Prediction of midazolam pediatric plasma profiles for multiple routes of administration using physiologically based pharmacokinetic model

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GMP Webinar Session 3
PK challenges in pediatric drug development
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Talking Points

- Owing to ethical and logistical constraints, clinical investigation of drugs in the pediatric population is challenging
- Physiologically based pharmacokinetic (PBPK) modeling because of its ability to facilitate age-dependent extrapolation of data can be a valuable tool in pediatric drug development
- PBPK combined with mechanistic absorption models validated against adult datasets can describe API ADME in pediatrics for multiple routes of administration

Outline:

- Modeling & Simulation for pediatrics? Why?
- PBPK models, a quick ABCs
- Midazolam case study

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Pediatric special population

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines pediatric patients as persons aged 21 or younger at the time of their diagnosis or treatment (09/2019). Pediatric subpopulations are further categorized as follows

- Neonates 0-28 days
- Infants 29 days- 2 years
- Children 2 -12 years
- Adolescents 12-21 years

https://www.fda.gov/medical-devices/products-and-medical-procedures/pediatric-medical-devices#:~:text=The%20Federal%20Food%2C%20Drug%2C%20and,to%20less%20than%202%20years

Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry

A sponsor who is planning to submit a marketing application (or supplement to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an iPSP (08/2020)

➔ **Section 3 Overview of planned extrapolation to specific pediatric population:**

"The sponsor also should discuss use of modeling and simulation to optimize studies to support extrapolation"

https://www.fda.gov/media/86340/download

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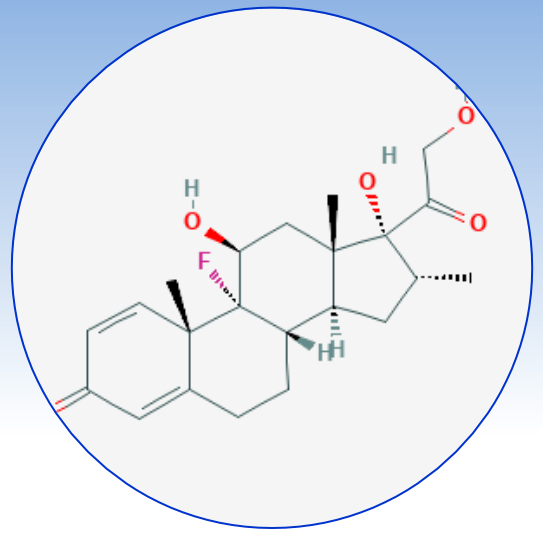
Setting the Scene: why modeling?

The Right Patient(s)

- Disease definition
- Targets?
- Disease progression
- Pharmacology response
- Other risks



The Right drug(s)

- Target interaction
- Action mechanism
- ADME
- On target binding
- Off target binding

The Right Dose

- Efficacious dose
- Right exposure
- Right time
- Interaction
- Route of administration

Modeling!!! Provides a simpler and integrated view!

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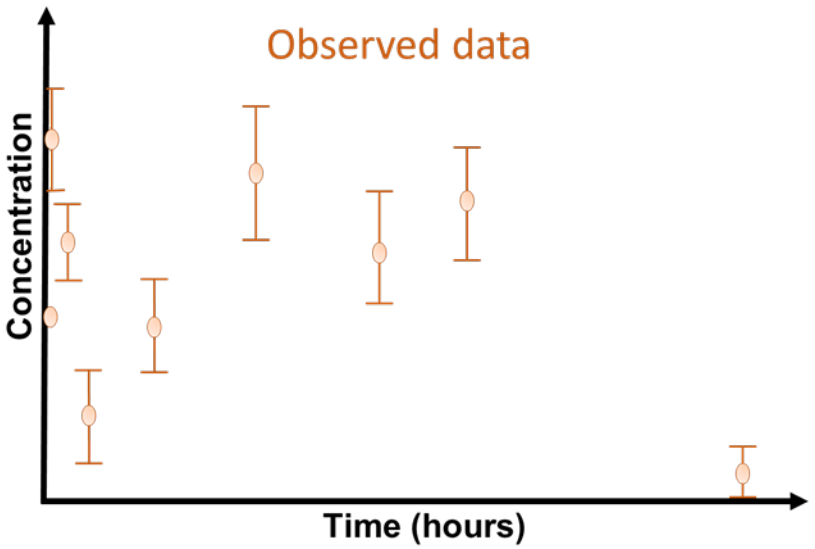
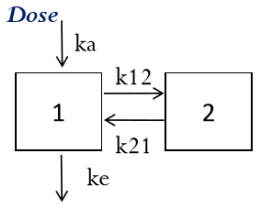
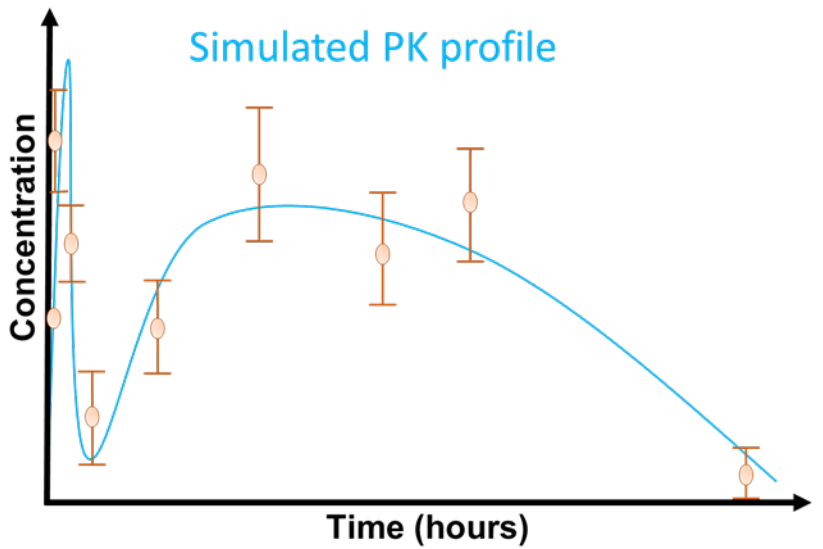
Modeling Approaches

Top-Down

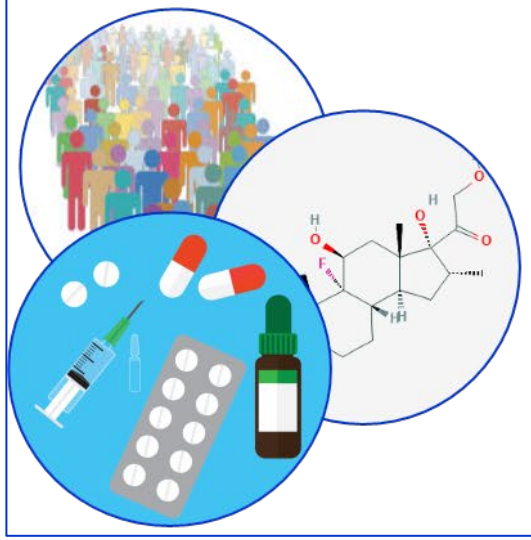


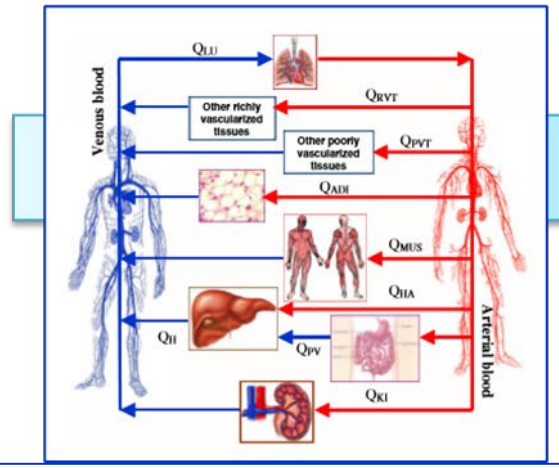
Ct = f(t, dose, route)

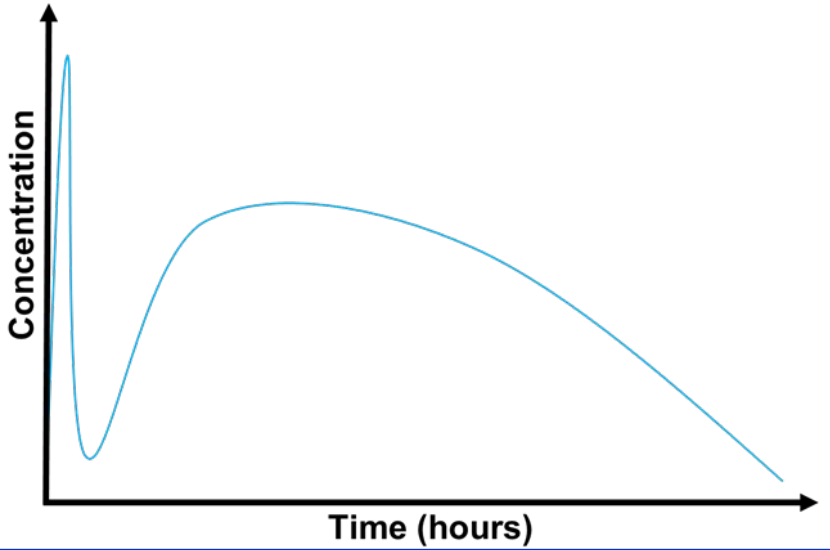




Bottom-Up







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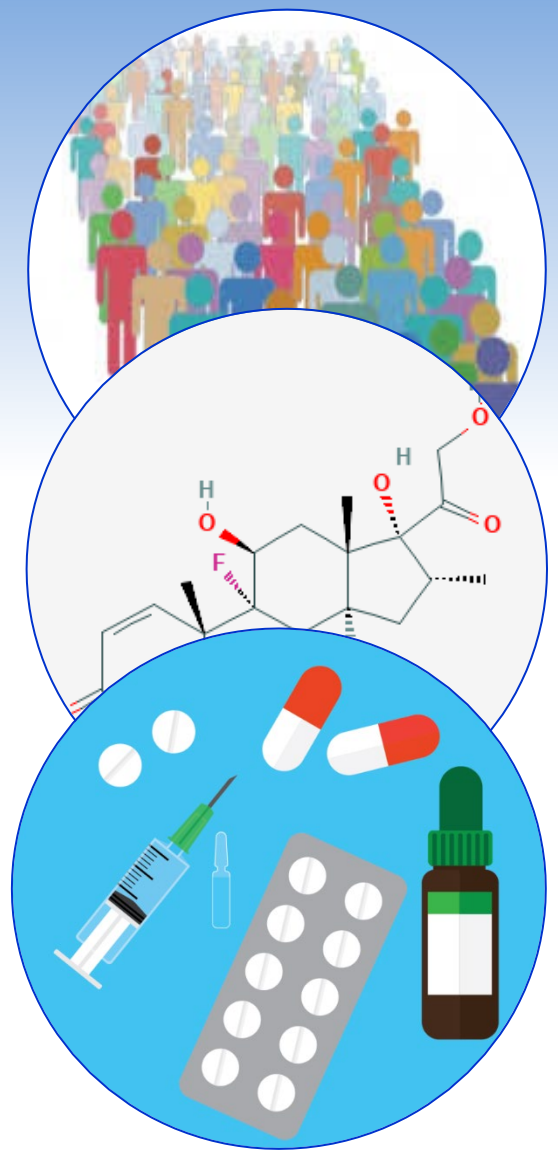
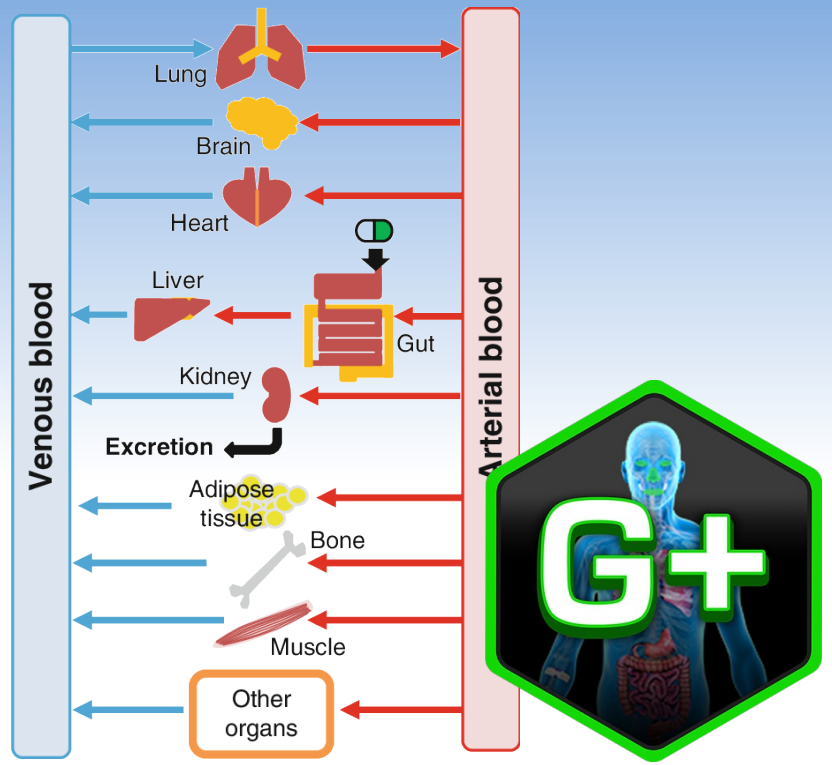
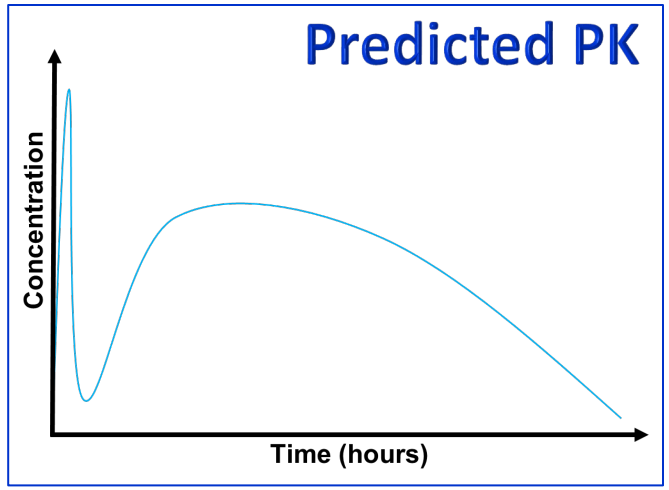
Bottom-Up Approach





Physiologically based Pharmacokinetics

- ✓ Interspecies scaling: FIH
- ✓ Special populations: **Pediatrics**, kidney and liver impaired
- ✓ Drug-drug interactions
- ✓ Food effect



Physiological frame

- ➢ Body/organ weight
- ➢ Blood flows
- ➢ Tissue composition
- ➢ Enzymatic abundance
- ➢ GIT

Drug parameters

- ➢ Phys-chem properties
- ➢ Protein binding
- ➢ Blood to plasma ratio
- ➢ Permeability
- ➢ Enzymatic clearance
- ➢ Transport clearance

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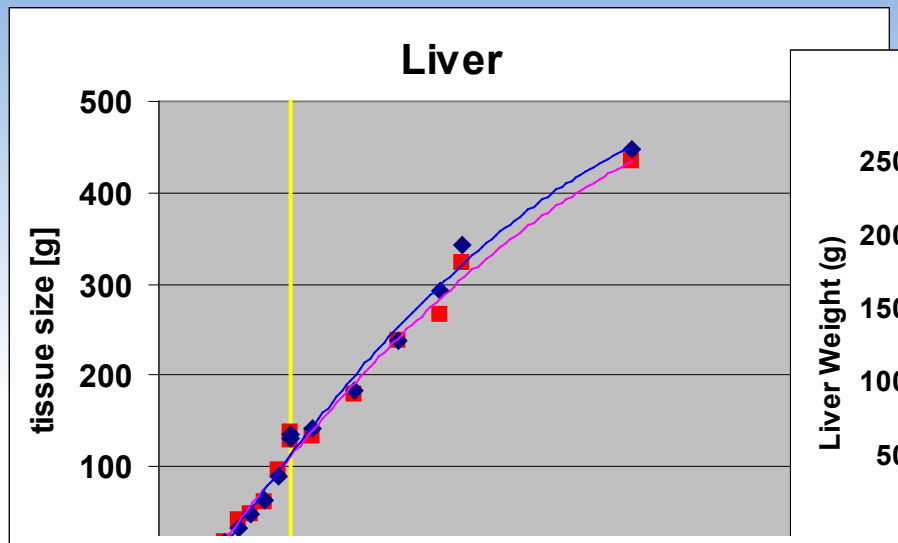
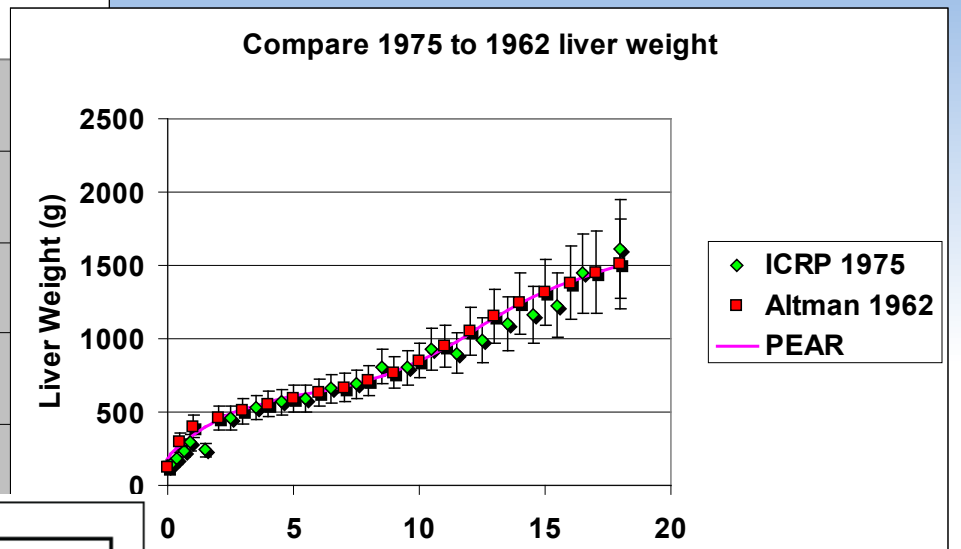
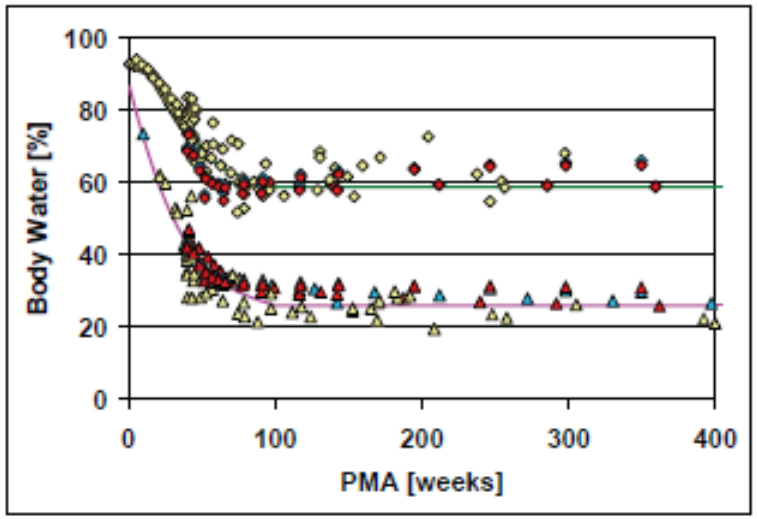
Pediatric physiology

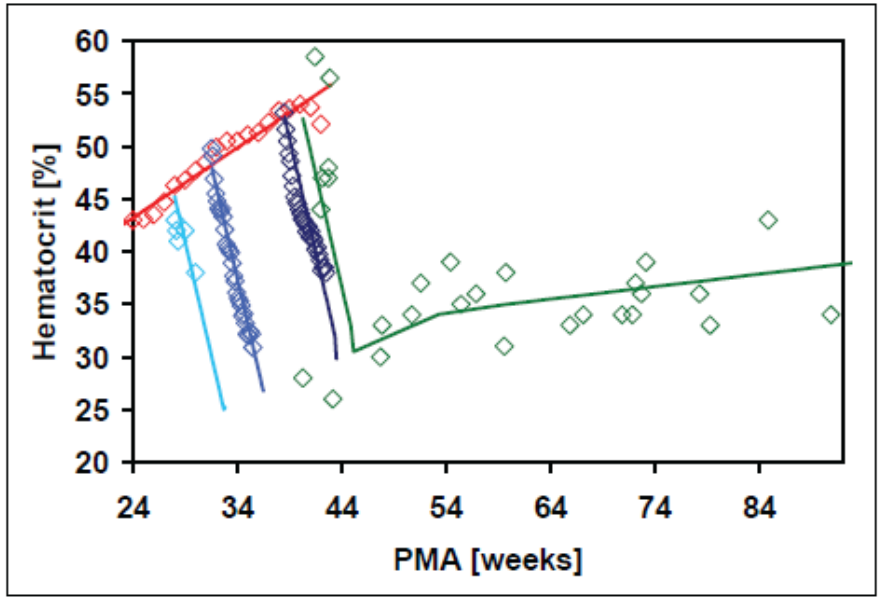
Main Pediatric Considerations for PBPK

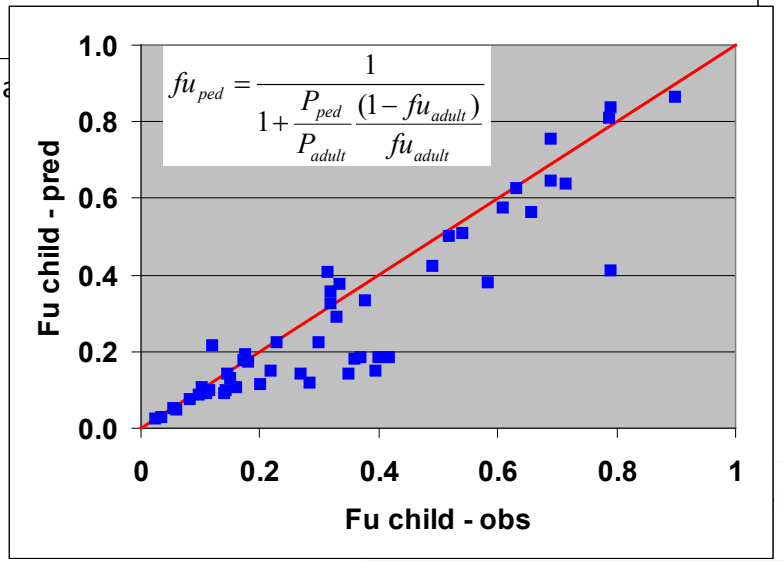
- Tissue sizes
- Organ flows
- GFR
- Tissue composition
- Hematocrit
- Plasma protein







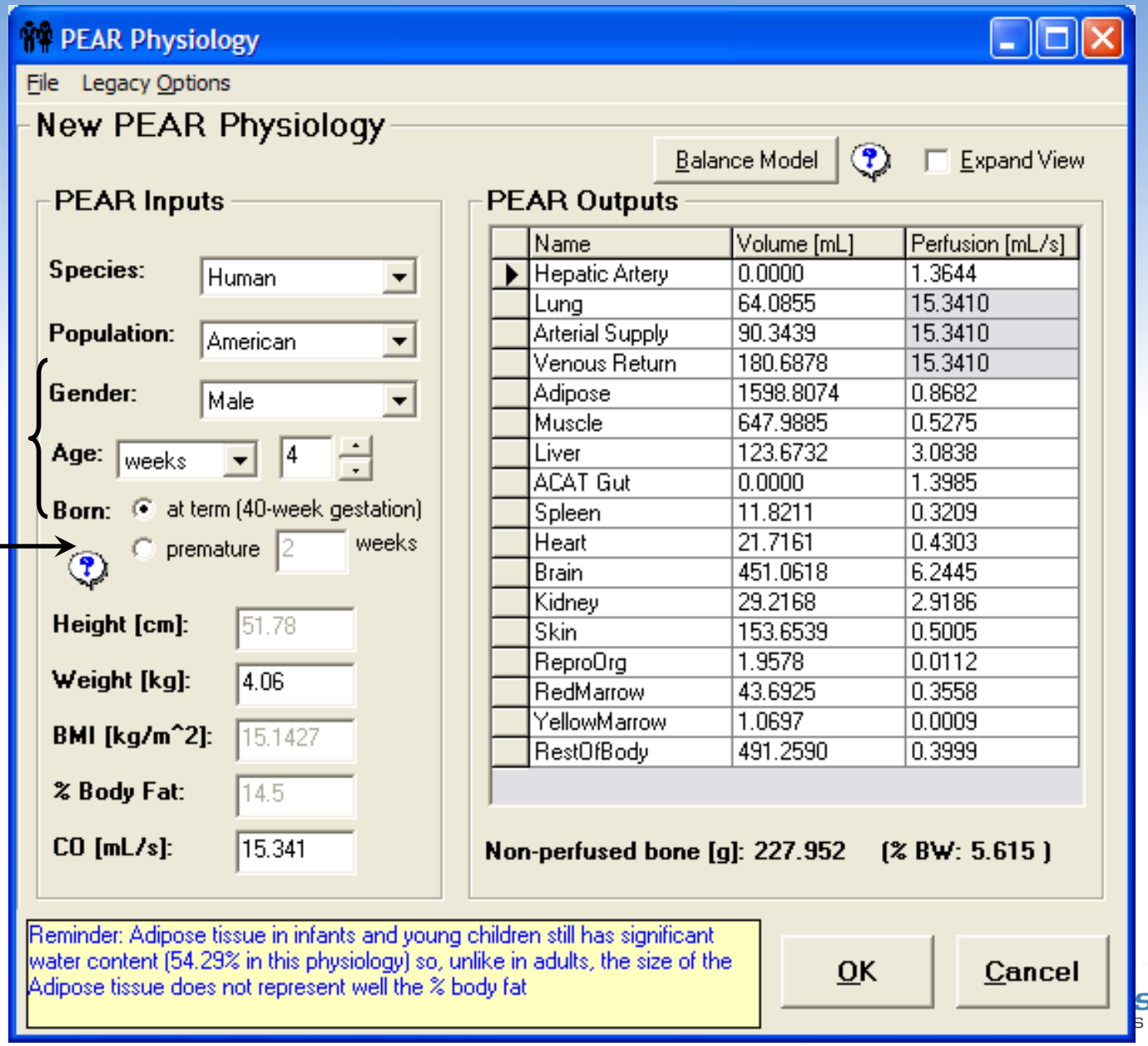




Pediatric physiology

For infants specify born **at term** or **premature** infant (up to 16 weeks premature)
(this option appears only when age is set to less than 1 year old)

Some physiological parameters are dependent on both, gestational age and postnatal age (i.e. % body fat, hematocrit, GFR)



Pediatric Intestinal physiology

- Limited information available for some parameters, i.e. gastric emptying or small intestine transit time (dependent on measurement method)
- For some parameters, the information is only qualitative (i.e. underdeveloped villi structure in infants < 3 years old or differences in bile salt composition and site of reabsorption)
- Intestinal Physiology Scaling in GastroPlus:
  - Stomach pH in neonates
  - Stomach volume
  - Intestinal length and radius (and subsequently volume)
  - Transit times
  - Enzyme and Transporter Expression Levels

Pediatric physiology: Enzyme Ontogeny

2 days old

Tissue Parameters for: Liver

Basic | Advanced | **Enzymes** | Transporters

Enzyme	Expression (mg-enz/g-tissue)	Expression CV	Turnover rate	Expression
2C19	6.99E-03			
2D6	1.49E-03			
2E1	1.70E-02			
3A4	2.61E-03			
3A5	1.03E-03			
3A7	3.35E-01			

Set Defaults | Add Enzyme

6 months old

Tissue Parameters for: Liver

Basic | Advanced | **Enzymes** | Transporters

Enzyme	Expression (mg-enz/g-tissue)	Expression CV (%)	Turnover rate [1/min]	Expression Source/Type
2C19	1.50E-02			
2D6	1.50E-02			
2E1	5.40E-02			
3A4	1.51E-01			
3A5	6.00E-02			
3A7	1.27E-01			

Set Defaults | Add Enzyme

1 year old

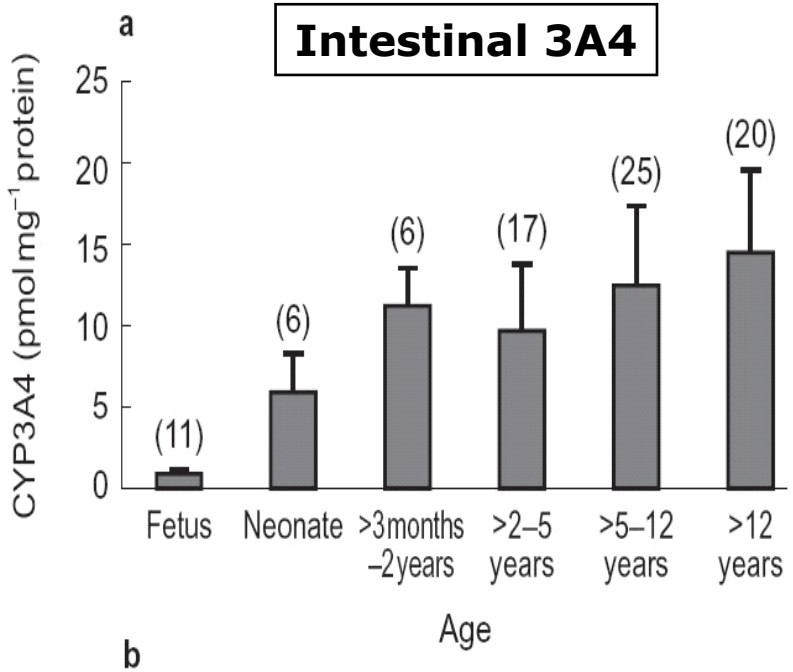
Tissue Parameters for: Liver

Basic | Advanced | **Enzymes** | Transporters

Enzyme	Expression (mg-enz/g-tissue)	Expression (%)
2C19	2.00E-02	106
2D6	1.60E-02	61
2E1	6.40E-02	61
3A4	1.92E-01	119
3A5	7.60E-02	119
3A7	7.00E-02	67

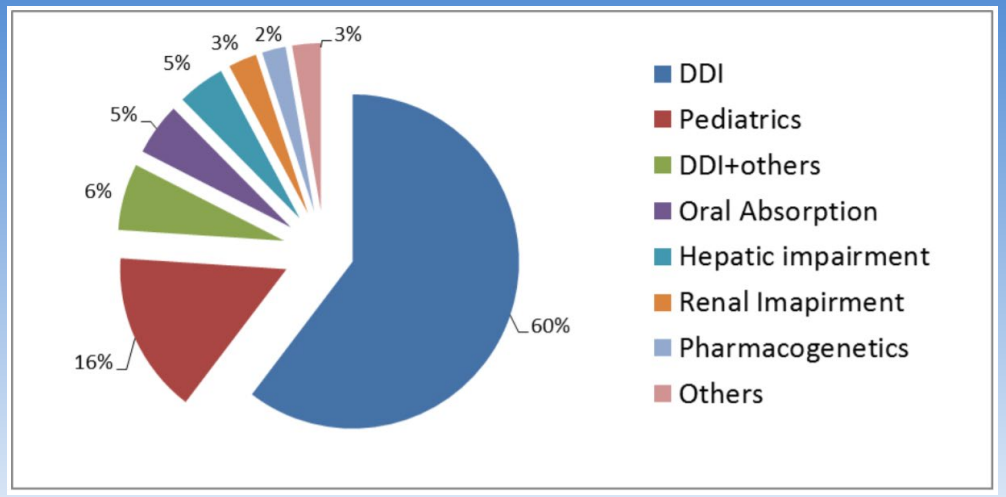
Set Defaults | Add Enzyme

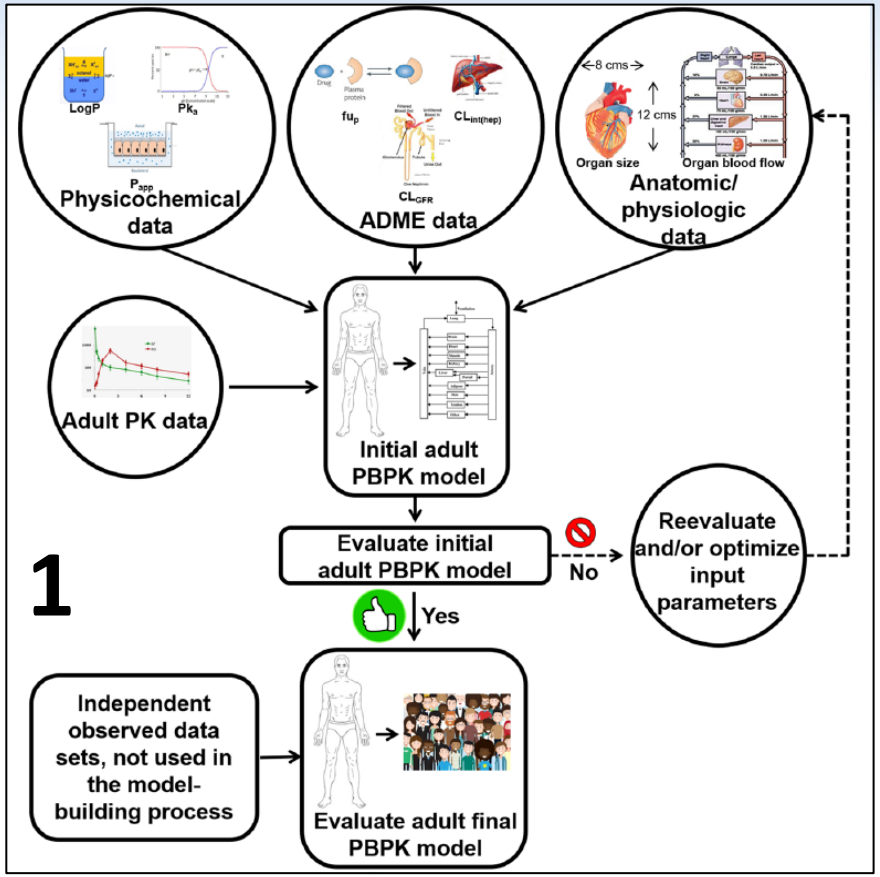
Intestinal 3A4

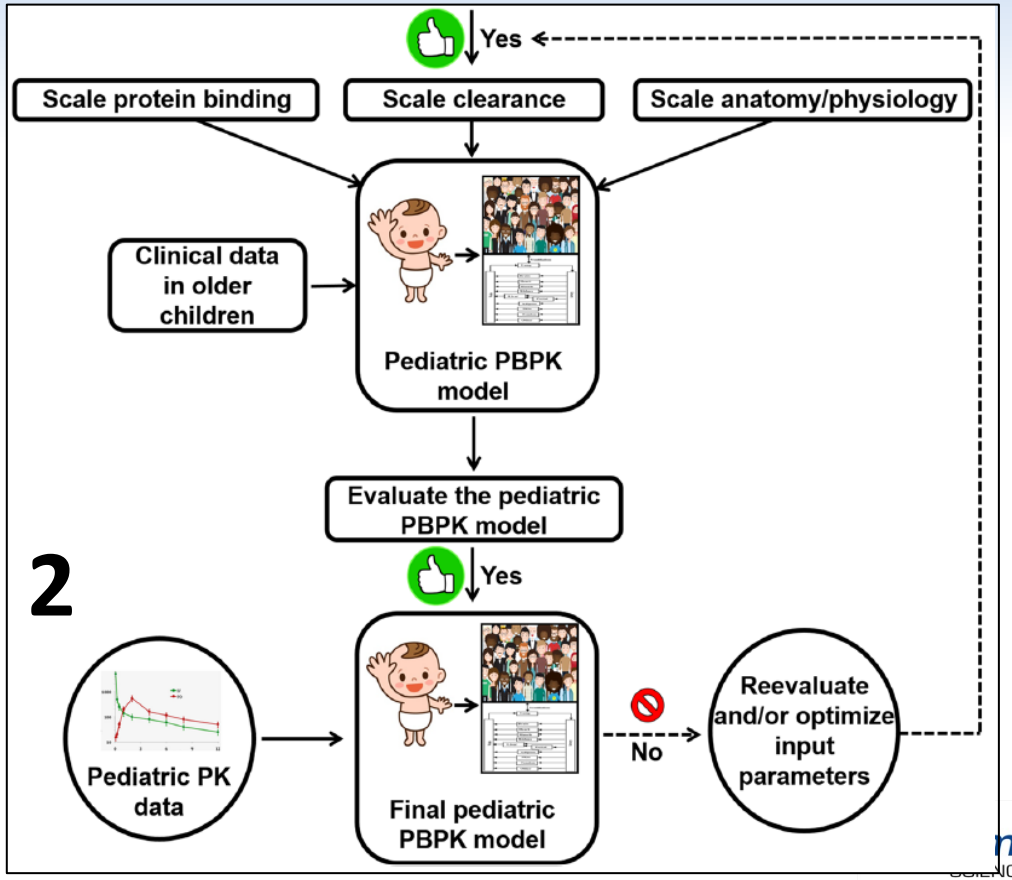


Pediatrics PBPK

- ➔ In 2016, Pediatrics application represented 16% of all applications using PBPK models. However only 2 cases were to support dosing recommendations in US prescribing information.
- ➔ Since then, PBPK knowledge has evolved



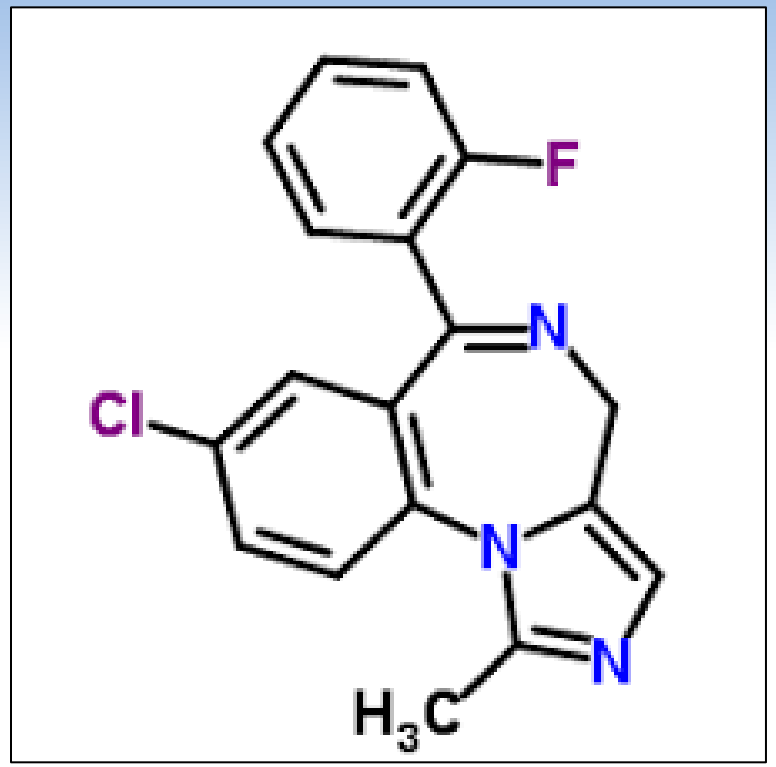




Yellepeddi et al. Clin Pharmacokinet (2019)

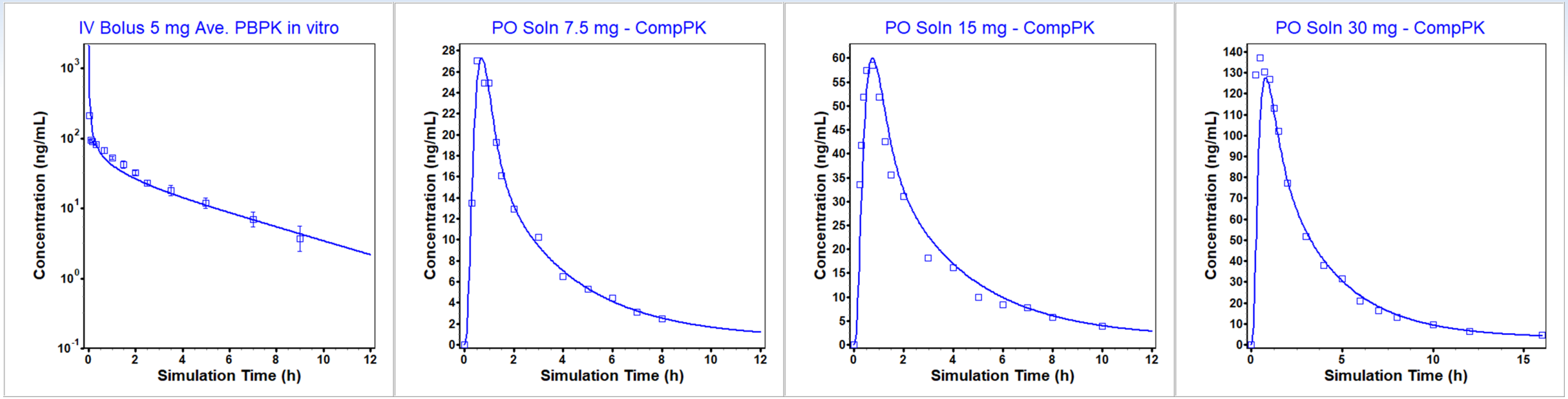
Midazolam case study

- BCS Class 1
- Well absorbed in the gastrointestinal tract
- Oral bioavailability = 35 % due to first pass metabolism
- Half life = 2 hours
- Metabolization by CYP3A4
- All in vitro parameters for volume of distribution and clearance estimation are available



Baseline adult model

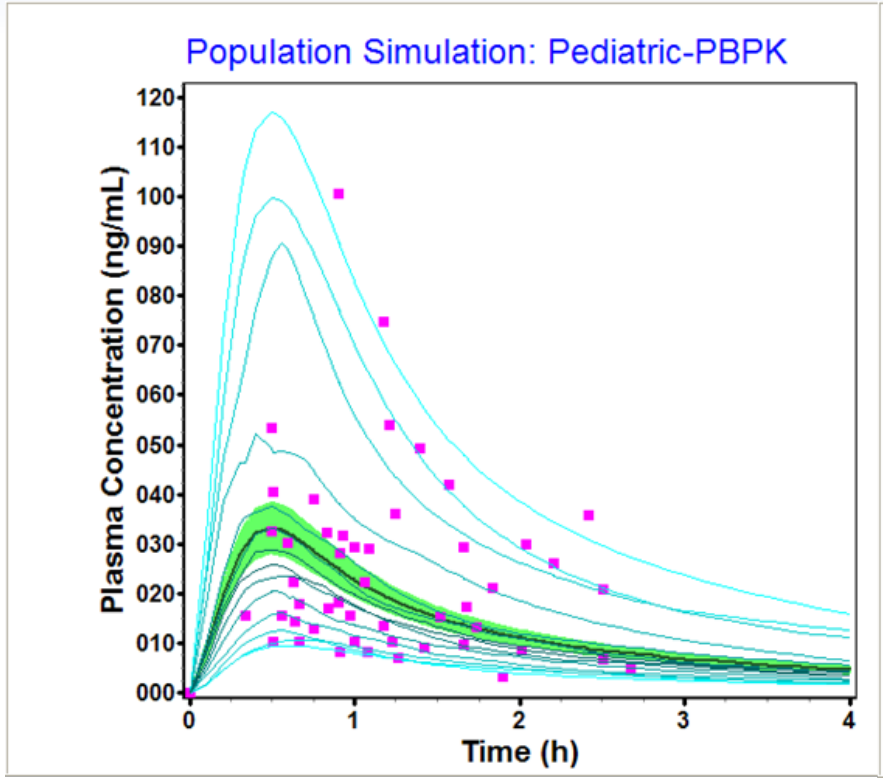
- In vitro parameters to estimate Vss (logD, pKa, fup, rbp)
- In vitro CYP3A4 Vmax and KM used to calibrate in vivo clearance
- Kidney clearance set to fup x GFR (minimal pathway)
- Studies population: Adult, 24 years old, 73 kg in average

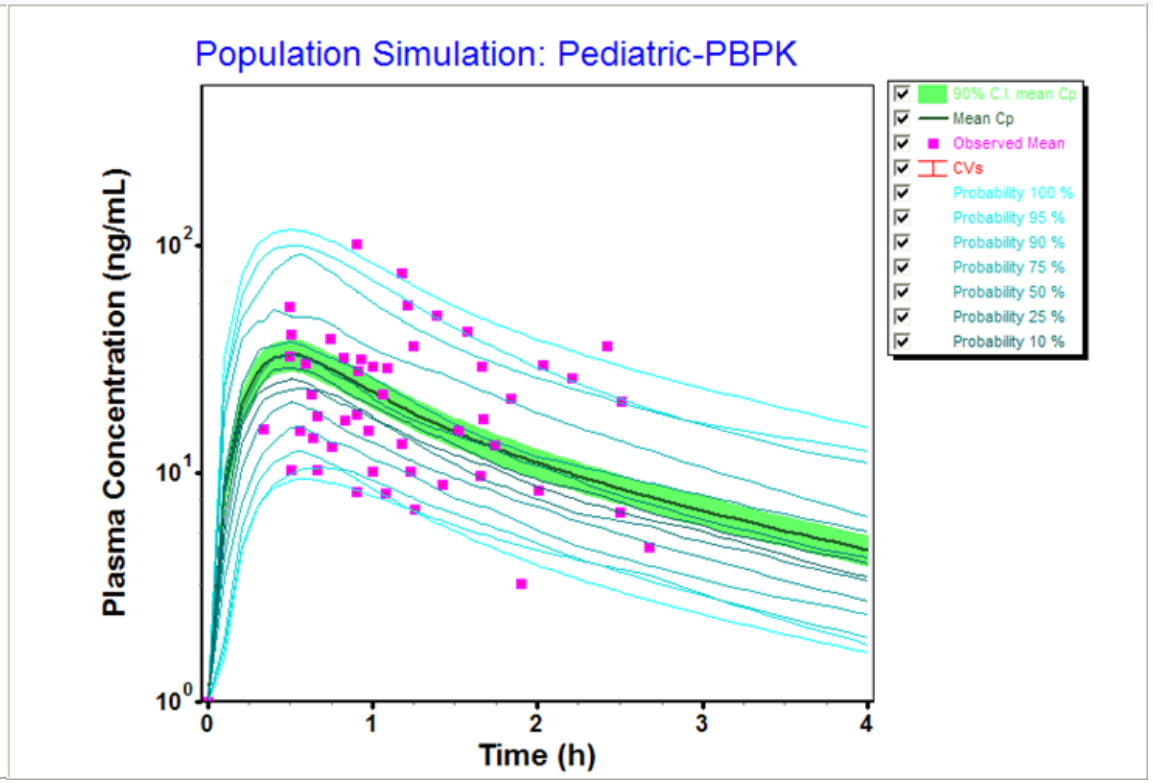


Overall, the model can describe the observed adult plasma concentration time course following the IV or PO administration of midazolam across a wide range of doses

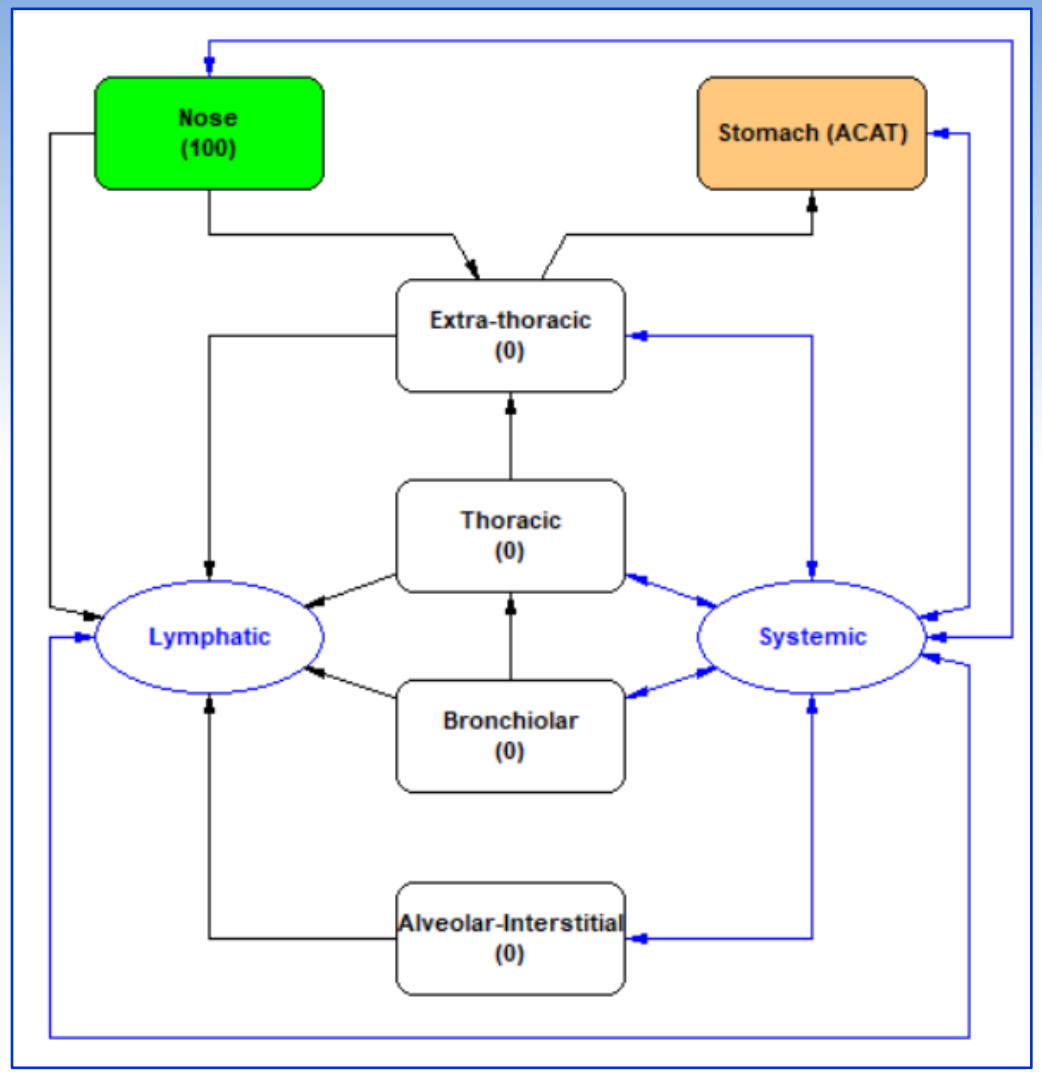
Pediatric PBPK: population simulation

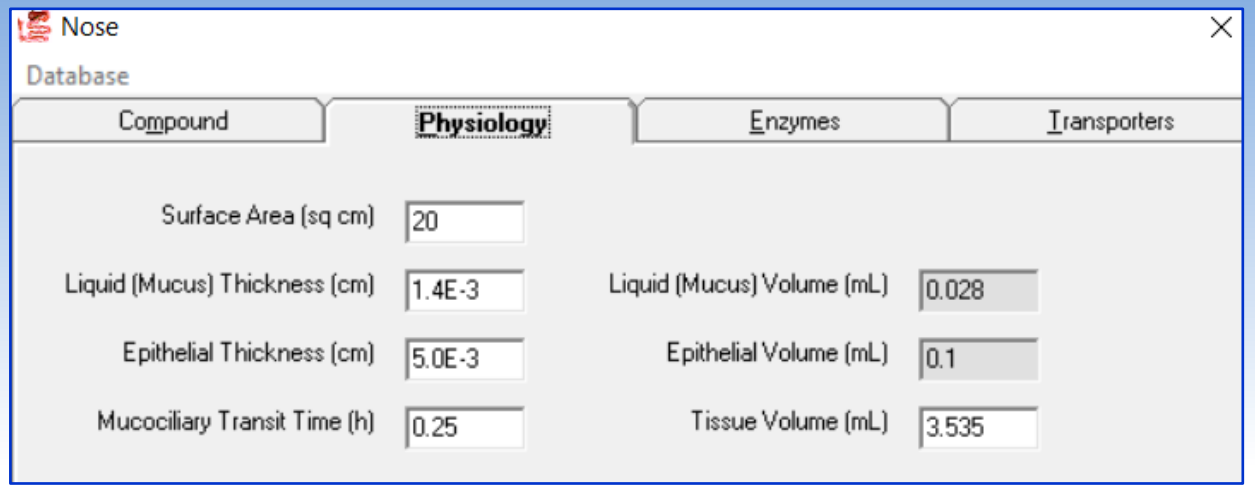
- In vitro parameters to estimate Vss (logD, pKa, fup, rbp)
- In vitro CYP3A4 Vmax and KM used to calibrate in vivo clearance
- Kidney clearance set to fup x GFR (minimal pathway)
- PBPK physiology set for pediatric population: Age range 1 – 12 yo
- Dose = 0.1 mg/kg PO





Intranasal administration PBPK

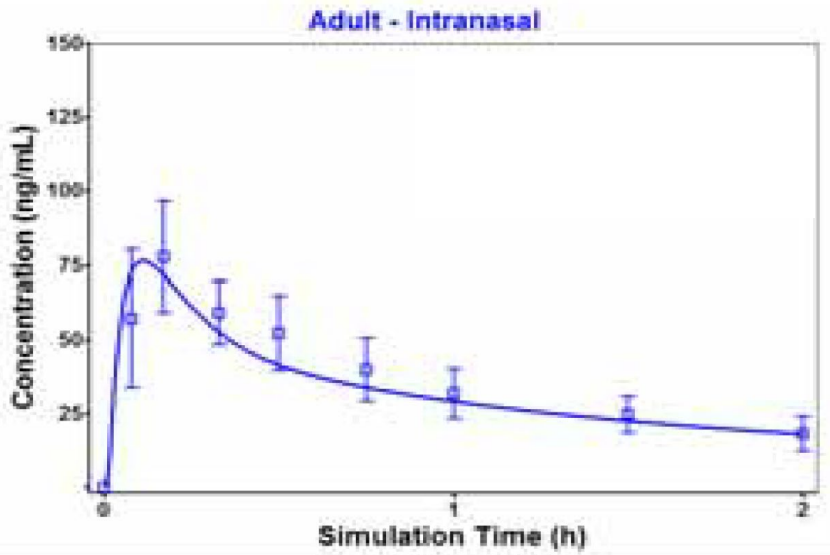




- Systemic compartment represents the systemic circulation in the PBPK model (verified using IV data)
- Stomach is the first compartment of the ACAT model (verified using PO data)
- Each tissue is defined by its own physiological parameters (age dependent)
- Once the drug is administered in the nose, it can (1) enter the systemic circulation (2) reach the stomach
- Intranasal-pulmonary model accounts for all absorption pathways

Intranasal administration: adult

- PBPK and mechanistic absorption (ACAT) models were used for simulation
- Intranasal-pulmonary model used to describe the administration of 5 mg

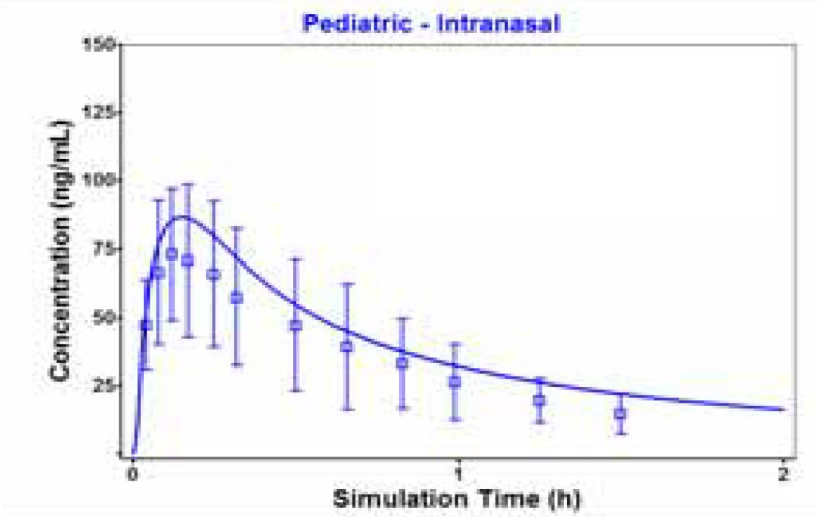


Adult	PO (5 mg)	IN (5 mg)
% absorbed from the nose	-	65.6
% absorbed from the gut	100	33.2
% reaching the portal vein	40.5	9.1
% bioavailable (F)	19.4	69.9

- Pulmonary systemic absorption rate were fitted using the observed data in adult
- Final model could describe the observed plasma PK data

Intranasal administration: pediatrics

- PBPK and mechanistic absorption (ACAT) models were used for simulation
- Intranasal-pulmonary model used to describe the administration of 0.1 mg/kg dose in pediatric subjects (2 years old, 12 kg)
- Pulmonary systemic absorption rates fitted using adult data were used



Pediatric	PO (1.2 mg)	IN (1.2 mg)
% absorbed from the nose	-	65.6
% absorbed from the gut	100	33.9
% reaching the portal vein	21.2	4.8
% bioavailable (F)	10.6	68.1

- Final model could describe the observed plasma PK data

Conclusions

- Pediatric study plans are mandatory by health authorities for drug approval
- These authorities recognize the role modeling and simulation can play to address efficacy and safety concerns for pediatric populations
- Because PBPK is based on physiology, these models can be scaled to describe a pediatric population
- PBPK combined with mechanistic absorption models validated against adult datasets can describe API ADME in pediatrics for multiple routes of administration

Thank you!

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