Supplemental Information

This supplemental section contains additional literature that can provide examples and further clarification on this important topic. This list is by no means comprehensive, but it can provide additional insight for interested readers.

1. Hornik CP, Wu H, Edginton AN, Watt K, Cohen-Wolkowiez M, Gonzalez D. Development of a Pediatric Physiologically-Based Pharmacokinetic Model of Clindamycin Using Opportunistic Pharmacokinetic Data. *Clin Pharmacokinet.* **56**,1343-1353 (2017).

   *This article provides an example of leveraging opportunistic data for physiologically-based pharmacokinetic (PBPK) model development and evaluation in pediatric patients.

2. Huang W, Nakano M, Sager J, Ragueneau-Majlessi I, Isoherranen N. Physiologically Based Pharmacokinetic Model of the CYP2D6 Probe Atomoxetine: Extrapolation to Special Populations and Drug-Drug Interactions. *Drug Metab Dispos*. **45**, 1156-1165 (2017).

   *This article evaluates the feasability of extrapolating a drug specific PBPK model developed in healthy adult volunteers to predict drug disposition and drug-drug interaction (DDI) potential in special populations including pediatric patients.

3. Khalil F, Läer S. Physiologically Based Pharmacokinetic Modeling: Methodology, Applications, and Limitations with a Focus on its Role in Pediatric Drug Development. *J Biomed Biotechnol*. **2011**, 907461 (2011).

   *An overview of the methodology, applications, opportunities, and limitations of PBPK modeling during pediatric drug development.

4. Kredo T, et al. The Interaction Between Artemether-Lumefantrine and Lopinavir/Ritonavir-based Antiretroviral Therapy in HIV-1 Infected Patients. *BMC Infect Dis.* **27**, 16:30 (2016).

   *A parallel-design adaptive study was conducted to evaluate the safety and pharmacokinetics of artemether-lumefantrine in HIV-infected adults (malaria-negative) receiving lopinavir based anti-retroviral treatment.

5. Leroux S, et al. Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. Clin Pharmacokinet. **54**, 1273-85 (2015).

   *An example of an opportunistic sampling strategy in combination with population based pharmacokinetic (PopPK) modeling for characterizing ciprofloxacin pharmacokinetics in neonates.

6. Li A, Yeo K, Welty D, Rong H. Development of Guanfacine Extended-Release Dosing Strategies in Children and Adolescents with ADHD Using a Physiologically Based Pharmacokinetic Model to Predict Drug-Drug Interactions with Moderate CYP3A4 Inhibitors or Inducers. *Paediatr Drugs.* **20**,181-194 (2018).

*This article provides an example where PBPK modeling was first developed using adult DDI data and then applied to predict DDI potential in children and adolescents without the requirement for additional studies.

7. Maharaj AR, Edginton AN. Physiologically Based Pharmacokinetic Modeling and Simulation in Pediatric Drug Development. *CPT Pharmacometrics Syst Pharmacol.* **3**, 1-13 (2014).

   *This tutorial discusses the advantages and limitations of PBPK modeling and describes the procedural steps for developing a pediatric PBPK model.

8. Mehrotra N, et al. Role of Quantitative Clinical Pharmacology in Pediatric Approval and Labeling. *Drug Metab Dispos.* **44**, 924-33 (2016).

   *This manuscript outlines some examples in which quantitative clinical pharmacology approaches were used to support approval and labeling in pediatrics.

9. Min JS, Bae SK. Prediction of Drug-Drug Interaction Potential Using Physiologically Based Pharmacokinetic Modeling. *Arch Pharm Res.* **40**, 1356-1379 (2017).

   *This review provides an overview of articles utilizing PBPK for the prediction of DDI potential published up to October 10, 2017.

10. Mulugeta Y, et al. Exposure Matching for Extrapolation of Efficacy in Pediatric Drug Development. *J Clin Pharmacol.* **56**, 1326-1334 (2016).

    *A systematic review of approaches used for matching adult systemic exposures as the basis for dose selection in pediatric trials submitted to the US Food and Drug Administration (FDA) between 1998 and 2012.

11. Rekić D, et al. Clinical Drug-Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access. *J Pharm Sci*. **106**, 2214-2218 (2017).

    *This commentary provides an overview of approaches and study types, including PBPK modeling, that can be used to evaluate DDI potential througout the drug development process.

12. Thakkar N, et al. An Opportunistic Study Evaluating Pharmacokinetics of Sildenafil for the Treatment of Pulmonary Hypertension in Infants. *J Perinatol.* **36**, 744-7 (2016).

    *An example of leveraging opportunistic data in preterm and term infants to evaluate DDI potential for drugs coadministered per standard of care (e.g., sildenafil plus cytochrome P450 inducers).

13. Tremoulet A, et al. Characterization of the Population Pharmacokinetics of Ampicillin in Neonates Using an Opportunistic Study Design. *Antimicrob Agents Chemother*. **58**, 3013-20 (2014).

    *An example of an opportunistic sampling strategy in combination with PopPK modeling for characterizing ampicillin pharmacokinetics in neonates.

14. Upreti VV, Wahlstrom JL. Meta-analysis of Hepatic Cytochrome P450 Ontogeny to Underwrite the Prediction of Pediatric Pharmacokinetics Using Physiologically Based Pharmacokinetic Modeling. *J Clin Pharmacol.* **56**, 266-83 (2016).

*This report describes the development of ontogeny functions for hepatic CYPs important for drug metabolism using *in vitro* or *in vivo* data, and then compares pediatric pharmacokinetic predictions for these ontogeny functions utilizing PBPK modeling.

15. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Summary minutes of the advisory committee for pharmaceutical science and clinical pharmacology. Accessed via: <https://wayback.archive-it.org/7993/20170404154933/https:/www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM306989.pdf> (2012). Accessed 04 June 2018.

*Summarizes a discussion held by the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology regarding aspects of pediatric clinical trial design and dosing to optimize pediatric drug development. The discussion included the role of modeling and simulation in pediatric drug development.

16. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Draft Guidance on Clinical Drug Interaction Studies — Study Design , Data Analysis , and Clinical Implications Guidance for Industry Clinical Drug Interaction Studies — Study Design , Data Analysis, and Clinical Implications Guidance for Industry. (2017). Accessed via: <https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf> Accessed 04 June 2018.

*Food and Drug Administration draft guidance on conducting clinical studies to evaluate DDI potential during drug development and to communicate the results from DDI studies.

17. Van Hasselt JG, Van Eijkelenburg NK, Beijnen JH, Schellens JH, Huitema AD. Design of a Drug-drug Interaction Study of Vincristine with Azole Antifungals in Pediatric Cancer Patients using Clinical Trial Simulation. *Pediatr Blood Cancer.* **61**, 2223-9 (2014).

*An example of performing clinical trial simulation analysis to optimize a pediatric DDI study in children receiving vincristine with azole antifungals.

18. Yeh ML, et al. Potential Drug-drug Interactions in Pediatric Outpatient Prescriptions for Newborns and Infants. *Comput Methods Programs Biomed.* **113**, 15-22 (2014).

*An example using electronic health record data to evaluate the prevalance of potential DDIs and estimates of off-label use percentage of pediatric outpatient prescriptions for newborns and infants from the National Health Insureance Research Database of Taiwan.