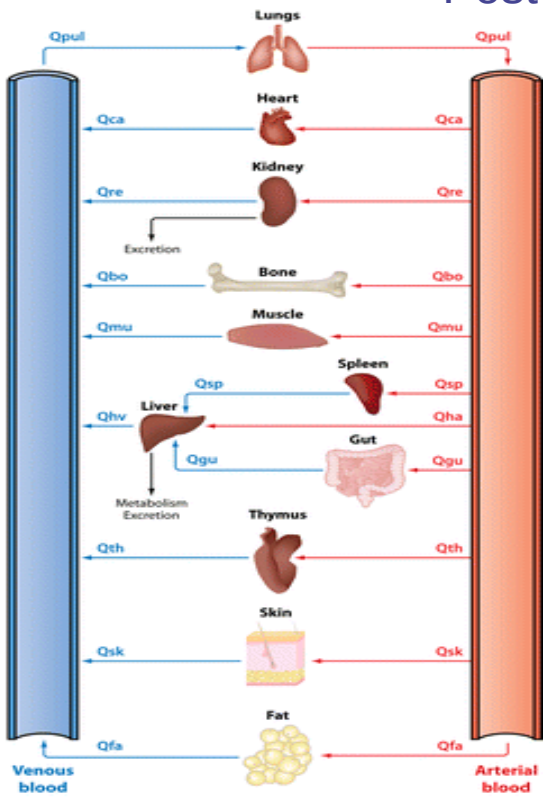
Transition to Pediatrics?

Industrial Focus – Research Initiative

- How do we address the transition gaps?
- What is the reasonable amount of uncertainty we can remove via targeted investigation?
  - Need to show the ROI
  - After we do this . . . what is the remaining risk?
- What will / should be our best practice?
- Back to the original question
  - Fit for purpose . . . what purpose?

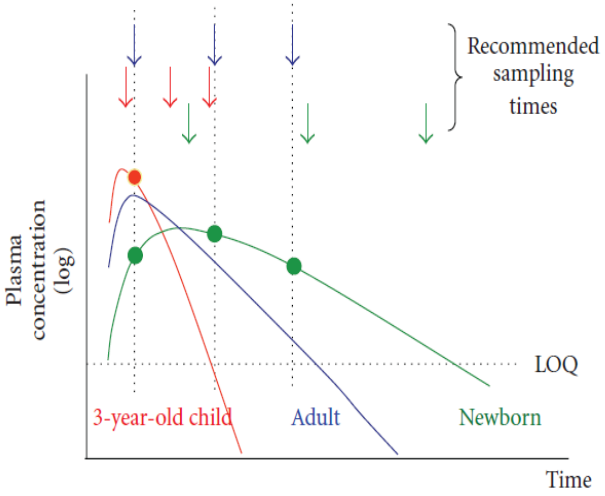
Questions about PBPK Advantages for Pediatric R&D Support

Post-doc Project: Hoai-Thu THAI



Adult PBPK model

age-dependent physiological characteristics



exposure in different pediatric age groups

- Take into account the effect of maturation on all ADME processes (absorption, distribution, metabolism, elimination)

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Project Overview

PBPK approach

Develop the adult PBPK model

Pediatric population

Pediatric PK prediction

Pop PK model

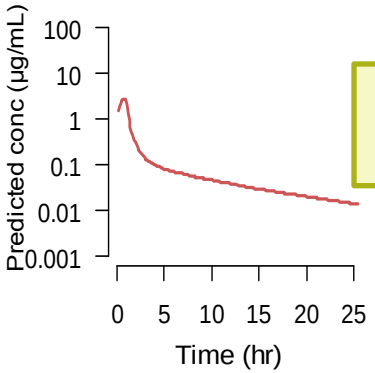
Allometric-PopPK approach

The adult popPK model

Allometric scaling for BSA with power=1

Paediatric PK prediction

Comparison



Concentration-time profiles

PK parameters

CL, V1

Optimal dose and sampling times

M&S softwares
Monolix: PopPK
Simcyp: PBPK
PFIM: Optimisation

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POST DOC PERSPECTIVES

- Optimizing sampling times using PBPK prediction if very young children are included
  - **Use semi-mechanistic PK model for fitting to account for maturation effect in addition to size effect**

$$CL_{child} = CL_{adult} \times \left(\frac{BSA_{child}}{BSA_{adult}}\right)^{1} \times \text{Maturation}$$

$$\text{Maturation} = \frac{PMA^{Hill}}{PMA^{Hill} + TM_{50}{}^{Hill}}$$

PMA: postmenstrual age (weeks)
TM_{50}: maturation half time

    - Require optimizing the design for a PK model with continuous covariate (only available in PopED developed by Uppsala)

  - **Find the sampling times empirically and optimize by simulation study**
- Use of PBPK-PD model since the exposure-effect relationship may be different between children and adults
- Adaptive approach when data for a given number of paediatric patients is available during the trial
  - **Refine paediatric PBPK model (learn and confirm)**
  - **Revise dose and sampling times**

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Pediatric Workflows
Process and Performance

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e80; doi:10.1038/psp.2013.55

www.nature.com/psp

ORIGINAL ARTICLE

Application of Physiologically Based Pharmacokinetic Modeling to Predict Acetaminophen Metabolism and Pharmacokinetics in Children

X-L Jiang[1], P Zhao[2], JS Barrett[3], LJ Lesko[1] and S Schmidt[1]

Acetaminophen (APAP) is a widely used analgesic and antipyretic drug that undergoes extensive phase I and II metabolism. To better understand the kinetics of this process and to characterize the dynamic changes in metabolism and pharmacokinetics (PK) between children and adults, we developed a physiologically based PK (PBPK) model for APAP integrating *in silico*, *in vitro*, and *in vivo* PK data into a single model. The model was developed and qualified for adults and subsequently expanded for application in children by accounting for maturational changes from birth. Once developed and qualified, it was able to predict clinical PK data in neonates (0–28 days), infants (29 days to <2 years), children (2 to <12 years), and adolescents (12–17 years) following intravenous and orally administered APAP. This approach represents a general strategy for projecting drug exposure in children, in the absence of pediatric PK information, using previous drug- and system-specific information of adults and children through PBPK modeling.

CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e80; doi:10.1038/psp.2013.55; published online 16 October 2013

Acetaminophen (APAP, Tylenol) is one of the most commonly used analgesic and antipyretic agents around the world.[1] In the United States, >300 million bottles or packets of APAP or APAP-containing products in different formulations are used by adults and children as over-the-counter or as prescription medicines annually.[2] In adults and adolescents (≥13 years old), the maximum recommended dose by the US Food and Drug Administration is 1,000 mg following single administration and 4,000 mg daily.[3] In children (2–12 years), dose reduction is recommended based on patient's age or body weight to account for differences in metabolism between adults and children.[4,5] Although APAP is generally considered safe and efficacious, drug-induced adverse events occur because of accidental or deliberate overdose, which can result in acute and serious liver failure. In some cases, even approved doses have resulted in liver damage, which were associated with both genetic and epigenetic factors.[6,7] In the wake of concerns about APAP overdoses and toxicity, the US Food and Drug Administration announced new requirements for the prescription of APAP products, adding to their warnings about liver damage from over-the-counter APAP products in January 2011.[8]

Liver injury from APAP is closely linked to its pharmacokinetics (PK) which is influenced by metabolism via phase I (cytochrome P450 (CYP) 1A2, 2E1, 3A4, etc.) and phase II enzymes (sulfotransferases and UDP-glucuronosyltransferases (UGTs)) in the liver.[4,6] Approximately 5–10% of APAP is metabolized by CYP enzymes to its toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI).[4,6] NAPQI is usually rapidly and efficiently detoxified to APAP-glutathione (APAP-GSH) conjugate, which is then further converted to 3′-[*S*-cysteinyl]-APAP, APAP mercapturate, 3′-[*S*-methyl]-APAP, and other inactive metabolites.[4,6,9] However, once this detoxification process becomes saturated because of the following reasons: (i) induction or stabilization of CYP enzymes that form NAPQI, (ii) depletion of GSH conjugation pathway, or (iii) a combination of these two processes, NAPQI may accumulate and covalently bind to hepatic and renal tubular cell proteins and cause cell necrosis.[4,6,10] Thus, simultaneous evaluation of a combination of metabolic enzyme pathways under different physiological and pathological conditions will help in elucidating potential bioactivation mechanisms related to APAP toxicity.

The enzymes involved in APAP metabolism undergo maturational changes from birth. For example, it has been reported that sulfation is the major conjugation pathway in children, whereas glucuronidation is the main pathway in adults.[4,6,11] This is due to the fact that sulfation is generally considered mature at birth,[4] whereas UGTs expression and activity undergo age-dependent changes. Recent *in vitro* enzyme kinetics studies with neonatal and pediatric liver microsomes showed that the metabolic capacity of UGT1A1, 1A9, and 1A6 reached adults levels at 3.8, 4, and 14 months postpartum, respectively,[12,13] whereas that of UGT1A4 and UGT2B7 was not fully developed until the age of 18 years.[14,15] The same holds true for the CYP isozymes, such as CYP1A2, CYP2E1, and CYP3A4, which also show variable ontogeny profiles.[2,16] The expression of CYP2E1, in particular, is thought to be low in children <1 year of age.[17] It should further be noted that the interindividual variability in the CYP enzymes–mediated NAPQI formation is not well understood, especially in children <2–3 years of age. A more mechanistic understanding

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Research Article
Theme: Challenges and Opportunities in Pediatric Drug Development
Guest Editors: Bernd Meibohm, Jeffrey S. Barrett, and Gregory Knipp

A Workflow Example of PBPK Modeling to Support Pediatric Research and Development: Case Study with Lorazepam

A. R. Maharaj,[1] J. S. Barrett,[2] and A. N. Edginton[1,3]

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Abstract. The use of physiologically based pharmacokinetic (PBPK) models in the field of pediatric drug development has garnered much interest of late due to a recent Food and Drug Administration recommendation. The purpose of this study is to illustrate the developmental processes involved in creation of a pediatric PBPK model incorporating existing adult drug data. Lorazepam, a benzodiazepine utilized in both adults and children, was used as an example. A population-PBPK model was developed in PK-Sim v4.2® and scaled to account for age-related changes in size and composition of tissue compartments, protein binding, and growth/maturation of elimination processes. Dose (milligrams per kilogram) requirements for children aged 0–18 years were calculated based on simulations that achieved targeted exposures based on adult references. Predictive accuracy of the PBPK model for producing comparable plasma concentrations among 63 pediatric subjects was assessed using average-fold error (AFE). Estimates of clearance (CL) and volume of distribution (V_{ss}) were compared with observed values for a subset of 15 children using fold error (FE). Pediatric dose requirements in young children (1–3 years) exceeded adult levels on a linear weight-adjusted (milligrams per kilogram) basis. AFE values for model-derived concentration estimates were within 1.5- and 2-fold deviation from observed values for 73% and 92% of patients, respectively. For CL, 60% and 80% of predictions were within 1.5 and 2 FE, respectively. Comparatively, predictions of V_{ss} were more accurate with 80% and 100% of estimates within 1.5 and 2 FE, respectively. Using the presented workflow, the developed pediatric model estimated lorazepam pharmacokinetics in children as a function of age.

KEY WORDS: lorazepam; PBPK; pediatrics.

INTRODUCTION

The Food and Drug Administration (FDA) enacted the Pediatric Research Equity Act in 2003, requiring pharmaceutical companies to assess pharmacokinetics (PK), safety, and efficacy of new drug products in pediatric subjects. Recently, several FDA pediatric submissions have incorporated physiologically based pharmacokinetic (PBPK) models, stimulating an interest in their utility among regulatory authorities (1). In a March 2012 meeting, the majority of the FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee voted to support the use of PBPK modeling for pediatric drug development; a decision with potential implications toward the manner in which pediatric drug information is derived.

PBPK modelling is characterized by the use of mathematical algorithms to predict the interplay between drug specific characteristics and organism anatomy and physiology. Similar to empirically derived compartmental models, the structure of PBPK models includes compartments in order to describe the processes of absorption, distribution, metabolism, and excretion (ADME). In a PBPK model, however, compartments are based on actual organs with inherent volumes and blood flows linked through the vasculature. The mechanistic nature of PBPK models permit rational scaling between organisms (*i.e.*, rat to human) as well as developmental stages (*i.e.*, adult to child). This is the result of defining ADME as a function of anatomy, physiology, and biochemistry: components not accounted for in traditional compartmental models.

Use of pediatric PBPK models offer researchers an *a priori* approach to predict a compound's PK behavior in children, with or without prior PK data in humans, though knowledge of the drug substance's physicochemical characteristics is essential. The developmental processes involved in the creation of pediatric PBPK models has been documented by several researchers and typically include defining physiology and anatomy, protein binding, and clearance, all as a function of age (2–4). Amongst the literature, pediatric PBPK models have been utilized in several different capacities: suggesting starting doses for children of different age groups, predictions of environmental contaminant exposure, optimization of clinical

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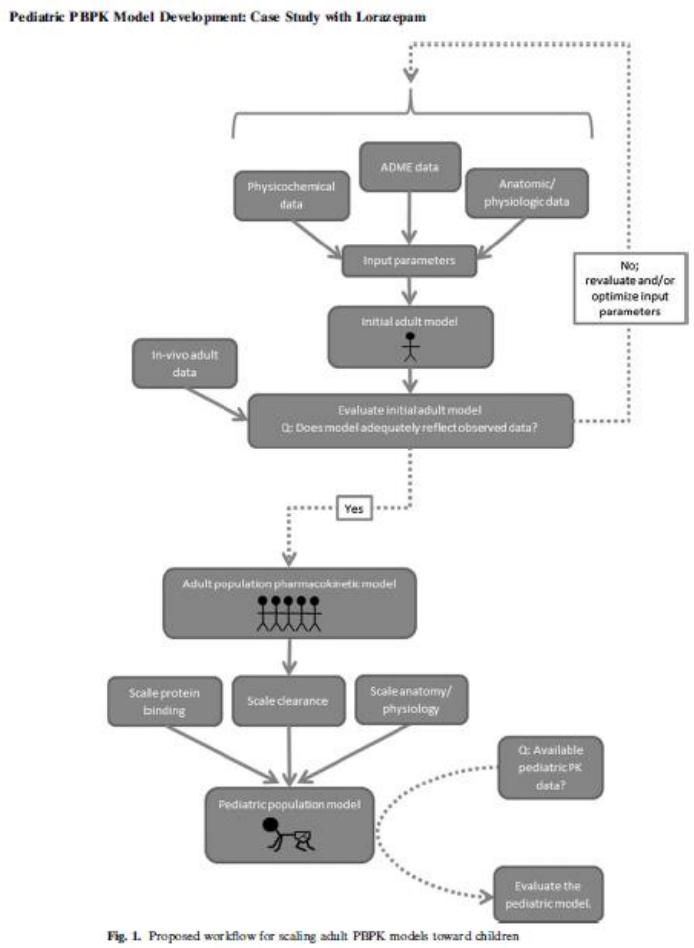
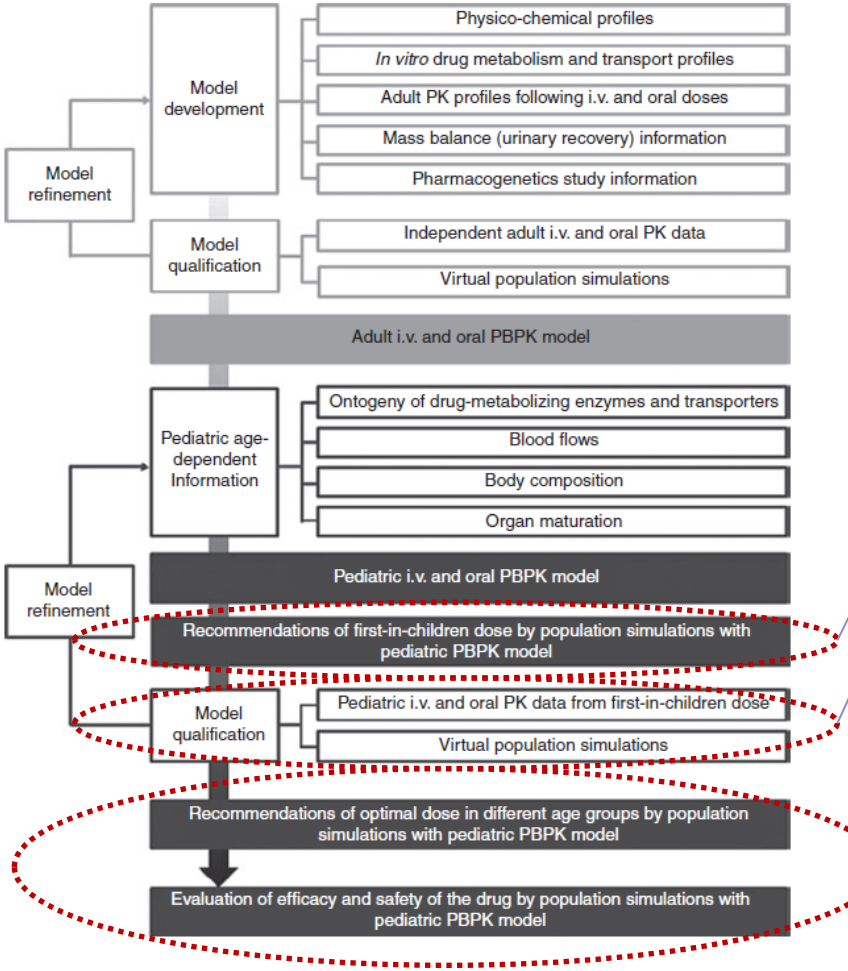
Evaluating Workflow Proposals
Process



- Is there an alternative to using the adult-scaled PBPK model as a bridge?
  - *What if I don't have any adult data yet?*
- Is it good enough to use systemic data only to guide the process?
  - *Do we know the risks of doing so?*
- What about route / formulation dependencies?
  - *Does that change the workflow?*
  - *Necessity of IV data anchor?*

Evaluating Workflow Proposals
Process



- Same questions regarding route and formulation
- How do you assess your virtual population simulations if the disease state is not well-defined in the simulator?

Purpose! *. . . the only purpose?*

Agree conceptually *. . . how realistic?*

Lots of assumptions here . . . *may be shooting too high for our current knowledge*

Evaluating Workflow Proposals
Performance – Lorazepam Example

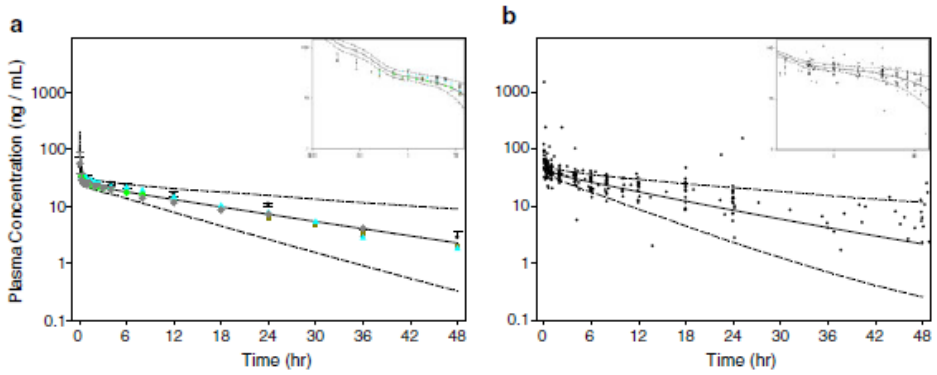


Fig. 2. **a** Predicted (*solid line* corresponds to geometric mean; *dashed lines* corresponds to 5th and 95th percentiles; virtual population n=100) *versus* observed (*symbols* – (15, 20–22)) plasma concentration versus time data following a 2-mg IV lorazepam bolus in adults. Log (concentration) *versus* Log (time) plot is displayed in *insert*. **b** Predicted (*solid line* corresponds to geometric mean; *dashed lines* corresponds to 5th and 95th percentiles; virtual population n=1140) *versus* observed (*symbols* – (30)) plasma concentration versus time data following a 0.05 mg/kg IV lorazepam bolus in children aged 0 to 18 years. Log (concentration) *versus* Log (time) plot is displayed in *insert*

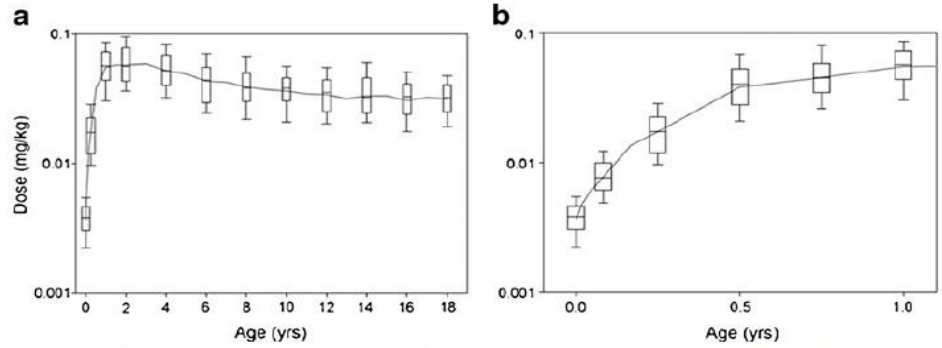


Fig. 3. Pediatric dose (milligrams per kilogram) required to achieve an equivalent $AUC_{0\rightarrow\infty}$ of a 2-mg dose in adults. **a** Entire pediatric age-range. **b** Children between 0 and 1 years old

- Same questions regarding route and formulation
- How do you assess your virtual population simulations if the disease state is not well-defined in the simulator?

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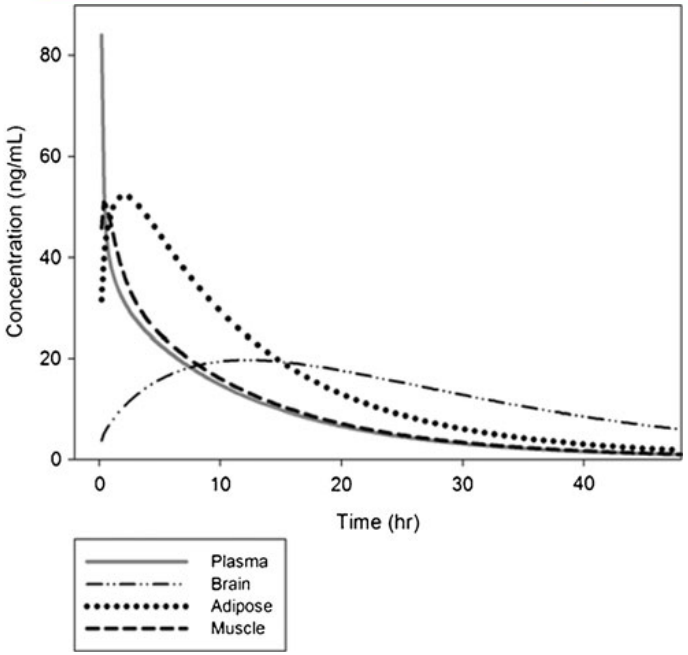
Evaluating Workflow Proposals
Performance – Lorazepam Example



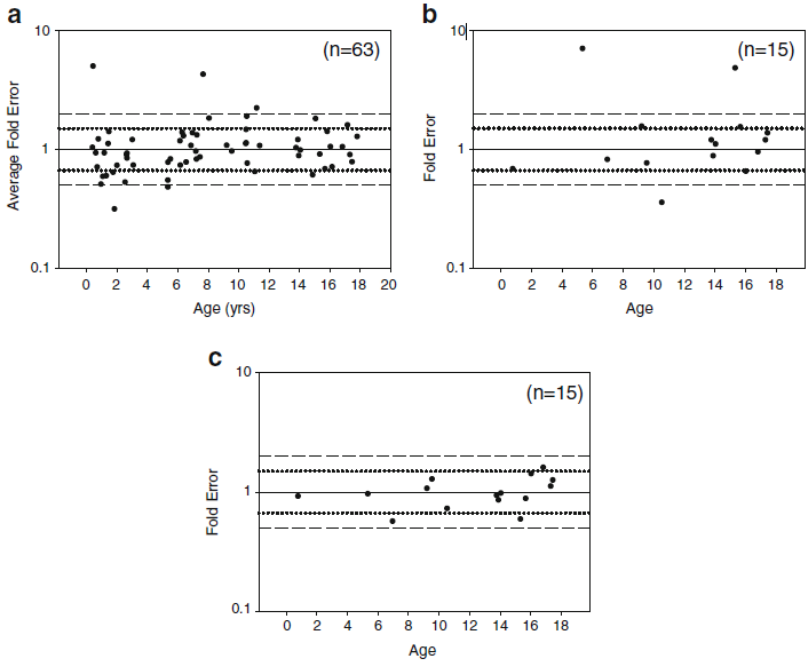


Fig. 5. Predictive accuracy plots: Individual AFE values for PBPK model concentration-time predictions for the 63 pediatric patients (plot *A*), fold error associated PBPK model clearance predictions for the 15 elective patients (plot *B*), and fold error associated PBPK model volume of distribution predictions for the 15 elective patients (plot *C*) (*dotted line* represents 1.5-fold error. *Dashed line* represents twofold error)

- Isn't this always relevant?
- How do you assess this projection in reality?
  - *Shouldn't there be an implicit plausibility check here!*

- Is this as good as it gets?
- Opportunity to explore measures of association statistics
- Relative to purpose . . . may be ok

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Evaluating Workflow Proposals

Performance – Acetaminophen Example

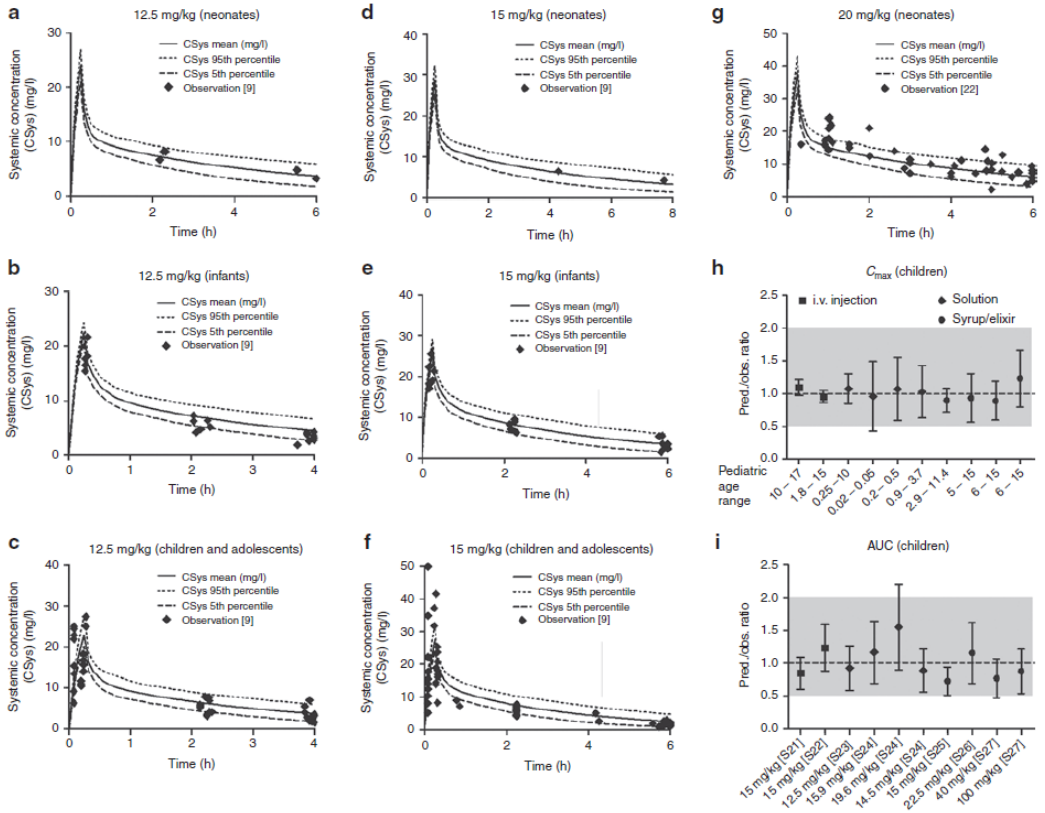

Figure 3 Observed vs. predicted plasma concentration profiles of acetaminophen (APAP) following (**a**,**b**,**c**) 12.5 mg/kg, (**d**,**e**,**f**) 15 mg/kg, or (**g**) 20 mg/kg of 15 min intravenous (i.v.) infusion of APAP in different pediatric age groups. Symbols represent individual observed data digitized from literature.[9,22] The solid, dashed, and dotted lines represent the predicted mean and 5 or 95% confidence interval of the current physiologically based pharmacokinetic (PBPK) model at respective doses and age ranges. Additional qualification of PBPK model performance in children was conducted by comparing prediction (pred.)/observtation (obs.) ratios of (**h**) mean peak plasma concentration (C_{max}) and (**i**) mean area under the curve (AUC) following i.v. and oral administrations of APAP from various clinical studies in pediatric subjects at respective doses and age ranges. The dashed line represents line of identity (pred./obs. ratio = 1); the gray shade represents 0.5–2.0 ratio window. Literature sources are presented in **Supplementary Material 2** online.

- Huge investment in time and effort
- Impressive accommodation of complicated metabolism, various formulations, age range, routes and biologic fluids / entities.
- Validates the approach when properly informed
- *Can this be managed during real-time drug development?*
- *What is the ROI?*

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Request for Clarification

- The application of PBPK to support pediatric research and development is still at its root a “fit-for-purpose” M&S endeavor → let’s treat it as such.
  - **Can we identify the specific purposes for pediatric-based PBPK M&S and identify the requirements aligned to the effort?**

- PBPK and Population-based PK Models are different yet they fundamentally allow prediction of the dose-exposure relationship in plasma → let’s not view these as alternative approaches. They are complimentary with some expectation of similarity in prediction. They can be used to refine each other . . . ***depending on the purpose!***
  - **Can we identify the “purposes” that align best with each approach based on the availability of certain data types?**
  - **Can we agree on which approach is best suited to answer specific (relevant) questions? Can regulatory authorities *help ☺* in this regard?**

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