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?

Diagram showing the flow of drug through different body tissues, including lung, liver, heart, kidney, and muscle, with pathways labeled for drug in and drug out.
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.
Experience of the Sanofi PBPK Working Group
Discovery / Preclinical Phase
Dynamic (MDM) and static (MSM) approaches

Available data
- Perpetrator parameters
  - $K_i$
  - $IC_{50}$
- Substrate parameters
  - $K_m$, $V_m$
  - $F_m$ values
  - Renal clearance in animal
- Fu values
- Active plasma concentration in the pharmacological model

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.
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.
Phase II / III
Dynamic (MDM) and static (MSM) approaches

Available data
- 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*.

Addressed questions

MSM approaches
- Rough DDI risk assessment toward potential co-medication
  - 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.

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

Validation of the DDI PBPK model for waiver, authorities experience
Submission phase
Dynamic (MDM) and static (MSM) approaches

Available data

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

Identification of covariates in POPPK approach, “top-down”
To be put in perspective with PBPK mode “bottom-up”
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

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**Post-doc Project: Hoai-Thu THAI**

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

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Adult PBPK model

- Exposure in different pediatric age groups

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**SANOFI**
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
- Optimal dose and sampling times

**PK parameters**
- CL, V1

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

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

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

S.L. Jiang, P. Zhao, J. Barrett, L.J. Lenox and S. Schettini

Acetaminophen (APAP), 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 vitro, and in vivo PK data into a single model. The model was validated and qualified for adults and subsequently expanded for application in children by accounting for maturation changes from birth. Once developed and qualified, it was able to predict clinical PK data in neonates (3-28 days), infants (39 days to 12 years), children (2-112 years), and adolescents (12-17 years) following aseptic and orally administered APAP. This Preprint represents a general strategy for phosphorylling drug exposures in children, in the absence of pediatric PK information, using prevacuous drug and systemic-specific information of adults and children through PBPK modeling.


Acetaminophen metabolism (APAP) is a well-known and well-studied topic in pediatric pharmacology. The metabolism of APAP is complex and involves multiple pathways. The primary metabolic pathway is the oxidation of APAP to N-acetyl-p-benzoquinone imine (NAPQI), which can undergo further metabolism to form toxic metabolites such as the mercapturate and sulfonic acid derivatives. These metabolites can cause hepatic toxicity if they are not properly detoxified. The detoxification of NAPQI involves the conjugation of glutathione (GSH), a tripeptide formed from cysteine, glycine, and glutamate. In children, the capacity to conjugate NAPQI with GSH is lower compared to adults, which may contribute to higher toxicity in children.

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 pharmacokinetic submissions have incorporated physiologically based pharmacokinetic (PBPK) models, highlighting their utility among regulatory authorities (1). In March 2012 meeting, the majority of the FDA’s Pediatric 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 future in which pharmacokinetic data is derived.

PBPK modeling is characterized by the use of mathematical algorithms to predict the interplay between drug-specific characteristics and organ-specific pathways. Similar to empirically derived compartmental models, the structure of PBPK models comprises compartments in which the processes of absorption, distribution, metabolism, and excretion (ADME) in a PBPK model, however, compartments are based on organ systems with inherent volumes and blood flow linked through the vasculature. The mechanistic nature of PBPK modeling allows for scaling the response of a phenomenon (e.g., liver damage or cardiovascular effects) to changes in organ size. This is the basis for defining ADME in a domain of organ size, physiology, and biochemistry not accounted for in traditional compartmental models.

Use of pediatric PBPK models offers several advantages over empirically derived compartmental models. PBPK models provide a framework for understanding the complex processes involved in drug disposition and pharmacokinetics, allowing for the prediction of drug behavior across different age groups. This is particularly important for drugs that have age-specific pharmacokinetic profiles. PBPK models can also be used to simulate the impact of changes in organ size or physiology on drug disposition, providing valuable insights for pediatric dosing recommendations.
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

- 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?

Fig. 2. a Predicted (solid line corresponds to geometric mean; dashed lines correspond 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 correspond 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$_{0-\infty}$ of a 2-mg dose in adults. a Entire pediatric age-range. b Children between 0 and 1 years old.
Evaluating Workflow Proposals
Performance – Lorazepam Example

- 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
Evaluating Workflow Proposals

Performance – Acetaminophen Example

- 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?
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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