PBPK Model Applications:
Supplementing Clinical Trials with limited Patient PK Data

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Unmet Needs with PBPK Models

- PBPK models have been used successfully for waivers of DDI trials and for PBBM absorption models (e.g. Shebley, M. (2018). Clin. Pharmacol. Ther., 104: 88-110. doi:10.1002/cpt.1013)

- For specific populations:
  - Often limited patient availability and sample PK collection
  - Pediatrics:
    - Dose Selections and Label Extension based on PBPK have been accepted with very limited PK data
    - PBPK models have successfully supplemented clinical trials for > 2 year old
    - Unmet Need: ADME not fully characterized in neonates and young infants
  - Organ Impairment:
    - PBPK modeling is often done a priori to inform the study
    - Unmet Need: Low confidence, Lack of Publications of PK in cirrhosis, Study waivers are still uncommon, even when limited data has been collected

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Case Study Nilotinib:

Physiologically Based Pharmacokinetic Modeling to Supplement Pharmacokinetics and Confirm Dose Selection in Pediatric Patients

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Health Authority Question for Nilotinib Pediatric Trial

"Data available in children below the age of 6 is seen as not sufficient to characterize PK *or to conclude whether a BSA dosing approach is adequate in this population. ..... provide a proposal how this data can be generated to allow a more valid modelling in the population below the age of 6"*

- In < 6 y patient, only one patient has a full PK profile, two patients have $C_{min,ss}$ data

Heimbach, Lin, et al, *Physiologically Based Pharmacokinetic Modeling to Supplement Nilotinib Pharmacokinetics and Confirm Dose Selection in Pediatric Patients,* Journal of Pharmaceutical Sciences, Volume 108, Issue 6,2019, Pages 2191-2198, https://doi.org/10.1016/j.xphs.2019.01.028

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Pediatric PBPK Model can simulate observed Cp-Time profile in 6 -17 years olds

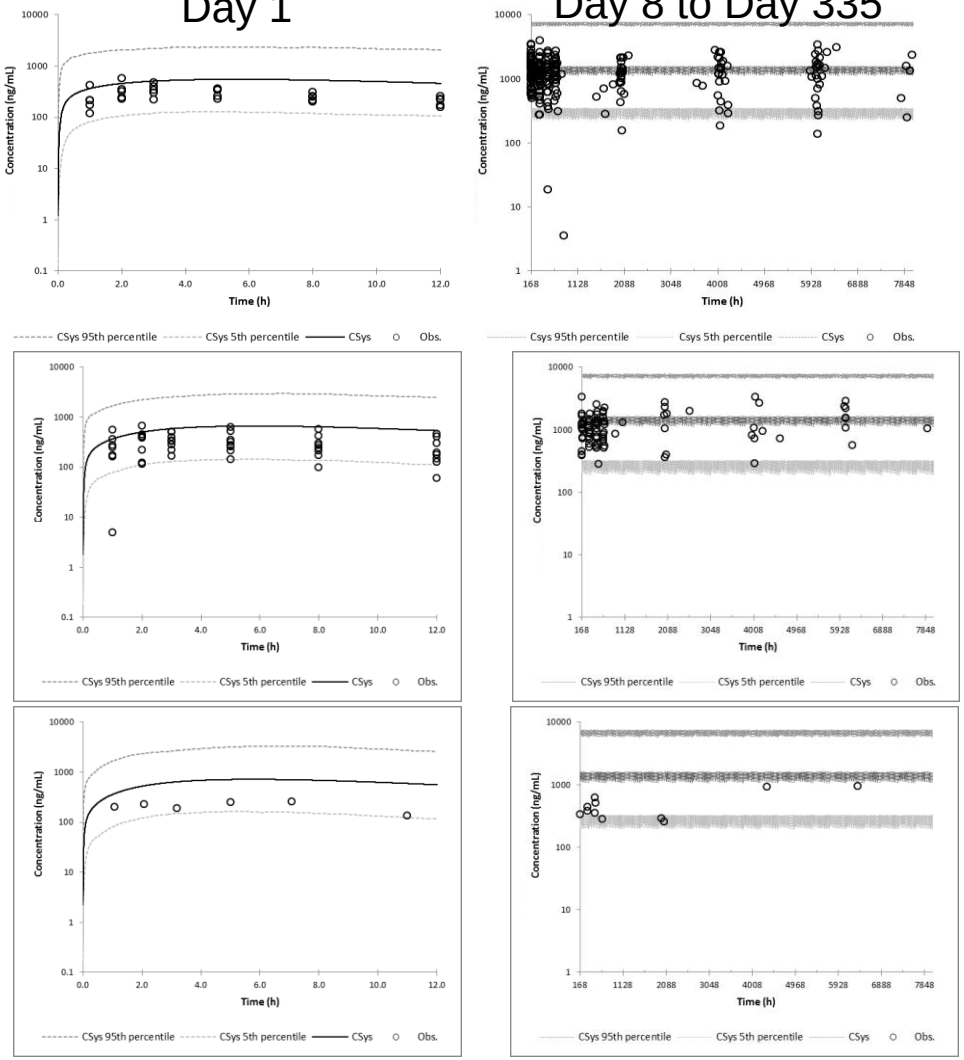
Day 1

Day 8 to Day 335

12 -< 18 yrs

6 -< 12 yrs

2 -< 6 yrs



Ontogeny profiles

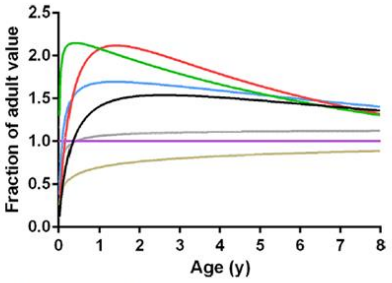


Figure 2. An integrated visualization of in vivo CYP ontogeny for the major hepatic CYPs: (A) CYP1A2 (black), (B) CYP2A6 (gray), (C) CYP2B6, CYP2D6 (purple), (D) CYP2C9 (green), (E) CYP2C19 (red), (F) CYP2E1 (gold), and (G) CYP3A (blue).

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Summary

- Pediatric PBPK model can well simulate Nilotinib PK on in 2 to < 6 yrs. olds, 6 to < 12 yrs. olds and 12 to <18 yrs. olds after a single or multiple doses
- The model predicted similar $AUC_{tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$ in 2 to < 6 years old patients as compared to those in 12 to < 18 years old and 6 to < 12 years old patients

Age group	$C_{max, ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	$AUC_{tau,ss}$ (ng•h /mL)
2 to < 6 years	1620	1067	17031
6 to < 12 years	1649	1131	17576
12 to < 18 years	1586	1130	17049

Conclusion: A BSA approach was appropriate in 2 to < 6 years old patients.

AUC, area under the curve; BSA, Body surface area; $C_{max, ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum plasma concentration at steady state; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics

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PKS / NIBR

Case Study Compound Z

Evaluation of Pharmacokinetics in Patients with Normal or Impaired Hepatic Function Using PBPK Modeling

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Compound Z ADME Characteristics

- *Absorption: Rapid absorption*
- *Distribution: Highly plasma protein bound*
- *Metabolism/elimination: Non-CYP-mediated metabolism, no renal CL*

<u>Question</u>: Can a PBPK model predict and supplement the limited clinical PK in patients with severe hepatic impairment, N=2?

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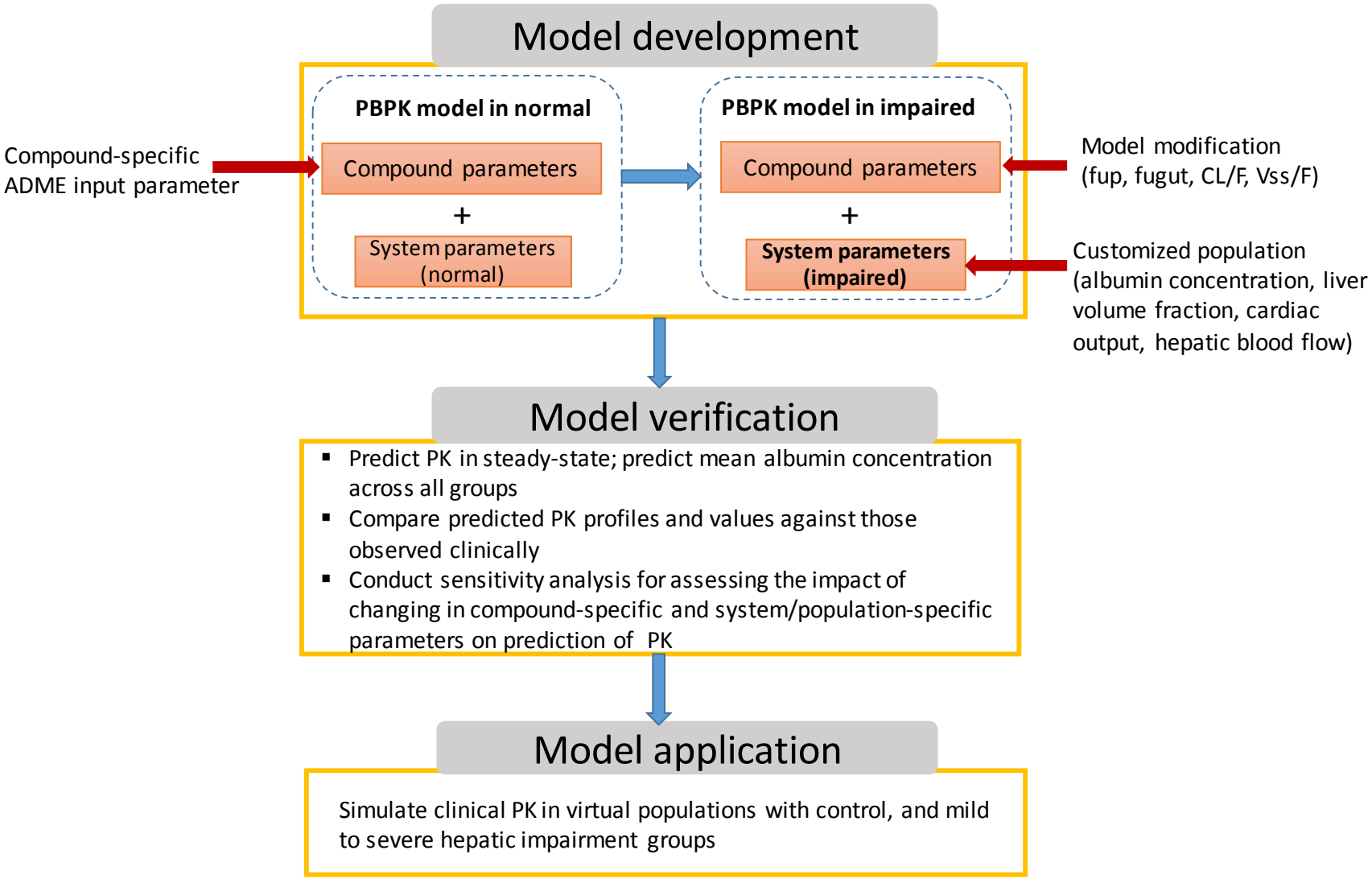
A PBPK modeling strategy



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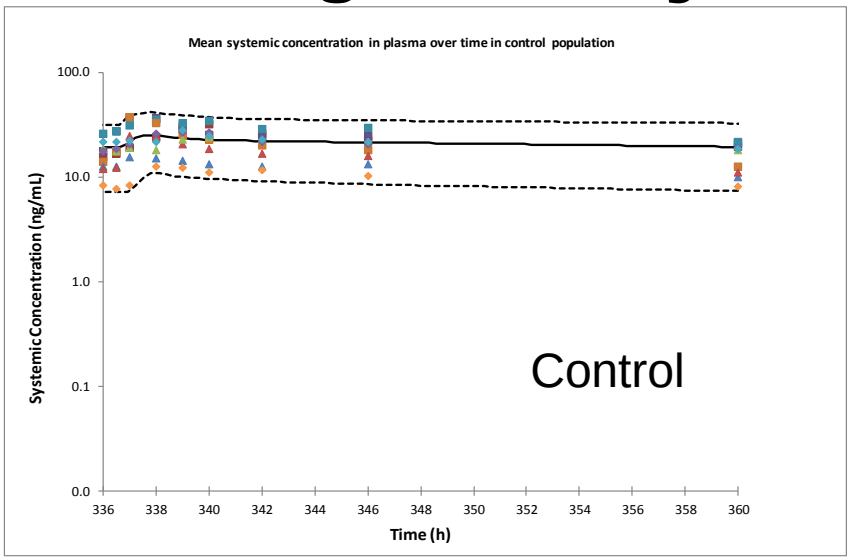
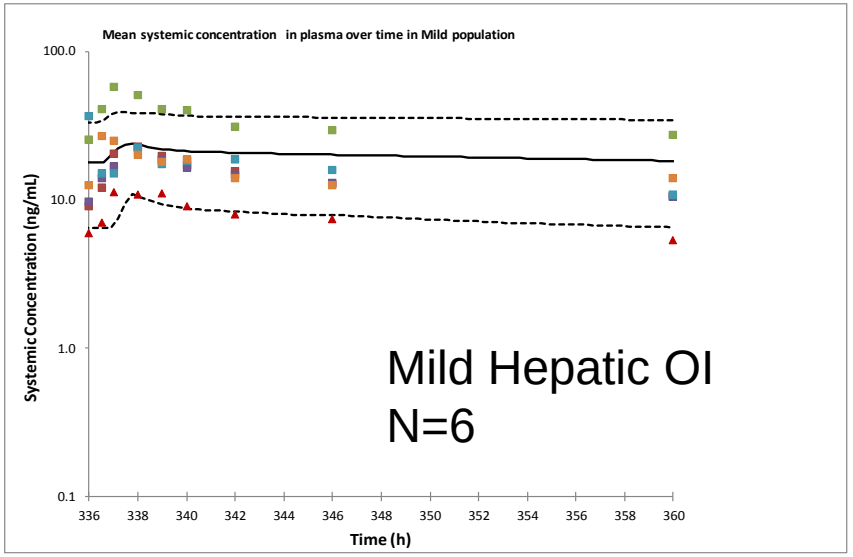
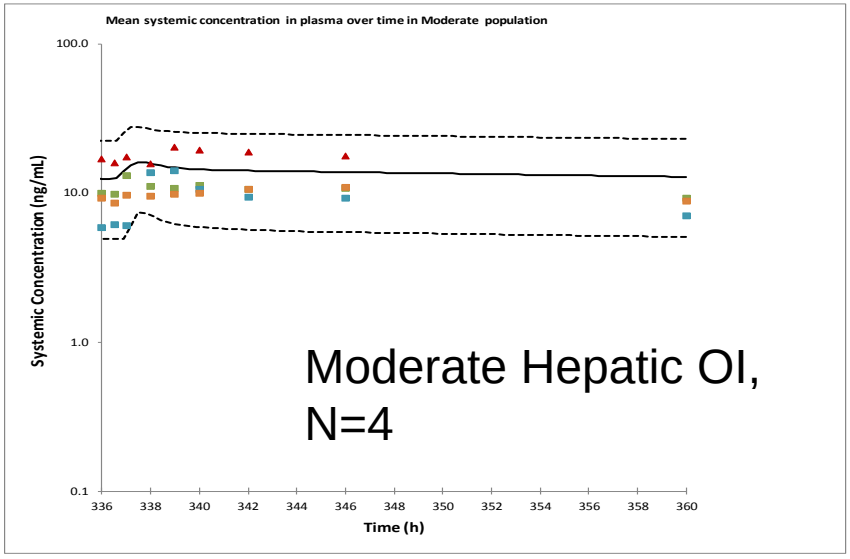
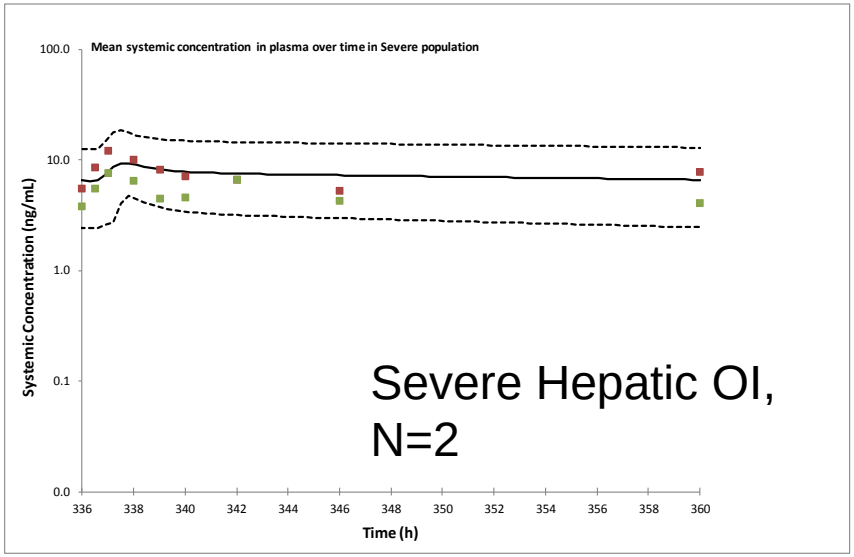
PBPK can describe observed plasma concentration-time profiles of Compound Z after QD dosing at steady-state









Conclusions

- A PBPK model was developed by taking into account nonCYP-mediated metabolism pathways, as well as the differences in the *ex vivo* protein binding across the groups
- The model performance was evaluated by comparing the simulated Compound Z PK data vs observed data which included plasma albumin concentrations
- The steady state total and unbound Compound Z exposure were predicted at different degree of hepatic impairment in a larger virtual population
- The approach can be potentially used to inform dose adjustment for patients with hepatic impairment

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Validation of Albumin Concentration in Hepatic OI Populations (obs vs. pred)

Actual measured vs. predicted albumin concentrations in patients with customized mild, moderate, and severe hepatic impairment populations

		Hepatic impairment		
Albumin (g/L)	Control	Mild	Moderate	Severe
Predicted (Mean ± SD)	50	41.4 ± 6.8	39.4 ± 7.4	31.5 ± 5.0
Measured (Mean ± SD)		37.8 ± 3.8	33.2 ± 6.0	32.0 ± 4.0
Ratio of predicted/measured		1.10	1.19	0.98

The changes in mean value of plasma albumin protein concentrations can be calculated using the following equation (Johnson et al 2010), using *ex vivo* plasma protein binding data measured in a clinical study

$$[Albumin]impaired = \frac{\left(\frac{1-fu,impaired\ obs}{fu,impaired\ obs}\right)\times[Albumin\ control]\times fu,control}{1-fu,control}$$

[Albumin]control and [Albumin]impaired are plasma protein concentrations in subjects with normal liver function and impairment, respectively, $f_{u\ control}$ and $f_{u,impaired}$ are the average measured unbound fraction of the compound in plasma for subjects with normal liver function and hepatic impairment, respectively.

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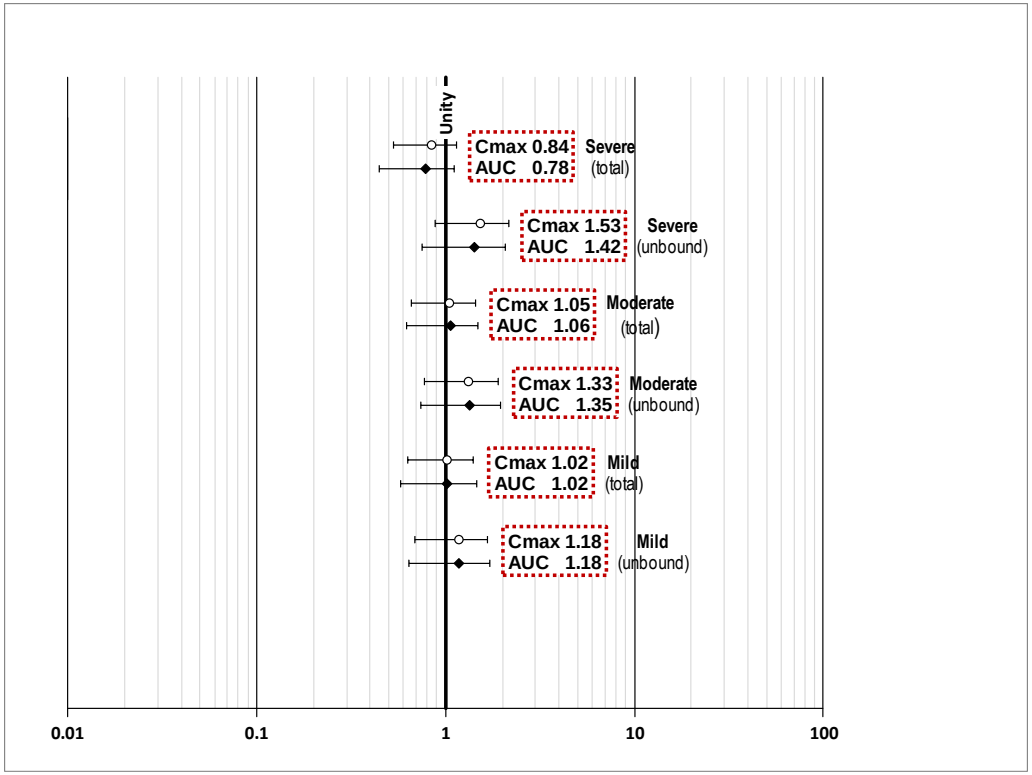
Predicted Steady State Exposure following QD dosing in mild, moderate, severe Hepatic Impairment Patients compared to Controls



The predictions were consistent with the observed data. No dose adjustment is warranted based on PBPK modeling.

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Supplementals

PBPK Unmet Needs

Modeling tools: Simcyp® Pediatric Module, GastroPlus®

- **Absorption: formulation relevant**
  - Age and meal type affect gastric emptying (GE) time in premature neonates, full-term neonates, infants and children? (Bonner J, et al, 2015)
    - Age was not but meal type was
    - GE by aqueous solution: 48 min; GE by solid food: 98 min
    - Studies of gastric emptying times across a wide age range with different meals and using scintigraphy are needed
  - Bile salts concentrations in premature neonates, full-term neonates, infants and children
    - For BCS II and IV compounds, age may impact bile salts enhancement on solubility and in vivo dissolution
    - Frequent feeding in neonates and young infants may bring about food effect
  - Ontogeny of intestinal transporters – PK study in juvenile animals may help predict the bioavailability change in infants, particularly for BCS III drugs
- **Distribution**
  - Brain distribution in infants: blood-brain barrier; transporters, etc; juvenile animals study
  - The impact of higher extracellular water on drug distribution pattern in pre- and full term neonates, young infants
- **Elimination**
  - In vivo ontogeny profiles for enzymes
  - Much less is known about the ontogeny of transporters